Restricted diets, micronutrient intake, and nutritional status

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FORWARD

This thesis contains original research in a style accepted for, submitted for, or appropriate for publication. All results chapters are presented in the format of a manuscript, comprising their own introduction, method, results, and discussion. A standalone methods section has been included to provide a comprehensive overview of the procedures used. Where relevant, the appendix contains manuscripts in their published or accepted format.

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STATEMENT OF CONTRIBUTION

I declare that the research presented in thesis is my original work produced with the assistance and support of those acknowledged below. All other contributions (ideas, data, images, or text) are fully credited and referenced. This thesis has not been submitted in whole or in part for any other academic degree or professional qualification. I also agree to have my text assessed for originality.

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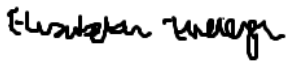
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PUBLICATIONS

Publications part of this thesis

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Eveleigh, ER, Coneyworth, L, Craigon, J, & Welham, SJM. (2023). Adoption of a short-term (4-week) vegan diet as part of 'Veganuary' significantly reduces saturated fatty acid (SFA), B12, and iodine intake in omnivorous individuals. *Suitable for submission in the European Journal of Nutrition.*

Eveleigh, ER, Coneyworth, L, & Welham, SJM. (2023). Iodine-fortified soya milk as a 'nutrient bridge' to improve iodine intake in vegan diets: A clinical trial protocol. *Suitable for submission in Nutrition and Health (Sage).*

Eveleigh, ER, Coneyworth, L, Craigon, J, & Welham, SJM. (2023). Systematic review and meta-analysis of iodine nutrition in modern vegan and vegetarian diets. *Br. J. Nutr*, 1-15.

Additional publications not part of this thesis

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Eveleigh, ER, Coneyworth, L, & Welham, SJM. (2023). Micronutrients in vegetarian and vegan diets. Dietary Supplements- Challenges and Future Research. London. IntechOpen.

ABBREVIATIONS

AMSR, Archive of Market and Social Research

ATA, American Thyroid Association

BDA, British Dietetics Society

BMIC, Breast milk iodine concentration

CI, Confidence interval

CNS, Central nervous system

CoFID, Composition of foods integrated dataset

COH, Carbohydrates

CRF, Case report form

D1, Deiodinase enzymes, type I

D2, Deiodinase enzymes, type II

D3, Deiodinase enzymes, type III

DDT, Organochlorines

DEFRA, Department for Environment Food and Rural Affairs

DIT, Diiodityrosine

DOB, Date of birth

DoH, Department of Health (UK)

DRV, Daily Recommended Value

EAR, Estimated Average Requirement

ECF, Extracellular fluid

EDTA, Ethylenediaminetetraacetic acid

EFSA, The European Food Safety Authority

EIrep:EE ratio, Reported Energy Intake to Energy Expenditure Ratio

ELISA, Enzyme-Linked Immunosorbent Assay

EPIC, European Perspective in Cancer

EU, European Union

FCQ, Food Choice Questionnaire

FD, Food diaries

FFQ, Food frequency questionnaires

FMHS, Faculty of Medicine & Health Sciences Research Ethics Committee Nottingham University Hospitals

FSA, Food Standards Agency

fT3, Free Triiodothyronine

fT4, Free Thyroxine

GDPR, General data protection regulation

GI, Gastrointestinal

hCG, Human chorionic gonadotropin

HPA, The hypothalamic-pituitary axis

I_2, Diiodine

I^-, Iodide

I/Creat, Iodine: Creatinine

ICCIDD, International Council for the Control of Iodine Deficiency Disorders

ICP-MS, Inductively coupled plasma mass spectrometry

IDD, Iodine deficiency disorders

IGN, Iodine Global Network

IO_3^-, Iodate

IO_4^-, Metaperiodate

IO_5^-, Orthoperiodate

IPAQ-SF, International Physical Activity Questionnaire Short Form

LRNI, Lower Reference Nutrient Intake

MIT, Monoiodotyrosine

MRC, Medical Research Council

MRC-HNR, Medical Research Council Collaborative Centre for Human Nutrition Research

MSC, Microbiological Safety Cabinet

MUFA, Monounsaturated fatty acids

mUIC, Median urinary iodine concentration

n-6, Omega 6

n-3, Omega 3

Na+/K+, ATPase-dependent sodium-potassium pump

NDNS, The National Diet and Nutrition Survey

NHLBI, National Heart, Lung, and Blood Institute

NICE, National Institute for Health and Care Excellence

NHI, National Institutes of Health

NIS, Na+/I− Symporters

NSP, Non-starch-polysaccharide

PBB, Polybrominated biphenyls

PCB, Polychlorinated biphenyls

PICOS, Population, Intervention, Comparison, Outcomes, and Study Framework

PHSRN, Population Health Services Research Network

PI, Principal Investigator

PPE, Personal protective equipment

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PUFA, Polyunsaturated fatty acids

QMC, Queen's Medical Centre

RCF, Relative centrifugal force

RCT, Randomised control trial

RDA, Recommended Dietary Allowance

RNI, Reference Nutrient Intake

rT3, Reverse T3

SACN, Scientific Advisory Committee on Nutrition

SAE, Serious Adverse Event

SFA, Saturated fatty acids

SIC, Salivary iodine concentration

SP, Salivary protein

SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials

SUSAR, Suspected Unexpected Serious Adverse Reaction

T3, Triiodothyronine

T4, Thyroxine

TBA, Thyroxine-binding albumin

TBG, Thyroxine-binding globulin

TBPA, Thyroxine binding prealbumin

Tg, Thyroglobulin

TMB, 3,3',5,5'-tetramethylbenzidine

TPO, Thyroperoxidase

TRH, Thyroid-releasing hormone

TRs, Thyroid hormone receptors

TSH, Thyroid-stimulating hormone

TTF-2, Thyroid transcription factor 2

UCreat, Urinary creatinine concentration

UIC, Urinary iodine concentration

UK, United Kingdom

UN, United Nations

UNICEF, United Nations Children's Fund

USI, Universal Salt Iodisation

WHO, World Health Organisation

ABSTRACT

Iodine deficiency in the UK has re-emerged in vulnerable groups. Dietary iodine has an essential role in the formation of thyroid hormones which regulate growth and metabolism. Iodine deficiency is particularly problematic for women of childbearing age and those who are pregnant and/or lactating as optimal thyroid function is vital for foetal neurodevelopment. Today, iodine deficiency is still considered the biggest single preventable cause of brain damage globally (WHO, 2007).

Vegans and vegetarians have been identified as a sub-group with an increased risk of iodine deficiency due to restricting foods that are typically known for being iodine rich (e.g. cow's milk, dairy products, white fish, and eggs). The risk of iodine deficiency is particularly problematic in vegan and vegetarian populations due to the uptake of these diets in young women. Globally, we are experiencing a transition to more sustainable diets and likely, the proportion of the world's population adhering to vegan/vegetarian diets will increase in the next decade. However, there are still few studies addressing iodine nutrition in individuals following vegan and vegetarian diets.

The research offered within this thesis aimed to investigate and expand the field of iodine in vegan and vegetarian diets. To do this, we addressed: (i) the world's literature on the topic of iodine in vegan and vegetarian diets; (ii) the prevalence of low iodine intake, status, and knowledge of habitual vegans and vegetarians living in an area historically associated with iodine deficiency (Nottinghamshire); (ii) the influence of short-term (4-week) vegan diets on iodine and micronutrient intake, and status; (iv) approaches to improve the iodine nutrition of individuals following vegan diets.

The first research article systematically reviewed 15 studies exploring the iodine intake and status of individuals following vegan and vegetarian diets residing in industrialised countries. Vegans were found to have an increased risk of low iodine status, deficiency, and inadequate intake compared with adults following less restrictive diets. This article also found that the level of iodine deficiency in vegans appears to relate closely to national iodine status.

The second research project (a cross-sectional study of iodine nutrition in Nottinghamshire) determined that although vegans and vegetarians had the lowest iodine intake and status compared to omnivores, median dietary iodine was below the Reference Nutrient Intake (RNI) for all groups. We also discuss that iodine knowledge is very poor among British participants. The third study identified that following a short-term vegan diet as part of global campaigns such as 'Veganuary' significantly reduced the iodine and B12 intake of omnivorous participants. However, long-term markers of iodine status and thyroid function did not change, suggesting that the endocrine systems can adapt to some extent to a temporary decline in dietary iodine. The fourth study proposes a clinical trial protocol to address the effectiveness of iodine-fortified alternative milk as a vehicle to improve iodine intake in vegans. Our final study re-evaluates the literature in the field of iodine in vegan and vegetarian diets. Results from our meta-analysis suggest that vegans are significantly more likely to have low iodine intake compared to omnivores. We also identify that voluntary salt fortification schemes may overlook vegan and vegetarian individuals within the population. The research presented in this thesis confirms that vegans and vegetarians are a sub-group with an increased risk of iodine deficiency. Our findings could have devastating public health consequences given that these diets are frequented by women of childbearing age. We also confirm that iodine deficiency is re-emerging in the UK. There is an urgent need to implement national strategies and policies to improve iodine awareness and promote the consumption of appropriate iodine sources for all dietary groups. Continued monitoring of individuals following vegan and vegetarian diets is required as more individuals transition to sustainable diets globally.

1. INTRODUCTION

1.1 Iodine

1.1.1 Definition

Iodine is an element with the atomic symbol of I, an atomic number of 53, and an atomic weight of 126.9 (PubChem, 2022). Iodine is the heaviest of the stable halogens (group 17 of the periodic table). Unlike other stable halogens (fluorine, chlorine, and bromine), iodine exists as a solid at room temperature (PubChem, 2022). Iodine can form a diatomic molecule, diiodine (I_2), and can exist in oxidation states as iodide (I^-), iodate (IO_3^-), or as periodate anions (e.g., metaperiodate IO_4^- and orthoperiodate IO_5^-) (PubChem, 2022).

1.1.2 The iodine cycle

The iodine cycle describes the geochemical movement of iodine through the natural environment and is a vital link to the food chain (**Figure 1.1**). Seawater is the main terrestrial source of bioavailable iodine (Fuge and Johnson, 2015; Ito, 1971). The iodine rich content of seawater is achieved by leaching of terrestrial soil surfaces by rainfall (wet precipitation), snow, or glaciation (Fuge and Johnson, 2015). Rivers and estuaries return iodine from these sources into seawater (Fuge and Johnson, 2015). Iodine within seawater is transferred to the atmosphere and dispersed to land areas by volatilisation (Fuge and Johnson, 2015). The volatilisation process is facilitated by biological sources (e.g. macroalgae) and oxidisation of ozone (Fuge and Johnson, 2015; Pillar-Little *et al*., 2013). Iodine within the atmosphere is transferred to terrestrial locations by wet and dry precipitation, or sea spray (Whitehead, 1984). Wet precipitation is the main method of iodine removal from the atmosphere, with rainfall being the top means (Whitehead, 1984), whereas dry deposition describes the transfer of iodine directly from the atmosphere to terrestrial areas (Whitehead, 1984). In terrestrial areas, the iodine in soils and plant-systems is mostly derived from wet and dry deposition (Fuge and Johnson, 2015). Soil can be fixated with iodine if distributed on iodine rich materials (e.g. limestone) (Fuge and Johnson, 2015).

The iodine concentration of plants is relative to the iodine content of the soil in the region in which it has been grown (Fuge, 2013). Plant foods typically have a low iodine content unless bio-fortified (Fordyce, 2003). This is partly because soil iodine is bound and is not easily transferred to plant roots (Fordyce, 2003). Additionally, soil iodine is depleted by glacial leaching, flooding, and erosion (Fuge and Johnson, 2015; Johnson, 2003).

Historically, the global geochemical cycle of iodine and the distribution of iodine in the marine and terrestrial environment was associated with the prevalence of iodine deficiency (Lazarus, 2015). However, nowadays, the prevalence of poor iodine nutrition, particularly in affluent areas such as Europe, does not associate strongly with the environmental transfer of iodine and is more closely related to changes in diet (Lazarus, 2015).

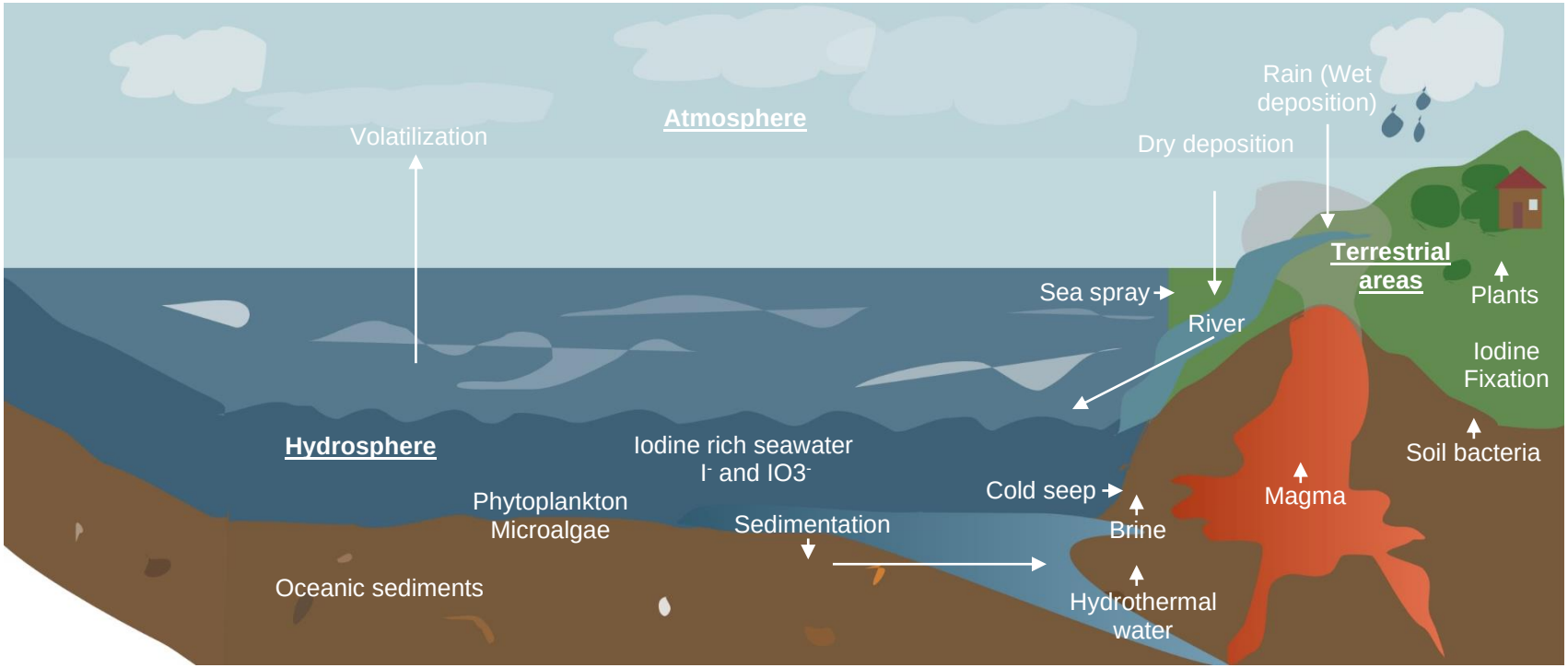


Figure 1.1. The iodine cycle.

Seawater is the largest store of iodine (Hydrosphere) (7.9 × 1016 g). Volatilization is the main route of iodine transfer into the atmosphere (~5 × 1012 g) and requires action of Phytoplankton and Microalgae. Atmospheric iodine is transferred to terrestrial areas by dry and wet participation or sea spray. Other routes of terrestrial iodine are from the iodine fixation of soils on materials that are iodine rich (e.g. limestone). Adapted from: Medrano *et al.*, 2016.

1.1.3 Physiology and functions of iodine in human health

Iodine is required for the optimal functioning of endocrine systems and has essential roles in other structures including the digestive and reproductive systems (Ahad and Ganie, 2010). A healthy human body contains 15000 – 20000 μg of iodine, of which 70-80% is concentrated in the thyroid gland (Ahad and Ganie, 2010). Iodine must be provided via the diet and cannot be endogenously synthesised by organisms (Ahad and Ganie, 2010). An adequate intake of iodine is required through all stages of development, or else deficiency will present serious growth and metabolic consequences (see Introduction Section 1.1.5) (Ahad and Ganie, 2010; Eastman and Zimmermann, 2018; Kapil, 2007; Zimmermann, 2009a; Zimmermann and Boelaert, 2015).

1.1.3.1 Iodine absorption

The bioavailability of iodine describes the available iodine provided and absorbed from the diet (Ahad and Ganie, 2010). Iodide is the predominant form of iodine in foods (EFSA, 2014). Other forms of iodine within foods are reduced to iodide before absorption (EFSA, 2014; Public Health England, 2014). After consumption, dietary iodide is readily absorbed in the small intestine of the gastrointestinal (GI) tract (Josefsson *et al*., 2002). The absorption of dietary iodide is tightly controlled by regulation of intestinal Na^+/I^- symporters (NIS) in enterocytes (Josefsson *et al*., 2002; Portulano *et al*., 2014).

NIS are plasma membrane glycoproteins that mediate the active transport of iodide (Josefsson *et al*., 2002; Portulano *et al*., 2014). When the diet provided is rich in iodide and the thyroidal iodine requirements are met, intestinal NIS expression is reduced and excess iodide (90% of ingested iodine) is excreted by the kidneys into the urine (Nicola *et al*., 2012). The salivary gland and the stomach similarly are involved in the clearance of iodide in faeces and sweat (Rousset *et al*., 2015). Once absorbed, iodide is distributed around the body by the circulatory system (Public Health England, 2014; Rousset *et al*., 2015). Of absorbed iodine, 30% is extracted from the plasma by the thyroid gland to be used in thyroid hormone synthesis (Josefsson *et al*., 2002).

1.1.3.2 Iodine bioavailability

Early studies of iodine bioavailability determined that of a 100 µg portion of iodide, around 20% would be utilised by the thyroid gland (Hurrell, 1997). Rat balance studies have also been conducted to assess iodine bioavailability (Hurrell, 1997). Balance studies from the 1920s found iodine absorption was approximately 90% in most foods with watercress being the exception (100% absorption) (Hurrell, 1997). Other studies have addressed human iodine bioavailability in foods that are considered important dietary sources of iodine such as cow's milk and seaweed (Combet *et al*., 2014; van der Reijden *et al*., 2019). Katamine *et al* (1987) established that not all food iodide is completely absorbed, the structure of foods could prevent iodine bioavailability, and cooking practices (e.g. heating) may liberate iodine within foods. Other investigations of iodine bioavailability from food in humans have involved studies with radioactive isotopes of iodine (e.g. 131I) (Hurrell, 1997).

1.1.3.3 The thyroid gland

The thyroid gland is the site of iodine metabolism and production of the thyroid hormones (**Figure 1.2).** The thyroid gland is arranged into the right and left lobules comprised of multiple follicles (Allen and Fingeret, 2021; Beynon and Pinneri, 2016). The follicles are lined by follicular cells on a basement membrane which can secret the thyroid hormones (Beynon and Pinneri, 2016; Rousset *et al*., 2015). Amongst the follicular cell walls are smaller cells called Parafollicular cells that have a role in calcium and phosphate deposition in skeletal and other tissues (Bhagavan and Ha, 2015). Thyroid follicles are filled with a material called colloid, which is made up of a glycoprotein called thyroglobulin (Tg) which is required to produce the thyroid hormones (Beynon and Pinneri, 2016).

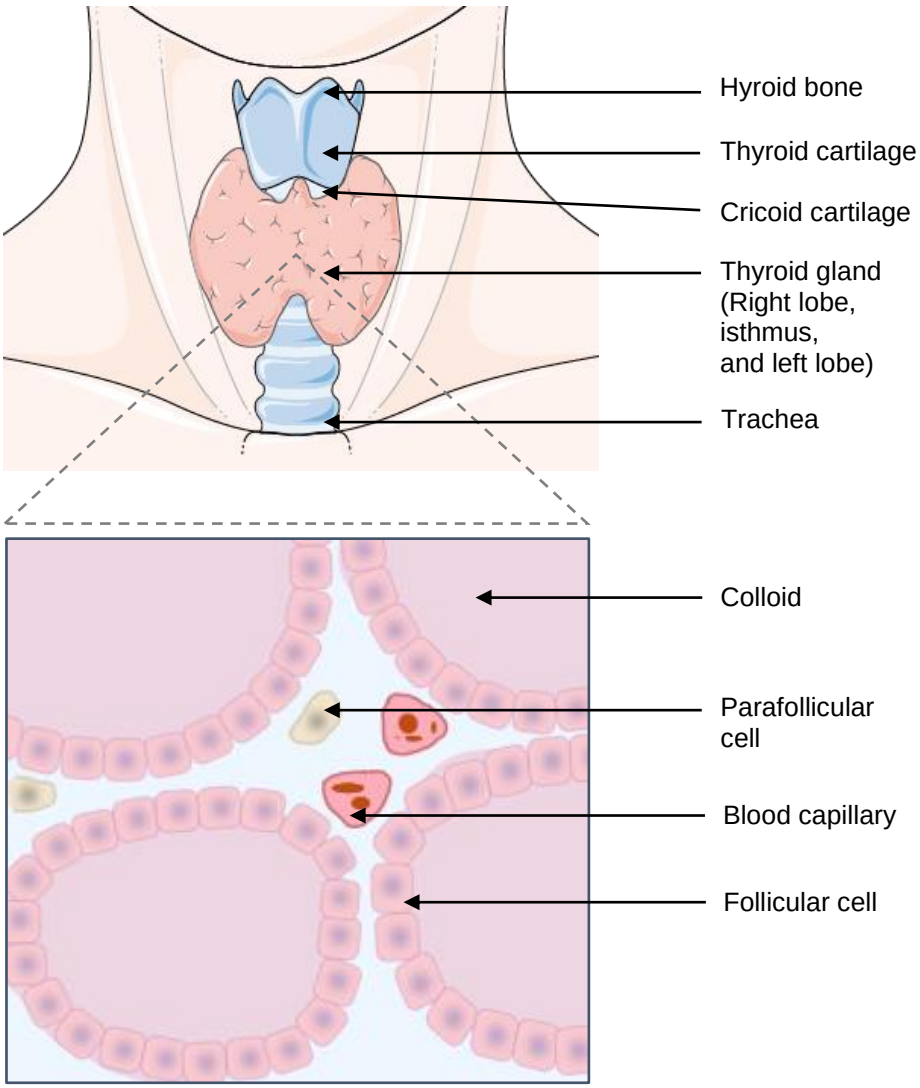


Figure 1.2. Structure of the thyroid gland and thyroid follicles.

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1.1.3.4 The thyroid hormones

The thyroid hormones, Triiodothyronine (T_3) (molecular formula – $C_{15}H_{11}I_4NO_4$) and Thyroxine (T_4) (molecular formula – $C_{15}H_{12}I_3NO_4$) are tyrosine-based hormones that act on almost all cells in the human body (Rousset *et al*., 2015) (**Figure 1.3).** In healthy adults with adequate iodine intake, 80% of bodily thyroid hormone exists as the active form of T3 (Rousset *et al*., 2015).

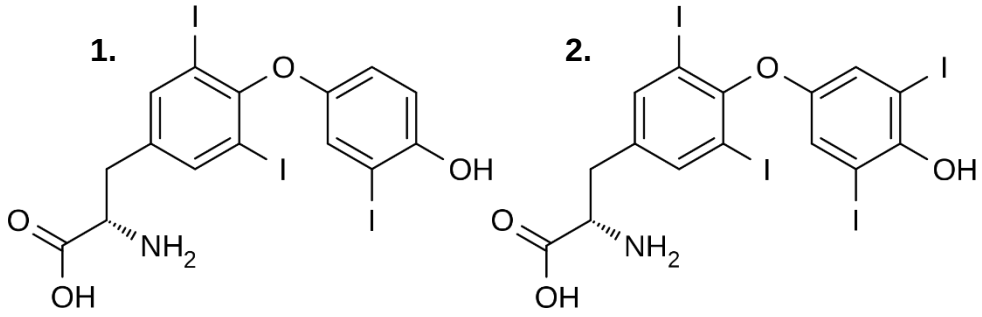


Figure 1.3. Molecular structure of the thyroid hormones; 1. Triiodothyronine (T3) and 2. Thyroxine (T4).

1.1.3.5 Iodine metabolism, thyroid hormone synthesis, and regulation

The first stage of iodine metabolism and thyroid hormone synthesis is iodine trapping (**Figure 1.4**). Iodide is actively transported from the extracellular fluid (or plasma) into the thyroid follicular cell (thyrocytes) using NIS located on the basolateral plasma membrane. An ATPase-dependent sodium-potassium pump (Na^+/K^+) provides energy to facilitate the active transport of iodide into the follicular cell (Josefsson *et al*., 2002). Following transport via the NIS (Josefsson *et al*., 2002), iodide is passively transported across the apical plasma membrane into the thyroid follicle lumen using the favourable electrical and concentration gradients created (Rousset *et al*., 2015). Select research has proposed the presence of a possible iodide transporter called Pendrin, a membrane glycoprotein located at the apical plasma membrane (Twyffels *et al*., 2011). However, the role of this protein in the efflux of iodide across the apical membrane of thyrocytes into the follicular lumen is still disputed (Twyffels *et al*., 2011).

Once entering the follicular cell colloid, iodide is oxidised by an enzyme called thyroperoxidase (TPO). The oxidation of iodide to neutral iodine happens in the presence of H_2O_2. Iodine is then bound to specific tyrosyl residues within the Tg molecules located in the thyroid follicles (Ruf and Carayon, 2006). Iodide is rapidly oxidised and only contributes approximately 1% of total iodine within the thyroid (Rousset *et al*., 2015). Iodination of the tyrosine residues of Tg begins at position 3 to form monoiodotyrosine (MIT) and then at position 5 to form diiodityrosine (DIT) (iodotyrosyl residues) (Rousset *et al*., 2015). The thyroid hormones, triiodothyronine (T3) and thyroxine (T4) are then synthesised by the coupling of iodotyrosyl residues (MIT and DIT) (Rousset *et al*., 2015). Two DIT form T4 and one MIT and one DIT form T3 (Rousset *et al*., 2015). The thyroid hormones are stored in thyroid follicles as colloid and can be used when required. Typically, stored hormones can supply requirements for approximately 3 months (Ahad and Ganie, 2010).

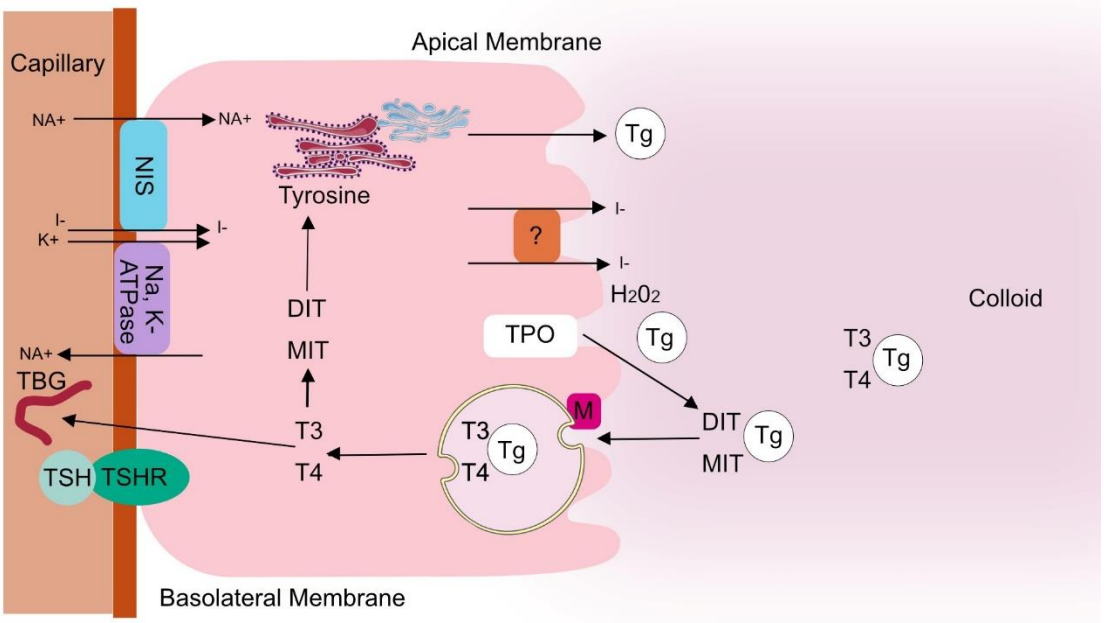


Figure 1.4. Iodine metabolism and thyroid hormone synthesis.

NIS, Na+/I− symporter; Na K- ATPase, ATPase-dependent sodium-potassium pump (Na+/K+); TPO, Thyroperoxidase; MIT, Monoiodotyrosine; DIT, Diiodityrosine; Tg, Thyroglobulin; M, Megalin; T3, Tri-iodothyronine; T4, Thyroxine; TSH, Thyroid stimulating hormone; TSHR, Thyroid stimulating hormone receptor; TBG, Thyroxine-binding globulin. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

The iodinated Tg is transferred from the thyroid colloid in the follicular lumen to the follicular cell by endocytosis (Rousset *et al*., 2015). A receptor called megalin is located on the apical membrane of thyocytes and supports the transfer of the iodinated Tg (Rousset *et al*., 2015). Once entering the cytoplasm of the follicular cell, the iodinated Tg moves towards the basal membrane (Rousset *et al*., 2015). Lysosome vesicles fuse with the colloid material (Rousset *et al*., 2015). Proteases contained within the lysosome vesicles digest the Tg molecule and release T4, T3, DIT and MIT into the cytoplasm (Rousset *et al*., 2015). The thyroid hormones T4 and T3 move to the basal surface of the follicular cell and diffuse into the blood capillary for transport in circulation (Rousset *et al*., 2015). MIT and DIT do not transfer into the blood capillary and are instead deiodinated by a deiodinase enzyme to release iodide and tyrosine to be recycled for further thyroid hormone production (Rousset *et al*., 2015).

T4 and T3 in the bloodstream are transported bound to binding proteins such as thyroxine-binding globulin (TBG), thyroxine-binding prealbumin (TBPA), and thyroxine-binding albumin (TBA) (Rousset *et al*., 2015). Only 1% of T4 and T3 circulate unbound and are biologically active to prevent urinary losses (Rousset *et al*., 2015). T3 is the active form of thyroid hormones and can be cleaved from T4 in the circulation by peripheral deiodination (Rousset *et al*., 2015).

The thyroid gland requires 80 μg day^{-1} of iodine for thyroid hormone production, 60 μg day^{-1} of iodine is replenished in the extracellular fluid (ECF) by the degradation of T4 and T3 in the liver, and 20 μg day^{-1} is excreted in faecal matter (Ahad and Ganie, 2010). Iodine balance is tightly regulated in the thyroid cells and ECF. In iodine excess, thyroid hormone synthesis is inhibited, this autoregulation is known as the Wolff–Chaikoff effect and Jöd-Basedow phenomenon (see Introduction, Section 1.1.9) (Bürgi, 2010; Wolff and Chaikoff, 1948).

However, asides from iodine concentration, the primary limiting factor in thyroid hormone production is thyroid stimulating hormone (thyrotropin) (TSH) (Pirahanchi *et al*., 2022). TSH is a peptide hormone produced by the anterior pituitary gland that triggers thyroid follicular cells to release T4 and T3 (Pirahanchi *et al*., 2022). The hypothalamic-pituitary axis (HPA) regulates TSH release in hypothalamic neurons via the secretion of thyroid-releasing hormone (TRH) (Mariotti and Beck-Peccoz, 2021) (**Figure 1.5**). T4 and T3 in the circulation control TSH levels by negative feedback, whereby, low levels of T3 and T4 increase TSH release (Pirahanchi *et al*., 2022). TSH facilitates the thyroidal functionality of iodine by stimulating the expression of NIS, TPO, Tg, and H_2O_2 involved in iodine trapping (Pirahanchi *et al*., 2022). Moreover, TSH promotes the formation of the active T3 comparative to T4, prioritises the iodination of tyrosyls, and increased the rate at which Tg is internalised by thyrocytes before hormone release (Rousset *et al*., 2015). Each of these roles of TSH can control the amount of iodine available to cells and subsequently improve the effectiveness of thyroid hormone production.

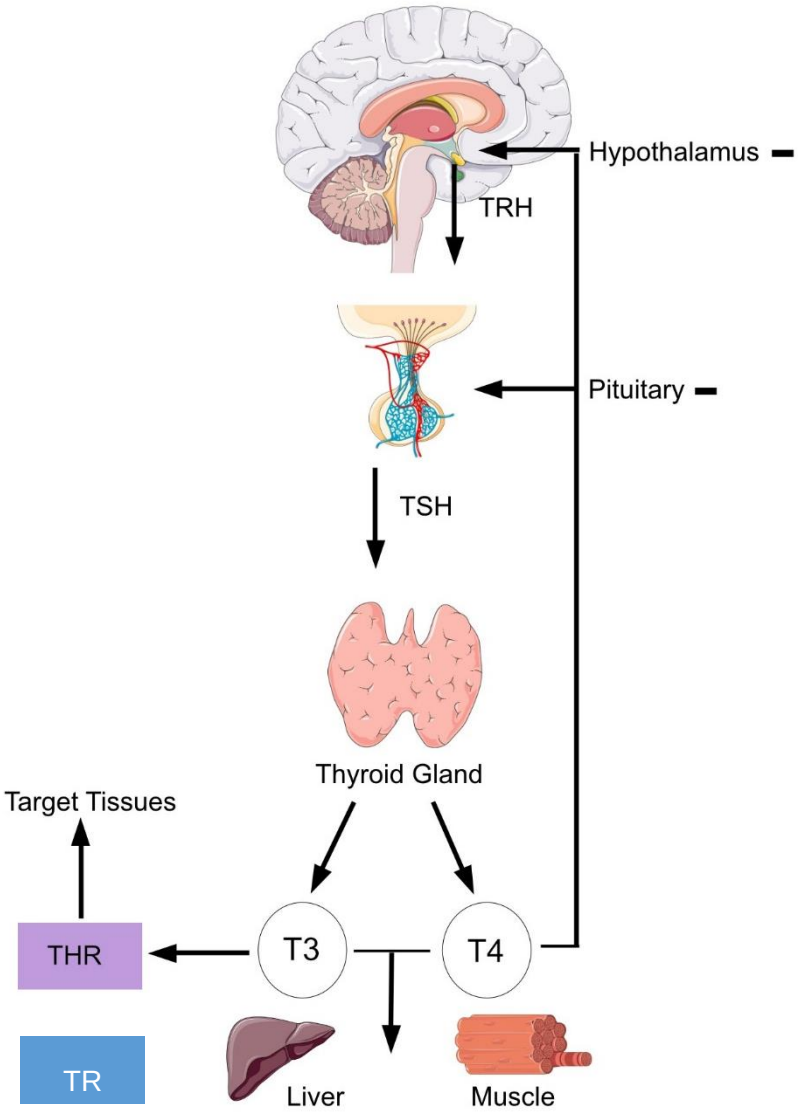


Figure 1.5. Schematic of the Hypothalamic-Pituitary-Thyroid Axis (HPA).
TRH, Thyrotropin-releasing hormone; TSH, Thyroid stimulating hormone; T3, Tri-iodothyronine; T4, Thyroxine; TR, Thyroid hormone receptors. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

1.1.3.1 Thyroid hormone function

T3 and T4 are lipophilic molecules, but unlike other lipophilic substances, they cannot transverse cell membranes passively and require ATP-dependent carrier-mediated transport to enter cells (Rousset *et al*., 2015). Thyroid hormones bind to nuclear hormone receptors called thyroid hormone receptors (TRs) that are expressed on certain tissues (Bakker, 2004). Only the active form of thyroid hormone T3 can bind to TRs, hence, most tissues that respond to thyroid hormones contain deiodinases, which catalyse the removal of an iodine atom from the T4s structure (Bakker, 2004). There are three related isoforms of deiodinase enzymes, type I (D1), II (D2), and III (D3) (Bernal, 2016). D1 is expressed in the liver, kidneys, and thyroid gland (Bernal, 2016; Zhang *et al*., 2003). D2 is expressed in the central nervous system (CNS), the pituitary gland, brown adipose, and skeletal muscle (Bernal, 2016; Zhang *et al*., 2003). D3 contributes to the breakdown of the thyroid hormones and is expressed in the brain, placenta, and foetal tissues (Bernal, 2016; Zhang *et al*., 2003).

1.1.3.1 The role of other micronutrients in thyroid hormone function

Coexisting micronutrient deficiencies may exacerbate iodine deficiency and contribute to altered thyroid function. **Table 1.1** outlines the role of specific micronutrients, other than iodine, involved in the synthesis and action of thyroid hormones.

1.1.3.2 Non-hormonal iodine

Non-hormonal iodine accounts for 20-30% of a healthy adult's bodily iodine content and is distributed in different tissues including the mammary glands, salivary glands, and gastric mucosa (Ahad and Ganie, 2010). In the mammary glands, iodine accumulates and is excreted in breast milk (Arias-Borrego *et al*., 2022; Azizi and Smyth, 2009; Nazeri *et al*., 2018). Iodide is the main form of iodine excreted in breast milk and makes up around 80% of total breast milk iodine concentration (BMIC) (Andersson and Braegger, 2022). The iodine content of human milk is directly relative to the maternal iodine intake (Andersson and Braegger, 2022; Henjum *et al*., 2017). The nature of iodide secretion in saliva has been of interest in recent years and is thought to act as a microbial agent (Guo *et al*., 2021, 2020). Similarly, in the gastric mucosa iodide secretions are thought to take part in pathogenic defence (Sorrenti *et al*., 2021).

Table 1.1. The role of micronutrients involved in thyroid hormone function.

Micronutrient	Role	Reference
Selenium	A component of several selenoproteins that support the regulation of thyroid hormone synthesis and protect the thyroid gland from oxidative stress. Aids conversion of Thyroxine (T4) to Triiodothyronine (T3) by two selenium-dependent thyroid deiodinases (D1 and D2). Protects thyroid from hydrogen peroxide (H2O2) by Glutathione Peroxidase 3 (GPx3).	(Arthur *et al*., 1999; Schmutzler *et al*., 2007)
Zinc	Contributes to Thyrotropin-releasing hormone (TRH) and Thyroid-stimulating hormone (TSH) synthesis. Transcription and gene expression of proteins required for thyroid hormone synthesis including the thyroid transcription factor 2 (TTF-2), Thyroglobulin (Tg) and Thyroperoxidase (TPO). A cofactor for type I (D1) and II (D2) deiodinases, which convert T4 to T3. A structural component of the T3 receptors or Thyroid hormone receptors (TRs).	(Batista Beserra *et al*., 2011)
Iron	Co-enzyme in haem dependant enzyme Thyroid peroxidase (TPO) used to catalyse the synthesis of thyroid hormones.	(Hess, 2010; Zimmermann and Köhrle, 2002)
Copper	Synthesis of phospholipids, which stimulate TSH production.	(Aihara *et al*., 1984)
Vitamin A	Synthesis of Tg. Supports the uptake of thyroidal iodine.	(Drill, 1943)

1.1.4 Iodine requirements

The recommended daily requirement of iodine differs according to country; however, it is between 100 – 150 μg day^{-1} for non-pregnant or non-lactating healthy adults in most European countries (Department of Health (DoH), 1991; European Food Safety Authority (EFSA), 2014). The World Health Organization (WHO) recommended dietary allowance (RDA) for iodine is 150 μg day^{-1} for adults and adolescents (WHO, 2013). In the UK, a Daily Recommended Value (DRV) of 140 μg day^{-1} has been given for adults and adolescence which was set by the DoH in 1991 (DoH, 1991). There are no changes in the adult recommended daily requirement of iodine according to age, sex, or body weight (DoH, 1991). Children aged 6-12 years do not require as much iodine for daily functioning and are recommended to consume 120 μg day^{-1} (WHO, 2013).

Women of childbearing age must consume adequate quantities of dietary iodine (140 μg day^{-1}) for several months prior to conception to maximise their intra-thyroidal iodine stores (Ahad and Ganie, 2010). Intra-thyroidal iodine stores act as a reservoir that can be liberated throughout pregnancy to uphold thyroid hormone production (Ahad and Ganie, 2010). Although, iodine stores diminished in a period of iodine insufficiency can be drawn upon, low stores may not be able to support the increased demand for iodine throughout pregnancy (Zimmermann, 2009b). In 2018, it was recorded that around 45% of UK pregnancies were unplanned at the time of conception (Public Health England, 2018). More recently, in 2020, during the first wave of the UK COVID-19 pandemic, the proportion of unplanned pregnancies almost doubled compared to rates recorded prior to the pandemic (Balachandren *et al*., 2021). Unplanned pregnancies represent a missed opportunity to optimise pre-pregnancy iodine. Most pregnancies are not confirmed until several weeks into the first trimester, which is a key period for thyroid hormone mediated growth and development of the foetus (Bath *et al*., 2014a). Even if iodine supplementation is implemented early in pregnancy, women may still have reduced thyroid hormone production compared to those who regularly consume an adequate amount of iodine leading up to conception (Moleti *et al*., 2011).

The WHO iodine requirement for pregnant and lactating women is greater than those for the general population at 250 μg day^{-1} to support the demands of a growing foetus (WHO, 2013). During pregnancy there is an increase in maternal T4 production to provide the mother and the developing foetus with a supply of thyroid hormones in the first trimester (before the thyroid gland is developed at 18-20 weeks gestation) (Moog *et al*., 2017). Iodine is also transferred to the foetus in later gestation via the placental NIS to support thyroid hormone synthesis, which is coupled with an increase of renal clearance of maternal iodine (Moog *et al*., 2017). The mother also experiences physiological changes during pregnancy that stimulate the thyroid gland resulting in an increase of thyroid hormone production (e.g. high estrogen concentration, elevated human chorionic gonadotropin (hCG), changes in peripheral thyroid-hormone metabolism, renal blood flow and glomerular filtration rate) (Glinoer 2004). Adequate supply of iodine and the thyroid hormones are essential for regular embryonic and foetal neurological development (Zoller and Rovet, 2004; Moog *et al*., 2017). However, the UK DRVs do not currently propose an increase in iodine intake for pregnant or lactating women and therefore remain at 140 μg day^{-1} (DoH, 1991). In 2014, the Scientific Advisory Committee on Nutrition (SACN) reviewed the evidence for increasing the iodine recommendation for pregnant and lactating women but found that there was insufficient evidence to revise the UK recommendations (SACN, 2014).

The current iodine requirements have been set to outline the average daily intake level which is sufficient to meet the nutrient requirements of nearly all healthy individuals in a population (97-98%) (DoH, 1991). In the context of iodine, another reference used to evaluate prevalence of deficiency is the Estimated Average Requirement (EAR). The EAR represents the average daily nutrient intake that is estimated to meet the requirements of 50% of the healthy individuals in a life stage and gender group (Institute of Medicine, 2001). The EAR for iodine was calculated using iodine balance studies and studies of radioiodine in individuals with (Zimmermann and Andersson, 2012). Currently, the EAR for iodine intake in adults is considered as 95 μg day^{-1} (Institute of Medicine, 2001). The EAR is equivalent to the average turnover of iodine by the thyroid (Zimmermann and Andersson, 2012).

The percentage of individuals in a group with daily intake below the EAR are at risk of nutrient inadequacy (Zimmermann and Andersson, 2012).

1.1.5 Sources of dietary iodine

Table 1.2 outlines the key sources of iodine in the UK diet. Cow's milk and dairy products remain the major sources of iodine in the UK (Bath *et al*., 2022). As mentioned previously (see Introduction, Section 1.1.8), the iodine content of cow's milk can be improved with supplementation of cattle fodder or using hygiene products, for this reason, the iodine content of cow's milk has a substantial seasonal variation (Bath *et al*., 2012). The iodine content of cow's milk is greater in the winter months due to the increase in feed supplementation (Bath *et al*., 2012). Whereas conventional cow's milk has a greater iodine content compared to organic cow's milk due to a lack of cattle feed supplementation (Bath *et al*., 2012). Other farming factors such as the number of goitrogens (compounds that prevent iodine absorption) in cattle feed rations, milk yield and processing further alter the iodine content of cow's milk (Trøan *et al*., 2015).

Fish, seafood, eggs, and seaweed are also iodine-rich food sources. Fish receive iodine from seawater and their food (Nerhus *et al*., 2018). The iodine content of fish and seafood varies according to species, seasonality, and location (Nerhus *et al*., 2018). A recent review of the iodine content of fish and seafood in the UK concluded that the UK dietary guidelines for fish consumption (inclusion of at least 2 portions (140g each) of fish a week, including 1 of oily fish) would provide 980 µg of iodine per week (66.7% of weekly iodine) (Sprague, Chong Chau, and Givens, 2022). Nonetheless, the mean fish and seafood intake of adults is currently well below the UK recommendations (Public Health England, 2020). The average UK consumption of white fish is approximately 15g per week^{-1} and 3g per week^{-1} for oily fish (De *et al*., 2021).

Seaweed can efficiently concentrate iodine from seawater and is a very variable but rich source of iodine (Smyth and Karger, 2021). There are three main types of seaweed: Phaeophyceae (brown), Rhodophyta (red), and Chlorophyta (green) (Smyth and Karger, 2021). The iodine content of seaweed can range between 20 – 10,000 µg g^{-1} and is dependent on the seaweed species and cooking practices (Smyth and Karger, 2021).

Brown seaweeds such as Kombu have the greatest iodine content (2,500–10,000 µg g^{-1}) and are not recommended to be consumed to improve iodine intake (Smyth and Karger, 2021), as the high iodine levels could have adverse effects on thyroid function (Sá Monteiro *et al*., 2019; Smyth and Karger, 2021). Seaweed and seaweed-containing snacks are becoming more common in the UK (Bouga and Combet, 2015). However, the iodine content in these products is not often recorded on the back of packet information and could provide an iodine content exceeding the adult upper level of tolerance (1100 µg day^{-1}) (Bouga and Combet, 2015).

As mentioned previously, (see Introduction, Section 1.12), asides from seaweed, plant-based foods typically are of lower iodine origin, unless bio-fortified with iodine, due to a low iodine concentration in soil (Bath and Rayman, 2016; Golubkina *et al*., 2021).

Table 1.2. Sources of iodine in the UK diet adapted from the British Dietetics Association (BDA) Fact Sheet for iodine (BDA, 2022).

Food item	Average iodine content (µg per portion)
Cow's milk (200 ml)	50-100[1]
Organic cow's milk (200 ml)	30-60[1]
Yoghurt (150 g)	50-100[1]
Cheese (40 g)	15
Haddock (120 g)	390
Cod (120 g)	230
Prawns (60g)	6
Eggs (1 egg, 50 g)	25
Meat/Poultry (100 g)	10
Nuts (25 g)	5
Bread (1 slice, 36 g)	5
Fruit and vegetables (80 g)	3

[1]Depending on the season, higher value in winter (Bath and Rayman, 2016).

1.1.5.1 Iodine fortified foods

Food fortification describes the addition of nutrients to foods and is known to be a cost-effective and sustainable public health method to improve micronutrient intake in populations (WHO, 2022). The term 'salt iodisation' is used to describe the fortification of salt with iodine (Bath *et al*., 2014b; Wu *et al*., 2002). Salt iodisation has been recommended by the WHO as an effective method to eradicate and control iodine deficiency (WHO, 2007). Salt is often used as a vehicle for fortification as the sensory components of the product are not affected by iodisation, usage is not seasonal ensuring iodine intake remains stable over time, and salt programmes can be well monitored by health officials (WHO, 2007). Iodised salt can be added directly to meals or into the processing and production of foods (WHO, 2007). Many countries worldwide have legislation for the universal mandatory iodine fortification of salt (Zimmermann and Andersson, 2021). In 2021, 124 countries were reported to have introduced mandatory salt iodisation programs (Zimmermann and Andersson, 2021). A further 21 countries globally have voluntary iodised salt legislation (Zimmermann and Andersson, 2021). To be considered as part of the Universal Salt Iodisation (USI) system, salt must contain 15-40 µg g^{-1} of iodine in the form of potassium iodide or iodate (Zimmermann and Andersson, 2021). A maximum limit was set at 40 µg g^{-1} to prevent inducing iodine excess in populations with a high dietary intake of iodine or fortified table salt (Jodmangel, 2005).

Aforementioned (see Introduction, Section 1.1.8), the UK currently has never implemented a universal iodised salt programme (Bath *et al*., 2014b). Today, iodised salt is sold commercially, however, its availability is low, and purchase is costly for most consumers (Bath *et al*., 2014b). In 2014, the top brand of iodised salt available for purchase in the UK (Cerebos) was recorded to provide only 12 µg per portion (1g) (Bath *et al*., 2014b). At present, Cerebos iodised table salt provides approximately 20 µg per portion (1g), which may provide more meaningful quantities of dietary iodine (Premier Foods, 2023). There has yet to be a more recent assessment of iodised salt in supermarkets. The average salt intake in the UK is currently recorded at 8.4 g day^{-1}, which is 2.4 g greater than the current Government salt recommendation of 6 g day^{-1} (Burt *et al*., 2022).

Bath *et al* suggested in their 2014 paper that encouraging iodised salt consumption might contradict salt-lowering efforts in the UK (Bath *et al*., 2014). Any implemented iodisation must coordinate with salt reduction programmes to prevent negative repercussions of salt intake (Burt *et al*., 2022). With no iodised salt programme in the UK, achieving adequate iodine intake is dependent on an individual's food choices and intake.

Other foods have been used as vehicles for iodine fortification, for example, refined water, tea, cereals such as wheat, rice, and maize, sugar, seasonings, and milk-powders, (Santos *et al*., 2019). For iodine fortification to be successful, the selected food items must be appropriate and suitable for the target population (Santos *et al*., 2019). For example, fortification of pork sausages with iodine would not be fitting for those avoiding animal products for cultural, religious, and/or ethical reasons. Again, these iodine fortification approaches have not been widely adopted in the UK.

Recently, iodine-fortified cow's milk alternatives (containing potassium iodide or iodate) have been identified as a "nutrient bridge" to improve dietary iodine intake in individuals who do not consume cow's milk (Govindji, 2020). A "nutrient bridge" is a concept designed by Registered Dietitian Azmina Govindji used to describe the addition or substitution of foods to vegan meals to improve nutrient intake or bio-availability (Govindji, 2020). Plant-based cow's milk alternatives e.g. soya, oat, rice, hemp, hazelnut, etc. are typically low in iodine unless fortified with potassium iodide or iodate (Bath *et al*., 2017). An assessment of alternative milk in the UK in 2015 found that the average iodine content for non-fortified alternative milk drinks was 7.3 µg kg^{-1} compared to 344 µg kg^{-1} for conventional cows' milk samples (97.9 % lower in iodine) (Bath *et al*., 2017). Fortified varieties of milk alternatives were able to provide 77.3–83.4 % of the iodine concentration of conventional cow's milk (Bath *et al*., 2017). However, in 2015, only 6% of alternative milk was fortified with iodine (3/47) (Bath *et al*., 2017). The study by Bath *et al.* also demonstrated that the usage of red seaweed (*Lithothamnium calcareum*) as an ingredient and source of calcium (Ca) could raise the iodine concentration of alternative milk drinks (Bath *et al*., 2017).

Dineva *et al* (2020) conducted a secondary analysis of the NDNS from Years 7 to 9 (2014-2017) and found that iodine intake was significantly lower in individuals who solely consumed alternative milk rather than cows' milk. Studies have also shown that plant-based alternatives of fish, cheese, and yoghurts, sold in the UK also are predominantly iodine-unfortified, and consumption may act as a barrier to adequate iodine intake (Nicol *et al*., 2022). Fortification of alternative milk with iodine is not yet mandatory in the UK. However, in 2021 the British Dietetics Associations' (BDA) England Board and the Maternal & Fertility Nutrition Specialist Group began to discuss the case for a wider iodine fortification of milk alternatives (BDA, 2022b). In parallel, the BDA is developing a campaign to increase awareness of iodine to ensure manufacturers' iodine fortify future staple alternative products (e.g. dairy-free/ plant milk, cheeses, yoghurts etc.) (BDA, 2022b). Similarly, in 2022, the Committee on Toxicity (COT) and SACN actioned a call for evidence to assess the mandatory fortification of alternative milk with iodine (SACN and COT, 2022).

1.1.5.2 Iodine-containing dietary supplements

Iodine is available in the form of dietary supplements such as potassium iodide or sodium iodide (National Institute of Health (NIH) Office of Dietary Supplements, 2022). Many multivitamin-mineral supplements in the UK also contain iodine. In Years 7 to 9 of the NDNS (2014-2017) only 3.7% of the UK population reported using iodine-containing supplements (n = 147) (Dineva *et al*., 2020b). The BDA endorses supplementation of iodine (150 µg day^{-1}) throughout pregnancy and lactation when it may be challenging to meet iodine targets through the diet (250 µg day^{-1}) (Bath and Rayman, 2016). However, supplements are not routinely prescribed for improving iodine in the UK for those who are not pregnant or planning for pregnancy despite being an effective method of combating iodine deficiency in other groups worldwide (Nazeri *et al*., 2021; NHS, 2020). This may be due to the lack of good-quality evidence to support the promotion of iodine supplementation in mildly-to-moderately iodine-deficient pregnant women (Dineva *et al*., 2020b). Studies have also demonstrated that rapid increases in maternal iodine intake caused by supplement use may have adverse effects on thyroid function, particularly in individuals with low iodine intake (Moleti *et al*., 2011; Dineva *et al*., 2020b).

Iodised oil supplements, orally or intramuscularly provided, have been used as an alternative to iodised salt to improve iodine nutrition in developing countries where immediate action is needed to prevent IDDs (Benmiloud *et al*., 1994; Zimmermann *et al*., 2000). However, there is no evidence of the use of iodised oil in individuals with mild to moderate deficiency in industrialised countries. A select number of studies have investigated the use of seaweed as a method of improving iodine intake in at-risk populations, with positive results (Cherry *et al*., 2019; Combet *et al*., 2014).

1.1.5.3 Goitrogenic substances

Goitrogenic substances (goitrogens) and their precursors are found in many plant foods, synthetic materials, and drugs (Bajaj *et al*., 2016). Goitrogens interfere with the uptake of iodine by the thyroid gland and disrupt thyroid hormone synthesis. Clinical consequences of goitrogen consumption are only exhibited in populations where iodine deficiency is prevalent and/or staple foods are rich in goitrogenic substances (Bajaj *et al*., 2016). The effect of goitrogenic substances can be overcome by increasing dietary iodine intake (Bajaj *et al*., 2016).

The main class of goitrogen in plant foods are glucosinolates, which produce thiocyanates and oxazolidine-2-thiones (e.g. goitrin). Thiocyanate is a cyanide metabolite found in Brassica vegetables such as cabbage, cauliflower, Brussel sprouts, and turnip. Other cyanide metabolites such as isocyanates are found in mustard oil. Thiocyanates and cyanide metabolites block the transport of iodine into the thyroid gland by competitively inhibiting uptake at the NIS. Goitrin is found in Brassica seeds, cow's milk (not in high concentrations), and seaweeds of the Laminaria species (e.g. Kombu) (Lightowler, 2009). Goitrin inhibits TPO, the enzyme central in the organification of iodine, and T4 formation in the thyroid (Bischoff, 2016). Other goitrogens include flavonoids (polyphenols), polychlorinated (PCB) and polybrominated biphenyls (PBB), and organochlorines (DDT) (Bajaj *et al*., 2016).

1.1.6 Iodine excess

Along with iodine deficiency, iodine excess is also a problem and can result in iodine-induced conditions. The safe tolerable limit for iodine intake has been identified as 600 µg day^{-1} for adults (>12 years) and pregnant women in the UK by the European Commission (Scientific Committee on Food, 2002). According to the American Thyroid Association (ATA) 1,000 µg day^{-1} is the upper tolerable limit for iodine consumption (American Thyroid Association, 2013). The thyroid can adapt to excess iodine and has several control mechanisms to maintain thyroid hormone synthesis (American Thyroid Association, 2013; Bürgi, 2010; Leung and Braverman, 2014). The main regulation of thyroidal iodine uptake in situations of iodine excess is the Wolff and Chaikoff phenomenon discovered in 1948 (Wolff and Chaikoff, 1948).

The Wolff and Chaikoff effect describes the autoregulatory process that results in a reduction in thyroid hormone production and secretion (Bürgi, 2010; Leung and Braverman, 2014; Wolff and Chaikoff, 1948). The proposed mechanism is mediated by the NIS (Bürgi, 2010). In environments of iodine excess, the NIS shuttles iodide into the thyroidal cells (Bürgi, 2010). The high intracellular concentration of iodide ($\geq 10^{-3}$ molar) inhibits the rate-limiting step of thyroid hormone synthesis, the organification of iodide (Bürgi, 2010). This effect is transient (0-10 days), and once iodide levels have lowered an 'escape' takes place to restore normal thyroid function (Bürgi, 2010). This is the most recent theory and the precise mechanism of the Wolff and Chaikoff phenomena is still unclear (Bürgi, 2010; Leung and Braverman, 2014). The Wolff and Chiakoff phenomenon has been identified as a cause of iodine-induced hypothyroidism and/or goitre in individuals consuming iodine-containing drugs such as amiodarone (antiarrhythmic drug) (Bürgi, 2010). Moreover, hypothyroidism and/or goitre may be experienced in select individuals (radioiodine provision in Graves' disease or autoimmune thyroiditis) in which the NIS fails to reduce the influx of iodide into the thyroid cell (Bürgi, 2010). In euthyroid individuals, iodine-induced hypothyroidism is rare (Bürgi, 2010; Leung and Braverman, 2014).

Iodine excess can also induce hyperthyroidism (Jod-Basedow Syndrome) (Bürgi, 2010; Roti and Degli Uberti, 2001). Iodine-induced hyperthyroidism is frequently observed in individuals experiencing iodine deficiency (with or without nodular goitres) who are abruptly exposed to excess iodine (Roti and Degli Uberti, 2001). However, iodine-induced thyrotoxicosis can also occur in euthyroid individuals who are not experiencing iodine deficiency (Roti and Degli Uberti, 2001).

Recent studies have proposed that abrupt introduction of dietary iodine during early pregnancy (e.g. from dietary supplements or iodised salt), in populations that are mild-to-moderately iodine deficient, may cause a thyroid 'stunning effect'. The 'stunning effect' describes the temporary suspension of thyroid hormone production and circulating fT4 (Næss *et al*., 2021). Although the specific mechanism of action for thyroid stunning is unknown, it has been proposed that it shares a similar mechanism to the Wolff–Chaikoff effect (Næss *et al*., 2021), which occurs after acute excess iodine intake to prevent overproduction of thyroid hormones (Næss *et al*., 2021).

1.1.6.1 Sources of excess iodine exposure

Iodine excess has been identified in populations that consume large quantities of iodine-rich foods as part of the habitual diet. Studies globally have recorded iodine excess relating to excessive seaweed or microalgae consumption (Aakre *et al*., 2020; Di Matola *et al*., 2014; Gherbon *et al*., 2019).

Consequences of iodine excess have also been observed following the enrolment of iodine supplementation and salt iodisation fortification programmes (Connolly *et al*., 1970; Delange *et al*., 1999; Kolcsár and Gáll, 2019; Mostbeck *et al*., 1998; Sarwar *et al*., 2013; Speeckaert *et al*., 2011). Other consumables such as water (Liu *et al*., 2009), breast milk and infant formulae (Bürgi, 2010; Roti and Degli Uberti, 2001), and food dyes (e.g. erythrosine) have been associated with iodine excess in humans (Bürgi, 2010; Roti and Degli Uberti, 2001). Other sources of excess iodine include organic iodine compounds in pharmaceuticals including topical disinfectants (e.g. iodporidone), radiographic contrast agents (e.g. iopanoic acid), and certain drugs (e.g. amiodarone or asthma syrups containing potassium iodide) (Bürgi, 2010).

1.1.7 Iodine deficiency disorders (IDD)

The term iodine deficiency disorders (IDD) is used to describe the negative health consequences of inadequate (<150 μg day^{-1}) or excess iodine intake (see Introduction, Section 1.1.6). In rare cases, IDD may develop because of genetic mutations that affect proteins involved in T3 and T4 synthesis and action (e.g. NIS, TPO, and Tg) (Rousset *et al*., 2015). IDD can present as a spectrum of disorders that generate different diagnoses according to life stage (**Table 1.3**).

Table 1.3. The spectrum of iodine deficiency disorders (IDD) by age stage adapted from World Health Organisation (WHO, 2007).

Age stage	IDD symptom or disorder
Foetus	Miscarriage
	Stillbirths
	Congenital anomalies
	Increased perinatal morbidity and mortality
Infancy	Endemic cretinism
	Goitre
	Hypothyroidism
	Endemic neurocognitive impairment
	Increased susceptibility of the thyroid gland to nuclear radiation
Child and adolescence	Goitre
	(Subclinical) hypothyroidism
	Impaired mental function
	Retarded physical development
	Increased susceptibility of the thyroid gland to nuclear radiation
Adult	Goitre
	Hypothyroidism
	Impaired mental function
	Unprompted hyperthyroidism in the elderly
	Iodine-induced hyperthyroidism
	Increased susceptibility of the thyroid gland to nuclear radiation
	Thyroid nodules

Endemic goitre (the enlargement of the thyroid gland) is the most obvious and visible sign of severe iodine deficiency and can develop in all life stages (Ahad and Ganie, 2010; Eastman and Zimmermann, 2018; Kapil, 2007; Zimmermann, 2009a).

However, the public health repercussions of IDD are most critical in pregnant women and those of childbearing age (Bath and Rayman, 2015; Farebrother *et al*., 2020; Henjum *et al*., 2018; Yang *et al*., 2018). Healthy pregnant women with sufficient iodine intake and adequate stores of iodine before conception can use their supplies to sustain the increased iodine demands and maintain thyroid hormone balance throughout pregnancy (Thilly *et al*., 1978). Conversely, pregnant women experiencing iodine deficiency at any stage (conception onwards) may experience an inadequate thyroid adaption response and may develop IDD depending on the timescale and severity of deficiency.

Foetal neurodevelopment must follow a precise chronology; if maternal thyroid hormone is altered (e.g. during maternal hypothyroxinaemia characterised by normal TSH concentrations but lowered circulating fT4) or is inadequate (e.g. in iodine deficiency), neurological structure and function can be permanently compromised (Moog *et al*., 2017). This is because TRs are expressed on neurons and in glial cells in the developing brain (Zoller and Rovet, 2004). The binding of T3 to the TR at the neuronal level activates the expression of genes involved in cerebral cortical development, including those relating to axonal and dendrite protuberance, synapse organisation, myelination, cell migration, and cell proliferation (Moog et al., 2017).

Individuals experiencing severe iodine deficiency during pregnancy experience the most serious foetal and maternal consequences for example, miscarriage, stillbirth, congenital anomalies, and increased perinatal morbidity and mortality (Table 1.3). Iodine deficient mothers are at risk of birthing infants suffering from cognitive and developmental defects (cretinism) (Ahad and Ganie, 2010; Kapil, 2007). IDD has been labelled the world's ‘greatest single cause of preventable brain damage and mental retardation’ (Delange, 2001). The relationship between severe iodine deficiency and foetal neurodevelopment has been extensively researched (Zhou *et al*., 2018; Bath, 2019).

Recently, the influence of mild-to-moderate iodine deficiency during pregnancy on neurodevelopment of the child has been of scientific interest (Zhou *et al*., 2018; Bath, 2019; Dineva *et al*., 2020a; Dineva *et al*., 2023). The evidence indicates that mild-to-moderate iodine deficiency during pregnancy is related to reduced cognition, hearing ability, and school performance (Zhou *et al*., 2018; Bath, 2019; Dineva *et al*., 2020a; Dineva *et al*., 2023). However, there is still a lack of good-quality research on this topic and further investigation is needed.

1.1.8 Identifying iodine deficiency disorders IDD and iodine nutrition in populations and individuals

The WHO, UNICEF (United Nations Children's Fund) and International Council for the Control of Iodine Deficiency Disorders (ICCIDD) 2007 report titled 'Assessment of Iodine Deficiency Disorders and Monitoring their Elimination: A Guide for Programme Managers' covers the most recent guidelines for identification and monitoring of IDD and iodine status in populations. The 2007 report is the 3rd addressing this topic (WHO, 2017). At the time of writing, this report is >15 years old, newer research has likely been published which may influence the current methodology and monitoring criteria of IDD. A newer report on this subject is due to be published in 2023. The following sections will outline the current advice for assessment and monitoring of IDD in populations from WHO, UNICEF, and the former ICCIDD which has been renamed (see Introduction, Section 1.1.7.2) (WHO, 2017).

1.1.8.1 Thyroid size

Assessment of thyroid size by palpation and/or ultrasonography are traditional methods for assessing IID prevalence (WHO, 2007). The measurement of thyroid size is assessing for the presence of thyroid enlargement or a 'goitre' (WHO, 2007). The thyroid gland can remain enlarged for months or years, even after iodine deficiency has been corrected. Many other factors may influence the occurrence and duration of thyroid enlargement including severity and duration of iodine deficiency, and age (WHO, 2007). All of which limit the effectiveness and usefulness of assessments of thyroid size as a marker of IDD. Thyroid size by palpation describes the clinical examination of the thyroid gland using the fingers. Using the palpation method, lobes of the thyroid gland that are larger than the tip of the thumb of the examiner are considered goitrous (WHO, 2007).

After palpation, the severity of the goitre is graded from 0-2, with 0 normal thyroid size and 2, goitre is present (WHO, 2007). The palpation method is cost-effective, if given the availability of trained examiners, and can be conducted readily in accessible groups such as school-age children (6-12 y) and adults (18-60 y), including pregnant and lactating women but not for neonates) (WHO, 2007). However, the palpation technique is subject to inter-observer variation and therefore can be easily misclassified (WHO, 2007).

Ultrasonography is considered the most sensitive method for examination of the thyroid gland and is a non-invasive and cost-effective tool (WHO, 2007). The ultrasound technique is achieved using a linear-array transducer (7-15 MHz) that can generate real-time images of the thyroid gland (WHO, 2007). Next, reference values (by age and sex) from iodine-sufficient populations are used to compare thyroid volume measures to the population of interest (WHO, 2007). Normal thyroid lobe dimensions in an adult are typically 40-60 mm (length) and 13-18 mm (depth) (**Figure 1.6**) (WHO, 2007). Once the depth, width, and length are assessed, the thyroid volume is calculated as the sum of both lobes using a standard formula (

Equation 1.1) (WHO, 2007).

Ultrasonography may be a preferred method of thyroid size in areas of mild-to-moderate IDD where visible goitres may not be present or may be difficult to identify via palpation, or when alterations in thyroid size are very small (WHO, 2007).

$$\mathbf{V\ (ml) = 0.479*D*W*L\ (cm)}$$

Equation 1.1. Calculation of normal thyroid lobe dimension and thyroid volume.

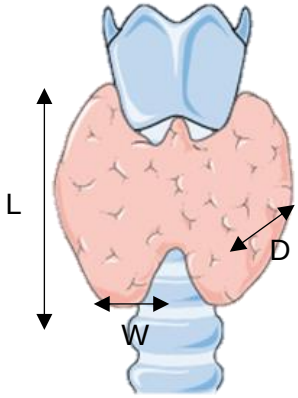


Figure 1.6. The anatomical dimensions of the thyroid gland.

L, Length; D, Depth; W, Width

1.1.8.2 Thyroid function by blood constituents

Constituents in the blood can be used to identify IDD or to assess thyroid function. Blood spots on filter paper or blood samples (collected via venepuncture or finger prick) are typically used in surveillance to detect quantities of TSH and Tg (WHO, 2007).

In iodine-deficient states, circulating TSH increases, and T4 decreases (Ahad and Ganie, 2010). Iodine deficiency can therefore be identified in individuals with raised TSH (Ahad and Ganie, 2010). However, TSH is not used as a biomarker in adults or school-aged children because overlap can occur (WHO, 2007). Instead, TSH is normally used to identify iodine deficiency in neonates as there is rapid iodine turnover in the first weeks of life (Di Dalmazi *et al*., 2020). In addition, an increase in TSH concentration, termed transient hyperthyrotopinemia, can be a sign of neonatal iodine deficiency (Di Dalmazi *et al*., 2020; Gaudino *et al*., 2005). Congenital hypothyroidism is a developmental condition present in neonates characterised by an absent or under-developed thyroid gland (dysgenesis) (Gaudino *et al*., 2005). Congenital hypothyroidism prevalence has been shown to relate to maternal iodine deficiency (Mills *et al*., 2020). However, in countries experiencing mild-to-moderate iodine deficiency, maternal iodine intake has been suggested not to relate to congenital hypothyroidism prevalence (Mills *et al*., 2020).

In many countries, neonates are screened for congenital hypothyroidism using bloodspot TSH on filter paper (WHO, 2007). Newborn TSH can be used as an indicator of population iodine status, whereby, iodine sufficiency is specified if the proportion of newborn TSH >5 mIU L^{-1} in the population is <3% (WHO, 2007).

Tg levels in the serum increase in response to iodine deficiency and goitre presence (Ma and Skeaff, 2014; Zimmermann *et al*., 2006). Raised Tg in the serum is related to long-term poor iodine nutrition (Ma and Skeaff, 2014). Tg concentration also increases in iodine excess (Dineva *et al*., 2023). Serum Tg can be detected in all healthy individuals in the population; however, it is most used to monitor iodine deficiency in school-aged children (Zimmermann *et al*., 2006). Recent studies have also indicated the usefulness of Tg as a measure of iodine status in adults and pregnant women (Dineva *et al*., 2023). Tg international reference values are used to assess relative levels of iodine sufficiency in populations of school-aged children of 4–40 µg L^{-1} (Zimmermann *et al*., 2006). However, specific ranges have not been adopted for adults and/or pregnant women (Dineva *et al*., 2023). Serum Tg can be assessed through dried whole blood spots at high sensitivity (Zimmermann *et al*., 2006). The use of dried blood spots for Tg measurement is efficient, simple and can be easily stored and transported for analysis so sampling in rural areas is possible (Zimmermann *et al*., 2006). However, the use of Tg as a biomarker has limitations. For instance, environmental contaminants and goitrogens (Thiocyanate from cigarettes) which interfere with iodine transport (see Introduction, Section 1.1.5.3) also cause an increase in serum Tg which could affect estimates (Dineva *et al*., 2023). Additionally, Tg cannot be dependably assessed in people with detectable anti-Tg antibodies (TgAb) (10% of the adult population) (Pearce and Cadwell, 2016).

Constituents in the blood serum such as TSH, fT4, and sometimes fT3 can be used to assess thyroid function (WHO, 2007). Assessing thyroid function permits an understanding of whether the thyroid gland is responding adequately to iodine intake (WHO, 2007). In clinical settings, fT4 and fT3 will only be measured if TSH values are above or below the reference range for a healthy adult population (**Table 1.4**).

There are separate reference values available for the measure of thyroid function in pregnant women (Kostecka-Matyja *et al*., 2017). Hypothyroidism is identified when TSH levels are high and fT4 is low. According to the National Institute for Health and Care Excellence (NICE), subclinical hypothyroidism is characterised by TSH levels that are slightly raised and when fT4 is still within the normal reference range (NICE, 2022). Use of serum concentrations of T4 and T3 are not commonly used in the monitoring of iodine nutrition. This is due to the expense, difficulty, and sensitivity of the measure (WHO, 2007). Instead, an assessment of fT4 and fT3 is used to assess the presence of thyroid functionality at the individual level (WHO, 2007).

Table 1.4. Reference ranges for thyroid function tests in healthy adult populations (18-60 years) (British Thyroid Foundation, 2021).

Test	Range	Unit
TSH	0.4 – 4.0	mU L^{-1}
FT4	9.0 – 25.0	pmol L^{-1}
FT3	3.5 – 7.8	pmol L^{-1}

TSH, Thyroid-stimulating hormone; fT4, Free Thyroxine; FT3, Free Triiodothyronine.

1.1.8.3 Urinary iodine concentration (UIC)

Consumed and absorbed iodine appears readily in the urine (Hussain *et al*., 2019; Pearce and Caldwell, 2016; Soldin, 2002). Urinary iodine concentration (UIC) is therefore a very efficient method to estimate recent dietary iodine intake and is recommended to assess the iodine status of populations (WHO, 2013; WHO, 2007). UIC measures are non-invasive, cost-effective and valid methods to assess the iodine status of a population, however, are not a useful measure for assessment at the individual level (WHO, 2007). UIC tends to have diurnal fluctuations, can vary substantially between daily records, and is affected by fluid intake (Doggui *et al*., 2018; Yeh *et al*., 2015). UIC tends to be higher after the consumption of a meal and in the evening (Als *et al*., 2000). Therefore, UIC may be exaggerated by the recent consumption of iodine-rich foods (Als *et al*., 2000). Similarly, morning first-pass UIC samples may tend to have a lower iodine concentration (Als *et al*., 2000).

Nevertheless, research has indicated that UIC samples are relatively stable over time and do not exhibit significant day-to-day fluctuations (Wang *et al*., 2013).

Spot (single-time) UIC samples are good measures of a population's iodine nutrition, given that many samples can be collected. However around 10 samples are required for best estimates of population iodine status (König *et al*., 2011). Spot UICs are limited by only providing a snapshot of the iodine intake of an individual at the point of sampling (Hussain *et al*., 2019; WHO, 2013; WHO, 2007). Spot UIC samples are often reported as the age- and sex-adjusted iodine: creatinine ratios (I/Creat) to account for fluid intake (Moore and Sharer, 2017). Additionally, many equations are available for estimating predicted 24h creatinine excretion in various populations (Kawasaki *et al*., 1993; Tanaka *et al*., 2002). Creatinine is a product of creatine phosphate from muscle and protein metabolism (Wyss and Kaddurah-Daouk, 2000). The concentration of creatinine in the body is controlled by renal excretion at the kidneys (Wyss and Kaddurah-Daouk, 2000). In healthy individuals, creatinine is filtered freely through the glomeruli of the kidneys and only a very small proportion is reabsorbed in the tubules. Therefore, almost all the creatinine produced is excreted from the body at the urinary tract (Wyss and Kaddurah-Daouk, 2000).

In normal conditions, the urine creatinine concentration is equivalent to the quantity of urine excreted and therefore is a suitable marker for fluid correction (Wyss and Kaddurah-Daouk, 2000). However, the correction of UIC samples with I/Creat has been criticised. One of the issues associated with this measurement is that creatinine excretion is not universal and differs considerably between individuals (Haddow *et al*., 2007). For example, men tend to excrete large quantities of creatinine compared to women (Haddow *et al*., 2007). Further, supplements and other foods, such as meat and fish, may increase the concentration of urinary creatinine and conceal the level of dilution of UIC samples (Franz *et al*., 2022; Abraham *et al*., 2023). This may lead to misinterpretation of I/Creat particularly when comparing omnivorous diets with vegan and/or vegetarian diets (Abraham *et al*., 2023). Select research has also indicated that I/Creat may not be appropriate for largescale population studies as they may be misleading (Haddow *et al*., 2007).

The WHO epidemiological criteria for assessing iodine nutrition based on median UIC is used to assess the relative status of iodine sufficiency in populations (WHO, 2013; WHO, 2007) (**Table 1.5**). The median UIC (mUIC) is used instead of the mean UIC, as the frequency distribution of iodine within samples is typically skewed towards higher values (WHO, 2007; Zimmermann, 2008).

The use of mUIC by WHO has been criticised and research indicates that this method may overestimate the prevalence of IDD particularly in populations of women of childbearing age and/or pregnant/lactating women (Andersson, 2022; Zimmermann and Andersson, 2012). The use of EAR as a cut-off for UIC in vulnerable populations has been outlined as a possible alternative method for detecting IDD (Zimmermann and Andersson, 2012).

The rational of the EAR cut-off method has been described in detail by Zimmerman and colleagues (Andersson, 2022; Zimmermann and Andersson, 2012). To apply the EAR cut-off method to UIC samples to assess deficiency, UIC samples must be converted into estimated daily iodine intake (μg day^{-1}) by dividing by 0.92 (for 92% of dietary iodine is absorbed following intake) (Zimmermann and Andersson, 2012). The proportion of individuals in the population that do not meet the EAR cut-off for iodine (95 μg day^{-1}) represents the magnitude of iodine deficiency (Institute of Medicine, 2001; Zimmermann and Andersson, 2012).

UIC can also be measured in 24h urine collections. These are often regarded as being an improvement on spot UIC samples as well as being recognised as the "reference standard" of measurement (König *et al*., 2011). 24h measures can reflect a whole day of an individual's daily excretion and are not subject to sample variation (Chen *et al*., 2016; Vejbjerg *et al*., 2009). The UIC from 24h samples also show substantial daily, seasonal, and individual variation (Chen *et al*., 2016; Vejbjerg *et al*., 2009). The 24h measurement for UIC is not often used in population studies, as measurements are time-consuming and highly burdensome for participants (Vejbjerg *et al*., 2009). Hence, spot UIC is often the favoured technique.

Table 1.5. The World Health Organisation (WHO) epidemiologic criteria for assessing iodine nutrition and status based on median urinary iodine concentrations (UIC) in different populations (Zimmermann *et al*., 2013)[1].

Median UIC (μg L^{-1})	**Iodine intake**	**Status**
Individuals of 6+ years		
<20	Insufficient	Severe iodine deficiency
20-49	Insufficient	Moderate iodine deficiency
50-99	Insufficient	Mild iodine deficiency
100-299	Adequate	Optimum
≥300	Excessive[2]	Risk of adverse health (iodine-induced hyperthyroidism, autoimmune thyroid disease)
Pregnant women		
<150	Insufficient	Iodine deficiency
150-249	Adequate	Adequate
250-499	Above requirements	May pose a health risk
≥500	Excessive[2]	Risk of adverse health (iodine-induced hyperthyroidism, autoimmune thyroid disease)

[1]For lactating women and children <2 years a median UIC of 100 μg L^{-1} is used to define adequate iodine intake, no other criteria for iodine deficiency exist in these population groups. Lactating women have the same iodine requirements as pregnant women, but UIC values tend to be lower due to lactation.

[2]The term 'excessive' means more than the quantity of iodine that is recommended to prevent deficiency.

1.1.8.4 Breast milk iodine concentration (BMIC)

Breast milk iodine concentration (BMIC) has been recently discussed as a promising indicator of iodine status in lactating women and children <2 years of age (Dold *et al*., 2017). BMIC has been addressed as a more accurate method to determine the iodine status of lactating women than UIC as a higher proportion of iodine is excreted into breast milk in comparison to the urine (Dold *et al*., 2017; Liu *et al*., 2022). BMIC varies substantially; current estimates suggest the median BMIC of lactating women ranges between 18-1153 µg L^{-1} (Liu *et al*., 2022). No official criteria or guidelines exist for the use of BMIC as a biomarker to detect iodine deficiency (Liu *et al*., 2022). However, a BMIC cut-off of ≥100 µg L^{-1} has been proposed to determine iodine sufficiency (Liu *et al*., 2022). This cut-off has been selected with the knowledge that an infant (at full-term) requires 15 µg per kg day^{-1} to sustain thyroid hormone production (Liu *et al*., 2022). Other possible cut-offs for iodine sufficiency based on BMIC have been proposed in the literature, ranging from 50-465 µg L^{-1} (Dold *et al*., 2017; Liu *et al*., 2022). The WHO has expressed the need for further studies investigating BMIC as a biomarker (Andersson *et al*., 2007a).

1.1.8.5 Salivary iodine concentration (SIC)

Salivary iodine concentration (SIC) has also been discussed as an alternative measure of iodine status. Salivary glands, like the thyroid gland and stomach, have the capacity to concentrate iodine and are involved in the gastro-intestinal cycle of iodides (Hays and Solomon, 1965). The salivary glands express several transporters involved in the concentration and secretion of iodine for instance, NIS, cystic fibrosis transmembrane conductance regulator, and anoctamin 1 (Dekker *et al*., 2021). The ability of the salivary glands to concentrate iodide has permitted SIC to be used as a diagnostic tool for congenital hypothyroidism in newborns according to the plasma iodide ratio (Portulano, Paroder-Belenitsky, and Carrasco, 2014). Studies have also shown strong correlations between SIC and UIC in healthy adults and school children with varying daily iodine intake (Dekker *et al*., 2021; Guo *et al*., 2020). Guo and colleagues proposed a cut-off for iodine deficiency according to SIC of <105 µg L^{-1} for children (Guo *et al*., 2020).

However, no official criteria or guidelines exist for the use of SIC as a biomarker to detect iodine deficiency in adults. To improve estimates, SIC measures can be corrected for fluid accumulation, which may occur from stimulation of the salivary glands during sample collection, by calculating ratios of SIC to salivary protein (SP) (SIC: SP (μg g^{-1})) and urea (SIC:U (μg:mmol)).

1.1.8.6 Dietary iodine intake

The dietary iodine intake of individuals within a population can vary significantly. The main reasons for the dissimilarity in dietary iodine intake are due to the types of foods consumed and their iodine concentration, the presence of iodine fortification (voluntary or involuntary), possible dietary restrictions, intolerances, or allergies (Bath *et al*., 2022; Leniszewski and Mauseth, 2009; Thomassen *et al*., 2017). The common methods to assess dietary iodine intake are food frequency questionnaires (FFQ), food diaries (FD), 24h food recalls, and weighed food records (Zimmermann and Andersson, 2012). Dietary intake methods are designed to assess the habitual (long-term) or short-term intake of iodine from foods by recording the frequency and amount of consumption (Shim *et al*., 2014). All dietary methods have issues such as poor dietary recall, participant desirability, and recall bias, and therefore are not accurate methods to estimate daily iodine intake (Hooson *et al*., 2020; Shim *et al*., 2014). These pitfalls, along with others, are associated with all estimates of dietary nutrients.

FFQs are designed to measure the long-term frequency and quantity of consumption of food items within a particular category over a set period (usually a year of intake) (Combet and Lean, 2014; Condo *et al*., 2015; Næss *et al*., 2019; Rasmussen *et al*., 2001; Shim *et al*., 2014). FFQs are useful for the assessment of iodine-rich foods that are infrequently consumed such as seaweed, which may be missed or under-represented using methods that estimate short-term dietary iodine intake (National Institute of Health Research, 2022a). Additionally, FFQ can capture the day-to-day variation in iodine and food consumption in an individual's diet (National Institute of Health Research, 2022a). Further questions added to FFQs can access information about dietary intake, for example, the use of iodine-containing supplements, iodised salt, or other fortified foods (National Institute of Health Research, 2022a).

Iodine-specific FFQs have been developed to assess dietary iodine intake in specific populations (Combet and Lean, 2014; Næss *et al*., 2019; Rasmussen *et al*., 2001), for example, women of childbearing age and pregnant women (Combet and Lean, 2014; Condo *et al*., 2015; Næss *et al*., 2019). Iodine-specific FFQs only establish dietary iodine intake, and not the intake of other nutrients, hence these only contain a limited list of foods that may be possible sources of dietary iodine (Combet and Lean, 2014; Condo *et al*., 2015; Forster *et al*., 2014; Næss *et al*., 2019; Rasmussen *et al*., 2001). Iodine-specific FFQs must be developed for a particular population, or else key sources of iodine in the diet may be missed or underrepresented.

FDs are used to record daily food intake and consumption, the average time-period for this method is 3-4 days of reporting, however for the best estimates, a longer duration may be used (Shim *et al*., 2014). Short FDs may miss iodine provided by foods that are not commonly consumed as part of the habitual diet (Shim *et al*., 2014). FDs have been shown to correlate well with UIC measures in populations and are a commonly-used method in studies of iodine intake (Brantsæter *et al*., 2009; Lightowler and Davies, 1998).

The 24h food recall method aims to record the dietary iodine intake within a short time frame of consumption. Participants are asked to recall the quantity and food groups consumed in a 24h period (one day) in a structured interview (National Institute of Health Research, 2022b; Shim *et al*., 2014). The 24h recall method is a quick way of establishing short-term intake, is subject to a lower risk of incomplete or inaccurate recall and is less burdensome for participants (National Institute of Health Research, 2022b; Shim *et al*., 2014). The 24h method only shows a snapshot of intake and may not demonstrate long-term iodine intake (National Institute of Health Research, 2022b).

Weighed food records involve the participant weighing and recording the quantity of food consumed (Bingham *et al*., 1995; Lightowler and Davies, 2002; Shim *et al*., 2014). Weighed food records are highly accurate because they do not require the individual to estimate food intake (Shim *et al*., 2014). However, weighed food records can be time-consuming and burdensome for the participant and may change behaviour (National Institute of Health Research, 2022c).

Variation in iodine food composition data has a major impact on dietary estimates of iodine (Zimmermann and Andersson, 2012). In the UK, the most well-known nutrient database is the Composition of Foods Integrated Dataset (CoFID) also named McCance and Widdowson's 'composition of foods integrated dataset' and is frequently used in nutritional studies (Public Health England, 2021). The British Geological Survey also generated an iodine content database using data from published literature up until 2003 (Fordyce, 2003). Today, many online databases are available to researchers to evaluate iodine intake. Database iodine values may result in considerable variation in estimates and must be well monitored and regularly updated to prevent inaccuracies in iodine intake.

Iodine intake (μg day^{-1}) can additionally be estimated from spot UIC, measures of 24-hour UIC and UIC adjusted for creatinine (König *et al*., 2011; Næss *et al*., 2019; Charlton *et al*., 2018). Various calculations are used in the literature as methods for estimating iodine intake (König *et al*., 2011; Næss *et al*., 2019; Charlton *et al*., 2018).

1.1.9 Global status of iodine deficiency disorders (IDD)

The WHO reviewed the global status of IDD in 1960 and published a report called "Endemic goitre" (Delange, 2002). However, the effects of IDD were not widely acknowledged until the 1980s (Lazarus, 2015). In 1986, The International Council for the Control of Iodine Deficiency Disorders (ICCIDDs) was established to address the effects of iodine deficiency at the individual, social, and national levels (ICCIDD, 2011). The ICCIDD is now known as The Iodine Global Network (IGN). The IGN is an organisation that collaborates with WHO and UNICEF to address IDD globally including the enrolment of strategies to eliminate IDD (Lazarus, 2015).

The IGN monitors studies of population iodine nutrition and complies data into a global Scorecard. The IGN estimates of countries with adequate intake have improved over the past 10 years from 105 in 2011 to 111 in 2021 (Andersson *et al*., 2012; IGN, 2021). However, these estimates may be misreporting the scale of global iodine adequacy because large-scale population monitoring is not present in many underdeveloped countries (IGN, 2021).

In countries with monitoring schemes, specific vulnerable population groups at risk of iodine deficiency may also be missed in estimates (Public Health England, 2014). Additionally, many population studies of iodine nutrition are outdated (>5 years) (IGN, 2021). Finally, current iodine deficiency may be overlooked in countries in Europe where population iodine adequacy fluctuates between adequate and mild-moderate deficiency (Andersson *et al*., 2007b; IGN, 2021). Although progress has been made towards the elimination of IDD, poor iodine nutrition is still a serious global public health issue.

1.1.10 Prevalence of iodine deficiency disorders (IDD) in the UK

Historically, iodine deficiency was prevalent in the UK (Lazarus, 2015; Slavin, 2005). Endemic goitre was first detected and reported in adults and children living in the UK in the late 1800s (Berry, 1901). Goitre was particularly common in limestone-heavy regions of England including the West Country, Gloucestershire, and Derbyshire, which were collectively branded as the 'goitre belt' (Phillips, 1997). In the 18th and 19th centuries, goitre was so widely recognised in Derbyshire that the presence of an enlarged thyroid was termed 'Derbyshire neck' (Slavin, 2005). Later in the mid-1900s a 'Goitre sub-committee was launched as part of the Medical Research Council (MRC) (Slavin, 2005). The MRC recommended iodised salt as a method to prevent iodine deficiency, but universal iodisation was never established (Slavin, 2005). Goitre was thought to be eradicated in Derbyshire in the 1930s, however, evidence of goitre was still present in areas of the UK until the 1960s (Slavin, 2005). Improvement in population iodine in the 19th century was a consequence of increased cow's milk iodine concentration and human consumption (Bath and Rayman, 2012; 2018). Iodophor disinfectants and cattle feeds were introduced to the dairy sector which naturally increased the iodine content of cow's milk (Bath and Rayman, 2012; 2018). Cow milk became a vital and rich source of iodine in the diet (Bath and Rayman, 2012; 2018). Meanwhile, the Government was promoting the consumption of cow's milk in UK-wide campaigns (Bath and Rayman, 2012; 2018). In the last 10 years, there has been increased awareness and research into IDD in the UK which began following research by Vanderpump and colleagues in 2009 (Vanderpump *et al*., 2011).

Vanderpump determined the iodine status of 737 secondary school girls (14-15 years) and found that mUIC in the sample was 80.1 μg L^{-1} which is indicative of mild iodine deficiency (50–99 μg L^{-1}) according to the WHO thresholds (Vanderpump *et al*., 2011; WHO, 2007). Similarly, maternal iodine status (mUIC) was reviewed in all available UK studies in 2015 and were found to be below the WHO threshold for adequacy of 150 μg L^{-1} (Bristol; 91.1 μg L^{-1}, Cardiff; 117 μg L^{-1}, Scotland; 137 μg L^{-1}, Surrey; 85.3 μg L^{-1}, Oxford; 42.0-69.4 μg L^{-1}) (WHO 2007; Bath and Rayman, 2015). Collectively, these studies evidence that some UK populations are iodine deficient and call for further investigation of iodine nutrition.

In 2014, SACN released a position paper on iodine and health in response to the publication of the Vanderpump *et al* research paper in 2011 (Public Health England, 2014). The SACN report outlined the current evidence and the adequacy of UK iodine intake, concluding that adolescent girls and individuals who avoid cow's milk and fish (including vegans and vegetarians) have the greatest risk of iodine deficiency (Public Health England, 2014).

Since the release of the SACN report, many UK studies have been published assessing iodine deficiency in vulnerable populations including pregnant women and women of childbearing age (Bath *et al*., 2014a; Farebrother *et al*., 2020; McMullan *et al*., 2019; Mullan *et al*., 2020; O'Kane *et al*., 2018, 2016; Snart *et al*., 2020; Threapleton *et al*., 2021). The findings of these studies are consistent with the general trend of low iodine intake and status in these groups.

The National Diet and Nutrition Survey (NDNS) rolling programme (Public Health England) is a continuous cross-sectional survey that measures the nutrient intake of the UK population (Public Health England and Food Standards Agency, 2019). The most recent NDNS report (years 9 – 11) showed that iodine status is above the WHO cut-off for iodine adequacy (100-299 μg L^{-1}) for all age and sex groups, except of women aged 16-49 years (women of childbearing age) (Public Health England, 2020). Individuals in this age group had a mUIC of 98 μg L^{-1} corresponding to mild iodine deficiency (Public Health England, 2020). Severe iodine deficiency (< 50 μg L^{-1}) was recorded in 21% of this age group, which is worrying given the health consequences of iodine deficiency at this life stage on foetal brain and neurodevelopment (Public Health England, 2020).

A review in 2020 addressed the possible reasons for the decline in iodine nutrition and the re-emergence of iodine deficiency in vulnerable groups in the UK (Woodside and Mullan, 2020). It concluded that alterations in iodine were due to changing farming practices, dietary choices, and public health priorities (Woodside and Mullan, 2020). In 2005, legislation was implemented to halve the iodine content of animal feeds from 10 mg K^{-1} to 5 mg K^{-1} thus reducing the iodine content of cow's milk (Public Health England, 2014). Equally, cow's milk intake has been on the decline in the UK, chiefly among women, children, and adolescents (Mintel, 2019a).

Cow's milk and dairy intake has been shown to have a direct relationship with iodine intake (Bath *et al*., 2014a, 2014c; Brantsæter *et al*., 2009; O'Kane *et al*., 2018b; Vanderpump *et al*., 2011), whereby, those with the lowest intake tend to have the lowest dietary iodine intake (Vanderpump *et al*., 2011). Individuals in the UK are also making behavioural shifts to more sustainable diets that are excluding foods rich in iodine (Woodside and Mullan, 2020). Additionally, public health campaigns that helped boost iodine intake in the 90s are no longer present. For example, the school milk scheme was ended in 2020 following the UK's withdrawal from the European Union (EU) (Woodside and Mullan, 2020). Additionally, public health education has not emphasised the role of iodine, particularly for pregnant women and women of childbearing age (Woodside and Mullan, 2020). Studies investigating awareness of iodine in the UK have found that iodine knowledge is generally low, and that the role of iodine is not well understood by the general public (Eveleigh *et al*., 2022; McMullan *et al*., 2019; O'Kane *et al*., 2016). Lastly, the UK does not have any formal fortification scheme for iodine like other countries in the EU (Bath *et al*., 2014b). There are currently no concerns about excess iodine intake in the UK population.

1.2 Vegan and Vegetarian Diets

1.2.1 Definitions

Vegan and vegetarian diets are defined by varying levels of restriction of animal products (**Table 1.6)**. In the 20th century, definitions of vegetarian and vegan diets were homogeneous and consisted of those who did not consume animal products (vegans) and those who also may consume dairy and eggs (vegetarians) (Phillips, 2005). Subculture diets of the vegetarian diet were later classified based on the type of animal product chosen to consume (**Table 1.6**) (Phillips, 2005). Subcultures are groups with identities that differ from the dominant culture. In the context of vegan/vegetarian diets, subculture diets describe those that share common dietary restrictions e.g. do not consume meat but vary slightly from the primary definitions. These include macrobiotic, raw, and fruitarian (Phillips, 2005). Variations in these classifications are significant when discussing the nutritional influence of vegetarian and vegan diets.

Table 1.6. Definition of common vegetarian and vegan diet types.

Type[1]	Definition
Flexitarian	Occasionally excludes meat and poultry but continues consumption of fish, eggs, and dairy
Pescatarian	Excludes meat and poultry but continues consumption of fish, eggs, and dairy
Lacto-ovo vegetarian	Excludes meat, poultry and fish but continues consumption of dairy and eggs
Lacto vegetarian	Excludes meat, poultry, fish, and eggs but continues consumption of dairy
Ovo vegetarian	Excludes meat, poultry, fish and dairy but continues consumption of eggs
Vegan	Excludes all animal products (meat, poultry, fish, eggs, and dairy)

[1]Diet definitions Phillips, 2005.

Definitions of vegan and vegetarian diets are not absolute and can vary (Sabaté *et al*., 2001). Sabate *et al* (2001) defined vegetarians as individuals who consume meat, poultry, or fish less than once a week, which by current definitions outlined in **Table 1.6** would consider an individual a flexitarian. Beardsworth and Keil (1991) considered that dietary preferences such as vegetarian and vegan exist on a scale of dietary restrictions ranging from 'least strict' to 'most strict'. Whereby omnivorous diets or diets that consumed meat were considered the least strict, and vegan diets where only plant-based foods are consumed were the strictest. In Beardsworth and Keil's model, different vegetarian diets were regarded to move along the scale (pescatarian, lacto-ovo vegetarian, lacto vegetarian, ovo vegetarian). Studies have documented that individuals identified as vegetarians and/or vegans do eat meat occasionally (Rosenfeld and Tomiyama, 2019). The reasoning for the violation of meat-free diets can vary, for example, a vegetarian individual may consume meat when celebrating a special occasion or may accidentally consume meat as part of a meal unknowingly (Rosenfeld and Tomiyama, 2019). This phenomenon further challenges the rigid definitions of vegan and vegetarian diets. Individuals may also report their dietary preference e.g. vegetarian as a loose definition to outline flexible food guidelines (Rosenfeld and Tomiyama, 2019). It is also important to acknowledge that according to self-categorization theory, individuals may self-define as a vegetarian or a vegan to identify with vegetarian/vegan beliefs rather than to describe their eating behaviour (Rosenfeld and Tomiyama, 2019). These additional factors must be considered when defining vegan and vegetarian diets.

1.2.2 Global prevalence

The prevalence of vegan and vegetarian diets differs globally (**Table 1.7**).

Table 1.7. Current global prevalence of vegan and vegetarian diets.

Country	Vegans approximate no. individuals (% of population)	Vegetarians approximate no. individuals (% of population)	Year of data	Reference
Argentina	-	5,400,000 (12)	2020	(Unión Vegana Argentina, 2020)
Brazil	6,330,660 (3)	29330000 (14)	2018	(Statista, 2018a)
Canada	1,768,000 (5)	2,888,000 (8)	2020	(Dale Cudmore, 2021)
China	27,960,000 (2)	195,720,000 (14)	2019	(Statista, 2019a)
Denmark	230,000 (4)	580,000 (10)	2020	(Ipsos, 2020)
Finland	120,000 (2)	660,000 (12)	2021	(Ipsos and Horgmo, E., 2021)
France	726,000 (1)	3,400,000 (5)	2018	(FranceAgriMer, 2018)
Germany	1,660,000 (2)	8,300,000 (10)	2021	(Forsa, 2021)
India	121,500,000 (9)	276,000,000 (20-39)	2021	(Statista, 2021)
Ireland	100,200 (2)	400,800 (8)	2021	(BORD BIA, 2021)
Italy	602,723 (1)	3013615 (5)	2022	(Statista, 2022)
Japan	2,500,000 (2)	11,367,000 (9)	2019	(BORD BIA, 2020)
Netherlands	150,000 (1)	850,000 (5)	2020	(Vegetariersbond, 2022)
Norway	53,120 (1)	159,360 (3)	2018	(Groufh-Jacobsen *et al*., 2022)
Spain	235,650 (0.5)	942,600 (2)	2019	(Statista, 2019b)
Sweden	415,000 (4)	1,248,000 (12)	2020	(Ipsos, 2020)
United Kingdom	2,016,600 (2-4)	3,697,100 (5-6)	2022	(YougGov, 2022)
United-States	7,588,000 (3)	16,000,000 (5)	2018	(Reinhart, 2018)

-, Not applicable.

Currently, India is the leading nation by share of vegetarian and vegan diets (**Table 1.7**). India's high prevalence of meat-free diets is principally due to a large proportion of the population following Hinduism (Britannica, 2022). Asides from religious reasons, individuals residing in lower-income countries may follow vegan and/or vegetarian diets because of low meat availability or the costly price of meat (Leahy, 2010).

There are inconsistencies in reports on the prevalence of vegan and vegetarian diets. Data on the prevalence of vegan and vegetarian diets come from a limited sample of respondents from a snapshot period in time. Population surveys do not account for the dynamic nature of dietary choice, whereby rates of vegetarianism and veganism fluctuate jointly over time (Waters, 2018). Similarly, surveys cannot account for the possible transition in eating behaviours; while omnivorous diets are largely stable over time, vegan and vegetarian diets are less so (Milfont *et al*., 2021; Springmann *et al*., 2021). Population rates of vegan and vegetarian diets may also improve after campaigns promoting meat-free diets (Waters, 2018). For example, meat-free Mondays or Veganuary (De Backer and Hudders, 2014; Veganuary, 2022). Other unknown factors are likely to influence the uptake of vegan and vegetarian diets (Waters, 2018).

The prevalence of vegan and vegetarian diets is likely to increase as industrialised countries move towards more sustainable diets that typically contain lower quantities of meat and animal products.

1.2.3 British vegan and vegetarian diets, past and present

There are many historic accounts of vegetarian and vegan diets across the world dating from the sixth century BC (Leitzmann, 2014). In the 19th century, several groups in the UK actively followed and promoted diets lacking in meat and animal products (Davis and International Vegetarian Union, 2022). Vegetarian diets were first described in print in the UK in 1847 (Davis and International Vegetarian Union, 2022), the same year as the founding of the Vegetarian Society. In early accounts, before the term vegetarianism or veganism was created, the 'vegetable diet' described food regimes that did not contain animal meat (Davis and International Vegetarian Union, 2022). The vegetable diet included foods such as cereals (oats, wheat, barley, and rice), starches (sago and tapioca), peas (kidney-beans, broad beans and green peas), vegetables and fruits (Davis and International Vegetarian Union, 2022). The vegetable diet was like the 'traditional' vegan and vegetarian diets that are observed in our society today, reliant on grains, beans, fruits and vegetables (Davis and International Vegetarian Union, 2022).

In the 20th century, there were increasing numbers of epidemiological studies investigating the nutritional intake of vegan and vegetarian diets (Leitzmann, 2014). Researchers were particularly interested in the beneficial health effects of meat-free diets and their ability to reduce the incidence of chronic and degenerative diseases (Leitzmann, 2014). At this time, around 6% of the UK population described their diet as being vegetarian according to the Archive of Market and Social Research (AMSR) (AMSR, 2022). Although vegetarian and vegan food substitutes (alternative milk and meats) were more available, individuals following meat-free diets still had a limited repertoire of foods to choose from, particularly when shopping in supermarkets or eating outside of the home (AMSR, 2022).

There continued to be further innovation in the manufacturing of plant foods in the 2000s, whereby, the UK vegetarian and vegan food sector was valued at £428 million (Mintel, 2019a). In the UK, the milk-alternative beverages market grew by 155% from 2011 to 2013 (Mintel, 2019a). Additionally, there was a 185% increase in new UK vegan products between 2012 and 2016 (Mintel. 2019a).

Modern-day vegetarians and vegans are much more heterogeneous than in the past. Individuals now have a more diverse pool of foods to choose from that are suitable for their dietary preferences, permitting huge variations in food intake. Four distinct dietary patterns within the definition of a vegan diet in UK vegans have been identified (Gallagher *et al*., 2022). The least common diet pattern observed was the 'traditional' vegan pattern comparable to the vegan diets followed in the 1980s, as described previously. This suggests that innovation in the vegetarian and vegan food sector is beginning to shift from the healthy 'traditional' diet. This change in eating could potentially compromise the nutritional quality of vegetarian and vegan diets and risk micronutrient deficiencies if diets are not appropriately planned.

1.2.4 Motivations

As previously mentioned, (see Introduction, Section 1.2.2), in many areas of the world, vegetarian and vegan diets are frequently adopted due to the low availability of animal foods and/or for monetary or religious reasons. In Western nations, individuals typically choose to follow vegetarian and vegan diets voluntarily or may adopt them due to food aversion, food allergies, or intolerances (Hargreaves *et al*., 2021). Adherence to vegetarian and vegan diets in Western countries often goes beyond food choice and is closely related with social identity (Nezlek and Forestell, 2020).

The top motivations for following vegetarian and vegan diets are ethical and health driven (Allen *et al*., 2000; De Backer and Hudders, 2014; Fox and Ward, 2008; Hoffman *et al*., 2013; Hopwood *et al*., 2020; Janssen *et al*., 2016; MacInnis and Hodson, 2021; Miki *et al*., 2020; North *et al*., 2021; Rosenfeld and Burrow, 2017). Ethical motives include environmental and animal welfare concerns relating to the production of animal-based foods. Health motives often involve the promise of improved health outcomes, weight loss, and reduction of chronic disease states (Fox and Ward, 2008; Rosenfeld and Burrow, 2017). However, many studies have shown that the adoption of vegan and vegetarian diets may be due to a combination of different motives (Allen *et al*., 2000; De Backer and Hudders, 2014; Fox and Ward, 2008; Hoffman *et al*., 2013; Janssen *et al*., 2016; MacInnis and Hodson, 2021; Miki *et al*., 2020; North *et al*., 2021)

1.2.1 Iodine nutrition

Individuals following meat-free diets are more dependent on plant foods to achieve dietary nutrient recommendations. As mentioned, (see Introduction, Section 1.1.2), the iodine content of fruits and vegetables is low and highly variable (Fuge and Johnson, 2015). Vegan and vegetarian individuals may not consume typically rich sources of iodine (cow's milk, dairy products, eggs and fish) and consequently are more likely to have low dietary iodine intake (Public Health England, 2014).

Dietary iodine may be improved by consuming vegan/vegetarian acceptable iodine-containing foods such as iodine-containing food supplements, iodine-fortified foods (including iodised salt), seaweeds or seaweed-containing foods. Moreover, individuals consuming vegan or vegetarian diets may consume higher quantities of dietary goitrogens from increased ingestion of plant foods (e.g. brassica) that may limit iodine bioavailability (Leung *et al*., 2011). Individuals following vegan and vegetarian diets may have coexisting micronutrient deficiencies limiting thyroid hormone synthesis and action (see Introduction, Section 1.1.6) (Fallon and Dillon, 2020; García-Morant *et al*., 2020).

Lifestyle factors that are frequented by vegans and vegetarians may further limit iodine intake, for example, the avoidance of dietary supplements and fortified foods, low salt intake (as a barrier to iodised salt consumption), low body mass index (BMI), and low food intake (Bowman, 2020, Eveleigh *et al*., 2020).

1.2.1.1 Epidemiological evidence

The first reported studies of iodine nutrition in vegan and vegetarian diets were conducted in Europe (Sweden, UK, Finland, and Germany) in the 1980s and 1990s when it was estimated that 1,572 million people were affected by iodine deficiency (Kapil, U, 2007; Abdulla *et al.*, 1981; Appleby *et al*., 1999; Draper and Lewis, 1993; Lightowler and Davies, 1998; Rauma *et al.*, 1994). Around this time, the Icelandic Nutrition Council also identified that young women consuming low levels of fish and dairy products were a subgroup with an increased risk of deficiency (Gunnarsdottir *et al*., 2009), but the link between low animal product intake and possible dietary restrictions in these groups was not established.

Further studies addressed iodine intake and status in vegetarian and vegan diets in the early 2000s (Lightowler and Davies, 2002), confirming that animal-free diets still posed an issue to iodine nutrition. The authors of these early iodine studies acknowledged that plant foods had a very low iodine content due to low soil iodine content and that animal product foods rich in iodine were not suitable for individuals following vegan and vegetarian diets. Concluding that, vegans and vegetarians who were not consuming seaweed, iodised salt, or supplements were at risk of iodine deficiency.

In 2005, Field *et al* published a review containing evidence from seven research papers, highlighting that vegetarians and vegans do not need to have lowered iodine intake, published the first review of iodine in vegetarian and vegan diets. Field and Borak in the 'Comprehensive Handbook of Iodine' further updated the review in 2009. In 2014, SACN raised the risk of iodine deficiency in individuals following vegan and vegetarian diets (Public Health England, 2014). Since its publication, studies have shown that individuals following meat-free diets are deficient in iodine.

1.3 Objectives and hypothesis

There has been a re-emergence of studies investigating iodine in these subgroups and the need to re-investigate the literature and establish the state of iodine nutrition in modern-day vegan diets (>2020). There are still few studies monitoring iodine intake in vegetarian and vegan populations in the UK. At present, little is known about the iodine nutrition of vegans and vegetarians living in areas with a historic prevalence of iodine deficiency such as Nottinghamshire. Moreover, there is a lack of knowledge regarding the iodine intake and status of those who follow a vegetarian or vegan diet in the short term after public campaigns promoting veganism (Waters, 2018).

This research project had the following aims: (1) To determine the micronutrient intake and status, predominantly of iodine, of individuals following a restricted diet (vegan and vegetarian) in the short and long term, and compare population data with omnivorous individuals, (2) To evaluate the understanding of iodine and its role in the diet among individuals who adhere to a vegan or vegetarian diet, and (3) To investigate food fortification as a possible method to improve iodine intake and status of individuals following vegan or vegetarian diets.

I hypothesise that iodine intake and status in vegan and vegetarian groups in the UK and globally will be deficient in iodine and will not meet the recommended intake for iodine of 140 - 150 µg day^{-1}. I hypothesis that UIC will be low throughout the vegetarian and vegan groups studied. Additionally, individuals following a short-term vegan diet will experience a decline in iodine intake but not status (status reflects longer-term intake).

This thesis contains several novel ideas: it will be the first project to assess the global literature on iodine nutrition in modern-day vegan diets; it will also be the first to observe the relationship between short-term vegan diets and micronutrient intake and status in the UK in individuals choosing to follow a 4-week vegan diet during a charity pledge of Veganuary.

2. MATERIALS AND METHODS

2.1 Data sources

All data and biological samples used in this thesis (**Manuscripts 2 and 3**), were collected as part of two observational human research trials designed and managed by the author of this thesis. The cohorts for each human research trial were recruited separately and will be described in **Manuscripts 2 and 3**. Details of the key methodology used for each human research trial are outlined in the relevant sections below and are summarised in **Table 2.1.**

Table 2.1. Summary details for each cohort.

	Cohort 1	**Cohort 2**	**Cohort 3**	**Cohort 4[1]**
Manuscript presented	2	2	3	3
Setting	Nottingham, UK	Nottingham, UK	National, UK	National, UK
Recruitment years	2016-17	2019	2019-2020	2020-2021
Sample (n)	60	36	81	73
Urine sample collection	One spot-urine sample was collected at 12.00 pm	One spot-urine sample was collected at 12.00 pm	Three spot-urine samples were collected over one day in the morning, afternoon, and evening.	NA
Urinary iodine measure	ICP-MS	ICP-MS	ICP-MS	NA
Urinary creatinine measure	NA	NA	Jaffe principle	NA
Plasma Thyroglobulin measure	NA	NA	ELISA	NA
Plasma fT4 measure	NA	NA	ELISA	NA
Plasma micronutrients measure	NA	NA	ICP-MS	NA
Dietary assessment measure (time-point)	Self-administered online iodine-specific FFQ and paper-copied 3-day FD	Self-administered online iodine-specific FFQ and paper-copied 3-day FD	Self-administered online FFQ and paper-copied 3-day FD	Self-administered online iodine-specific FFQ
Iodine/micronutrient knowledge measure	Self-administered online iodine knowledge questionnaire	Self-administered online iodine knowledge questionnaire	Self-administered online micronutrient knowledge questionnaire	Self-administered online iodine knowledge questionnaire

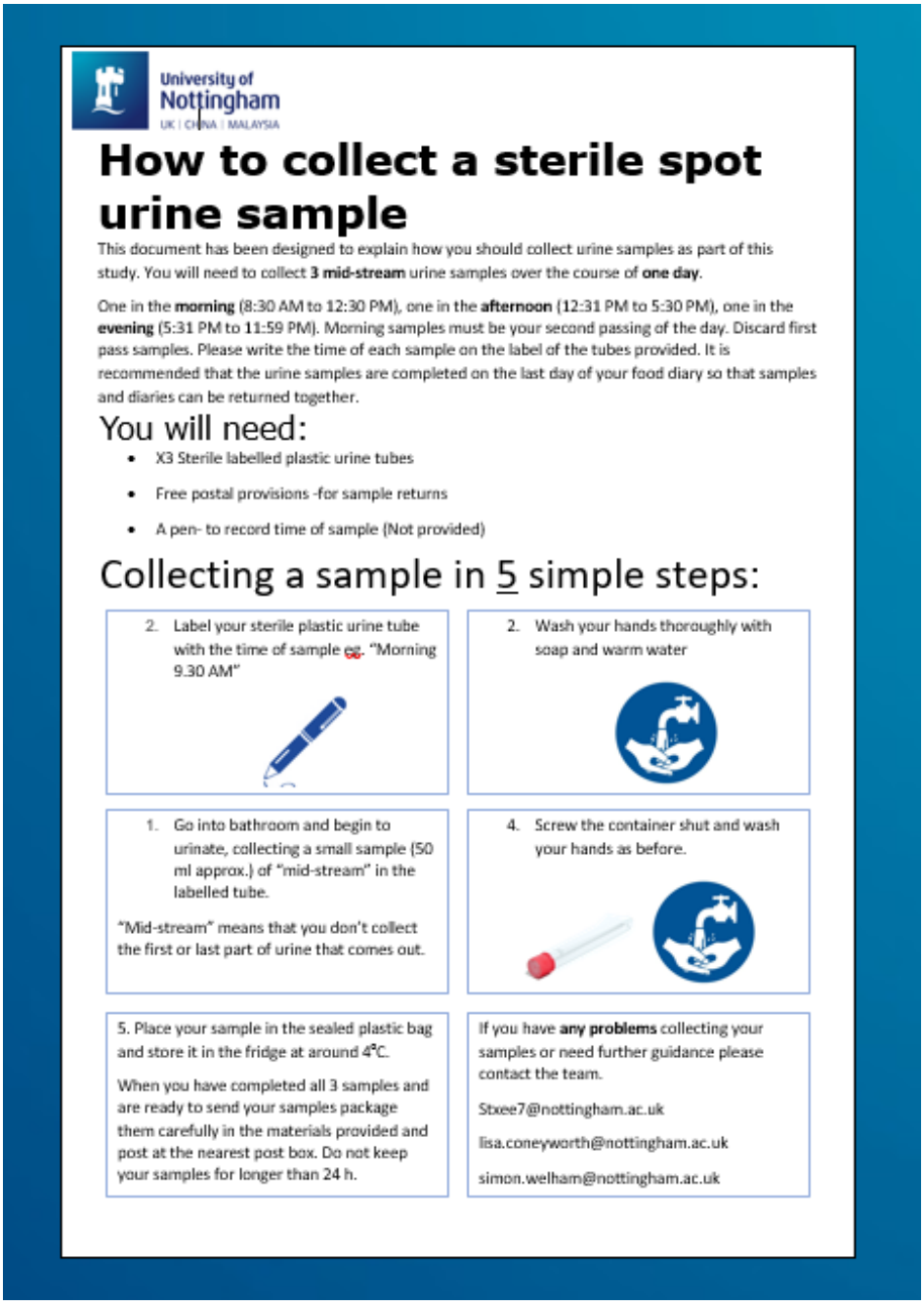
[1]Data were collected during the SARS-CoV-2 virus (COVID-19) pandemic, therefore, no biological samples were permitted; ICP-MS, Inductively coupled plasma mass spectrometry; ELISA, Enzyme-linked immunosorbent assay; FFQ, Food Frequency Questionnaire; FD, food diary; NA, not applicable.

2.2 Laboratory methods

2.2.1 Urinary iodine concentration (UIC) analysis

Midstream non-first pass spot urine samples were collected in a 50 ml universal sterile (ThermoFisher Scientific™) by participants. In **Manuscript 2,** verbal descriptions of how to take a urine sample were provided to participants by the author of this thesis. In **Manuscript 3**, individuals were provided with paper copy instructions describing the correct urine collection procedure (**Figure 2.1**).

After collection, urine samples were packaged in plastic zip lock bags in a leak-proof lined specimen container labelled with biological hazard symbols and description of samples inside, to be transported to North Laboratory, School of Biosciences, at the University of Nottingham for analysis. If collected outside of working hours, samples were stored upright in laboratory fridges (-4°C), for next-day analysis. Urine specimens were centrifuged (Beckman GS-6R Refrigerated Centrifuge GS1M31) for 10 minutes at 252 g at room temperature. Separated urine samples were handled in a class II Microbiological Safety Cabinet (MSC) (ESCO ACZ-4E8). The a-cellular layer was collected with an appropriate transfer pipette without disturbing the cellular debris at the bottom of the tube. Ten percent of samples were analysed by Mark Pope at the Child Health Laboratory, Queen's Medical Centre (QMC) to confirm that no cellular material was contained within samples before storage. Samples were pipetted into appropriately sized aliquots in labelled Eppendorf tubes (ThermoFisher Scientific™). Aliquot volume is estimated to be approximately 1 ml per sample. This process was completed within 1 hour of sample centrifugation. Aliquots of urine were transferred and stored in North Laboratory fridges at -80°C until analysis. Urine samples were diluted 1:10 with Milli-Q® H_20 and placed into Polypropylene Autosampler Tube (ThermoFisher Scientific™) before Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis. All samples were analysed in triplicate. No additional digestion steps were conducted. UIC was assessed by ICP-MS (ThermoFisher Scientific™ iCAP Q) with standard mode (no cell gas) and an internal standard of 5 µg L^{-1} for correction (Seronorm). ICP-MS analysis was conducted by Saul Vazquez Reina at The University of Nottingham, School of Bioscience following dilution.



University of Nottingham
UK | CHINA | MALAYSIA

How to collect a sterile spot urine sample

This document has been designed to explain how you should collect urine samples as part of this study. You will need to collect **3 mid-stream** urine samples over the course of **one day**.

One in the **morning** (8:30 AM to 12:30 PM), one in the **afternoon** (12:31 PM to 5:30 PM), one in the **evening** (5:31 PM to 11:59 PM). Morning samples must be your second passing of the day. Discard first pass samples. Please write the time of each sample on the label of the tubes provided. It is recommended that the urine samples are completed on the last day of your food diary so that samples and diaries can be returned together.

You will need:

- X3 Sterile labelled plastic urine tubes
- Free postal provisions -for sample returns
- A pen- to record time of sample (Not provided)

Collecting a sample in 5 simple steps:

2. Label your sterile plastic urine tube with the time of sample eg. "Morning 9.30 AM"

2. Wash your hands thoroughly with soap and warm water

1. Go into bathroom and begin to urinate, collecting a small sample (50 ml approx.) of "mid-stream" in the labelled tube.

"Mid-stream" means that you don't collect the first or last part of urine that comes out.

4. Screw the container shut and wash your hands as before.

5. Place your sample in the sealed plastic bag and store it in the fridge at around 4°C.

When you have completed all 3 samples and are ready to send your samples package them carefully in the materials provided and post at the nearest post box. Do not keep your samples for longer than 24 h.

If you have **any problems** collecting your samples or need further guidance please contact the team.

Stxee7@nottingham.ac.uk

lisa.coneyworth@nottingham.ac.uk

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Figure 2.1. Paper copy instructions given to participants to aid the collection of midstream non-first-pass urine samples for urinary iodine concentration (UIC) analysis.

2.2.2 Iodine:Creatinine (I/Creat) analysis

Urinary iodine is expressed per unit volume and reflects recent fluid intake, for this reason, iodine: creatinine (I/Creat ratio) can be used to correct for fluid volume. To determine I/Creat in provided urine samples (**Manuscript 3** only) we developed a protocol based on the Jaffe method as modified by J. Moore *et al* (2017). The Jaffe Principle describes the reaction of creatinine (Jaffe, 1886), with picric acid in an alkaline solution, which produces a soluble red colour complex. Colorimetric analysis of samples against creatinine standards can be used to estimate creatinine concentration.

Urine samples were collected and frozen before I/Creat analysis (see Materials and methods, Section 2.2.1). Samples were defrosted overnight at -4°C, for next-day analysis. Defrosted urine specimens were centrifuged, to remove cellular debris, (Beckman GS-6R Refrigerated Centrifuge) for 30 seconds at 252 g at room temperature to ensure dispersion of constituents. All preparation of materials took place in a Class II MSC (ESCO ACZ-4E8). Urine specimens were diluted 1:10 for analysis. A solution of 0.75 Sodium Hydroxide (NaOH) was prepared by dilution of 6g NaOH in Milli-Q® H_20. Next, a solution of Picric Acid and NaOH was produced by mixing 2.75 ml of 1.3% Picric Acid with 2.75 ml of 0.75 NaOH solution. Creatinine standards were prepared from 10 mg of creatinine (Sigma-Aldrich Lot: SLBW4791) in 50 ml Milli-Q® H_20 (20 mg dL^{-1} of creatinine in H_20). A standard curve was generated using creatinine standards (**Table 2.2, Figure 2.2**) on a 96 well plate specified for dilution of reagents. The diluted urine samples were also pipetted into wells of the dilution plate. A dilution plate was used to reduce the disparity in reaction time between samples. To perform the assay, 160 µL of each solution from the dilution plate was directly transferred into the corresponding wells of a new transparent plastic 96-well plate labelled the reagents plate. Next, 100 µL of Picric Acid NaOH solution was added into each well of a new plate using a multichannel pipette to reduce variation by time. Absorbance was assessed using a FLUOstar Omega plate reader (BMG LABTECH) set at 520 nm at room temperature.

Following the addition of reagents, absorbance was recorded immediately and every 5 minutes for a maximum of 30 minutes of incubation. Incubation time was measured to prevent additional factors influencing colour production.

Staggering of absorbance readings was used to ensure dependable reaction times. Unknown sample creatinine concentration was determined by the following calculation (**Equation 2.1**):

$$\mathbf{X = Au/As * Cs}$$

Where:

X = Unknown sample concentration,

Au = Sample Absorbance,

As = Absorbance of standard,

Cs = Standard concentration

Equation 2.1. Unknown sample creatinine concentration calculation.

Table 2.2. Concentration of creatinine standards for assessment of Iodine:Creatinine (I/Creat).

Standard	Creatinine standard (µL)	Milli-Q® H_20	Final concentration (mg dL^{-1}) creatinine
1	0	500	0
2	50	450	2
3	100	400	4
4	150	350	6
5	200	300	8
6	300	200	12
7	375	125	15

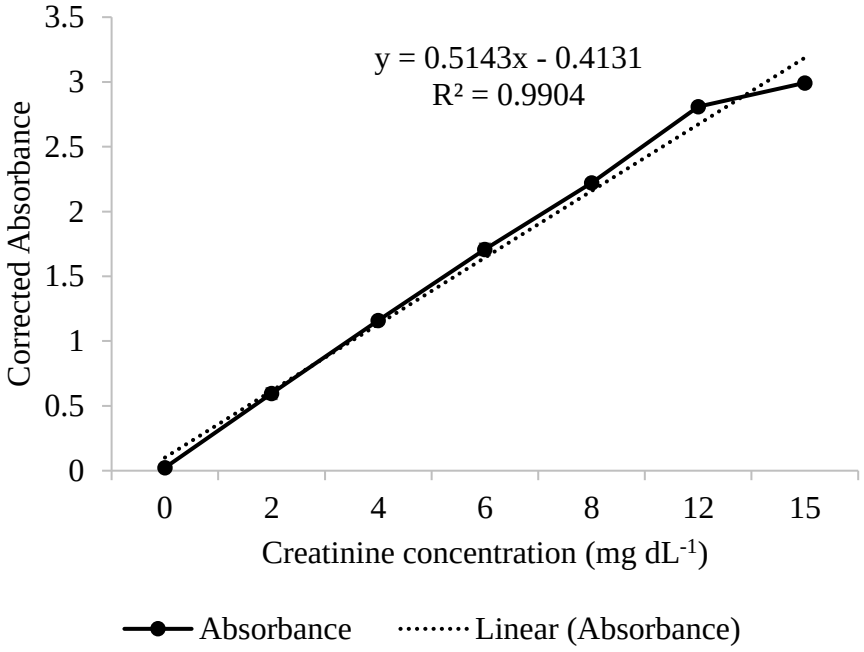


Figure 2.2. Example composite standard curve from a total of 4 Iodine:Creatinine (I/Creat) assays.
Data presented are mean ± SD.

2.2.3 Blood collection protocol

Blood samples were collected from participants by trained phlebotomists at the QMC Nottingham. Phlebotomists used purple topped Ethylenediaminetetraacetic acid (EDTA) blood vacutainer tubes (BD Vacutainer 10 ml EDTA Purple Blood Collection Tubes) to collect 10 ml of venous blood from participants. Researchers asked phlebotomists to remove the tourniquet before blood dispersion to prevent haemolysis. After collection, the blood samples were gently mixed by inverting the tube 8 to 10 times. Participants were asked to sit and rest for 10 minutes following blood samples. EDTA tubes containing blood were transported upright packaged in zip plastic zip lock bags in a leak-proof lined specimen container labelled with biological hazard symbols and description of samples inside, to the Child Health Laboratory at the QMC. Blood samples were centrifuged (Heraeus Multifuge 3SR Plus, Thermo Scientific, Loughborough, UK) for 15 minutes at 1100 g at room temperature within 1 hour of blood collection. Once separated, the plasma layer was carefully collected with a transfer pipette ensuring the 'buffy coat' layer was not disturbed. The buffy coat layer describes the white layer of mononuclear cells and platelets in separated blood samples. Plasma was pipetted into Eppendorf tubes placed on ice (ThermoFisher Scientific™). Aliquot volume was selected to be approximately 1 ml per sample. All aliquots were stored upright in a specimen box in an -80ºC freezer at the Child Health Laboratory. All specimens remained at -80ºC or colder before shipping to North Laboratory, School of Biosciences, at the University of Nottingham. Once transported samples remained frozen at -80ºC and were not thawed until constituent analysis.

2.2.3.1 Blood plasma free Thyroxine (fT4) analysis

Human blood plasma fT4 was quantified using Abcam Ltd. Thyroxine (fT4) ELISA Kit (ab108686). The assay kit uses a coated 96-well plate with anti-Thyroxine antibodies, and the fT4 in the sample competes for antibody binding. The 1x Wash Solution were prepared on the day of analysis by diluting 10 ml of 50x Washing Solution with Milli-Q® H20 to yield 500 ml volume. All other solutions were supplied and ready to use (**Table 2.3**). All materials were equilibrated to room temperature before assay completion.

Human plasma samples were defrosted at room temperature and all samples were prepared for analysis with a minimum of two replicates. Standards and samples were added to their respective wells of the test kit (25 µL of each). Thyroxine-HRP Conjugate was added to each well (100 µL) with a single well blank (substrate blank). Wells were covered with foil provided by the test strip and incubated at room temperature for 1 hour. Once the incubation period lapsed, the foil was removed, and wells were washed three times with 300 µL diluted washing solution. Next, 100 µL TMB Substrate Solution was added to all wells. The plate was incubated at room temperature in the dark for a further 15 minutes. Stop Solution (100 µL) was then added to all the wells maintaining order and plates were read at 450 nm using a plate reader (FLUOstar Omega BMG LABTECH). Mean values were calculated and subtracted from the zero standard optical density using the standard curve of absorbance (**Figure 2.3**).

Table 2.3. Concentration of standards for assessment of human blood plasma Thyroglobulin (Tg) using Abcam Ltd. Free Thyroxine (fT4) ELISA Kit (ab108686).

Standard	Total volume (mL)	Final concentration (pg mL^{-1})
0	1	0.0
1	1	3.0
2	1	9.5
3	1	21.0
4	1	36.0
5	1	70.0

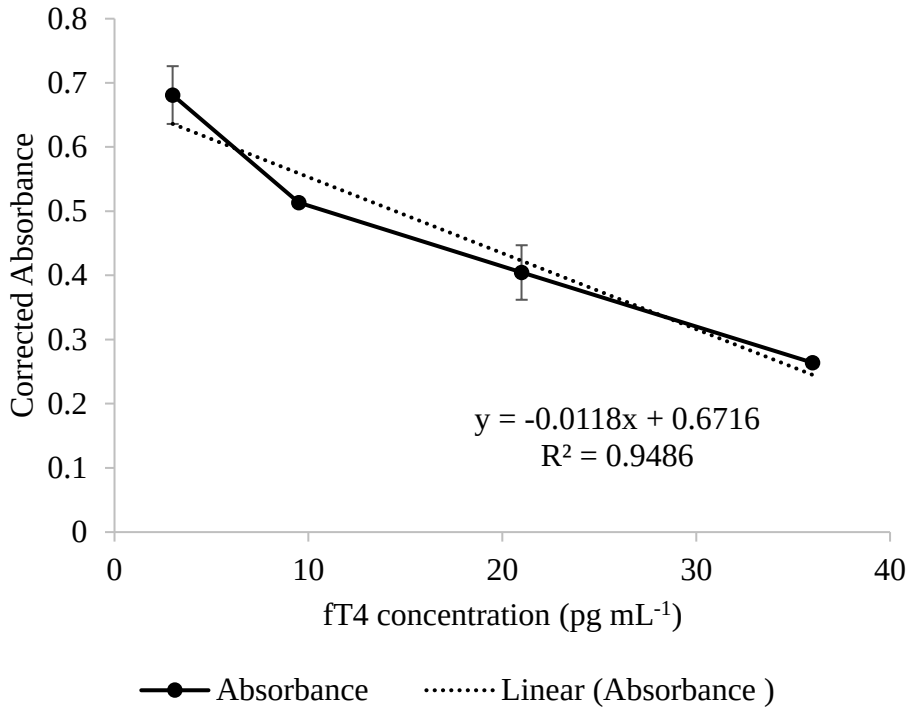


Figure 2.3. Composite standard curve from Human blood plasma Free Thyroxine (fT4) analysis.
Data presented are mean ± SD.

2.2.3.2 Blood plasma thyroglobulin (Tg) analysis

Blood plasma Tg was measured using the Abcam Ltd. Human Thyroglobulin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (ab155441) according to the manufacturer's instructions. The assay kit uses a coated 96-well plate with antibodies specific for Human Tg. The Tg in blood plasma samples binds to the immobilised antibody in the wells. The kit constituents (1x assay diluent B, 1x wash solution, 1x biotinylated thyroglobulin detection antibody, and 600x HRP-streptavidin solution) were prepared on the day of analysis. The 1x assay diluent B was produced by a 5-fold dilution of 5x Assay Diluent B with Milli-Q® H_20. The 1x wash solution was produced by diluting 20 ml of 20x wash buffer concentrate with Milli-Q® H_20 to yield 400 ml volume. The biotinylated anti-Human thyroglobulin vial was briefly spun, before the addition of the prepared 1x assay Diluent B. The mixture was briefly pipetted up and down to ensure the mixing of the solutions. The HRP-streptavidin concentrate was diluted 600-fold with 1x Assay Diluent B after being gently mixed with a pipette before use. Standards were serially diluted as per instructions (**Table 2.4, Figure 2.4**). Human plasma samples were defrosted at room temperature and were diluted 2 fold with Milli-Q® H_20 as advised by manufactures details. Samples of blood plasma were prepared for analysis with a minimum of two replicates. Standards and sample (100 µL of each) was pipetted into appropriate wells in the 96 well plate provided in the test kit. Standards and samples were incubated for 2.5 hours at room temperature in (Corning™ LSE™ Platform Rocker) and were gently rocked. Following incubation, the solution was discarded, and the plate was washed 4 times with 1x wash solution (300 µL per well) using a multi-channel pipette. After washing, the plate was inverted and blotted against clean paper towelling. Next, 100 µL of streptavidin solution was added to each well and incubated at room temperature for 45 minutes, again with gentle rocking. The solution was then discarded, and the washing step described above was repeated. After washing, 100 µL of 3,3',5,5'-tetramethylbenzidine (TMB) one-step substrate reagent was added to each well and was incubated for 30 minutes in a dark room at room temperature with gentle rocking.

Lastly, 50 µL of stop solution was added to each well, and plates were read at 450 nm using a plate reader (FLUOstar Omega BMG LABTECH).

Mean values were calculated and subtracted from the zero standard optical density using the standard curve of absorbance as described for the assessment of creatinine (**Equation 2.1**).

Table 2.4. Concentration of standards for assessment of human blood plasma Thyroglobulin (Tg) using Abcam Ltd. Human Thyroglobulin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (ab155441).

Standard	Volume to dilute (µL)	Diluent (µL)	Total volume (µL)	Starting concentration (ng mL^{-1})	Final concentration (ng mL^{-1})
1	Lyophilised thyroglobulin standard (50 ng mL^{-1})	400	400	50	50
2	200	300	500	50	20
3	200	300	500	20	8
4	200	300	500	8	3.2
5	200	300	500	3.2	1.28
6	200	300	500	1.28	0.512
7	200	300	500	0.512	0.205
8	0	300	300	0	0

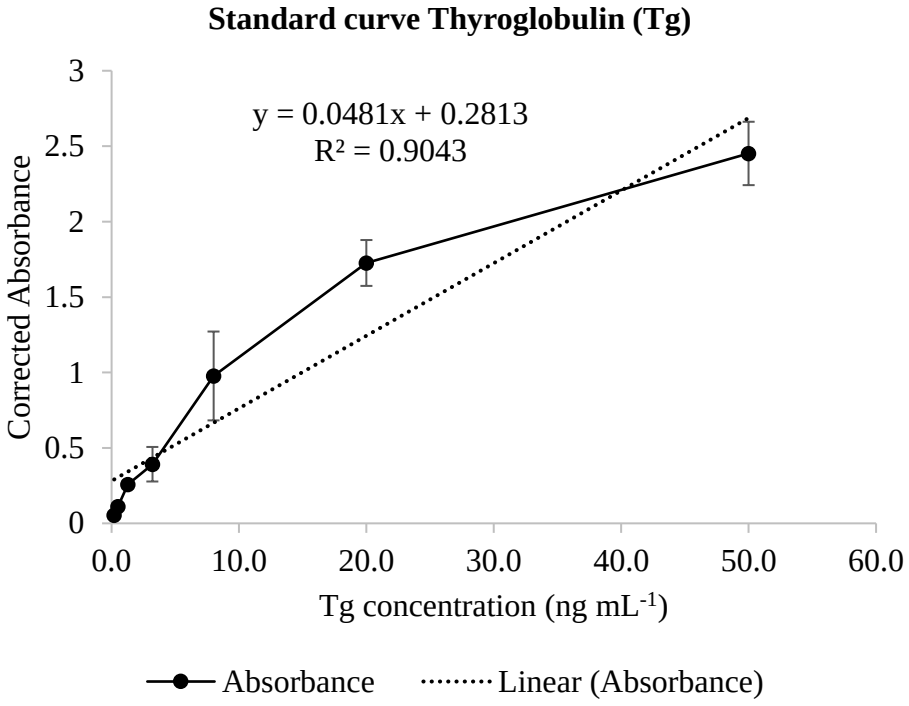


Figure 2.4. Composite standard curve from Human blood plasma thyroglobulin (Tg) analysis.
Data presented are mean ± SD.

2.2.4 Alternative milk iodine analysis

In **Manuscript 4**, an analysis of the iodine concentration of soya milk available from UK supermarkets was conducted in February-March 2022. Alternative milk samples were diluted 1:10 with Milli-Q® H_20 and placed into Polypropylene Autosampler Tube (ThermoFisher Scientific™) before Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis. All samples were analysed in triplicate. No additional digestion steps were conducted. Iodine concentration was assessed by ICP-MS (ThermoFisher Scientific™ iCAP Q) with standard mode (no cell gas), internal standard of 5 µg L^{-1} for correction and Seronorm. ICP-MS analysis was conducted by Saul Vazquez Reina at The University of Nottingham, School of Bioscience following dilution.

2.3 Dietary intake methods

2.3.1 Food diaries (FD)

A4 paper and online 3-day FDs were used to assess dietary intake in **Manuscript 2**. The FD used were those produced by the Medical Research Council Collaborative Centre for Human Nutrition Research (MRC-HNR) as part of the NDNS (Version: P2709 Diary_Adult_A5_Instructions, Ref. 07/H0602/113). The NDNS FD is free to download and use for research studies. Participants were asked to record all food and drink consumed over 3 days (inside and outside the home), portion sizes (or weights of foods consumed), time of consumption, recipes used (if applicable), and any additional details about the eating scenario (for example eating with friends or alone etc.). We also included questions about usual food habits and any dietary supplements used (and their details). We did not include specific questions about the type of milk or fat spread used. Instead, participants were relied upon to provide accurate description of milks and fat spreads used within the diary itself. The NDNS FD contains detailed instructions for participants to read to aid reporting along with photos. Further details regarding the methodology of FDs are outlined later in **Manuscript 2** to prevent duplication of information.

2.3.1.1 Nutritics analysis of food diaries (FD)

FDs responses from participants were coded in EXCEL before being entered into the dietary assessment software Nutritics (Version: 5.79 Research Edition). Before analysis, the data sources used by Nutritics were selected to UK/Ireland to restrict the input of foods that cannot be regularly purchased in the UK. For each participant, age, weight, gender, activity level, dietary preference (vegetarian, vegan, dairy-free, etc.), and allergies were imputed into Nutritics to produce the most accurate nutritional outputs. Adding dietary preferences and allergies ensured that selected foods were appropriate, as foods containing items listed as restricted did not come up on search results. Foods from the FD were imputed into Nutritics by day and a time stamp was generated allowing researchers to observe when foods were consumed. Where possible foods were entered as separate items, for example, a cup of tea with semi-skimmed milk would be separated into its components: tea black brewed and semi-skimmed milk. The separation of food components allowed the calculation of the relative contribution of different foods to micronutrient intake. Portion sizes were selected as given by participants in FDs.

Foods selected and imputed were the best estimates of actual intake. If foods were given in the FD that were not present in the Nutritics database e.g. vegan alternatives, then a food item closely matching the expected nutritional profile was selected. The BRANDB database was restricted unless no alternative food item was present in the database, this is because the BRANDB database often is missing micronutrient values for certain foods. Moreover, before foods were selected, the nutritional information was checked to ensure it was complete to prevent possible underestimation of nutritional intake. Recipes given by participants in FDs were also imputed into Nutritics. All supplements, where possible, were added into FD estimates in Nutritics. Once all food items and recipes were coded into Nutritics, an average of the 3-day FD was generated and was used for future analysis. We additionally assessed the rate of underreporting in our FDs which is outlined in detail in Manuscript 2, Section 4.3.9.

2.3.2 Iodine-specific food frequency questionnaire (FFQ)

Iodine-specific FFQs were used in **Manuscripts 2 and 3** to assess the habitual iodine intake from iodine-rich food groups (cow's milk and dairy products, seafood, eggs, seaweed), supplements, potential vegan sources of iodine (alternative meats, milk, and dairy), iodised salt and dietary goitrogens. The FFQ was developed using "Online surveys" (previously "Bristol Online Surveys"; (Online Surveys, 2022)) and was based on the validated FFQ used in the Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC Oxford) study (EPIC Oxford, 2020). In **Manuscript 2**, the FFQ was used to assess 6 months of intake and in **Manuscript 3** it was used to assess a month's intake. The FFQ included 45 items and was associated with frequency categories. The frequency categories range between "never or less than once/month" to "6+ times per day". Frequently consumed food items, such as cow's milk, were listed in separate questions accounting for variations in serving sizes. The medium serving size was indicated using labelled food images employed by the NDNS (Lennox *et al*., 2008). For each food item, frequency categories were converted to daily iodine intake (μg day^{-1}). The category: "two to four times per week" was adjusted to three per week or equivalent to 0.4 servings per day.

It was assumed that those selecting the "Less than once or never" option for rare foods such as samphire, or animal products for vegans were not consumed within the past 6 months, thus, generating a value of 0.0. Food items were assigned iodine values per portion from an in-house database created using data from Nutritics 4.3 software and McCance and Widdowson's 'composition of foods integrated dataset (Public Health England, 2021; Nutritics, 2021). Iodine values and portion sizes of items included in the FFQ can be viewed in **Table 2.5**. Iodine values for specific kinds of milk used e.g. organic semi-skimmed cow's milk and types of alternative milk can be viewed in **Table 2.6**.

Table 2.5. Food items addressed in the iodine-specific Food Frequency Questionnaire (FFQ).

Food item	Portion (g)[1]	Iodine per 100g (µg day-[1])	Iodine according to the frequency of consumption (µg day^{-1})[1].								
			Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Cow's milk and dairy products											
Semi-skimmed cow's milk, with tea/coffee	30.0	39.0	0.4	0.8	1.7	5.0	9.2	11.7	29.3	52.7	70.2
Semi-skimmed cow's milk, with breakfast cereals	135.0	39.0	1.8	3.5	7.5	22.6	41.4	52.7	131.6	236.9	315.9
Semi-skimmed cow's milk, in a latte, cappuccino, or hot chocolate	160.0	39.0	2.1	4.2	8.9	26.7	49.0	62.4	156.0	280.8	374.4
Semi-skimmed cow's milk, just on its own	200.0	39.0	2.6	5.2	11.1	33.4	61.3	78.0	195.0	351.0	468.0
Yoghurts (e.g. full fat, Greek yoghurt, fromage frais, low fat)	125.0	63.2	2.6	5.3	11.3	33.9	62.1	79.0	197.5	355.5	474.0
Cheese (e.g. cheddar, brie, edam)	30.0	40.0	0.4	0.8	1.7	5.1	9.4	12.0	30.0	54.0	72.0
Milk or cream-based desserts (e.g. ice cream, panna cotta, chocolate)	75.0	5.1	0.1	0.3	0.5	1.6	2.9	3.8	9.4	16.9	22.5
Cheese-based dishes (e.g. cauliflower cheese, cheese, and potato pie)	62.0	9.0	0.2	0.4	0.8	2.4	4.4	5.6	14.0	25.1	33.5
Eggs (chicken) and egg dishes											
Eggs (e.g. boiled, fried, scrambled)	50.0	104.0	1.7	3.5	7.4	22.3	40.9	52.0	130.0	234.0	312.0
Omelette (plain)	125.0	44.0	1.8	3.7	7.9	23.6	43.2	55.0	137.5	247.5	330.0
Egg-based dessert	100.0	17.6	0.6	1.2	2.5	7.5	13.8	17.6	44.0	79.2	105.6

Table continued…

	Portion (g)[1]	Iodine per 100g (µg day-[1])	Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Meat, fish, and seafood											
White sea fish, fresh, or frozen (e.g. cod, haddock, plaice, sole, halibut)	140.0	124.3	5.8	11.6	24.9	74.6	136.7	174.0	435.0	783.0	1044.0
Oily fish, fresh or canned (e.g. mackerel, kippers, tuna, salmon, sardines, herring)	140.0	44.3	2.1	4.1	8.9	26.6	48.7	62.0	155.0	279.0	372.0
Other seafood (e.g. crab, prawn, mussels, fish roe, taramasalata)	140.0	13.0	0.6	1.2	2.6	7.8	14.3	18.2	45.5	81.9	109.2
Processed meat (e.g. bacon, ham, sausages)	70.0	6.6	0.2	0.3	0.7	2.0	3.6	4.6	11.5	20.7	27.6
Alternative milk and dairy-free alternative products											
Alternative milk, with breakfast cereals[2]	160.0	0.9	0.0	0.1	0.2	0.6	1.1	1.4	3.6	6.5	8.6
Alternative milk, in a latte, cappuccino, or hot chocolate[2]	200.0	0.9	0.1	0.1	0.3	0.8	1.4	1.8	4.5	8.1	10.8
Alternative milk, just on its own[2]	125.0	0.9	0.0	0.1	0.2	0.5	0.9	1.1	2.8	5.1	6.8
Alternative milk, yogurt (e.g. full fat, Greek yoghurt, fromage frais, low fat)[2]	125.0	10.0	0.4	0.8	1.8	5.4	9.8	12.5	31.3	56.3	75.0
Vegan/ dairy-free cheese	30.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Alternative milk desserts (e.g. ice cream, panna cotta, chocolate)	75.0	26.9	0.7	1.3	2.9	8.6	15.8	20.2	50.4	90.7	120.9
Vegan/ dairy-free cheese-based dishes, (e.g. cauliflower cheese, cheese, and potato pie)	62.0	24.2	0.5	1.0	2.1	6.4	11.8	15.0	37.5	67.5	90.0

Table continued…

	Portion (g)[1]	Iodine per 100g (µg day-[1])	Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Fruit and vegetables											
Broccoli, cauliflower	90.0	2.2	0.1	0.1	0.3	0.9	1.6	2.0	5.0	9.0	12.0
Cabbage, Brussels sprouts	80.0	1.3	0.0	0.1	0.1	0.4	0.8	1.0	2.5	4.5	6.0
Kale	18.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Mustard greens	80.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Spinach	80.0	2.5	0.1	0.1	0.3	0.9	1.6	2.0	5.0	9.0	12.0
Nuts (e.g. peanuts)	20.0	28.5	0.2	0.4	0.8	2.4	4.5	5.7	14.3	25.7	34.2
Turnip, pak choi, swede	80.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Beansprouts, sweet potatoes	80.0	6.0	0.2	0.3	0.7	2.1	3.8	4.8	12.0	21.6	28.8
Seaweed nori sheets (e.g. with sushi)	3.0	1470.0	1.5	2.9	6.3	18.9	34.7	44.1	110.3	198.5	264.6
Seaweed kombu or sea kelp	7.0	6295.7	14.7	29.4	63.0	188.9	346.2	440.7	1101.7	1983.0	2644.0
Snacks and convenience											
Seaweed snacks (e.g. crackers, rice cakes)	30.0	147.0	1.5	2.9	6.3	18.9	34.7	44.1	110.3	198.5	264.6
Soya products (e.g. tofu, veggie burgers)	150.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Snack foods (e.g. crisps, cereal bars, chips)	50.0	1.8	0.0	0.1	0.1	0.4	0.7	0.9	2.3	4.1	5.4
Convenience foods (e.g. pizza, ready-meals)	380.0	13.4	1.7	3.4	7.3	21.9	40.1	51.0	127.5	229.5	306.0
Bread and bakery products (e.g. cakes, pastries, cookies, biscuits, crumpets)	50.0	4.8	0.1	0.2	0.3	1.0	1.9	2.4	6.0	10.8	14.4

Table continued…

	Portion (g)[1]	Iodine per 100g (µg day-[1])	Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Vegan/dairy-free bread and bakery products (e.g. cakes, pastries, cookies, biscuits, crumpets)	50.0	3.6	0.1	0.1	0.3	0.8	1.4	1.8	4.5	8.1	10.8
Vegan/dairy-free convenience foods (e.g. pizza, ready-meals)	380.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Vegan snack foods (e.g. crisps, cereal bars, crisps)	50.0	1.8	0.0	0.1	0.1	0.4	0.7	0.9	2.3	4.1	5.4
Sauces and spreads (e.g. mayonnaise, salad dressings, sauces, stocks, and spreads)	15.0	7.3	0.0	0.1	0.2	0.5	0.9	1.1	2.8	5.0	6.6
Vegan/ dairy-free sauces and spreads (e.g. mayonnaise, salad dressings, sauces, stocks, and spreads)	150.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Salt (table)	5.0	44.0	0.1	0.1	0.3	0.9	1.7	2.2	5.5	9.9	13.2
Iodised salt	5.0	2200.0	3.7	7.3	15.7	47.1	86.4	110.0	275.0	495.0	660.0

[1]Values are taken from Nutritics 4.3 software and McCance and Widdowson's composition of foods integrated dataset (Public Health England, 2021; Nutritics, 2021); [2]Generic alternative milk types, the iodine content of specific milk (including organic cow's milk) is listed in **Table 2.6**.

Table 2.6. Alternative milk types addressed in the iodine-specific Food Frequency Questionnaire (FFQ).

Food item	Portion (g)[1]	Iodine per 100g (µg day^{-1})	Iodine according to the frequency of consumption (µg)[1].								
			Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Organic semi-skimmed cow's milk											
Organic semi-skimmed cow's milk, with tea/coffee	30.0	32.4	0.3	0.6	1.4	4.2	7.6	9.7	24.3	43.7	58.3
Organic semi-skimmed cow's milk, with breakfast cereals	135.0	32.4	1.5	2.9	6.2	18.7	34.4	43.7	109.4	196.8	262.4
Organic semi-skimmed cow's milk, in a latte, cappuccino, or hot chocolate	160.0	32.4	1.7	3.5	7.4	22.2	40.7	51.8	129.6	233.3	311.0
Organic semi-skimmed cow's milk, just on its own	200.0	32.4	2.2	4.3	9.3	27.8	50.9	64.8	162.0	291.6	388.8
Soya milk, sweetened or un-sweetened fortified with calcium, and vitamins D and B12											
Soya milk, with tea/coffee	30.0	1.0	0.0	0.0	0.0	0.1	0.2	0.3	0.8	1.4	1.8
Soya milk, with breakfast cereals	135.0	1.0	0.0	0.1	0.2	0.6	1.1	1.4	3.4	6.1	8.1
Soya milk, in a latte, cappuccino, or hot chocolate	160.0	1.0	0.1	0.1	0.2	0.7	1.3	1.6	4.0	7.2	9.6
Soya milk, just on its own	200.0	1.0	0.1	0.1	0.3	0.9	1.6	2.0	5.0	9.0	12.0

Table continued…

	Portion (g)[1]	Iodine per 100g (µg day^{-1})	Never or less than once a month	1-3 times per month	Once a week	2-4 times per week	5-6 times per week	Once per day	2-3 times per day	4-5 times per day	6+ times per day
Soya milk, sweetened or un-sweetened fortified with calcium, iodine and vitamins D and B12											
Soya milk, with tea/coffee	30.0	22.5	0.2	0.5	1.0	2.9	5.3	6.8	16.9	30.4	40.5
Soya milk, with breakfast cereals	135.0	22.5	1.0	2.0	4.3	13.0	23.9	30.4	75.9	136.7	182.3
Soya milk, in a latte, cappuccino, or hot chocolate	160.0	22.5	1.2	2.4	5.1	15.4	28.3	36.0	90.0	162.0	216.0
Soya milk, just on its own	200.0	22.5	1.5	3.0	6.4	19.3	35.4	45.0	112.5	202.5	270.0
Oat milk, sweetened or un-sweetened fortified with calcium, and vitamins D and B12											
Oat milk, with tea/coffee	30.0	1.0	1.0	0.0	0.0	0.0	0.1	0.2	0.3	0.8	1.4
Oat milk, with breakfast cereals	135.0	1.0	1.0	0.0	0.1	0.2	0.6	1.1	1.4	3.4	6.1
Oat milk, in a latte, cappuccino, or hot chocolate	160.0	1.0	1.0	0.1	0.1	0.2	0.7	1.3	1.6	4.0	7.2
Oat milk, just on its own	200.0	1.0	1.0	0.1	0.1	0.3	0.9	1.6	2.0	5.0	9.0
Almond milk, sweetened or un-sweetened fortified with calcium, and vitamins D and B12											
Almond milk, with tea/coffee	30.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.2
Almond milk, with breakfast cereals	135.0	0.1	0.0	0.0	0.0	0.1	0.1	0.1	0.3	0.6	0.8
Almond milk, in a latte, cappuccino, or hot chocolate	160.0	0.1	0.0	0.0	0.0	0.1	0.1	0.2	0.4	0.7	1.0
Almond milk, just on its own	200.0	0.1	0.0	0.0	0.0	0.1	0.2	0.2	0.5	0.9	1.2

[1]Values are taken from Nutritics 4.3 software and the McCance and Widdowson's composition of foods integrated dataset (Public Health England, 2021; Nutritics, 2021).

2.3.1 Modification of the European Perspective in Cancer (EPIC) food frequency questionnaire (FFQ)

To assess nutrient intake in **Manuscript 3** we modified the European Perspective Cancer (EPIC)- Norfolk food frequency questionnaire (FFQ). The original EPIC-Norfolk FFQ is an A4 document that contains a list of 130 food items associated with nine frequency categories. The frequency categories range between "never or less than once/month" to "6+ times per day". Participants are asked to select the frequency of different foods (specific quantities representing average portions are given). The EPIC-Norfolk FFQ also includes a section where details include the type of breakfast cereal used, the type and quantity of milk consumed, the type of fat used (in cooking or not), and if visible fat is eaten.

Although the EPIC-Norfolk FFQ was validated for carbohydrate intake, it has been used previously to assess the micronutrient intake of individuals in the UK with different dietary preferences. We further modified the EPIC-Norfolk FFQ to include food sources commonly consumed by vegetarians and vegans in the UK such as alternative milk, meat, other snacks, and composite meals to ensure that the FFQ was suitable for the population of interest. The modifications we implemented will be discussed further in the following sections. We did not differentiate between home-cooked and retail cakes, biscuits, and pies. Additionally, we removed questions asking about condiments to reduce the length of the survey and participant burden. We did not ask additional questions relating to the type of breakfast cereal used, the type of fat used (in cooking or not), or visible fat consumption. However, we did ask additional questions regarding dietary supplement intake, milk type, and quantity used to accurately assess dietary intake. Our FFQ was conducted on Online surveys (formally Bristol Online Surveys). Where possible, photographs of portion sizes from the NDNS were given along with the frequency of consumption items to allow the participant to better estimate dietary intake. We additionally asked participants to estimate dietary intake over the past 6 months and last month (**Figure 2.5**). The reason for the difference in time scale will be discussed in **Manuscript 3.**

7.a.i. How often did you eat these foods? Tick one column for each food (per day, per week or per mon

Please don't select more than 1 answer(s) per row.

Please select at least 3 answer(s).

	Never or less than once a month	1-3 per month	Once a week	2-4 per week	5-6 per week	Once per day	2-3 per day	4-5 pe day
Cheese (hard or soft)	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurts	☐	☐	☐	☐	☐	☐	☐	☐
Milk or cream-based puddings (eg custard, ice cream)	☐	☐	☐	☐	☐	☐	☐	☐

Guide

Food Item | Portion Size

Cheese (hard or soft)



30g (about the size of a matchbox)

Figure 2.5. Example of our online Food Frequency Questionnaire (FFQ) based on the European Perspective Cancer (EPIC) - Norfolk FFQ.

2.3.1.1 Modification of FETA look-up files

FETA is an open-source tool that has been produced MRC Population Health Services Research Network (PHSRN) and can be downloaded to rapidly calculate nutrient data collected by the EPIC - Norfolk FFQ. The FETA software uses a data entry template in EXCEL in which researchers manually input data using assigned codes for frequency of consumption and additional details such as milk, cereal, and fat type used by participants. Once the data entry table is completed, the EXCEL file is run through FETA and a nutritional output is generated for each participant. The FETA software can be modified by researchers to add or remove food items, modify portions, update nutrient information, or alter FFQ lines to suit the research question of interest. Further details on FETA will be described in **Manuscript 3.**

We modified the FETA look-up files to ensure that foods that were consumed regularly by vegetarian and vegan participants were represented in the FETA output. Asides from plant foods that naturally are free from animal products and tofu/veggie burgers, there were no alternative products designed for consumption by individuals following a vegan diet included in the FETA software e.g. alternative meat (Quorn, tempeh, etc.), dairy-free yogurts, etc. despite these foods taking up a large proportion of the food sector in the UK. We used nutritional and portion data for various alternative and dairy-free products provided by Nutritics to create 16 new food codes for FETA analysis (**Table 2.7**). If more than one food code from Nutritics was available for a specific food item, an average nutrient value was calculated. Where compound foods were not included in Nutritics e.g. 'Plant-based lasagne or moussaka with dairy-free cheese' we imputed suitable recipes found on BBC Good Food and the Vegan Society to generate nutrient outputs (BBC Good Food, 2019; Vegan Society, 2019). Nutritional data for new food codes are presented in **Table 2.8.** Modifications to FETA look-up files are presented in **Table 2.9 and Table 2.10 (**Note nutritional information provided in look-up file: FOOD_NUTRIENTS.CSV is presented in **Table 2.8** and is not repeated).

Table 2.7. Code name, description, item name, and Nutritics code for new FETA foods.

Code	Description	Item name	Nutritics code
a2011	Plant-based (dairy-free) chocolates, single or squares	ND_CHOCOLATE	N/8631
a2012	Plant-based (dairy-free) ice cream or choc ices	ND_ICECREAM	GB15/65730
a2013	Plant-based (dairy-free) fruit pies, tarts, crumbles, or sponge puddings	ND_FRUIT_PIE	GB15/65814
a2014	Plant-based (dairy-free), pastries e.g. croissants or doughnuts	ND_PASTRIES	BRANDB2562519
a2015	Plant-based (dairy-free) salad cream or mayonnaise (tablespoon)	ND_CONDIMENT	N/16345
a2016	Plant-based cheese (dairy-free) e.g. Cheddar, Brie, Edam, Cottage cheese, or low-fat soft cheese	ND_CHEESE	GB15/65645
a2017	Plant-based (dairy-free) desserts (125g carton or medium serving)	ND_DESSERT	N/1093357
a2018	Plant-based (dairy-free) full-fat or Greek yogurt (25g carton)	ND_YOGURT	N/8176
a2019	Plant-based (dairy-free) low-fat yogurt or fromage frais (125g carton)	ND_LOWFATYOGURT	N/40968
a2020	Plant-based (dairy-free) double or clotted cream e.g. soya or oat (tablespoon)	ND_DOUBLECREAM	BRANDB/2610555
a2021	Plant-based (dairy-free) single or sour cream e.g. soya or oat (tablespoon)	ND_SINGLECREAM	BRANDB/2610555
a2022	Plant-based lasagne or moussaka with dairy-free cheese	ND_MEAL	Recipe inputted from BBC Good Food (2019)
a2023	Pizza with dairy-free cheese	ND_PIZZA	N/5432 and GB15/65645
a2024	Meat alternative battered, e.g. plant-based meat substitutes, mycoprotein, or processed soya	ND_MEATALTBATTERED	N/4261303 and IE09/3639
a2025	Meat alternative non-battered, e.g. plant-based meat substitutes, mycoprotein or processed soya	ND_MEATALT	N/4259743, IE09 / 3930, N/4125415, N/8749N, N/927547, N/78496, and N/11106
a2026	Plant-based (dairy-free) cakes e.g. fruit or sponge	ND_CAKE	Recipe inputted from the Vegan Society (2019)

Table 2.8. Nutrient information for new FETA foods.

Nutrient	Code[1]															
	a2011	a2012	a2013	a2014	a2015	a2016	a2017	a2018	a2019	a2020	a2021	a2022	a2023	a2024	a2025	a2026
Energy (kcal)	542.0	211.0	79.0	420.0	508.0	319.0	230.0	35.8	78.0	144.0	144.0	19.4	171.6	207.3	150.7	342.6
Energy (kj)	2253.0	880.0	337.0	1757.0	2092.0	1321.0	961.0	150.0	330.0	595.0	595.0	81.0	724.0	868.4	631.0	1432.4
Carbohydrate (COH) (g)	32.0	22.5	19.4	45.0	4.5	0.0	23.0	1.6	11.5	5.8	5.8	2.1	25.4	18.2	6.8	52.5
Protein (g)	9.1	2.3	0.4	6.1	1.0	18.3	2.2	3.2	3.8	0.9	0.9	0.7	5.4	11.0	14.6	4.0
Fat (g)	42.0	12.4	0.0	24.0	54.0	27.3	14.4	1.8	1.9	13.0	13.0	0.9	5.1	10.1	7.3	12.9
Starch (g)	5.0	0.3	5.0	38.4	4.0	0.0	1.0	0.0	0.8	2.2	2.2	1.2	22.4	15.8	4.8	25.6
Oligosaccharide (g)	-	1.5	-	-	0.0	-	-	0.0	0.3	-	-	-	0.0	0.0	0.6	0.1
Fibre (g)	11.0	0.4	1.6	1.8	0.5	0.0	1.5	1.0	1.2	0.8	-	-	1.6	4.1	4.2	1.6
Non-starch polysaccharides (NSP) (g)	7.0	0.1	1.0	1.4	0.4	0.0	1.2	0.7	0.9	0.6	0.8	0.3	1.5	3.3	3.2	1.2
Sugar (g)	27.0	20.6	14.4	6.6	0.5	0.0	22.0	1.6	10.5	3.6	3.6	0.8	3.0	-	1.0	26.8
Glucose (g)	0.0	5.3	5.2	-	0.0	0.0	0.0	0.0	0.3	-	0.0	0.3	0.8	0.0	0.2	0.0
Galactose (g)	0.0	0.0	-	-	0.0	0.0	-	0.0	0.0	-	0.0	0.0	0.0	0.0	0.0	0.0
Fructose (g)	0.0	1.6	5.5	-	0.0	0.0	0.0	0.0	1.2	-	0.0	0.2	1.0	0.0	0.1	0.0
Sucrose (g)	27.0	12.5	3.7	-	0.0	0.0	2.1	1.6	0.7	-	0.0	0.3	0.0	0.0	0.0	0.2
Maltose (g)	0.0	1.2	0.0	-	0.0	0.0	-	0.0	0.0	-	0.0	0.0	1.2	0.0	0.0	0.0
Lactose (g)	0.0	0.0	0.0	-	0.0	0.0	-	0.0	0.0	-	0.0	0.0	0.0	0.0	0.1	0.0
Saturated fat (SFA) (g)	25.6	3.7	-	8.7	6.5	-	11.2	0.3	0.4	1.6	1.6	0.1	0.1	1.1	1.1	2.9
Monounsaturated fat (MUFA) (g)	17.8	5.8	-	-	11.1	-	3.0	0.4	0.4	-	0.0	0.5	0.5	0.4	2.1	3.2

Table continued…

Nutrient	Code[1]															
	a2011	a2012	a2013	a2014	a2015	a2016	a2017	a2018	a2019	a2020	a2021	a2022	a2023	a2024	a2025	a2026
Polyunsaturated fat (PUFA) (g)	1.5	2.3	-	-	33.6	-	0.3	1.1	1.2	-	0.0	0.1	0.1	1.0	0.8	6.0
Omega3 (n-3) (mg)	0.0	0.1	-	-	0.1	-	-	0.0	0.0	-	-	-	0.0	0.0	0.1	0.8
Omega6 (n-6) (mg)	0.0	1.7	-	-	33.5	-	0.3	1.1	0.0	-	-	-	0.1	0.0	0.5	5.0
Trans fat (g)	0.0	0.7	0.0	-	0.0	-	-	0.0	0.0	-	-	-	0.0	0.0	0.4	0.7
Cholesterol (mg)	4.5	1.1	0.0	-	0.0	0.0	-	0.0	0.0	-	0.0	0.0	0.0	0.0	0.6	0.0
Sodium (mg)	0.4	87.0	43.0	360.0	550.0	600.0	39.4	80.0	124.0	44.0	44.0	25.4	235.5	515.0	456.6	269.9
Potassium (mg)	641.0	103.0	84.0	0.0	25.7	130.0	177.0	70.0	119.0	0.0	0.0	63.0	169.5	60.0	128.4	95.0
Chloride (mg)	137.0	-	45.0	545.0	839.0	870.0	61.0	200.0	310.0	67.0	67.0	48.0	180.8	288.0	1120.4	245.9
Calcium (mg)	68.0	16.0	30.0	0.0	5.1	450.0	0.0	96.0	120.0	0.0	0.0	9.6	77.9	14.5	48.9	114.2
Phosphorus (mg)	284.0	45.0	15.0	0.0	5.5	350.0	44.0	61.0	89.0	0.0	0.0	17.5	77.5	118.5	105.0	240.5
Magnesium (mg)	202.0	18.0	5.0	0.0	4.8	29.0	20.0	12.0	18.0	0.0	0.0	4.5	16.2	18.5	24.0	14.7
Iron (mg)	9.1	1.2	1.0	0.0	0.2	1.1	1.0	0.4	0.3	0.0	0.0	0.2	1.0	0.3	1.0	0.8
Zinc (mg)	3.0	0.3	0.0	0.0	0.1	1.8	0.3	0.2	0.3	0.0	0.0	0.4	0.5	3.5	1.9	0.4
Copper (mg)	1.5	0.1	0.0	0.0	0.0	0.0	0.2	0.0	0.1	0.0	0.0	0.0	0.1	0.1	0.2	0.1
Manganese (mg)	1.6	0.2	0.1	0.0	0.1	0.1	0.5	0.1	0.2	0.0	0.0	0.0	0.3	1.4	0.7	0.4
Selenium (µg)	7.6	2.0	0.0	0.0	0.1	0.0	0.4	0.0	4.0	0.0	0.0	0.6	0.4	0.0	5.6	2.5
Iodine (µg)	0.0	-	0.0	0.0	0.6	0.0	0.7	7.0	1.0	0.0	0.0	0.3	1.0	0.0	0.8	0.4
Vitamin A (µg)	2.5	0.0	3.0	0.0	0.0	0.0	0.6	19.1	0.0	0.0	0.0	44.0	64.0	0.0	0.0	120.2
Retinol (µg)	0.0	0.0	0.0	0.0	0.0	0.0	-	19.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table continued…

Nutrient	Code[1]															
	a2011	a2012	a2013	a2014	a2015	a2016	a2017	a2018	a2019	a2020	a2021	a2022	a2023	a2024	a2025	a2026
Carotene (µg)	22.0	0.0	17.0	0.0	0.1	0.0	3.7	1.8	0.0	0.0	0.0	267.0	385.0	0.0	0.0	721.0
Vitamin D (µg)	0.0	-	0.0	0.0	0.0	0.0	0.8	0.6	0.8	0.0	0.0	0.0	0.0	0.0	0.0	1.3
Vitamin E (mg)	0.6	1.2	0.0	0.0	26.1	0.0	0.4	0.6	0.3	0.0	0.0	0.2	0.5	0.0	0.1	5.3
Vitamin K (µg)	7.3	-	-	-	3.3	0.0	-	0.0	0.7	-	-	-	2.2	0.0	0.0	11.2
Thiamin (B1) (mg)	0.0	0.1	0.0	0.0	0.0	0.3	0.0	0.1	0.1	0.0	0.0	0.1	0.2	0.1	3.7	0.1
Riboflavin (B2) (mg)	0.1	0.0	0.0	-	0.0	0.6	0.0	0.0	0.2	0.0	0.0	0.1	0.1	0.2	0.1	0.0
Niacin total (B3) (mg)	1.0	1.1	0.3	-	0.1	4.0	0.6	0.7	0.8	-	-	0.7	1.6	1.5	1.5	1.6
Niacin (mg)	0.0	0.2	0.2	0.0	0.0	1.1	0.3	0.0	0.1	0.0	0.0	-	1.3	0.2	0.3	0.6
Tryptophan (mg)	0.0	54.0	6.0	-	6.5	174.0	-	0.0	42.0	-	-	-	17.6	81.0	46.8	57.7
Pantothenic Acid (B5) (mg)	0.4	0.4	0.0	-	0.0	0.0	0.2	0.1	0.0	-	-	-	0.1	0.2	0.1	0.1
Pyridoxine (B6) (mg)	0.0	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1
Folates (B9) (µg)	0.0	13.0	3.0	-	0.6	35.0	14.0	3.4	9.0	-	-	13.1	13.7	10.5	11.1	7.1
Vitamin B12 (µg)	0.2	-	0.0	0.0	0.0	2.5	0.4	0.4	0.4	0.0	0.0	0.1	0.2	0.2	0.0	0.9
Biotin (B7) (µg)	0.0	1.1	0.0	-	0.3	0.0	0.1	0.8	0.0	-	-	-	0.8	3.0	3.8	1.0
Vitamin C (mg)	0.0	-	7.0	0.0	0.1	0.0	4.4	0.0	1.0	0.0	0.0	2.0	30.5	0.0	0.0	0.0

[1]Descriptions of the foods associated with codes a2011-a2026 are provided in **Table 2.7**; -, Not applicable.

Table 2.9. Modifications added to FETA look-up file: FOOD.CSV.

Code[1]	Description
a2011	Plant-based (dairy-free) chocolates, single or squares
a2012	Plant-based (dairy-free) ice cream or choc ices
a2013	Plant-based (dairy-free) fruit pies, tarts, crumbles, or sponge puddings
a2014	Plant-based (dairy-free), pastries e.g. croissants or doughnuts
a2015	Plant-based (dairy-free) salad cream or mayonnaise (tablespoon)
a2016	Plant-based cheese (dairy-free) e.g. Cheddar, Brie, Edam I , Cottage cheese, or low fat soft cheese
a2017	Plant-based (dairy-free) desserts (125g carton or medium serving)
a2018	Plant-based (dairy-free) full fat or Greek yogurt (25g carton)
a2019	Plant-based (dairy free) low fat yogurt or fromage frais (125g carton)
a2020	Plant-based (dairy-free) double or clotted cream e.g. soya or oat (tablespoon)
a2021	Plant-based (dairy-free) single or sour cream e.g. soya or oat (tablespoon)
a2022	Plant-based lasagne or moussaka with dairy-free cheese
a2023	Pizza with dairy-free cheese
a2024	Meat alternative battered, e.g. plant-based meat substitutes, mycoprotein, or processed soya
a2025	Meat alternative non-battered, e.g. plant-based meat substitutes, mycoprotein or processed soya
a2026	Plant-based (dairy-free) cakes e.g. fruit, sponge

[1]Descriptions of the foods associated with codes a2011-a2026 are provided in **Table 2.7**.

Table 2.10. Modifications added to FETA look-up file: MEALS.CSV.

Line number	Item name[1]	Description
112	ND_CHOCOLATE	Plant-based (dairy-free) chocolates, single or squares
113	ND_ICECREAM	Plant-based (dairy-free) ice cream or choc ices
114	ND_FRUIT_PIE	Plant-based (dairy-free) fruit pies, tarts, crumbles, or sponge puddings
115	ND_PASTRIES	Plant-based (dairy-free), pastries e.g. croissants or doughnuts
116	ND_CONDIMENT	Plant-based (dairy-free) salad cream or mayonnaise (tablespoon)
117	ND_CHEESE	Plant-based cheese (dairy-free) e.g. Cheddar, Brie, Edam I , Cottage cheese, or low fat soft cheese
118	ND_DESSERT	Plant-based (dairy-free) desserts (125g carton or medium serving)
119	ND_YOGURT	Plant-based (dairy-free) full fat or Greek yogurt (25g carton)
120	ND_LOWFATYOGURT	Plant-based (dairy free) low fat yogurt or fromage frais (125g carton)
121	ND_DOUBLECREAM	Plant-based (dairy-free) double or clotted cream e.g. soya or oat (tablespoon)
122	ND_SINGLECREAM	Plant-based (dairy-free) single or sour cream e.g. soya or oat (tablespoon)
123	ND_MEAL	Plant-based lasagne or moussaka with dairy-free cheese
124	ND_PIZZA	Pizza with dairy-free cheese
125	ND_MEATALTBATTERED	Meat alternative battered, e.g. plant-based meat substitutes, mycoprotein, or processed soya
126	ND_MEATALT	Meat alternative non-battered, e.g. plant-based meat substitutes, mycoprotein or processed soya
127	ND_CAKE	Plant-based (dairy-free) cakes e.g. fruit or sponge

[1]Descriptions of the foods associated with item names are provided in **Table 2.7.**

The FETA software also has a limited number of milk product codes that can be assigned to the data entry table. Only one milk code per participant can be selected and therefore FETA cannot account for the consumption of individuals who consume a variety of different kinds of milk. Codes include varieties of milk such as full cream, skimmed, dried milk, semi-skimmed, Channel Islands, soya, none, non-specific milk, other- with free text, and other- with no free text. The soya milk code was the only dairy-free code available and did not contain any information regarding the fortification status. Given that there is a huge range of dairy-free milk alternatives available, we created new milk codes to reflect different products available to purchase in the UK. We used nutritional and portion data for various alternative and dairy-free products provided by Nutritics to create 8 new milk codes for FETA analysis (**Table 2.11**). Modifications to FETA milk look-up files are presented in **Table 2.12.** The new milk codes included: soya (sweetened, fortified), soya (un-sweetened, fortified), soya (un-sweetened, un-fortified), oat (Oatly brand), oat (un-sweetened, Oatly brand) almond (Almond Breeze brand), soya (Alpro brand, fortified inc. iodine) and cow's milk (organic). Fortified varieties covered alternative milk that were fortified with B12, calcium, and vitamin D as standard. Nutritional data for each milk code is presented in **Table 2.13**. Similar to the addition of new foods, if multiple Nutritics codes were used, an average nutrient value was generated. Individuals were given the option of using free text boxes to describe the dairy-free alternative milk or other milk consumed, from this information researchers selected the most appropriate milk code, if individuals were unsure or did not record which milk was used the non-specific milk code was given.

Table 2.11. Code name, description, and Nutritics code for new FETA milks.

Code	Description	Nutritics code
a2004	Soya, Sweetened Fortified	GB15/64336
a2005	Soya, Un-Sweetened Fortified	GB15/64337
a2006	Soya, Un-Sweetened Un-Fortified	GB15/65768
a2007	Oat, Oatly, Oat Milk Vitamins and Minerals	N/8001
a2008	Almond, Almond Breeze	N/15521
a2009	Soya, Alpro Original, Fortified Inc. Iodine	BRANDB2356427
a2010	Oat, Oatly Un-Sweetened	N/7977

Table 2.12. Modifications added to FETA look-up file: MILKS.CSV.

Code	Food code[1]
17	a2004
18	a2005
19	a2006
20	a2007
21	a2008
22	a2009
23	a2010

[1]Descriptions of the milks associated with item names are provided in **Table 2.11.**

Table 2.13. Nutrient information for new FETA milks.

Nutrient	Code[1]						
	a2004	a2005	a2006	a2007	a2008	a2009	a2010
Energy (kcal)	44.0	26.0	26.0	43.0	12.7	38.2	35.7
Energy (kj)	184.0	109.0	109.0	180.0	53.0	160.0	151.0
Carbohydrate (COH) (g)	2.5	0.5	0.5	6.3	0.2	2.5	6.3
Protein (g)	3.1	2.4	2.4	1.0	0.5	3.0	1.0
Fat (g)	2.4	1.6	1.6	1.5	1.1	1.8	0.7
Starch (g)	0.0	0.0	0.0	2.5	-	0.0	2.5
Oligosaccharide (g)	0.3	0.3	0.3	0.0	-		0.0
Fibre (g)	0.5	0.5	0.5	0.9	-	0.5	0.9
Non-starch polysaccharides (NSP) (g)	0.2	0.2	0.2	0.6	-	0.4	0.6
Sugars (g)	2.2	0.2	0.2	3.8	0.1	2.5	3.8
Free sugars (g)	0.0	0.0	0.0	0.0	0.0	-	0.0
Glucose (g)	0.3	0.0	0.0	0.0	0.0	-	0.0
Galactose (g)	0.0	0.0	0.0	0.0	0.0	-	0.0
Fructose (g)	1.2	0.0	0.0	0.0	0.0	-	0.0
Sucrose (g)	0.7	0.2	0.2	0.0	0.3	-	0.0
Maltose (g)	0.0	0.0	0.0	3.8	0.0	-	3.8
Lactose (g)	0.0	0.0	0.0	0.0	0.0	-	0.0
Saturated fat (SFA) (g)	0.4	0.2	0.2	0.2	0.1	0.3	0.1
Monounsaturated fat (MUFA) (g)	0.5	0.3	0.3	1.0	2.5	-	0.3
Polyunsaturated fat (PUFA) (g)	1.4	1.1	1.1	0.3	0.7	-	0.3
Omega3 (n-3) (mg)	-	0.1	0.1	0.0	0.0	-	0.0
Omega6 (n-6) (mg)	-	0.8	0.8	0.3	0.7	-	0.3
Trans fat (g)	0.0	0.0	0.0	0.0	0.0	-	0.0
Cholesterol (mg)	0.0	0.0	0.0	0.0	0.0	-	0.0
Sodium (mg)	56.0	0.0	32.0	49.0	50.0	32.0	49.0
Potassium (mg)	119.0	74.0	74.0	30.6	59.0	-	30.6
Chloride (mg)	3.0	3.0	3.0	77.0	125.0	48.0	77.0
Calcium (mg)	130.0	120.0	13.0	120.0	18.8	120.0	4.5
Phosphorus	89.0	48.0	48.0	31.3	38.7	-	31.3
Magnesium (mg)	18.0	15.0	15.0	9.2	18.9	-	9.2
Iron (mg)	0.3	0.4	0.4	0.3	0.2	-	0.3
Zinc (mg)	0.3	0.3	0.3	0.3	0.2	-	0.3
Copper (mg)	0.1	0.1	0.1	0.0	0.1	-	0.0
Manganese (mg)	0.2	0.3	0.3	0.3	0.2	-	0.3
Selenium (µg)	4.0	4.0	4.0	0.3	0.1	-	0.3
Iodine (µg)	1.0	1.0	1.0	0.1	0.1	22.5	0.1
Vitamin A (µg)	0.0	0.0	0.0	0.0	0.0	-	0.0
Retinol (µg)	0.0	0.0	0.0	0.0	0.0	-	0.0
Carotene (µg)		0.0	0.0	0.0	0.0	-	0.0
Vitamin D (µg)	0.8	0.8	0.0	0.8	0.8	0.8	0.0
Vitamin E (mg)	0.3	0.3	0.3	0.1	1.8	-	0.1

Table continued…

Nutrient	Code						
	a2004	a2005	a2006	a2007	a2008	a2009	a2010
Vitamin K (µg)	0.7	1.7	1.7	0.0	0.0	-	0.0
Thiamine (B1) (mg)	0.1	0.1	0.1	0.0	0.0	-	0.0
Riboflavin (B2) (mg)	0.2	0.2	0.1	0.2	0.1	0.2	0.0
Niacin total (B3) (mg)	0.8	0.8	0.7	0.3	0.4	-	0.3
Niacin (mg)	0.1	0.1	0.1	0.1	0.2	-	0.1
Tryptophan (mg)	42.0	42.0	42.0	13.8	13.8	-	13.8
Pantothenic acid (B5) (mg)	0.0	0.0	0.0	0.1	0.1	-	0.1
Vitamin B6 (mg)	0.0	0.0	0.0	0.0	0.0	-	0.0
Folates (B9) (µg)	9.0	14.0	14.0	30.0	3.4	0.0	4.9
Vitamin B12 (µg)	0.4	0.4	0.0	0.4	0.4	0.4	0.0
Biotin (B7) (µg)	1.0	1.0	1.0	1.6	4.5	-	1.6
Vitamin C (mg)	1.0	0.0	0.0	0.0	0.0	-	0.0

[1]Descriptions of the milks associated with item names are provided in **Table 2.11**; -, Not applicable.

2.4 Additional tools

2.4.1 Sociodemographic questionnaires

In **Manuscripts 2 and 3**, we asked our participants to complete a questionnaire on sociodemographic variables (e.g. age, sex, household income, etc.) to investigate the relationship between sociodemographic and iodine/micronutrient intake. In addition, we used this data to compare demographics between dietary groups (e.g. vegan, vegetarian, and omnivore, etc.). Specific sociodemographic questions asked to participants in each study will be outlined in later sections (See Manuscript 2, Section 4.3.7; See Manuscript 3, Section 5.3.2).

2.4.2 Nutrition knowledge questionnaires

We were particularly interested in assessing our participants awareness of iodine and other micronutrients. In **Manuscripts 2 and 3** (Cohort 2), we asked participants about their knowledge of iodine based on a previous iodine knowledge questionnaire developed and validated by O'Kane *et al* for women of childbearing age (O'Kane *et al.* 2016). Questions addressed the symptoms related to IDD, iodine rich food sources, and the understanding of iodine throughout the life cycle. In **Manuscript 3** (Cohort 1), we asked general questions addressing micronutrient knowledge.

The specific questions asked will be outlined in future sections (See Manuscript 2, Section 4.3.7; Manuscript 3, Section 5.3.2).

2.4.3 Anthropometric measurements

All anthropometric measurements were self-reported by participants (**Manuscript 2 and 3**). Height was reported in cm and height in kg. A tool was provided to participants to allow conversion between common units.

2.5 Statistical methods

Different statistical methods and software were used for data analysis in each study (See Manuscript 2, Section 4.2.10; Manuscript 3, Section 5.3.10, Manuscript 5, Section 7.3.6). To assess normality, we employed the Shapiro–Wilk test. Measures of iodine are typically not evenly distributed within a population; hence, non-parametric methods were frequently used in analysis. We will outline the relevant statical methods used in detail in each manuscript.

3. Thesis aims according to manuscript number

Table 3.1 presents the thesis aims corresponding to the relevant manuscript number.

Table 3.1 Thesis aims according to manuscript number

Thesis aim	Manuscript number
(1) To determine the micronutrient intake and status, predominantly of iodine, of individuals following a restricted diet (vegan and vegetarian) in the short-and-long-term and compare population data with omnivorous individuals	1, 2, 3, and 5
(2) To evaluate the understanding of iodine and its role in the diet among individuals who adhere to a vegan or vegetarian diets	2 and 3
(3) To investigate food fortification as a possible method to improve iodine intake and status of individuals following vegan or vegetarian diets.	4

4. MANUSCRIPT 1

Eveleigh, ER, Coneyworth, L, Avery, A, & Welham, S. (2020). Vegans, vegetarians, and omnivores: How does dietary choice influence iodine intake? A systematic review. *Nutrients*, 12(6), 1606.

Author contributions can be found in **APPENDIX A.**

4.1 Abstract

Vegan and vegetarian diets are becoming increasingly popular. Dietary restrictions may increase the risk of iodine deficiency. This systematic review aims to assess iodine intake and status in adults following a vegan or vegetarian diet in industrialised countries. A systematic review and quality assessment were conducted in the period May 2019 – April 2020 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were identified in Ovid MEDLINE, Embase, Web of Science, PubMed, Scopus, and secondary sources. Fifteen articles met inclusion criteria. Participants included 127,094 adults (aged ≥ 18 years). Vegan groups presented the lowest median urinary iodine concentration, followed by vegetarians, and did not achieve optimal status. The highest iodine intake were recorded in female vegans (1448.0 ± 3879.0 µg day^{-1}) and the lowest in vegetarians (15.6 ± 21.0 µg day^{-1}). Omnivores recorded the greatest intake in 83% of studies. Seaweed contributed largely to diets of vegans with excessive iodine intake. Vegans appear to have increased risk of low iodine status, deficiency, and inadequate intake compared with adults following less restrictive diets. Adults following vegan and vegetarian diets living in countries with a high prevalence of deficiency may be more vulnerable. Therefore, further monitoring of iodine status in industrialised countries and research into improving the iodine intake and status of adults following vegan and vegetarian diets is required.

4.2 Introduction

Vegan and vegetarian diets have gained popularity over the past decade. Characteristically, vegans do not consume any animal-derived products including eggs, dairy, meat, and fish (Phillips, 2005). Vegetarians exclude meat and fish but may consume milk and eggs (Phillips, 2005). A subclass of the vegetarian diet may consume fish but not meat, termed pescatarians (Phillips, 2005). Despite these definitions, varying levels of strictness and adherence to dietary restriction exist at the level of the individual (Phillips, 2005).

The prevalence of vegetarian and vegan diets differs globally. In developing regions, meat-free diets are traditionally adopted owing to religious, social, ecological, or economic constraints as opposed to personal choice (Sebastiani and Barbero, 2019). In industrialised countries, most individuals are afforded the choice of food consumption and level of dietary restriction. Populations in developed countries may adopt these diets for environmental, ethical, religious, health beliefs or social reasons. Presently, well-planned vegan and vegetarian diets have been regarded by the BDA and other organizations in industrialised countries to be suitable throughout the lifespan, inclusive of infancy and pregnancy (BDA, 2017; Dietitians Association of Australia, 2019; Craig and Mangels, 2009). However, concerns have been raised regarding the ability of these diets to adequately provide essential micronutrients, such as iodine (Public Health England, 2014).

Iodine is an essential micronutrient, required in trace quantities, which is vital for the synthesis of thyroid hormones—triiodothyronine (T3) and thyroxine (T4) (Zimmermann, M., *et al*, 2008). The thyroid hormones are crucial for the regulation of metabolism, growth, and neurological development (Ahad and Ganie, 2010). Iodine deficiency presents as a spectrum of clinical disorders termed ‘iodine deficiency disorders’ (IDD’s) which occur when recommended intakes are not achieved (150 µg day^{-1}) (Ahad and Ganie, 2010). These include hypothyroidism, goitre abnormal thyroid nodular pathology, and cretinism in infants born to mothers with a low iodine status during pregnancy and lactation (Zimmermann, M., *et al*, 2008).

Low iodine intake may be a risk factor for thyroid nodule formation, particularly in females (Popoveniuc and Jonklaas, 2012; Zimmermann, 2014). Most nodules are harmless; however, some may result in thyroid dysfunction or malignancy (Popoveniuc and Jonklaas, 2012). Excessive iodine intake (>1000 μg day^{-1}) may lead to hyperthyroidism in individuals with pre-existing thyroid disease or iodine deficiency (Leung and Braverman, 2014). Iodine deficiency is not limited to developing countries—mild–moderate deficiency exists in industrialised nations including Europe, UK, Australia and select populations in the USA (Zimmermann *et al*., 2008). In 2011, iodine nutrition was highlighted as a significant public health concern following estimates indicating that 2 billion people globally were deficient (Li and Eastman, 2012). Recent data collected by the WHO show a global decline in iodine deficiency between 1993 and 2019, suggesting that less than 8.5% of the world's population are affected (IGN, 2019). However, subgroups of European populations are still at increased risk of iodine deficiency (Public Health England, 2014).

Iodine deficiency traditionally was assessed by monitoring the prevalence of visible goitre in populations (Zimmermann *et al*., 2008). After the development of newer methods for measuring iodine status, it was recognized that low-level deficiency may be present in industrialised populations not displaying obvious thyroid enlargement (WHO, 2007). Various biomarkers can be used to estimate population iodine status and intake (WHO, 2007). Urinary iodine concentration (UIC) is the most common and practical marker (Pearce and Caldwell, 2016). This is because >90% of the iodine ingested from dietary sources is readily excreted in the urine (Serra-Majem *et al*., 2009). Spot UIC and 24 h measures can be used to detect and monitor iodine adequacy and deficiency. However, these estimates only correspond to recent intake (Pearce and Caldwell, 2016). Additionally, thyroid function tests are required routinely to detect iodine adequacy in vulnerable populations such as pregnant and/or lactating women and infants (Pearce and Caldwell, 2016). Dietary iodine can be estimated indirectly by UIC or by common dietary assessment methods (WHO, 2007). Limitations of the methods used must be considered. Biomarkers of status and dietary intake methods are not always the same between studies which adds to the challenge of reliably comparing iodine amid populations (Gunnarsdottir and Dahl, 2012).

Individuals residing in developing countries, who are reliant on plant-based foods in their diet, have a higher prevalence of iodine deficiency (Fuge, 2013). The bioavailability of iodine from plant sources has been suggested to be determined by rainfall and water collection on crop leaves with much of the iodine within plants not being bioavailable (Humphrey *et al*., 2019). In industrialised countries where people consume a 'Western diet', the key dietary sources of iodine are bread fortified by iodised salt, cow's milk, and dairy products (Zimmermann, 2011). Seafood, eggs, and seaweed are also iodine rich but are not regularly consumed (Bath, S., & Rayman, M, 2016). Water and salt iodination strategies are present in most states in the US and select countries in Europe (Andersson *et al*., 2007b; Gärtner, 2016). Countries such as the UK have yet to establish a mandatory salt fortification program and despite regular manufacturing of iodised salt, it is not widely available for public purchase (Bath *et al*., 2014b)

For this reason, individuals who consume diets excluding iodine-rich food, principally dairy, eggs, and/or fish, have increased risk of iodine deficiency (Appleby *et al*., 1999). Further complicating this issue is the growing availability and acceptance of plant-based food 'alternatives', regularly consumed by vegans and vegetarians, that naturally have negligible iodine content and are not regularly fortified (Bath *et al*., 2017; Elsabie and Aboel Einen, 2016). The size of the plant-based 'alternatives' food market has been reported to have almost doubled between 2014 and 2017 in the UK (Mintel, 2019a).

Currently, two reviews exist investigating iodine in the diets of vegans and vegetarians, one in 2005, which was updated in 2009 by the same authors (Fields *et al*., 2005; Fields and Borak, 2009). The most recent review included eight studies, covering a period between 1981 and 2003, with the conclusion that strict vegans and vegetarians living in Europe have iodine values below recommended levels and are at risk of deficiency. In the years since publication, these diets have become more widely accepted and it is likely that food consumption practices have changed considerably since this last assessment of iodine intake in adults following vegan and vegetarian diets. Given the potential health consequences of iodine deficiency, it is important to re-examine whether adults following either a vegan or vegetarian diet are still at risk of iodine deficiency.

Thus, the aim of this review is to assess the iodine intake and status in adults following a vegan or vegetarian diet in industrialised countries across time. The objectives included (1) evaluation of the methods used to assess iodine; (2) determination of the iodine intake and food consumption in vegan and vegetarian adults; (3) assessment of the iodine status and prevalence of iodine deficiency using urinary iodine concentration (UIC); (4) comparison of the iodine intake, status and prevalence of deficiency between vegans, vegetarians and omnivores; and (5) consideration of gender differences in estimates of iodine nutrition.

4.3 Materials and methods

This systematic review was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher *et al*, 2009).

A systematic search of literature was performed from 20 May 2019 to April 2020. Electronic databases (Ovid MEDLINE, Embase, Web of Science, PubMed, and Scopus) were searched using text terms with appropriate truncation, and Medical Subject Headings. Search term sensitivity and relevance of article identification was tested using preliminary searches in Ovid MEDLINE (**Supplementary Table 1**). All database searches were refined by 'Humans, Adults (aged > 18 years) and English Language'. Identified relevant studies were saved onto EndNoteTM online and duplicates were removed (manually and automatically). To limit bias, relevance was confirmed by two investigators. Additional relevant articles were sourced from reference lists of included studies. The current systematic review addressed study eligibility using the population–intervention– comparison–outcome (PICOS) formulation (

Table 4.1) (Howard, 2019). Additionally, only articles with full paper availability published in/after 1990 were considered for inclusion. Data extraction was

Criteria Category	Inclusion	Exclusion
Population	Adults (aged ≥ 18 y) residing in industrialised nations.	Individuals (aged < 18 y), unless results display separate data; adults residing in developing countries; populations with a high prevalence of thyroid disorders.
Intervention/exposure	Participants with any type of dietary preference or restriction. Voluntary or otherwise.	Use of a dietary grouping without defining diet characteristics.
Comparators	Differing dietary preference or restriction.	None.
Outcome measure	Iodine intake or status measured by UIC or analysis of dietary records.	No analysis of iodine intake or status; use of thyroid measures alone for iodine intake and status.
Study design	Any study design with relevant outcomes.	None.

completed independently by one researcher. The terms used for data extraction were discussed and finalised by two secondary researchers. A modified version of "Data collection form for intervention review—RCTs and non-RCTs" by The Cochrane Collaboration was used for data extraction (Cochrane, 2019). Adaptions considered the characteristics of interest and study design. To permit comparison between groups, 'moderate vegans' were considered as vegetarians.

Table 4.1. Population–intervention–comparison–outcome (PICOS) criteria for study inclusion and exclusion.

Criteria Category	Inclusion	Exclusion
Population	Adults (aged ≥ 18 y) residing in industrialised nations.	Individuals (aged < 18 y), unless results display separate data; adults residing in developing countries; populations with a high prevalence of thyroid disorders.
Intervention/exposure	Participants with any type of dietary preference or restriction. Voluntary or otherwise.	Use of a dietary grouping without defining diet characteristics.
Comparators	Differing dietary preference or restriction.	None.
Outcome measure	Iodine intake or status measured by UIC or analysis of dietary records.	No analysis of iodine intake or status; use of thyroid measures alone for iodine intake and status.
Study design	Any study design with relevant outcomes.	None.

‘Mixed diet’ and ‘meat eaters’ as omnivores and ‘living food dieters’ as vegans. Due to variation in nomenclature, demi vegetarians will be considered separately. To make comparisons between genders, where possible, data on males and females were extracted separately.

Following data extraction, study quality was critically appraised by one author. Quality was assessed using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (NHLBI, 2019). According to Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies provided by NHLBI, fixed response was selected for three questions to account for the nature of cross-sectional studies. Exposures and outcomes are measured and assessed during the same timeframe excluding time to see an effect and often lack a follow up, hence questions 6 and 7 would automatically receive a “NO” response. Additionally, question 13 was given a fixed response of “NA” (**Supplementary Table 2**). Quality of matched-pair interventions was assessed using the Quality Assessment of Controlled Intervention Studies, and Matched-Pairs (Case-Control) by The Quality Assessment of Case-Control Studies NHLBI (NHLBI, 2019). Assessment was completed by one author and reviewed by another independent assessor prior to agreement (**Table 4.2**).

Table 4.2. National Heart, Lung, and Blood Institute (NHLBI) tool for quality assessment of included studies.

Study, Year	Question														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Observational Cohort Cross-Sectional Studies															
Alles *et al*, 2017	+	+	+	+	-	-	-	-	+	+	+	-	**a**	+	Fair
Draper , 1993	+	-	r	+	-	-	-	+	+	+	+	-	**a**	-	Fair
Henjum, 2018	+	+	r	+	-	-	-	+	+	+	+	-	**a**	+	Good
Krajcovicová-Kudlácková, 2003	+	-	r	+	-	-	-	+	+	+	+	-	**a**	-	Fair
Leung, 2011	+	-	r	+	-	-	-	+	+	+	+	-	**a**	+	Good
Lightowler, 1998	+	+	+	+	-	-	-	+	+	+	+	-	**a**	+	Fair
Lightowler, 2002	+	+	+	+	-	-	-	+	+	+	+	-	**a**	+	Good
Nebl, 2019	+	+	+	+	-	-	-	-	+	+	+	r	a	-	Good
Schűpbach, 2017	+	-	+	+	-	-	-	+	+	+	+	-	**a**	+	Good
Sobiecki, 2016	+	+	+	+	+	-	-	+	+	+	+	-	**a**	+	Good
Waldmann, 2003	+	-	+	+	-	-	-	+	+	+	+	-	**a**	+	Good
Controlled Intervention Studies															
Remer, 1999	-	?	-	-	-	+	+	+	+	+	+	+	+	+	Good
Case-Control Studies															
Elorinne, 2016	+	-	+	+	r	+	?	?	-	+	-	+	**a**	a	Fair
Kristensen, 2015	+	+	-	-	+	+	?	?	-	+	-	+	**a**	a	Fair
Rauma, 1994	+	-	-	+	-	+	?	?	-	+	-	-	**a**	a	Poor

+, yes; -, no; ?, cannot determine; a, not applicable; r, not reported; (outlined), fixed answers according to NHLBI recommendations.

The WHO criteria for assessing the severity of IDD (1994) stratified by median urinary iodine concentration (UIC) was used to assess the relative level of deficiency in each dietary group. According to this classification, the rate of deficiency is described as the percentage of individuals in each group with UIC below <100 or <50 μg L−1, in severe deficiency (WHO, 2007).

Funnel plots were generated for both UIC and dietary iodine intake data. For urinary iodine status, summary values and number of participants for each dietary group were used to generate an overall population mean value (μ).The standard error for each observation group was generated according to the equations (**Equation 4.1**):

$$SE = SQRT(SQRT(\mu \times \frac{1-\mu}{number\ of\ subjects})^2)$$

$$95\%\ Confidence\ interval\ (CI) = \mu \pm (1.96 \times SE)\ 99.7\%\ CI = \mu \pm (3 \times SE)$$

Equation 4.1. Standard error and confidence intervals (CI) for groups included.

Confidence limits were produced for each population studied and used to generate funnel plots of UIC or iodine intake shown against study size (**Supplementary Figure 1 & Supplementary Figure 2**).

4.4 Results

Following exclusion of studies qualitative synthesis was completed for fifteen studies. The technique of study selection along with the number of included and excluded studies recorded for this systematic review is shown in the PRISMA 2009 flow diagram (**Figure 4.1**) (Moher *et al*, 2009). Fifteen relevant studies were identified examining the iodine intake or status by dietary group. Descriptions of the included studies are shown in **Table 4.3**. Consistent with scientific literature, different descriptors and nomenclature were used to define vegetarian diet types (**Supplementary Table 3**). Three studies used objective assessments to group individuals (Nebl *et al*, 2019; Sobiecki *et al*, 2017; Waldmann *et al*, 2003).

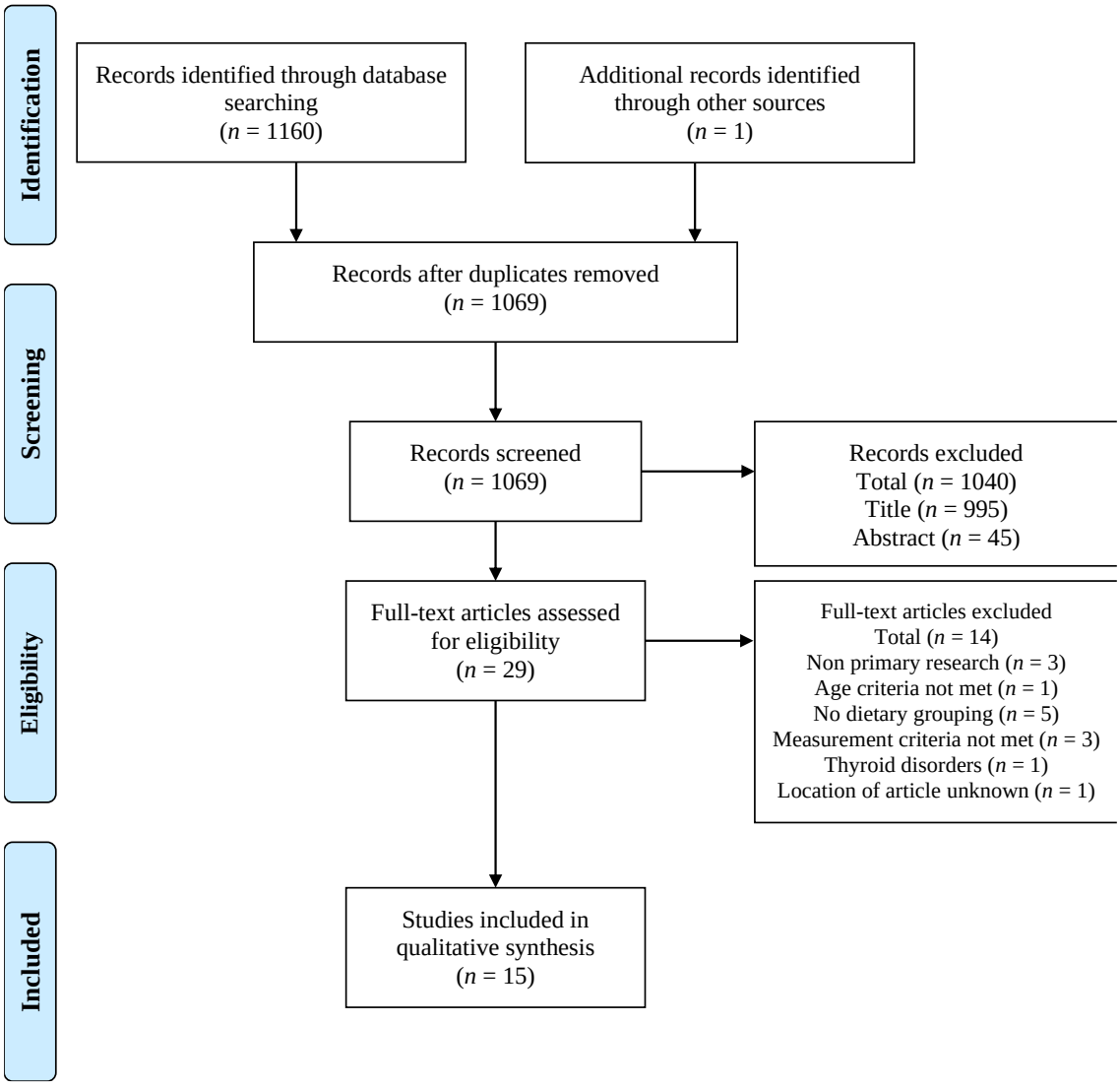


Figure 4.1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for included studies.

4.4.1 Urinary iodine status

Eight studies investigated iodine status by urinary iodine concentration (UIC) (**Table 4.4; Figure 4.2**). Four studies measured UIC using spot samples (Henjum *et al*, 2018; Leung e al, 2011; Schüpbach *et al*, 2017; Elorinne *et al*, 2016)—of which, one study collected multiple fasted samples to determine average values (Schüpbach *et al*, 2017).

The lowest median UIC (16.8 µg L^{-1}) was recorded by Lightowler in UK male adults following vegan diets (Lightowler and Davies 1998). Rauma reported the highest median UIC (<500.0 µg L^{-1}) in Finish omnivores (Rauma *et al*, 1994). Large variation in UIC existed in several studies (Leung *et al*, 2011; Schüpbach *et al*, 2017; Rauma *et al*, 1994), with one study showing variation in those following vegan diets between <200 and 1700 µg L^{-1} (Rauma *et al*, 1994).

Table 4.3. Studies investigating iodine among vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Study Design	Location	Dietary Groups	Sample (*n*) (Male, Female)	Method of Dietary Classification	Average Diet Adherence (Years)
Alles, 2017	Cross-Sectional	France	Vegan	789	Assessed by investigators pre-study	NA
			Vegetarian	2370		
			Omnivore	90,664		
Draper, 1993	Cross-sectional	London, UK	Vegan	38 (18,20)	Self-reported	1.0
			Lacto-Vegetarian	52 (16,36)		2.0
			Demi-vegetarian	37 (13,24)		5.0–9.0
Elorinne, 2016	Matched pairs by age and sex	Kuopio, Finland	Vegan	22 (16,6)	Self-reported	8.6
			Omnivore	19 (11,8)		NA
Henjum, 2018	Cross-Sectional	Norway, eastern and western geographical regions	Vegan	27	Self-reported	NA
			Vegetarian	9		
			Omnivore	367		
Kristensen, 2015	Matched pairs by age	Denmark	Vegan	75 (36,39)	Self-reported	≤ 1.0
			Omnivore	1627 (716, 911)		NA
Krajcovicová-Kudlácková, 2003	Cross-sectional	Slovakia	Vegan	15 (6,9)	Self-reported	9.7
			Vegetarian	31 (12,19)		9.0
			Omnivore (Mixed Diet)	35 (15,20)		NA
Leung, 2011	Cross-sectional	Boston, Massachusetts	Vegan	63	Self-reported	11.3 ± 11.7[1]
			Vegetarian	78		5.6 ± 5.7 [1]
Lightowler, 1998	Cross-sectional	London and surrounding counties, UK	Vegan	30 (11,19)	Self-reported	M, 10.0, F, 9.2
Lightowler, 2002	Cross-sectional	London and the south-east of England, UK	Vegan	26 (11, 15)	Self-reported	M, 9.9, F, 11.7

Table continued…

Study, Year	Study Design	Location	Dietary Groups	Sample (*n*) (Male, Female)	Method of Dietary Classification	Average Diet Adherence (Years)
Nebl, 2019	Cross-sectional	Hanover, Germany	Vegan	27 (11,16)	Assessed by investigators pre-study	> 2.0
			Vegetarian	25 (10, 15)		> 2.0
			Omnivore	27 (10,17)		> 3.0
Rauma, 1994	Matched pairs	Kuopio, Finland.	Vegan (Living Food Diet)	12	Self-reported	6.7 ± 3.8[1]
			Omnivore	12		NA
Remer, 1999	Repeated-measures	Germany	Vegetarian (Lacto)	6 (3,3)	Allocated by investigators	0.0
			Omnivore	6 (3,3)		
			Omnivore (High protein)	6 (3,3)		
Schüpbach, 2017	Cross-sectional	Lausanne and Zurich, Switzerland	Vegan	53 (20,33)	Self-reported	≤ 1.0
			Vegetarian	53 (17,36)		≤ 1.0
			Omnivore	100 (37,63)		≤ 1.0
Sobiecki, 2016	Cross-sectional	Oxford, UK	Vegan	803	Assessed by investigators pre-study	≤ 1.0
			Vegetarian	6673		≤ 1.0
			Pescatarian	4531		≤ 1.0
			Omnivore (Meat-eaters)	18,244		≤ 1.0
Waldmann, 2003	Cross-sectional	Hanover, Germany	Vegan (Strict)	98	Assessed by investigators pre-study	4.3
			Vegan (Moderate)	56		3.4

NA, not assessed; M, male; F, female; [1]mean ± SD.

Table 4.4. Iodine status and deficiency in vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Assessment Method	Dietary Group (n) (Male, Female)	Iodine Status by UIC ($\mu g\ L^{-1}$)	Criteria for Iodine Deficiency Disorders
Elorinne, 2016	Spot UIC Sandell–Kolthoff method.	Vegan (21)	15.0 (4.6, 21.8) [1,**]	Severe
		Omnivore (18)	37.4 (17.7, 86.5)[1]	Moderate
Henjum, 2018	Spot UIC.	Vegan (9) Vegetarian (27)	38.0[1,**]	Moderate
		Omnivore (367)	80.0[1]	Mild
Krajcovicová-Kudlácková, 2003	24 h UIC Sandell–Kolthoff method.	Vegan (15) (6,9)	71.0 (9.0–204.0)[2,**]	Mild
		Vegetarian (31) (12,19)	177.0 (44.0–273.0)[2,**]	Optimal
		Omnivore (Mixed Diet) (35) (15,20)	210.0 (76.0–423.0)[2]	Optimal with risk of health consequences
Leung, 2011	Spot UIC spectrophotometry.	Vegan (62) (19,43)	78.5 (6.8–964.7)[2,*]	Mild
		Vegetarian (78) (26,52)	147.0 (9.3–778.6)[2]	Optimal
Lightowler, 1998	Four 24 h UIC Sandell–Kolthoff method reaction.	Vegan (30) (11,19)	Total, 20.2[1], M, 16.8[1], F, 20.5[1]	Severe-Moderate
Rauma, 1994	24 h UIC.	Vegan (Living Food Diet) (10)	<450.0 (<200.0–1700.0)[2]	Optimal with risk of health consequences
		Omnivore (12)	<500.0 (300.0−1200.0) [2]	

Table continued…

Study, Year	Assessment Method	Dietary Group (n) (Male, Female)	Iodine Status by UIC (μg day^{-1})	Criteria for Iodine Deficiency Disorders
Remer, 1999	Two 24 h UIC.	Vegetarian (6) (3,3)	36.6 ± 8.8[3,*]	Moderate
		Omnivore (6) (3,3)	50.2 ± 14.0[3]	Mild
		Omnivore (High Protein) (6) (3,3)	61.0 ± 8[3]	Mild
Schüpbach, 2017	Four fasted spot UIC.	Vegan (53) (20,33)	56.0 (27.0–586.0)[2,*]	Mild
		Vegetarian (53) (17,36)	75.0 (1.0–610.0)[2]	Mild
		Omnivore (100) (37,63)	83.0 (22.0–228.0)[2]	Mild

M, male; F, female; 1median (25th–75th percentile), [2]median (range); [3]mean ± SD; *Significantly different between dietary group comparison, P = < 0.05; **, P < 0.001; criteria for iodine deficiency disorders (WHO, 2007), severe< 20 ug L^{-1}, moderate 20–49 ug L^{-1}, mild 50–99 ug L^{-1}, adequate 100–199 ug L^{-1}, excessive risk of adverse health consequences ≥ 300 ug L $^{-1}$.

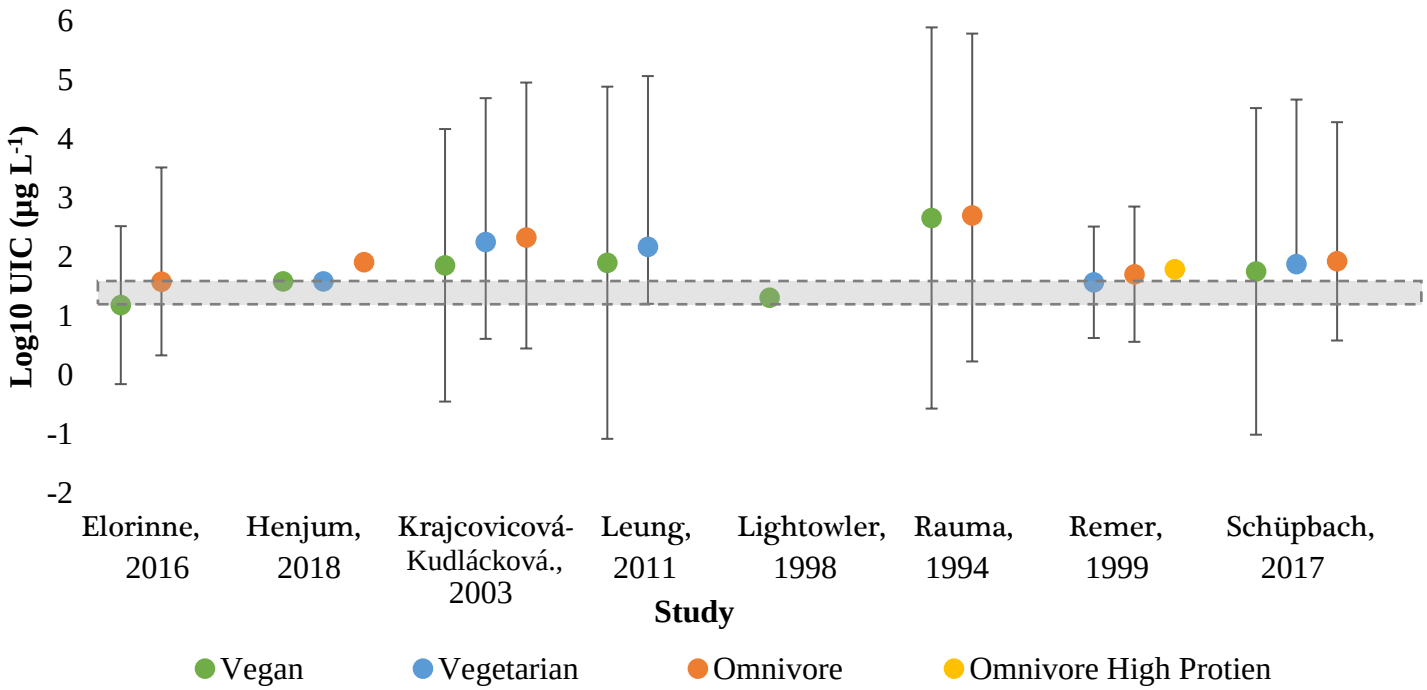


Figure 4.2. Visual representation of iodine status by median urinary iodine concentration (mUIC) for included studies. The shaded grey bar represents the optimal range for iodine status (100–299 µg L^{-1}) (WHO, 2007). Significance values are not presented within this figure. See **Table 4.4**.

The majority (75%) of the recorded values for UIC fell below the expected population mean of 95.6 µg L^{-1} (**Supplementary Figure 1**) and half of the values fell either on or outside of the 99.7% confidence limit.

In all studies giving intergroup comparisons, the lowest median UIC was recorded for those following vegan diets and the highest for omnivores (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Schüpbach *et al*, 2017; Remer *et al*, 1999; Elorinne *et al*, 2016; Rauma *et al*, 1994). Five out of eight studies recorded median UIC in vegans to be significantly lower than omnivores (P = < 0.005) (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Schüpbach *et al*, 2017; Remer *et al*, 1999). All studies observed UIC in those following vegetarian diets to be higher than vegan diets, yet lower than omnivorous diets (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Schüpbach *et al*, 2017; Remer *et al*, 1999). The difference between vegetarian and omnivorous diets was significant in three studies (P = < 0.05) (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Remer *et al*, 1999).

IDD assessment according to the WHO criteria ranged from severe (inadequate) to at 'risk' of adverse health consequences (excess) across studies (WHO, 2013). Supplementary Table S4 presents national data corresponding to countries of included studies. Optimal status (100–200 µg L^{-1}) was achieved in vegetarian groups in Slovakia and Boston (Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011). No adults following vegan diet had median UIC within the optimal range (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Schüpbach *et al*, 2017; Remer *et al*, 1999). Seven studies observed one or more dietary group below the cut off for optimal population UIC (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Lightowler and Davies 1998; Schüpbach *et al*, 2017; Remer *et al*, 1999; Elorinne *et al*, 2016). Iodine deficiency (mild) (50–99 µg L^{-1}–>20 µg L^{-1}) was recorded in adults following vegan diets in six studies (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Lightowler and Davies, 1998; Schüpbach *et al*, 2017; Elorinne *et al*, 2016), vegetarian diets in two studies (Schüpbach *et al*, 2017; Remer *et al*, 1999), and omnivorous diets in four studies (Henjum *et al*, 2018; Nebl *et al*., 2019; Remer *et al*, 1999,Elorinne *et al*, 2016).

Those following vegan diets were most frequently seen to exhibit either mild (50–99 μg L^{-1}) or moderate deficiency (20–49 μg L^{-1}) (Leung *et al*, 2011; Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Lightowler and Davis, 1998; Schüpbach *et al*, 2017; Elorinne *et al*, 2016), and in two studies were found to be severely deficient (<20 μg L^{-1}) (Leung *et al*, 2011; Remer *et al*, 1999). In one of these studies, >75% of those following vegan diets fell into the severely deficient category (Elorinne *et al*, 2016). Both those following vegan and vegetarian diets were more commonly observed to be moderately deficient, whilst, conversely, omnivores were found in two studies to exhibit excessive iodine status (Krajcovicová-Kudlácková *et al*, 2003; Rauma *et al*, 1994). This was also noted for those following vegan diets in one Finnish study Rauma *et al*, 1994).

4.4.2 Dietary iodine intake

Methods for assessing dietary intake are listed in **Supplementary Table 5.** Ten studies reported estimates for daily iodine intake (Allès *et al*, 2017; Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Remer *et al*, 1999; Kristensen *et al*, 2015, Rauma *et al*, 1994).—of which, four studies were investigating iodine specifically (Lightowler and Davis, 1998; Lightowler and Davis, 2002; Remer *et al*, 1999; Rauma *et al*, 1994). The additional studies investigated other macro- and micronutrient intakes besides iodine (**Table 4.5**; **Figure 4.3**; **Figure 4.4**) (Allès *et al*, 2017; Draper and Lewis, 1993; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Kristensen *et al*, 2015.

Table 4.5. Assessment of dietary iodine intake for vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Assessment of Dietary Iodine	Criteria for Recommended Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Allès, 2017	Three repeated 24 h dietary records.	150 µg day^{-1} RDI for the French population (2001)	Vegan (789)	248.3 ± 9.8 (a)[1]	Seaweed, salt, or supplements not measured.	Y
			Vegetarian (2370)	222.6 ± 5.7 (a)[1]		Y
			Omnivore (90,664)	180.1 ± 1.1 (a)[1,**]		Y
Draper, 1993	Three-day weighted food diaries. Analysed using UK Ministry of Agriculture, Fisheries and Food data.	DRV of 140 µg day^{-1} Department of Health (1991)	Vegan (38) (18,20)	M, 98.0 ± 42.0[2,**] F, 66.0 ± 22.0[2,**]	95% used sea salt or seaweed. 30%–40% consumed food supplements containing seaweed 1–2 days a month. 15.6 µg day^{-1} provided by dietary supplements.	N
			Lacto-Vegetarian (52) (16,36)	M, 216.0 ± 73.0 [2,**] F, 167.0 ± 59.0 [2,**]	No iodine provided by salt, seaweed or supplements.	Y
			Demi-Vegetarian (35) (13,24)	M, 253.0 ± 164.0[2, **] F, 172.0 ± 91.0 [2,**]	No iodine provided by salt, seaweed or supplements.	Y

Table continued…

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Kristensen, 2015	Four-day weighed food diary.	150 µg day^{-1} NNR (2012)	Vegan (70) (33,37)	M, 64.0 (43.0–91.0) [3,**] F, 65.0 (54.0–86.0)[3,**]	Salt not measured. Three vegans consumed seaweed. 9.0 µg day^{-1} (M) and 6.0 µg day^{-1} (F) was provided by dietary supplements.	N
			Omnivore (1257) (566,691)	M, 213.0 (180.0-269.0)[3] F, 178.0 (146.0-215.0)[3]	Salt not measured. No iodine provided by seaweed. 107 µg day^{-1} (M) and 78.9 µg day^{-1} (F) was provided by dietary supplements.	Y
Lightowler, 1998	Four-day weighed food diary with duplicate portion technique.	140 mg day^{-1} RNI Department of Health (1991)	Vegan (30) (11,19)	M, 138.0 ± 149.0[2] F, 187.0 ± 246.0[2]	Salt not measured. Three vegans consumed seaweed, resulting in significantly higher iodine intake (P = < 0.001) Seaweed consumers were over six times the RNI. Iodine-containing supplements were consumed by five (45%) males and seven females (37%).	M, N F, Y

Table continued…

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Lightowler, 2002	Four -day food diaries with duplicate portion technique. Analysed using CompEat 4 software.	140 mg day^{-1} RNI Department of Health (1991)	Vegan (26) (11,15)	Diet Diary M, 42.0 ± 46.0[2] F, 1448.0 ± 3879.0[2] Duplicate Diary M, 137.0 ± 147.0[2] F, 216.0 ± 386.0[2]	Salt not measured. Two vegans consumed seaweed, resulting in iodine intake to exceed the RNI. Dietary supplement intake was recorded but not included to dietary intake.	Diet Diary M, N F, Y Duplicate Diary M, N F, Y
Nebl, 2019	Three-day food diaries analysed by PROD16.4®.	200 µg day^{-1} RV German, Austrian and Swiss Nutrition Societies (2019)	Vegan (27) (10,17) Vegetarian (25) (10,15) Omnivore (27) (11,16)	57.7 (48.4, 67.0)[4,*] 61.6 (49.4, 73.7)[4,*] 88.8 (64.1, 114.0)[4] **	Salt or seaweed not measured. No iodine provided by supplements.	N N N
Rauma, 1994	Seven-day food diaries analysed by NUTRICA Finland.	0.1–0.2 mg day^{-1} RDA (120–200 µg day^{-1})	Vegan (Living Food Diet) (9) Omnivore (8)	29.0 ± 18.0[2] 222.0 ± 93.0[2]	25% of daily iodine in vegans was provided by seaweed (estimated >8.0 µg day^{-1}). Four vegans consumed seaweed, resulting in higher intake.	N Y

Table continued…

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Remer, 1999	Five-day dietary intervention of pre-selected food items representing each diet. Calculated using food tables.	NA	Vegetarian (Ovo-Vegetarian)(6) Omnivore (6)	15.6 ± 21.0[2] 35.2 ± 15.0[2]	No iodized salt, seaweed or supplements were permitted during the study. All drinks including water were low in iodine and other minerals.	N N
	Pre-study questionnaire	200 mg day^{-1} RI, German Society	Omnivore (High Protein) (6)	44.5 ± 16.5[2]		N
Waldmann, 2003	identifying regularly consumed foods. Two estimated nine-day FFQs using 7 days of records.	of Nutrition (2000)	Vegan (Strict) (98) (48,50)	M, 87.7 ± 30.6[2] F, 82.1 ± 34.4[2]	Salt not measured. Seaweed intake not measured.	N
			Vegan (Moderate) (56) (19,37)	M, 93.7 ± 27.8[2] F, 78.1 ± 25.6[2]	46% of participants used some form of nutritional supplement. Iodine-specific supplements were not recorded.	N

Table continued…

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Sobiecki, 2016	112-item semi-quantitative FFQ. Analysed based on UK Ministry of Agriculture, Fisheries and Food data.	150 µg day^{-1} RDA, dietary reference intakes for iodine (2001)	Vegan (803) (269,534)	M, 55.5 ± 40.0[2] F, 54.1 ± 40.0[2] Total, 58.5 (a)[2]	Salt not measured. Two participants who consumed seaweed had values close to the maximum tolerable daily intake for iodine. Supplement intakes recorded did not specify iodine content.	M, N F, Y (a), N
			Vegetarian (6673) (1516,5157)	M, 141.0 ± 77.4[2] F, 146.1 ± 78.8[2] Total, 148.1 (a)[2]		M, N F, N (a), N
			Pescatarian (4431) (782,3749)	M, 197.4 ± 84.7[2] F, 194.8 ± 85.9[2] Total, 196.8 (a)[2]		Y (a), Y
			Omnivore (Meat - Eaters) (18,244) (3798,14446)	M, 214.3 ± 85.6[2] F, 213.8 ± 85.2[2] Total, 212.2 (a)[2]		Y (a), Y

RDI, Recommended Daily Intake; DRV, Daily Recommended Value; NNR, Nordic Nutrition Recommendations; RNI, Recommended Nutrient Intake; RV, Recommended Value; RDA, Recommended Daily Allowance; RI, Recommended Intake; (a), adjusted by age and sex; [1]mean ± SEM; [2]mean ± SD; [3]median (25th–75th percentile); [4]mean (95% CI); *Significant difference with other dietary groups, P = < 0.005, **Significant difference with other dietary groups, P = < 0.001.

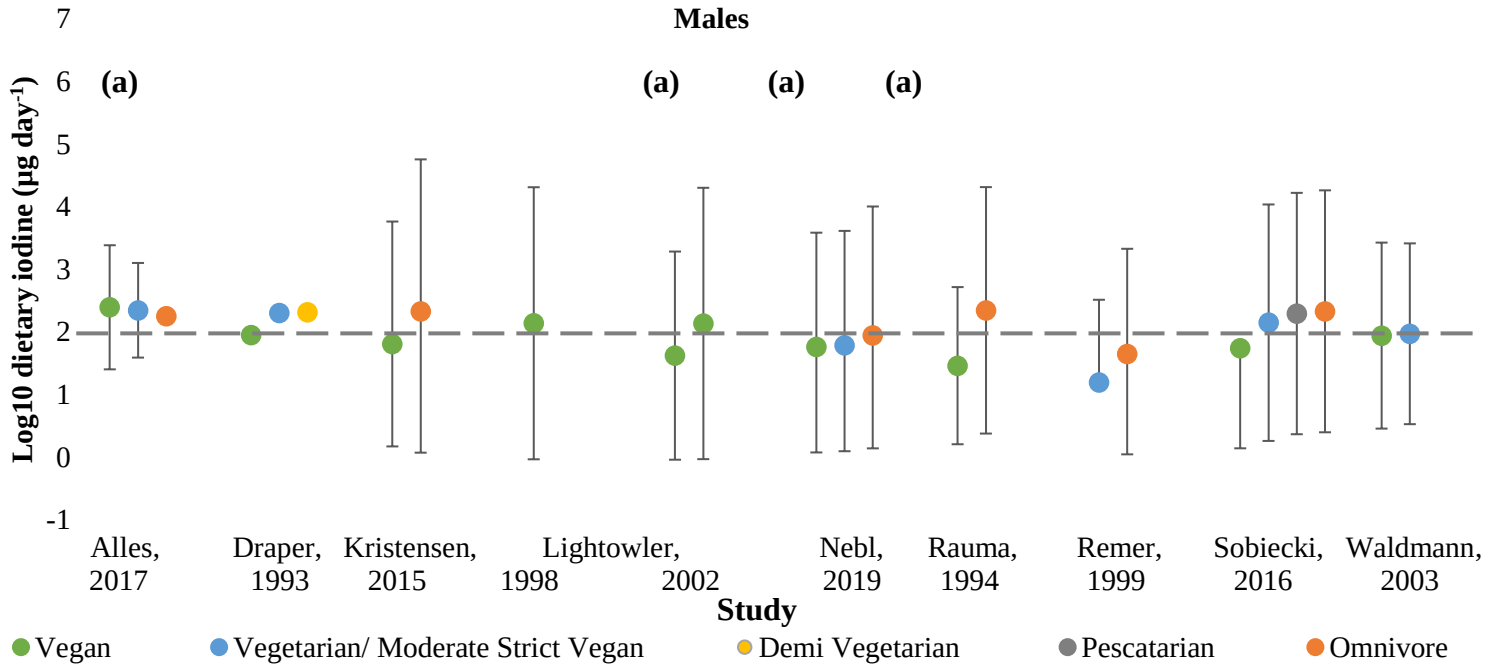


Figure 4.3. Visual representation of estimated average iodine intake (µg day^{-1}) for males in included studies. The grey dashed line represents the adequate intake recommended by the WHO of 150 µg day^{-1}; (a), mixed gender values; Significance values are not presented within this figure. See **Table 4.5**.

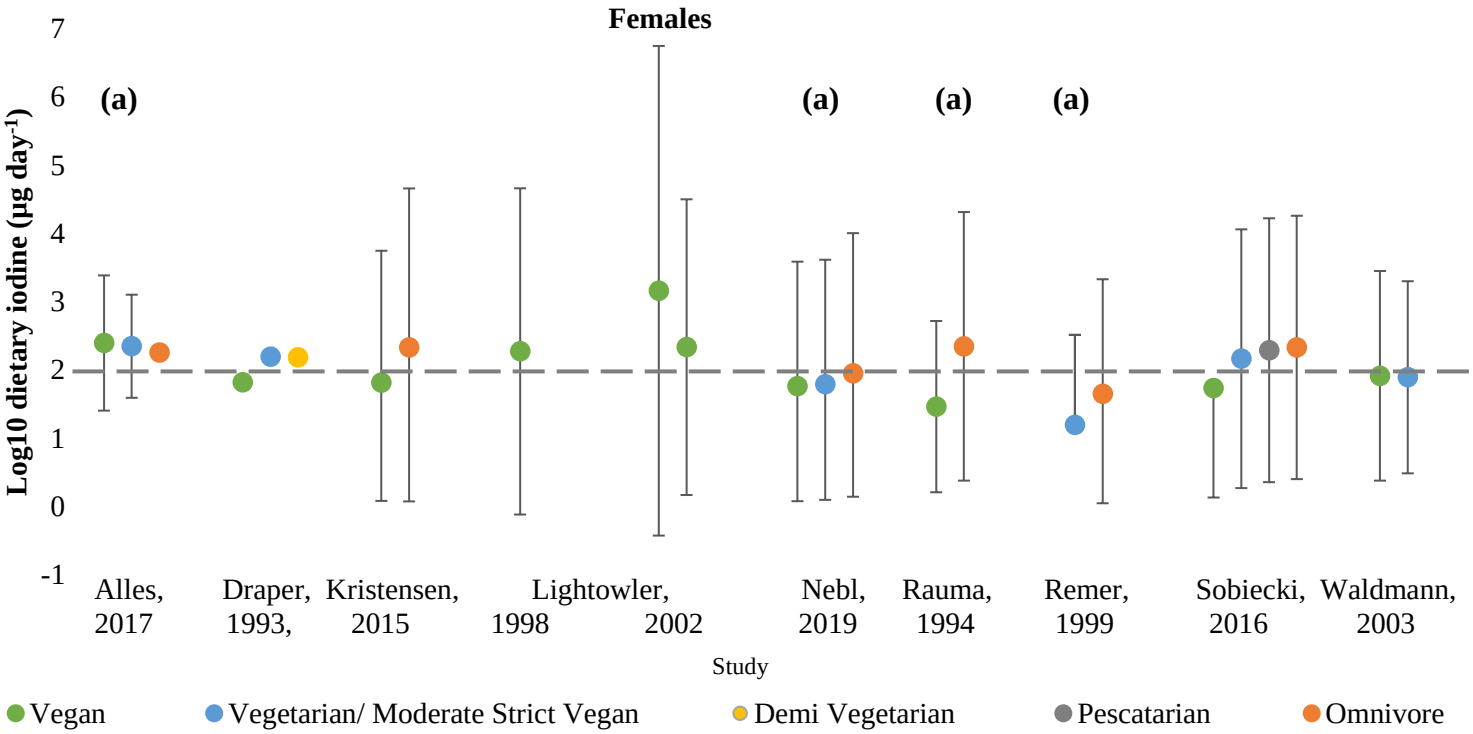


Figure 4.4. Visual representation of estimated average iodine intake (µg day^{-1}) for females in included studies. The grey dashed line represents the adequate intake recommended by the WHO of 150 µg day^{-1}; (a), mixed gender values; Significance values are not presented within this figure. See **Table 4.5**.

The highest daily iodine intake was recorded in females following vegan diets of 1448.0 ± 3879.0; 29.0 ± 18.0 μg day^{-1} (Lightowler and Davis, 2002; Rauma *et al*, 1994). The lowest dietary intake was found in those following vegetarian diets of 15.6 ± 21.0 μg day^{-1} (Remer *et al*, 1999). Seven studies assessed iodine intake between vegans and one or more dietary group (Allès *et al*, 2017; Draper and Lewis, 1993; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Kristensen *et al*, 2015; Rauma *et al*, 1994). Omnivores (male and female) had the highest estimated average intake in 85% of studies (Nebl *et al*, 2019; Sobiecki *et al*, 2016, Waldmann *et al*, 2003; Remer *et al*, 1999; Kristensen *et al*, 2015; Rauma *et al*, 1994). Vegan groups tended to have the lowest iodine intake. Males following vegan diets had average intakes lower than all comparative dietary groups in all studies, apart from that conducted by Allès (Allès *et al*, 2017). Females following vegan diets presented the lowest iodine intake in 75% of studies (Draper and Lewis, 1993; Sobiecki *et al*, 2016; Kristensen *et al*, 2015). Varied intakes were recorded for moderate vegans, vegetarians, and pescatarians across studies, with estimates ranging between 222.6 ± 1.1 and 15.6 ± 21.0 μg day^{-1} (Allès *et al*, 2017; Nebl *et al*, 2019; Remer *et al*, 1999). Most values fell around the expected population mean (184.1 μg day^{-1}), although there was a general tendency for values to be slightly below this level (**Supplementary Figure 2**).

Recommended criteria for iodine intake varied according to country of study. Comparisons were, therefore, drawn according to recommended intake values denoted by the WHO, with values above 150 μg day^{-1} for the group being classed as adequate (WHO, 2013). One study recorded estimates above the adequate range for all dietary groups (Allès *et al*, 2017). Omnivores most frequently achieved adequate intake, with only two studies recording intakes below 150 μg day^{-1} for both genders (Nebl *et al*, 2019; Remer *et al*, 1999). Those following vegan diets most frequently showed dietary iodine inadequacy. Adequate intake was recorded for 44% of female and 66% of mixed gender estimates (Allès *et al*, 2017; Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Kristensen *et al*, 2015; Rauma *et al*, 1994).

No groups of males only had intakes above the adequate cut off values (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Kristensen *et al*, 2015; Rauma *et al*, 1994). Intakes for moderate vegans (vegetarians), vegetarians, and pescatarians were similar between genders and were above adequate in half of studies (Allès *et al*, 2017; Draper and Lewis, 1993; Nebl *et al*, 2019).

Only four studies investigated the relative consumption of different food groups (Allès *et al*, 2017; Draper and Lewis, 1993; Nebl *et al*, 2019; Waldmann *et al*, 2003). None reported the actual contribution of each food group to dietary iodine independent of iodised salt and supplements. However, adults following vegan and vegetarian diets tended to report significantly higher consumption of plant-based food groups (fruit, vegetables, legumes, tubers cereals and grains) (Nebl *et al*, 2019; Waldmann *et al*, 2003), along with tofu and soya-based products which naturally have a low iodine content. One study reported the consumption of milk alternatives in each dietary group, and vegans had the largest consumption of plant-based milk alternatives (Allès *et al*, 2017). As expected, milk and dairy, egg, and fish consumption was significantly higher ($P = < 0.0001$) in vegetarians and omnivores compared to vegans (Allès *et al*, 2017; Nebl *et al*, 2019).

Six studies measured seaweed consumption (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Sobiecki *et al*, 2016; Kristensen *et al*, 2015; Rauma *et al*, 1994). Adults following vegan diets had the greatest seaweed intake, with four studies stating that consumption significantly increased dietary intake such that iodine intake would be considered ‘excessive’ (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Kristensen *et al*, 2015). Seaweed was not regularly consumed by omnivores and moderate vegans (vegetarians), vegetarians, demi vegetarians or pescatarians (Draper and Lewis, 1993; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Remer *et al*, 1999; Kristensen *et al*, 2015; Rauma *et al*, 1994).

Mandatory salt fortification programs were present in three countries of included studies (**Table 4.6**) (Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Kristensen *et al*, 2015).

Eight studies did not record the contribution of iodised salt to dietary iodine (Allès *et al*, 2017; Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis 2002; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Kristensen *et al*, 2015).

Table 4.6. Summary of salt fortification programs present in included studies[1].

Country	Year	Iodate and/or Iodide	Iodine Amount (ppm)	State of Legislation
Boston (U.S.)	1920	Iodide	43	Mandatory
Denmark	1999	Iodide	13	Mandatory
France	1997	Iodide	10–15	Voluntary
Finland	1963	Iodide	25	Voluntary
Germany	1981	Iodate	15–20	Voluntary
Norway	NA	Iodide	5	Voluntary
Slovakia	1966	Iodide	25 ± 10	Mandatory
Switzerland	1922	Both	20–30	Voluntary
UK	NA	Iodide	10–22	Voluntary

[1]Data is taken from the Iodine Global Network (IGN) Iodine Scorecard and Map.

Supplement intake was recorded in seven studies (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Kristensen *et al*, 2015). Two studies did not record iodine-specific supplementation (Sobiecki *et al*, 2016; Waldmann *et al*, 2003). One study prevented supplement intake during the study and another excluded supplement contribution in dietary analysis (Lightowler and Davis, 2002; Remer *et al*, 1999).

Three studies recorded supplement intake in adults following vegan diets, contributing between 9.0 and 54.0 μg day^{-1} to dietary intake (Draper and Lewis, 1993; Lightowler and Davis, 1998; Kristensen *et al*, 2015). Supplements contributed greater iodine to diets of omnivores (78.9 μg day^{-1}–107.0 μg day^{-1}) (Draper and Lewis, 1993; Kristensen *et al*, 2015). No supplement consumption was recorded for moderate vegans (vegetarians), vegetarians, demi vegetarians or pescatarians (Draper and Lewis, 1993; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Remer *et al*, 1999).

4.5 Discussion

The popularity of vegan and vegetarian diets has increased considerably in the past decade. The prospect of these diets acting as a barrier to adequate iodine nutrition could increase the risk of developing preventable health consequences associated with deficiency and furthering the worldwide public health issue of iodine (Black, 2003).

Given that these diets are commonly followed by females of childbearing age (16–24 years), lowered dietary iodine intake in these groups could significantly impact future generations and reduce societal productivity (Public Health England, 2014; Zimmermann, 2013; Martinelli and Berkmanienė, 2018).

The present systematic review is the most recent review to evaluate the evidence for iodine intake and status among adults following vegan and vegetarian diets (Fields and Borak, 2009). Our review showed that the discourse has not changed and that adults following a vegan diet, living in industrialised countries, not consuming seaweed, or iodine-containing supplements, appear to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared to less restrictive dietary groups. Comparison of dietary estimates supports the possibility of a gender difference within vegan groups, as no vegan males achieved adequate intake. Vegetarians or pescatarians are more at risk of low iodine status and intake compared to omnivores but not vegans.

These results are in accordance with the previous review by Fields, Dourson and Borak in 2009, whereby it was concluded that iodine adequacy decreased with increased dietary restriction (Fields and Borak, 2009). However, the previous review did not highlight that some study populations following omnivorous diets also had low iodine status and deficiency (Fields and Borak, 2009). The degree of vulnerability in all dietary groups appears to be impacted by not only individual dietary choices, practices, and restrictions, but country-specific dietary determinants and national food fortification strategies. For this reason, vegans and vegetarians living in industrialised regions where national population iodine measures are below adequate or where dietary intake is insufficient are more susceptible to iodine deficiency.

This trend can be observed by comparing mUIC of included studies with the corresponding national data from the country of origin. mUIC tends to closely represent that of omnivorous diets, owing to these practices being the dominant in most industrialised countries.

Vegan and vegetarian mUIC in all studies, apart from that conducted by Rauma (1994), fell below national values (Rauma *et al*, 1994). In half of studies, the extent was substantial enough for adults following vegan and vegetarian diets to be classified in a lower deficiency category, according to the WHO criteria, than omnivores and national data—for example, mild (omnivores)–moderate (vegans and vegetarians) (Henjum *et al*, 2018; Krajcovicová-Kudlácková *et al*, 2003; Leung *et al*, 2011; Elorinne *et al*, 2016). This trend can be explained by exploring values determined by Henjum (2018) of non-pregnant young women in Norway (Henjum *et al*, 2018). Omnivores in this study presented UIC values concordant with current Norwegian national data (80.0, 75.0 μg day^{-1}), which could be due to efficient data collection of northern, western, and eastern regions of Norway (WHO, 2007; Henjum *et al*, 2018). As omnivorous diets are the most dominant in industrialised countries, this sample is likely to be representative of the Norwegian population. Omnivorous MUIC and national data are indicative of mild deficiency, whereas for those following vegan and vegetarian diets, MUIC is suggestive of moderate deficiency, therefore indicating that the susceptibility of vegan and vegetarian populations to deficiency is in part dependent on national iodine status.

This trend is not apparent in woman of reproductive age in Switzerland, despite lower observed values in those following vegan diets, as all groups and national data would be classified as mildly deficient (Schüpbach *et al*, 2017). This could be explained by regular consumption of iodized salt in Swiss households, which is greater than 80% (Andersson *et al*, 2010). Fortified bread is a significant contributor to dietary iodine and can be consumed by all dietary groups (Andersson *et al*, 2010). A reduction or restricted legislation in iodine fortification could increase the risk of iodine deficiency. In Germany, Remer (1999) induced deficiency in vegetarian and omnivorous diets when preventing consumption of fortified and iodinated foods under controlled conditions (Remer *et al*, 1999).

In this study, daily iodine intake dropped below requirements required for optimal thyroidal function (50.0–80.0 μg day^{-1}). Disuse or lack of availability of iodine-fortified foods could produce similar consequences.

Shifting legislation reflects changes in iodine status by dietary group over time in Finland from a risk of excess to moderate–severe deficiency in 2016 (Elorinne *et al*, 2016; Rauma *et al*, 1994). This is following a reduction in iodised salt consumption possibly influenced by efforts to reduce salt consumption in the general public and replacement of the traditional diet rich in fish and dairy for diets providing improved fruit and vegetable intake (Nyström *et al*, 2016). The Finnish Vegan Society was founded in October 1993 (International Vegetarian Union, 2019), a year before Rauma's study was conducted, and food consumption is likely to have changed in this time, as these diets have become widely accepted. Papers published prior to 1990 were excluded, as meat-free diets did not appear in the mainstream until the 1980s, and it is likely that food choices and landscape have changed substantially since this period (Leitzmann, 2014). Recent studies published after 2010 represent almost half of the included studies which could account for the 'second-wave' vegetarian movement supported today (Leung *et al*, 2011; Henjum *et al*, 2018; Nebl *et al*, 2019; Schüpbach *et al*, 2017; Sobiecki *et al*, 2016; Elorinne *et al*, 2016; Kristensen *et al*, 2015).

Despite the popularity of vegan and vegetarian diets, there is no homogenous term to define these dietary groups, thus questioning the accuracy of group estimates in included studies. Three studies used objective assessments to group individuals by dietary preference (Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003). Self-reported measures are frequently inaccurate at determining dietary preference (Fields and Borak, 2009). Misreporting may additionally be a consequence of misinterpretation of the term "vegetarian" and its associated dietary restrictions or, additionally, over exaggeration of restrictive practices to align with vegetarian ideology (Fields and Borak, 2009; Juan, Yamini, and Britten, 2015). Juan, Yamini and Britten (2015) observed errors with adherence to vegetarian diets when investigating food consumption patterns of the U.S. population in the period 2007–2010 (Juan, Yamini, and Britten, 2015).

The authors determined that half of those identifying themselves as vegetarian consumed meat, poultry, or seafood and, therefore, would not be described as vegetarian using typical definitions.

This issue was discussed previously in the systematic review conducted by Fields, Dourson, and Borak, indicating that individual dietary intake based on the description of typical "vegetarian" regimes from self-reports may be inaccurate and indicates that consistent strict dietary adherence in the included studies is likely to be low (Fields and Borak, 2009).

The duration of practicing a specific dietary preference must be considered when examining the diets of vegan and vegetarians. Most studies (apart from that conducted in experimental conditions and studies of recreational runners) included participants with 1-year minimum dietary adherence (Nebl *et al*, 2019; Remer *et al*, 1999). Draper (1993) only recruited participants who had elected to adopt their diets in adulthood and had not grown up as vegetarian (Draper and Lewis, 1993). This raises the question as to whether the length of dietary adherence affects iodine measures. Long-term vegetarians could be better at planning their diet adequately if receiving guidance from their parents from a young age or iodine intake could reflect reduced diet diversity and long-term dietary compliance.

Reduced dietary intake for those following vegan diets may reflect difficulties in accurately measuring dietary intake. Intake can be measured using various methods. The "gold standard" for estimating iodine intake is a dietary record or food diary inclusive of one weekend day (Serra-Majem *et al*, 2009). Seven included studies followed this methodology, additionally pairing food diaries with weighed or duplicate records (Allès *et al*, 2017; Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Nebl *et al*, 2019; Remer *et al*, 1999; Kristensen *et al*, 2015). Food diary measurements reflect recent intake; therefore, 10 days are recommended for iodine to account for food items that are rich in iodine but not regularly consumed (Bingham *et al*, 1995). Only two studies collected records exceeding this duration (Waldmann *et al*, 2003; Rauma *et al*, 1994).

The most frequent length of estimates was 4 days, which is acknowledged as an adequate length to record dietary intake (Bingham *et al*, 1995). Duplicate diaries are suitable for valuation of minerals such as iodine (National Institute of Health research, 2022d). This technique is useful for foods with iodine values not contained within food tables or composition data. For this reason, this technique is useful to assess the dietary iodine of those following vegan diets who may consume foods that are novel or not frequently eaten by the public.

Two studies used validated FFQs to estimate iodine intake (Sobiecki *et al*, 2016; Waldmann *et al*, 2003). FFQs are often designed to be specific to a nutrient of interest and aim to include food items contributing to intake. Both studies had developed FFQs to address intake of multiple micronutrients and were not iodine specific. As FFQs are a comprehensive list and not all foods can be contained, they are, therefore, limited to the listed items. It is unlikely that these studies addressed foods that largely contribute to iodine intake but are not regularly consumed such as seaweed or novel foods consumed by vegans. In addition, FFQs have been recognised to frequently overestimate iodine intake as supported by previous validation studies (Rasmussen *et al*, 2001).

For all studies, estimations of iodine intake were calculated using mean iodine concentration of foods and beverages provided by regional food composition tables or databases and are, therefore, country specific (Allès *et al*, 2017; Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Nebl *et al*, 2019; Sobiecki *et al*, 2016; Waldmann *et al*, 2003; Remer *et al*, 1999; Rauma *et al*, 1994). Estimates based on one summary statistic cannot account for variation in iodine content between food items across time, season, and geographic location—for example, the iodine content of milk, which also varies according to processing and product origin (O'Kane *et al*, 2018b). In vegan adults, the lowest intakes were recorded in Finland (29.0 ± 18.0 μg day^{-1}) (Rauma *et al*, 1994). Krajcovicová-Kudlácková (2003) discussed that Finish food tables tended to estimate lower iodine intake compared to British food tables (Krajcovicová-Kudlácková *et al*, 2003), and variation in this case probably represents geographical diversity between countries and food availability.

Waldmann (2003) created a database accounting for vegan food items regularly consumed in Germany (Waldmann *et al*, 2003), thus improving estimates. Four studies were conducted in the 1990s (Draper and Lewis, 1993; Lightowler and Davis, 1998; Remer *et al*, 1999, Rauma *et al*, 1994).

It is likely that food tables and databases have improved iodine content of foods. However, these methods lack iodine values for newly consumed food and products, particularly those gaining in popularity such as plant-based alternatives.

Adults following vegan diets had the largest consumption of plant-based milk alternatives. Bath *et al*. investigated the iodine concentration of milk alternatives available in the UK in 2015 and determined the concentration of unfortified milk-alternative drinks (median 7.3 µg kg^{-1}) to be significantly lower than the dairy milks analysed (median 438.0 µg kg^{-1}) (Beth *et al*, 2017). Those consuming alternative milks may not be aware of the lower contribution of plant-based milks to iodine and need to ensure intake from other sources.

The highest iodine intake was recorded for females following vegan diets, living in London (1448.0 ± 3879.0 µg day^{-1}), whose regular consumption of seaweed increased intakes to over six times the RNI (Lightowler and Davis, 2002). Five studies recorded seaweed consumption in vegan diets only, observing intakes close to, or over, the maximum tolerant level (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Waldmann *et al*, 2003; Kristensen *et al*, 2015). Seaweed is a naturally rich source of iodine, but the relative content is highly variable and can provide excessive quantities and, therefore, regular consumption is not recommended (Yeh, Hung, and Lin, 2014). Seaweed is not customarily consumed in the Western diet. However, it has recently become popular in UK food products as a whole food and functional ingredient (Bouga and Combet, 2015). For example, carrageenan is widely used in newly formulated vegan and vegetarian products. Manufacturers use it to replace gelatine, as it is derived from plant origin (Bouga and Combet, 2015). . Draper (1993) observed low iodine intakes in adults following vegan diets in London despite 95% recording regular consumption of seaweed or foods containing seaweed powder (Draper and Lewis, 1993).

While the iodine content of seaweeds is often high, it is not a food that is consumed in large quantities, hence the contribution towards dietary intakes is likely to be small and inconstant (Lightowler, 2009). Moreover, iodine content significantly differs between seaweed species consumed (Yeh, Hung, and Lin, 2015).

Voluntary fortification is present in most countries (IGN, 2019), yet very few manufacturers add fortified salt to food items and iodinated salt is not easily available to consumers. This appears to be true in the study conducted by Rauma (1994), where only one Finish vegan reported consuming iodised salt regularly (Rauma *et al*, 1994). Furthermore, Bath *et al.* (2014) conducted a shelf survey of five major chain supermarkets in the UK and found that iodized salt was only sold in 42% (32 out of 77) of shops and that the iodine content of fortified salt sold was low (11.5 ± 4.2 μg g^{-1}) (Bath *et al.*, 2014b). Draper (1993) noted the consumption of 'sea salt' in 95% of UK adults following vegan diets [Draper and Lewis, 1993). Although 'sea salt' and other 'specialty' salts such as Himalayan Sea salt contain iodine, the concentration is relatively small compared to iodised salts (Dasgupta, Liu, Dyke, 2008). Additionally, of two studies reporting iodised salt intake (Draper and Lewis, 1993; Rauma *et al*, 1994), neither identified having adjusted intakes to account for volatile iodine losses experienced during cooking (Rana and Raghuvanshi, 2013). Kristensen (2015) attempted to quantify the involvement of iodised salt by measuring reported sodium intake (Kristensen *et al*, 2015). Despite, the routine uses of iodised salt in Danish households, 55 out of 70 vegans failed to meet dietary recommendations for iodine (Kristensen *et al*, 2015). Low dietary intake in vegans in this study may be explained by reduced dietary sodium intake reported by vegan participants and infrequent consumption of salt-rich processed food items. Moreover, vegan ready meals are not always readily available from retailers.

Limitations of the study. In addition to the limitations highlighted above, it should be noted that the values recorded in the included studies tended to be skewed below the mean estimated population levels for UIC (**Supplementary Figure 1**) and intake (**Supplementary Figure 2**).

This would suggest that for most studies, the sample population was not wholly reflective of the general population. This is a challenge for such studies, as the cohort of individuals prepared to participate is often characterised by those with an interest either in their dietary choice or dietary control for health reasons. Accessing the wider public is much more difficult and a challenge that needs to be addressed in future studies.

There was some overlap with the previous systematic review, and we found that recent studies investigating iodine nutrition were relatively scarce. Further, it was necessary to combine groups, thereby oversimplifying dietary practice to enable comparison of studies. Lastly, there was a lack of values for contribution of specific food groups (e.g. supplements) and iodised salt.

4.6 Conclusion

Iodine deficiency remains a public health problem worldwide and is of concern following the "re-emergence" of iodine deficiency, especially in industrialised countries (Rayman and Bath, 2015). This review agrees with findings from the previous systematic reviews exploring this topic (Fields, Dourson, and Borak, 2005; Fields and Borak, 2009) confirming that vegans and vegetarians, living in industrialised countries, not consuming seaweed, or iodine-containing supplements, appear to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared to adults following less restrictive diets. The evidence suggests that the degree of vulnerability appears to be relative to the prevalence of deficiency at the national level. This review also highlights the variety of methodological issues associated with estimating iodine in unique dietary groups. In conclusion, further monitoring of iodine status in industrialised countries and research into improving the intake and status of vegan and vegetarian diets is required. Efforts need to be made to devise a means of safe iodine consumption whether by fortification of staple foods or iodised salt provision, in addition to information delivery intended for tolerable consumption of seaweed varieties. Lastly, nutrients frequently lacking in vegan and vegetarian diets should be routinely labelled on foods regularly consumed by these groups in order to highlight to those making these purchases that there is a need to consider the levels that are being consumed.

5. MANUSCRIPT 2

Eveleigh, ER, Zhou, M, Burdett, H, Hoang Nguyen, V, & Welham, SJM. (2022). Vegans and vegetarians living in Nottingham (UK) continue to be at risk of iodine deficiency. *Br. J. Nutr*, 1–46.

Author contributions can be found in **APPENDIX A.**

5.1 Abstract

Iodine is essential for thyroid hormone synthesis. Individuals adhering to vegan and vegetarian diets have been found to be vulnerable to iodine deficiency. Yet, iodine has not been monitored in these groups across time. This study aims to investigate iodine status, intake and knowledge in vegans, vegetarians, and omnivores and determine changes between 2016-17 and 2019.

Dietary intake (μg day^{-1}) was estimated by three-day food diaries (FD), and iodine food frequency questionnaires (FFQ). Urinary iodine concentration (UIC), analysed by ICP-MS, assessed iodine status according to World Health Organisation (WHO) criteria. Iodine knowledge was scored by an adapted questionnaire. IBM SPSS was used for statistical analysis.

Ninety-six adults (18-60 y) were recruited in October 2016-17 (vegans; 12, vegetarians; 5, omnivores; Nebl *et al*, 2019) and June 2019 (vegans; 7, vegetarians; 10, omnivores; 19). Median dietary iodine was below the Reference Nutrient Intake (RNI) for all groups. Vegans and vegetarians had the lowest iodine intake. Vegans had significantly lower iodine intake than omnivores (2016-17; 47.6 μg day^{-1} vs. 111.9 μg day^{-1}, 2019; 17.3 μg day^{-1} vs. 126.0 μg day^{-1}). Omnivores had the highest iodine status (2016-17; 79.4 μg L^{-1}, 2019; 72.4 μg L^{-1}), and vegans the lowest (2016-17; 31.2 μg L^{-1}, 2019; 12.2 μg L^{-1}). Iodine knowledge was poor but did not differ between dietary groups (2016-17; $P = 0.219$, 2019; $P = 0.532$).

Vegans and vegetarians continue to be at risk of iodine deficiency. Further, iodine intake in the UK is poor independent of dietary choice. Iodine education is needed along with, research into improving iodine nutrition at national level.

5.2 Introduction

Iodine is an essential micronutrient required to produce thyroid hormones, thyroxine (T4) and triiodothyronine (T3) (Zimmermann and Boelaert, 2015). Thyroid hormones are necessary for normal neuronal development, metabolic function, and growth throughout the lifespan (Zimmermann and Boelaert, 2015). Iodine deficiency occurs when physiological requirements are not met, and thyroid hormone synthesis is low (Ahad and Ganie, 2010). Deficiency can result in a series of clinical abnormalities termed 'iodine deficiency disorders' (IDD's) and is most obviously manifested with the appearance of a goitre, the enlargement of the thyroid gland (Ahad and Ganie, 2010). In pregnancy, risk of stillbirth, spontaneous abortion and other birth defects is increased in iodine deficient states (Bath and Rayman, 2015). Infants exposed to deficiency *in utero* are at risk of impaired cognitive development resulting in irreversible neurological damage, leading to cretinism in its most severe form (Ahad and Ganie, 2010; Bath and Rayman, 2015; Zimmermann and Boelaert, 2015). Coexisting deficiencies of micronutrients such as iron, selenium and vitamin A may further impair iodine absorption and thyroid hormone production (O'Kane *et al*., 2018a). Deficiency, attributed to insufficient dietary iodine intake, is recognised as a major public health problem (Kapil, 2007).

The World Health Organisation (WHO) recommends a Reference Intake (RI) of 150 µg day^{-1} for adults (>12 y), to optimise thyroid hormone production (typically requiring around 70 µg day^{-1}) (WHO, 2013; Zimmermann and Andersson, 2012). In the UK, a Reference Nutrient Intake (RNI) of 140 µg day^{-1} has been selected (DoH, 1991). Historically iodine deficiency was prevalent in the UK, with some regions experiencing endemic goitre (Vanderpump *et al*., 2011). Eradication began in the 1960s due to government campaigns encouraging milk consumption, and changes in farming practice resulting in production of milk with a higher iodine content (Bath and Rayman, 2012; 2018). For many years following intervention, intake was considered sufficient, but is now a recognised public health issue after mild iodine deficiency was detected in schoolgirls and pregnant women in 2014–15 (Bath *et al*., 2014a; Vanderpump *et al*., 2011).

More recently, iodine intake was recognised as of concern for UK adults following a secondary analysis of the UK National Diet and Nutrition Survey (NDNS) in 2018 (Derbyshire, 2018). Iodine intake estimates for males and females (aged 20-59 y) were recorded to be significantly lower than the current RNI. Young adults (aged 20-29 y) were recognised to be substantially more at risk than older adults (aged 30-59 y), with 15% of males and 17% of females falling below the Lower Reference Nutrient Intake (LRNI) for iodine. The LRNI for iodine is the quantity that is considered adequate for around 3% of the population who have low needs. Recent studies suggest that lack of information and knowledge regarding iodine may be greater in individuals at risk of iodine deficiency (Henjum *et al*., 2018; O'Kane *et al*., 2016a). Current trends in food avoidance and dietary restriction, particularly of meat and dairy, have been recognised as a factor contributing to lowered iodine intake (Public Health England, 2014). Individuals who have low knowledge and are not aware of the importance of adequate iodine intake, may be less well equipped to make dietary changes that permit them to meet their iodine requirements.

In the UK, the main sources of dietary iodine are cow's milk and dairy products (Bath and Rayman, 2016). Seafood, eggs, seaweed, and iodine containing supplements are also iodine rich (Bath and Rayman, 2016). The relative iodine content of foods commonly consumed in the UK are presented in **Table 5.1.**

Table 5.1. Average Iodine content of foods consumed regularly in the UK.

Food	Serving size (ml g^{-1})	Average iodine/portion (µg g^{-1})	Contribution of food groups to average daily iodine intake by NDNS (2016-17 to 2018-19) (%)
Milk and dairy products			
Cow's milk (semi skimmed)	200	50-100[1 2]	13[5]
Organic cow's milk (semi skimmed)	200	30-60[1 2]	NA
Yoghurt	150	50-100[1 2]	6[5]
Cheese	40	15[2]	3[5]
Fish and seafood			
Whitefish	120	230-390[2]	8[5]
Salmon	100	14[2]	NA
Tinned tuna	100	12[2]	NA
Prawns	60	6[2]	NA
Eggs, meat, and poultry			
Eggs	50	25[2]	9[5]
Meat and poultry	100	10[2]	9[5]
Plant-based			
Fortified alternative milk	200	53-57[3]	NA
Unfortified alternative milk	200	1-4[3]	NA
Nuts	25	5[2]	0
Bread	36	5[2]	3
Fruit and vegetables	80	3[2]	6
Nori seaweed	26	382[4]	NA

NA, Not applicable; [1]Actual iodine content subject to seasonal variation (winter=higher) and organic farming practices (organic=lower); [2]Data from The British Dietetic Association (BDA) Iodine Fact Sheet (Bath and Rayman, 2016); [3]Data from Bath *et al*., 2017; [4]Data from Nutritics database UK (Public Health England, 2021); [5]Data from NDNS Years 9-11 Descriptive statistics tables (19-64 y used) (Public Health England, 2020).

Despite being the primary source of iodine, milk consumption has reduced considerably over the last decade. Particularly in those aged 16-24 y, whose cow's milk consumption has declined rapidly in recent years (Mintel, 2019b). The proportion of people in this age group consuming cow's milk decreased from 79% to 73% between years 2018-19 (Mintel, 2019b). This decrease could reflect the growth and appeal of the alternative milk market in the UK. Food purchasing data from average UK households indicated an upwards trend in purchasing of alternative milks since 2014 (Department for Environment Food and Rural Affairs (DEFRA), 2022) (**Table 5.2**).

Table 5.2. Purchasing data and trends from UK households: Family Food 2018-19 Living Costs and Food Survey (LCFS) (Department for Environment Food and Rural Affairs (DEFRA), 2022).

Food item (g day^{-1})	2015-16	2016-17	2017-18	2018-19	Change from 2015-16 to 2016-17 (%)	Change from 2016-17 to 2017-18 (%)	Trend between 2017-18 and 2018-19
Cow's milk and milk products[1]	258.09	259.78	255.17	262.80	+2	+3	-
Semi-skimmed cow's milk	134.99	135.78	132.05	128.98	-4	-2	-
Yoghurt and fromage frais	27.55	28.52	26.88	28.41	-3	+6	-
Cheese	16.46	17.69	17.82	17.64	+7	-1	↗
Fish	20.64	19.86	19.79	20.81	+1	+5	-
White fish[2]	2.51	1.95	2.21	2.10	-16	-5	-
Eggs	0.28	0.28	0.28	0.3	+9	+6	↗
Dairy milk alternatives	5.86	7.15	9.38	9.85	+71	+5	↗

[1]Excluding cheese; [2]Fresh, chilled, or frozen, upward arrows show significant increases in UK purchasing between 2017-18 and 2018-19 ($P = < 0.05$); -, No significant change in purchasing trends 2017-18 and 2018-19 ($P = < 0.05$); *Statistical significance difference at ($P = < 0.05$).

Alternative milks such as soya, oat, and coconut are now regularly consumed, are very low in iodine and not regularly iodine-fortified (Bath *et al*., 2017). Although iodine rich, the contribution of fish and seaweed to iodine intake in the UK is likely to be small reflecting low national consumption (Public Health England, 2016). The iodine content of seaweed is highly variable and if not monitored in the diet, over-consumption could induce excess iodine intake (Leung and Braverman, 2014; Smyth and Karger, 2021; Yeh *et al*., 2014). Many countries implement mandatory or voluntary iodised salt legislation (Zimmermann and Andersson, 2012). Fortified salt used at household level provides additional dietary iodine and has been shown to alleviate deficiency (Wu *et al*., 2002). Routine salt iodisation is not present in the UK currently and access to iodised salt in supermarkets is low (Bath *et al*., 2014b). Even if table salt was fully iodised, it is unlikely to provide adequate dietary iodine as table salt only comprises a small proportion (15%) of dietary sodium consumed in the UK diet, and over half of intake (>60%), is provided by ready-made and processed foods (Action on Salt, 2020; Mhurchu *et al*., 2011).

Inadequate iodine intake has been observed in individuals who consume diets excluding iodine rich foods, principally dairy and/or fish (Eveleigh *et al*., 2020). For this reason, vegans and vegetarians are recognised as a subgroup with increased risk of iodine deficiency (Public Health England, 2014), as confirmed by recent research conducted in European nations including the UK, Germany, Finland, Norway, Spain and Switzerland (Elorinne *et al*., 2016; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Schüpbach *et al*., 2017; Waldmann *et al*., 2003).

Despite the increasing acceptance of vegan and vegetarian diets in the UK and the emergence of iodine deficiency, there is a lack of data regarding the level of iodine knowledge and whether good understanding of the challenges, allows individuals to account for iodine when dietary restrictions are implemented. The purpose of this study was to investigate iodine status, intake and knowledge in vegans, vegetarians, and omnivores and determine if changes were observed with time (between 2016 and 2019).

We hypothesised that iodine intake and status would be positively associated with knowledge and that deficiency would be greater in vegans and vegetarians lacking good understanding compared with omnivores. We additionally proposed that, since a greater array of specialist foods would be available in 2019 than in 2016, iodine intake and status would be improved in vegans and vegetarians in the more recent cohort.

5.3 Methods

5.3.1 Ethical approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Faculty of Medicine & Health Sciences Research Ethics Committee Nottingham University Hospitals (Ethics Reference No. BS02082016). Written informed consent was obtained from all subjects.

5.3.2 Design and recruitment

Students and staff of The University of Nottingham (n = 96) were recruited to the study at 2 separate time-points, 2016-17 and 2019. The first phase of recruitment was conducted between 24 Oct 2016 – 01 Jan 2017 and the second 16 Jun - 13 Nov 2019. The study protocol is outlined in **Figure 5.1**. The study was advertised using posters, leaflets and emails distributed throughout the university. Adults following vegan and vegetarian diets were recruited by social media advertisement circulated through university societies.

Participants matching the inclusion criteria were invited to attend a one-off session at 12.00 pm each day, whereby the experimental methodology was explained, and baseline data collected. To maintain anonymity, a unique participant number was randomly selected at baseline. During these sessions, individuals were provided with a participant information pack containing the study information sheet, three-day food diary (FD), weblink to an online food frequency questionnaire (FFQ), a sterile universal urine tube and an ID number unknown to researchers. Participation was optional and written informed consent was obtained.

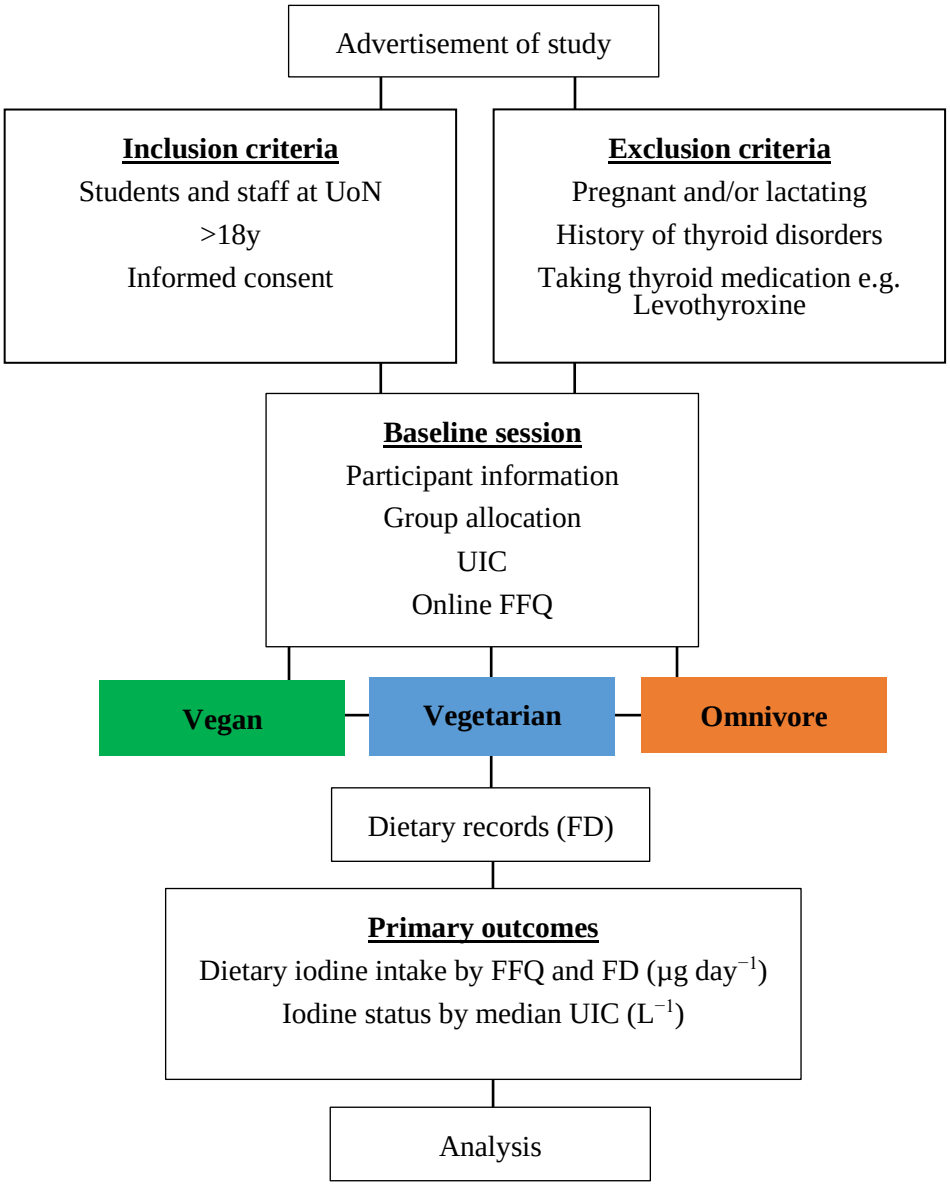


Figure 5.1. Flow chart of study protocol.
UIC, urinary iodine concentration; FD, food diary; FFQ, Food Frequency Questionnaire.

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5.3.3 Dietary grouping

Participants were categorized into three dietary groups: vegan, vegetarian and omnivore, based on responses to the online FFQ addressing current dietary preference and consumption of animal products in the past 6 months. Participants who reported no dietary restrictions relating to animal products were classified as omnivores. Participants who did not consume animal products of any form were classified as vegans. Vegetarians encompassed all descriptions of vegetarian diets and were those who consume milk, eggs and possibly fish (pescatarians) but not meat. The vegetarian group also comprised individuals who had recently (< 3 months) transitioned from vegetarian to a vegan diet.

5.3.4 Assessing dietary iodine intake

Dietary iodine consumption was assessed using an online FFQ and three-day FD introduced during baseline sessions. Adequate iodine intake was assessed using the current UK RNI of 140 µg day^{-1} and LRNI of 70 µg day^{-1} (DoH, 1991).

5.3.5 Food frequency questionnaire (FFQ)

The FFQ was developed using "Online surveys" (previously "Bristol Online Surveys"; (Online Surveys, 2022) to assess habitual dietary intake over the past 6 months and was based on the validated FFQ used in the Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC Oxford) study (EPIC Oxford, 2020). The FFQ addressed 45 different food items including sources of dietary iodine and goitrogenic foods (**Table 2.5**). Prior to study the FFQ was modified to address dietary preference and consumption of substitutes of specific foods that could be a potential source of iodine for those following vegan and vegetarian diets, such as alternative milk and dairy products. Frequently consumed food items, such as cow's milk, were listed in separate questions accounting for variations in serving sizes. Medium serving size was indicated using labelled food images employed by The National Diet and Nutrition Survey (NDNS) (Lennox *et al*., 2008; **Supplementary Figure 3**). For each food item, frequency categories were converted to daily iodine intake (µg day^{-1}). The category: "two to four times per week" was adjusted to three per week or equivalent to 0.4 servings per day.

It was assumed that those selecting the “Less than once or never” option for rare foods such as samphire, or animal products for vegans were not consumed within the past 6 months, thus, generating a value of 0.0. Food items were assigned iodine values per portion from an in-house database created using data from Nutritics 4.3 software and McCance and Widdowson's 'composition of foods integrated dataset (Public Health England, 2021; Nutritics, 2021).

5.3.5.1 Three-day food diary

Iodine consumption was measured by a three-day FD based on that used in the NDNS (Medical Research Council Collaborative Centre for Human Nutrition Research (MRC-HNR), 2008). Participants were asked to record estimated daily food and drink consumption, including descriptions of relative portion sizes, brand names of packaged items, home-cooked meal ingredients and supplement intake. Further questions addressed fluctuation from usual dietary patterns to establish if recorded intakes reflected that of a normal day. Participants were asked to complete the FD in the three consecutive days following recruitment sessions. To reduce disparity in diet patterns between the week and weekends, sessions were organised so that FD records contained at least one weekend day. If the consecutive days after recruitment did not contain a weekend, completion was postponed. Participants were asked to return completed FDs to accessible drop-off points. Nutritics 4.3 was used to estimate dietary intakes. Databases used were limited to include food values of UK foods only. Average portion sizes for items designated by Nutritics were selected if not specified by participants. It was assumed that, unless stated, all milk was semi skimmed non-organic cow’s milk, alternative milks were unfortified unless brand information or fortification status was specified, and salt added to meals was non-iodinated. Best estimates were made for vegan substitutes of food items not listed on Nutritics software using online information from retailers or back-of packet values. Recipes from the Vegan Society were used to calculate iodine values for vegan compound foods, such as cakes and biscuits, where there was no viable substitution in UK databases. All analysis considered edible portions for analysis and adjusted for cooking procedure when required. Where possible, Nutritics food codes with values for iodine were selected.

Iodine values were added manually using data from Nutritics if the selected food code was established from label based analysis. Nutritics outputs from FDs were used to calculate the average quantity (g) of iodine rich foods consumed and the contribution (%) of food groups to total iodine intake.

5.3.6 Assessing iodine status

5.3.6.1 Urinary iodine concentration (UIC)

Optional spot urine samples were collected to determine median UIC. Participants were asked to complete a 50 ml single spot urine sample during information sessions to reduce diurnal variation associated with estimates. Samples were centrifuged immediately after collection at 914 relative centrifugal force (RCF) for 5 minutes (Beckman GS-6R Refrigerated Centrifuge GS1M31) and supernatant frozen at -80ºC. Samples were defrosted overnight at 4°C. UIC was determined using inductively coupled plasma mass spectrometry (ICP-MS; ThermoFisher Scientific). Certified reference materials (Seronorm) were used as a control during analysis. Standards and samples were diluted 1:10 with Milli-Q H_20, transferred to analysis tubes and analysed in triplicate.

5.3.6.2 Classification of status

The WHO criteria were used to assess iodine status using UIC expressed as a median with inter-quartile range (IQR) (WHO, 2007). Groups with median with UIC <100 μg L^{-1} were considered "sufficient" and those with values <100 μg L^{-1} were considered "deficient". Relative levels of deficiency were classified as: 50-99 μg L^{-1} Mild, 20-49 μg L^{-1} Moderate and <20 μg L^{-1} Severe.

5.3.7 Iodine knowledge and demographic data

The FFQ additionally collected demographic information which may contribute to iodine status, including ethnicity, educational level, degree classification, employment status, smoking status, and alcohol consumption. Participants were also asked to complete 7 questions addressing iodine knowledge and factors influencing iodine nutrition, generating a total possible score of 17. Questions were modified from studies previously investigating iodine knowledge in the UK (O'Kane *et al*., 2016). Negative marking was used, and a point was deducted for each incorrect answer, this was so that individuals were discouraged from selecting all listed responses.

Iodine knowledge was considered ‘poor’ if scores were 5 or below, ‘fair’ if between 5-10 and ‘good’ if above 10.

5.3.8 Anthropometric data

All measurements of height (cm) and weight (kg) were self-recorded as part of the FFQ. Body Mass Index (BMI: weight/height^2, kg/m^2) was determined and classified according to WHO assessment (WHO, 2021).

5.3.9 Assessing under-reporting

FD estimates were used to assess under-reporting. FFQs could not be used as energy intake was not estimated. Schofield equations were applied to determine the ratio between basal metabolic rate (BMR) or energy expenditure (EE) and actual reported intake (EIrep:EE) using age and weight (kg) as a reference (Black, 2000). To identify records of poor validity, participants were classified according to EIrep:EE into under-reporters, acceptable reporters and over-reporters using the Goldberg Cut-off (Black, 2000; Goldberg and Black, 1998). Activity levels were not assessed during this study therefore a lower activity factor used to calculate the estimated energy requirement. A physical activity level (PAL) of 1.5 was used for adjustment (Statista, 2018b). This value describes a population with a low level of daily physical activity (not sick, disabled, or elderly). The calculations used to determine cut-offs are presented in **Equation 5.1**.

$$\textbf{95\% Confidence Limits} = \textbf{PAL} \times \exp(\pm 2 \times ((S/100)/\sqrt{n})$$

PAL= 1.5

n = Participant no. (45)

S = Factor accounting for variation in estimated intake (EI), BMR and PAL was estimated by:

$$S = \sqrt{[CV^2_{wEI}/d + CV^2_{wB} + CV^2_{tP}]}$$

Where,

$\mathbf{CV_{wEI}}$ = Within-subject variation in EI in our cohort (28%)

d = Number of days of dietary assessment (3 days)

$\mathbf{CV_{wB}}$ = Variation in repeat BMR measures (9%)

$\mathbf{CV_{tP}}$ = total variation in PAL (15%)

Equation 5.1. Assessing under-reporting to determine under and over-reporting in dietary surveys.

The coefficient of variation for within-individual variation for our cohort was determined as 18%. Coefficient of variation parameters (9% and 15%) were taken from those generated by Black (Black, 2000), and have been accepted as suitable for use in the Goldberg equation. Confidence intervals at 95% were applied, those with EIrep:EE of 1.41-1.71 were considered as acceptable reporters. Participants with values <1.41 were under-reporters and >1.71 as over-reporters.

5.3.10 Statistical analysis

Data analysis was performed using IBM SPSS Statistics V22.0. A significance of P = < 0.05 (two-tailed) was selected for all statistical analysis. Normality of the data was assessed using the Shapiro Wilkes test for normality. UIC and dietary iodine intake values were not normally distributed, therefore, medians are reported. Kruskal-Wallis H tests with Dunns post hoc tests were performed to compare intake and status where groups were two or more. Spearman's rank correlation was used to determine relationships between continuous data. Pearson's Chi-square test was used for comparison between categorical variables. The Bonferroni test for adjustment was used for correction. Sample size estimates were calculated based upon data obtained from a previous report which provided mean and standard deviation measurements for vegans and omnivores (Draper *et al.*, 1993). The effect size was recorded as 106 µg Day^{-1} with a population standard deviation of 91 µg Day^{-1} and a recruitment bias of 1. For a power of 80% and an α-error of 5% the sample size was calculated as a minimum of 24 (12 per group) for vegans and omnivores using the "ClinCalc" online calculator (Clincalc, 2021).

5.4 Results

5.4.1 Study population

Descriptive characteristics of participants (n = 96) are listed in **Table 5.3**. Two individuals in 2019 (one male and one female) had recently transitioned onto a vegan diet and were considered as vegetarians. All dietary groups were predominantly composed of females (84%). The average BMI for each dietary group was lower than the UK population (Statista, 2018b), but, within the healthy range (18.5 - 24.9) for most participants.

Exceptions included six overweight female omnivores (BMI; overweight - 25.0 - 29.9), as well as two female vegetarians and one female vegan who were below the normal range of BMI (17.0, 16.6 and 18.2 respectively). BMI values were significantly lower in vegetarians than omnivores in 2016-17 ($P = 0.019$). In 2019 there was no difference in BMI between dietary groups ($P = 0.066$). We were unable to assess differences in gender, nationality, and qualifications by Chi Squared as the minimum expected count was under 5 for these variables.

Table 5.3. Participant Characteristics (n = 96).

		2016-17			2019		
		Vegans (n = 12)	**Vegetarians (n = 5)**	**Omnivores (n = 43)**	**Vegans (n = 7)**	**Vegetarians (n = 10)**	**Omnivores (n = 19)**
Gender (*n*)[1]	Male	0 (0.0)	0 (0.0)	7 (16.3)	3 (42.9)	1 (10.0)	5 (26.3)
	Female	12 (100.0)	5 (100.0)	36 (83.7)	4 (57.1)	9 (90.0)	14 (73.7)
Age (y)[2]		21.5 (10.0)	22.0 (3.0)	21.0 (32.0)	23.0 (12.0)	23.0 (18.0)	25.0 (29.0)
BMI (kg m^2)[2]		21.0 (6.0)	19.4 (5.6)	22.0 (18.8)	20.4 (5.6)	21.7 (7.3)	22.9 (14.5)
Birth region (*n*)[1]	United Kingdom (UK)	11 (92.0)	5 (100.0)	24 (55.8)	4 (57.1)	7 (70.0)	9 (47.4)
	Europe	1 (8.0)	0 (0.0)	2 (4.7)	3 (42.9)	1 (10.0)	2 (10.5)
	East and Southeast Asia	0 (0.0)	0 (0.0)	8 (18.6)	0 (0.0)	2 (20.0)	6 (31.6)
	Western Asia	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)
	West Africa	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
	Caribbean	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
	Did not disclose		0 (0.0)	8 (18.6)	0 (0.0)	0 (0.0)	0 (0.0)
Education (*n*)[1]	BSc BA or lower	9 (75.0)	4 (80.0)	20 (46.5)	2 (28.6)	5 (50.0)	4 (21.1)
	PhD or MD	3 (25.0)	1 (20.0)	8 (18.6)	4 (57.1)	5 (50.0)	9 (47.4)
	Staff	0 (0.0)	0 (0.0)	5 (11.6)	0 (0.0)	0 (0.0)	1 (5.3)
	Did not disclose	0 (0.0)	0 (0.0)	10 (23.3)	1 (14.3)	0 (0.0)	5 (26.3)

[1]Values are *n* and (%); [2]Values are median (range); Normality was assessed by Shapiro-Wilk (P = 0.001); *Significance between dietary groups assessed by Kruskal-Wallis (P = < 0.05).

5.4.2 Dietary intake

Other specific diets were followed by three vegans in 2016-17, two of which, avoided starch and bread/flour products and one described having a lactose intolerance. Lactose intolerance was reported by one omnivore in 2019.

The prevalence of under-reporting was high in both years with 73% of participants recording an EIrep:EE ratio < 1.41. All male participants were classified as under-reporters, but under-reporting did not differ between dietary groups with vegans, vegetarians and omnivores having similar occurrence (2016-17; 75%, 50% and 68%, P = 0.830). In 2019, under-reporting was more prevalent, with 100% of vegans being classed as under-reporters compared to 71% of vegetarians and 86% of omnivores (P = 0.608). In both years, vegetarians had the largest proportion of acceptable reporters (2016-17; 50%, 2019; 28%), whilst none of the vegan participants in 2019 had values within this range. Over-reporting was low in both years, with none recorded in 2019 compared to 2 omnivores and 1 vegan in 2016-17.

Energy intake did not differ between dietary groups (2016-17; P = 0.438, 2019; P = 0.802, **Table 5.4**. We were unable to stratify by gender due to low numbers of males in our cohort. However, with the inclusion of males, average energy intake was greater than current estimates of the UK population for females (1632 kcal) but not males (2313 kcal) for most dietary groups (British Nutrition Foundation, 2021b). In both years, vegans had the greatest daily energy intake (2016-17; 1755.3 kcal, 2019; 1656.0 kcal). There was no relationship between energy and iodine intake by FD or FFQ in 2016-17 or 2019 (FD; r = 0.085, P = 0.610; FFQ; r = 0.044, P = 0.796 and FD; r = 0.067, P = 0.786; FFQ r = 0.012, P = 0.960).

Average daily intake of macronutrients by dietary group are presented in **Table 5.4**. In both years, vegans consumed significantly greater quantities of fibre than omnivores (2016-17; P < 0.001, 2019; P = 0.030). In 2016-17, polyunsaturated fat intake was significantly higher in vegans compared to omnivores (P = 0.011).

Table 5.4. Average daily macronutrient intake of vegans, vegetarians and omnivores by diet group in years 2016-17 and 2019 provided by Food Diary (FD) estimates.

	2016-17				2019			
	Vegans (n = 10)	**Vegetarians** (n = 4)	**Omnivores** (n = 27)	**P**	**Vegans** (n = 4)	**Vegetarians** (n = 6)	**Omnivores** (n = 11)	**P**
Energy (kcal)	1755.3 (1474.4)	1512.0 (1540.8)	1651.6 (3064.5)	0.438	1656.0 (1376.0)	1654.6 (1198.6)	1587.9 (1696.0)	0.802
Protein (g)	65.1 (102.8)	55.5 (27.9)	66.8 (186.8)	0.633	59.1 (37.0)	56.2 (45.8)	85.7 (84.9)	0.081
Fat total (g)	62.2 (100.0)	64.3 (46.6)	67.2 (142.6)	0.973	69.2 (69.9)	67.1614 (62.2)	64.1 (66.3)	0.806
Saturated (g)	14.6 (30.4)	20.3 (15.7)	23.3 (45.7)	0.139	22.3 (36.0)	20.3 (19.9)	21.0 (33.5)	0.995
Monosaturated (g)	23.3 (37.3)	19.9 (11.3)	21.0 (56.0)	0.747	18.8 (6.4)	22.7 (24.6)	20.6 (19.4)	0.739
Polyunsaturated (g)	18.6 (32.6)	9.1 (17.3)	10.2 (27.4)	0.012*	13.1 (12.5)	10.8 (24.8)	9.5 (10.9)	0.199
Carbohydrates (g)	237.4 (246.2)	184.0 (160.9)	198.3 (332.7)	0.268	202.5 (239.7)	206.9 (141.7)	176.1 (267.4)	0.525
Added sugars (g)	102.6 (111.5)	96.8 (68.0)	69.6 (181.1)	0.266	63.4 (110.0)	107.1 (84.1)	60.54 (105.0)	0.493
Fibres (g)	37.1 (46.9)	29.5 (16.4)	16.9 (33.5)	< 0.001	34.3 (24.6)	25.5 (26.4)	19.5 (25.6)	0.030*
Alcohol (ml)	2.4 (29.6)	4.1 (69.5)	0.0 (64.0)	0.128	0.3 (47.3)	0.0 (13.4)	0.0 (6.1)	0.528

Normality was assessed by Shapiro-Wilk (P = 0.001); *Significance between dietary groups assessed by Kruskal-Wallis (P = < 0.05).

5.4.2.1 Dietary iodine

Median iodine intake estimated by FFQ, and food diaries are shown in **Figure 5.2**. Intakes derived from the FFQ were higher (P = 0.020) and displayed larger variation than those provided by FD's.

Median iodine intake was below the RNI (150 µg day^{-1}) for all dietary groups in 2016-17 (vegans; 47.6 µg day^{-1}, vegetarians; 68.8 µg day^{-1} and omnivores; 111.9 µg day^{-1}) and 2019 (vegans; 17.3 µg day^{-1}, vegetarians; 71.4 µg day^{-1} and omnivores; 126.0 µg day^{-1}). The RNI was not achieved by any vegetarians in 2016-17 or vegans in 2019. Median values for vegans and vegetarians in 2016-17, and vegans in 2019, were below the LRNI of 70 µg day^{-1}. Average iodine intake in vegans and vegetarians were lower than current estimates of the UK population of 98 µg day^{-1} for women of childbearing age (19 - 49 y) and 106 µg day^{-1} for adults (19 - 64 y). Inadequate intake was more frequent in those following vegan and vegetarian diets than omnivorous diets. In both years, median intake was numerically lower in vegan and vegetarian groups and was significantly lower in vegans compared with omnivores both years (2016-17; P = 0.032, 2019; P = 0.001).

In both years FFQ median dietary iodine intake for vegetarians and omnivores wase above the RNI (2016-17; 202.9 µg day^{-1}, 299.6 µg day^{-1}, 2019; 230.0 µg day^{-1}, 221.9 µg day^{-1}). Dietary iodine intake for vegans did not meet the RNI (2016-17; 107.0 µg day^{-1}, 124.9 µg day^{-1}). Intakes between dietary groups displayed a similar trend as observed in food diaries. In 2016-17, median values were significantly lower in vegans compared to omnivores (P < 0.001). This trend was not seen in vegetarians, whose intake in 2016-17 were similar to those of omnivores (P = 1.000). In 2019, no significant differences in iodine intake were observed between dietary groups (P = 0.356).

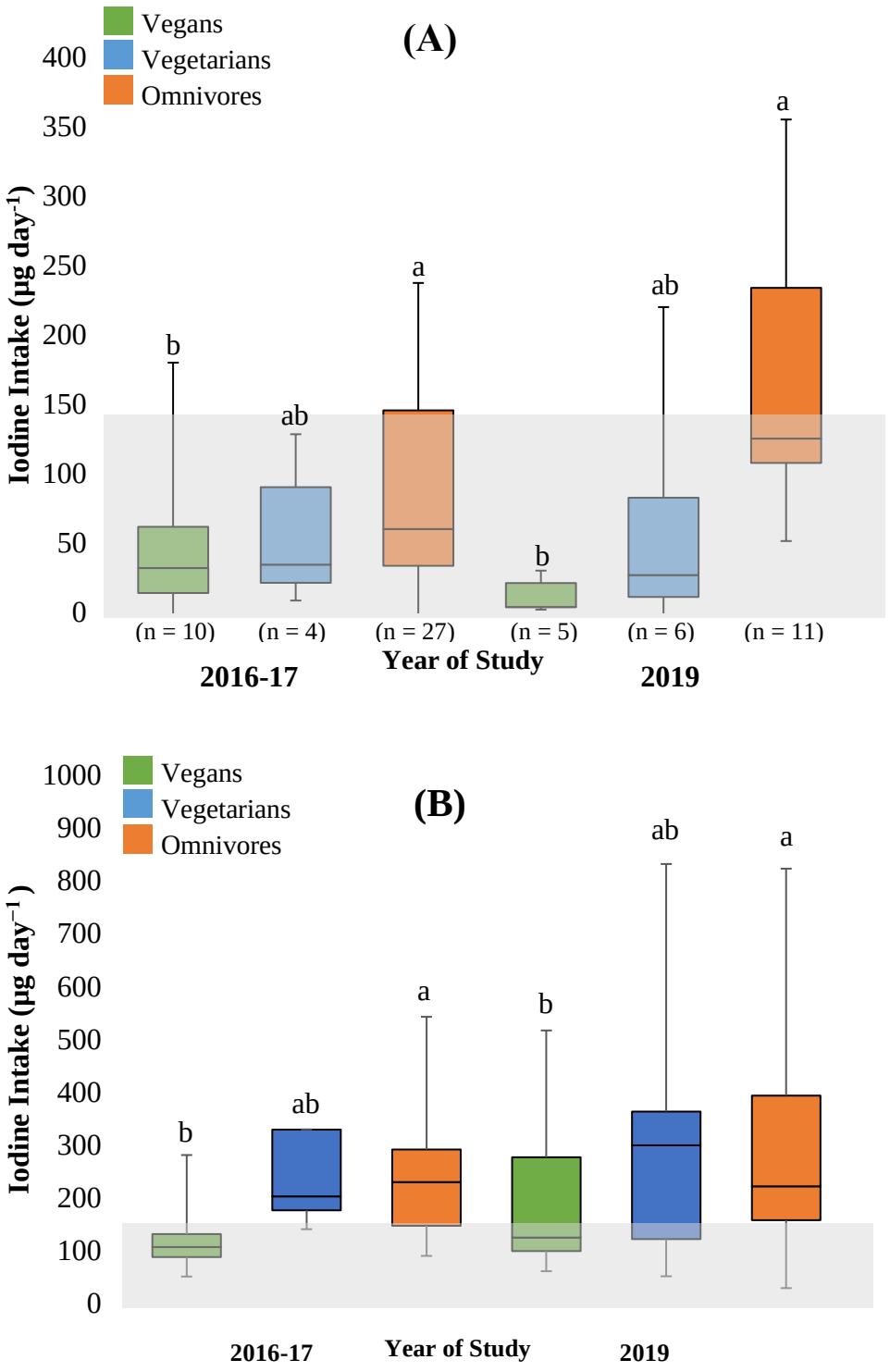


Figure 5.2. Estimated dietary iodine intake by (A) Food Diaries (FD) and (B) Food Frequency Questionnaire (FFQ) for vegans, vegetarians, and omnivores. Shaded areas represent intakes below the Reference Nutrient Intake (RNI) of 140 µg day^{-1}. Different letters (a and b) represent significant differences among dietary groups whereby a > b, ab = a, ab = b, a > c, b > c and ab > c (P = <0.05) (Kruskal-Wallis).

We assessed the average daily consumption of foods potentially contributing to iodine intake using data from food diaries (**Table 5.5**). In both years, omnivores had the greatest consumption of cow's milk, dairy products, and eggs. In 2019, fish and seafood were predominantly consumed by omnivores. Seaweed was only consumed as a supplement by two omnivores and is not considered a regular dietary source of iodine. In 2016-17, alternative milk, alternative milk product and seaweed consumption was significantly greater in vegans than omnivores ($P = 0.001$, $P = 0.016$ and $P = 0.040$). No significant differences in iodine rich food consumption were observed between dietary groups for either year when non-consumers were removed from analysis.

The major sources of dietary iodine in each cohort are displayed in **Table 5.6.** In 2016-17, the food groups contributing the largest proportion to iodine intake in omnivores was cow's milk (21%) and eggs (10%). In 2019, cow's milk (24%) and fish and seafood (12%) were major sources of dietary iodine. Cow's milk was a key source of iodine in the diets of vegetarians in both years rising from 10% in 2016-2017 to 14% in 2019. Eggs were also a good source of iodine in the diets of vegetarians in 2016-17 but not 2019 (7% and 0% respectively).

Plant-based sources were the major providers of iodine for vegans. Fruit and vegetables being the predominant source (21% and 27%), followed by breads, grains, and pulses (5% and 22%). Unlike cow's milk and dairy products, alternative milk (1%) and alternative milk products (0%) did not greatly contribute to dietary iodine, in any dietary groups, in either year.

Table 5.5. Daily consumption (g) of possible sources of iodine in the diets of vegans, vegetarians, and omnivores in years 2016-17 and 2019. Median (range).

	Vegans		**Vegetarians**		**Omnivores**		**P**	
	2016-17 (n = 10)	**2019** (n = 4)	**2016-17** (n = 4)	**2019** (n = 5)	**2016-17** (n = 27)	**2019** (n = 10)	**2016-17**	**2019**
Consumers								
Cow's milk	-	-	146.7 (98.3 - 195.0)	186.7 (40.0 - 358.0)	120.0 (10.0-413.3)	198.3 (6.17 - 476)	0.905	0.838
Dairy products	-	-	62.3 (21.2 - 103.3)	36.84 (4.67 - 89.7)	56.3 (1.7 - 201.7)	87.3 (10.0 - 199.0)	0.913	0.174
Fish and seafood	-	-	50.0 (33.3 - 66.7)	66.7 (40.0 - 93.3)	37.3 (3.3 - 100.0)	40.0 (18.3 - 206.7)	0.734	0.303
Eggs	-	-	30.0 (20.0 - 40.0)	62.5 (50.0 - 75.0)	21.0 (3.3 - 73.3)	66.7 (18.3 - 206.7)	0.724	1.000
Alternative milks	170.0 (46.7 - 471.7)	268.7 (120.7 - 306.7)	136.7 (11.7 - 270.0)	116.7 (66.7 - 116.7)	125.0 (11.6 - 350.0)	199.5 (161.7 - 237.3)	0.613	0.074
Alternative milk products	22.5 (14.0 - 120.0)	51.7 (50.0 - 53.3)	98.3 (90.0 - 106.7)	467.5 (41.7 – 93.3)	41.7 (13.3 - 166.7)	-	0.614	1.000
Seaweed	2.2 (1.7 - 2.7)	-	-	-	-	0.7 (0.0 - 0.67)	NA	NA

Table continued…

	Vegans		Vegetarians		Omnivores		P	
	2016-17 (n = 10)	**2019** (n = 4)	**2016-17** (n = 4)	**2019** (n = 5)	**2016-17** (n = 27)	**2019** (n = 10)	**2016-17**	**2019**
Inclusive of Non-Consumers								
Cow's milk	-	-	49.2 (0.0 - 195.0)	40.0 (0.0 - 358.0)	60.0 (0.0 – 413.3)	161.8 (0.0 - 476.0)	0.549	0.458
Dairy products	-	-	10.6 (0.0 - 103.3)	30.0 (0.0 - 89.7)	41.6 (0.0 - 201.7)	56.5 (0.0 - 199.0)	0.405	0.325
Fish and seafood	-	-	16.7 (0.0 - 66.7)	0.0 (0.0 – 93.3)	0.0 (0.0 - 100.0)	21.6 (0.0 - 71.7)	0.849	0.613
Eggs	-	-	10.0 (0.0 - 40.0)	0.0 (0.0 – 75.0)	20.0 (0.0 - 73.3)	19.2 (0.0 - 206.7)	0.358	0.519
Alternative milks	168.3 (0.0 - 471.7)	194.7 (0.0 - 306.7)	74.2 (0.0 - 270.0)	66.7 (0.0 - 116.7)	0.0 (0.0 - 350.0)	0.0 (0.0 - 237.3)	0.001*	0.101
Alternative milk products	17.0 (0.0 - 120.0)	25.0 (0.0 - 53.3)	45.0 (0.0 - 106.7)	0.0 (0.0 – 93.3)	0.0 (0.0 - 166.7)	0.0 (0.0 - 0.0)	0.009*	0.068
Seaweed	0.0 (0.0 - 2.67)	0.0 (0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.6)	0.042*	0.638

NA, at least one variable was continuous; -, No consumers included Normality was assessed by Shapiro-Wilk (P = 0.001); *Significant between dietary groups for nominal data assessed by Chi Squared and continuous by Kruskal-Wallis (P = < 0.05).

In 2016-17, the iodine contribution of alternative milks was significantly greater in vegans and vegetarians (P = < 0.001, P = 0.016). Alternative meats provided significantly greater contribution to dietary iodine in vegans compared with omnivores (P = 0.018). Seaweed supplied a significantly greater iodine contribution to the diets of vegans compared to omnivores (P = 0.040). Multivitamin supplements provided significantly greater iodine to the diets of vegans compared to omnivores and vegetarians (P = < 0.001, P = 0.033).

In both years, the contribution of fruit and vegetables to dietary iodine was greater for vegans than omnivores (P = 0.001, P = 0.029). In 2019, breads, grains and pulses and drinks contributed significantly greater iodine to the diet of vegans than omnivores (P = 0.011, P = 0.007). Iodised salt was only consumed by one female participant in 2016-17 following an omnivorous diet.

Table 5.6. Percentage (%) iodine intake from different food groups in vegans, vegetarians, and omnivores in years 2016-17 and 2019. Inclusive of both consumers and non-consumers. Median percentage (range).

Percentage Iodine Intake (%)								
	Vegans		Vegetarians		Omnivores		P	
	2016-17 (n = 10)	2019 (n = 4)	2016-17 (n = 4)	2019 (n = 5)	2016-17 (n = 27)	2019 (n = 10)	2016-17	2019
Food Group								
Cow's milk	-	-	9.5 (0.0 - 65.0)	14.0 (0.0 - 74.9)	21.0 (0.0 - 65.0)	23.5 (0.0 – 51.6)	0.697	0.704
Dairy products	-	-	0.0 (0.0 - 0.0)	3.3 (0.0 - 58.0)	0.0 (0.0 – 41.0)	1.8 (0.0 – 43.8)	0.130	0.708
Fish and seafood	-	-	0.9 (0.0 - 2.2)	0.0 (0.0 - 15.8)	0.0 (0.4 - 85.0)	12.0 (0.0 - 47.5)	0.573	0.184
Eggs	-	-	6.8 (0.0 - 14.4)	0.0 (0.0 - 28.0)	9.8 (0.0 - 35.7)	11.7 (0.0 – 29.3)	0.512	0.343
Alternative milks	0.6 (0.0 - 16.7)	0.6 (0.0 - 3.6)	0.3 (0.1 - 38.3)	0.0 (0.0 - 1.4)	0.0 (0.0 - 60.4)	0.0 (0.0 - 1.9)	0.001*	0.129
Alternative milk products	0.0 (0.0 - 3.4)	0.0 (0.0 - 36.3)	0.0 (0.0 - 0.0)	0.0 (0.0 – 6.8)	0.0 (0.0 - 1.3)	0.0 (0.0 - 0.0)	0.210	0.114
Meat and poultry	-	-	-	-	5.3 (0.0 - 63.9)	6.7 (0.0 - 16.3)	NA	NA
Alternative Meat	1.6 (0.0 - 51.6)	4.3 (0.0 - 24.8)	4.4 (0.0 - 16.6)	0.0 (0.0 - 0.9)	0.0 (0.0 – 11.3)	0.0 (0.0 - 0.0)	0.007*	0.057

Table continued…

	Vegans		Vegetarians		Omnivores		P	
	2016-17 (n = 10)	**2019 (n = 4)**	**2016-17 (n = 4)**	**2019 (n = 5)**	**2016-17 (n = 27)**	**2019 (n = 10)**	**2016-17**	**2019**
Food Group								
Fruit and vegetables	21.3 (2.9 - 76.9)	26.8 (7.7-69.4)	9.1 (8.1 - 21.1)	8.8 (1.1 -93.6)	5.9 (0.5 - 33.6)	2.7 (1.0 - 8.0)	0.001*	0.025*
Breads, grains, pulses etc.	5.0 (1.9 - 36.9)	21.9 (17.8 - 45.6)	6.0 (0.8 - 27.3)	2.7 (0.0 - 12.5)	2.8 (0.0 - 20.0)	3.0 (0.0-8.0)	0.105	0.012*
Snacks, crisps, cakes and nuts/seeds	3.6 (0.0 - 58.9)	11.4 (0.0 - 37.8)	2.6 (1.3 – 18.8)	5.7 (0.0 - 28.5)	2.7 (0.0 - 16.8)	1.3 (0.0 - 35.0)	0.253	0.633
Drinks	0.3 (0.0 -58.9)	0.3 (0.0 -26.1)	0.0 (0.0 - 36.4)	0.0 (0.0 - 0.4)	0.0 (0.0 - 2.0)	0.0 (0.0 - 0.0)	0.172	0.009*
Salt and spices	0.0 (0.0 - 2.7)	0.1 (0.0 - 0.5)	0.3 (0.0 - 0.5)	0.0 (0.0 - 0.8)	0.0 (0.0 - 5.5)	0.0 (0.0 – 2.6)	0.371	0.869
Iodised salt	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 50.0)	0.0 (0.0 - 0.0)	0.588	1.000
Seaweed	0.0 (0.0 – 79.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 8.0)	0.042*	0.638
Supplements	2.0 (0.0 - 86.6)	0.0 (0.0 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 0.0)	0.0 (0.0 - 42.0)	0.001*	0.638

Normality was assessed by Shapiro-Wilk (P = 0.001); *Significant between dietary groups by Kruskal-Wallis (P = < 0.05).

5.4.3 Supplement usage

Supplement usage was determined by FFQ. Overall, 42% of participants recorded consumption of a dietary supplement, either daily, weekly or sporadically. The most frequently used supplement for all groups was B12 (27%), followed by non-iodine-containing multivitamin formulations (17%) and Vitamin D (12%). Multivitamins containing iodine were consumed by 12% of participants providing an average of 140 µg day^{-1} to dietary iodine. Seaweed supplements kelp and/or kombu was consumed by two omnivores in 2019, providing an average iodine intake estimate of 1541 µg day^{-1}.

When comparing supplement use between years the only significant difference observed was that vegans supplemented to a greater extent than omnivores in 2016-17 ($P = 0.001$). The iodine content provided by all consumed supplements differed according to dietary group in 2016-17 ($P = 0.013$) but not 2019 ($P = 0.910$). The iodine content of supplements consumed by vegetarians in 2016-17 was significantly lower than those consumed by omnivores ($P = 0.022$). Pearson's Chi-square was used to assess iodine-containing supplement consumption (providing > 20 µg day^{-1}) by dietary group.

A significantly greater proportion of vegetarians consumed iodine-containing supplements in 2016-17 ($P = 0.009$) but not 2019 ($P = 0.942$). Whilst supplement usage was recorded by participants in FFQs, only 4 participants recorded consumption in their FD.

5.4.4 Iodine Status

Iodine status assessed by UIC is presented in **Figure 5.3**. Nine participants did not provide a urine sample (2016-17; n = 8, 2019; n = 1). In both years, omnivores had the greatest UIC (2016-17; 79.4 µg L^{-1}, 2019; 72.4 µg L^{-1}), followed by vegetarians (2016-17; 32.7 µg L^{-1}, 2019; 13.4 µg L^{-1}) and the lowest were recorded in vegans (2016-17; 31.2 µg L^{-1}, 2019; 12.2 µg L^{-1}). In 2016-17, omnivores had significantly greater median UIC than vegans (P = 0.003) but not vegetarians (P = 0.083). A similar trend was observed in 2019, where omnivores had significantly higher median UIC than vegans and vegetarians (P = 0.029, P = 0.044). The greatest variation in UIC (IQR) was observed for omnivores in 2016-17 and 2019 (76.3 - 100.9 µg L^{-1}), compared to vegans (30.5 - 36.5 µg L^{-1}) and vegetarians (33.3 - 43.6 µg L^{-1}).

None of the samples given by vegan participants in either years, or vegetarians in 2016-17, were above the cut off for iodine adequacy (100 µg L^{-1}). Vegans and vegetarians had median values signifying moderate deficiency (20-49 µg L^{-1}) in both years studied.

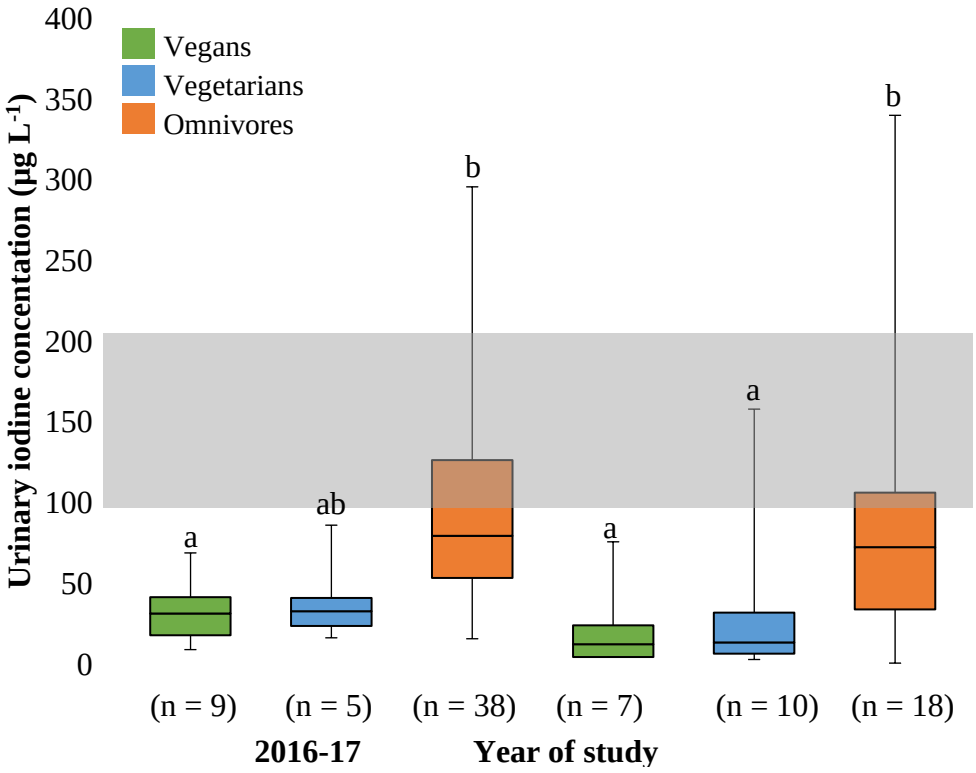


Figure 5.3. Iodine status of vegans, vegetarians, and omnivores by urinary iodine concentration (UIC). Shaded areas show the proportion of participants within the World Health Organisation (WHO) adequate range for median UIC (100 µg L^{-1}). Bars show variation (minimum and maximum). Different letters (a, b and c) represent significant differences among dietary groups, whereby a > b, ab = a, ab = b, a > c, b > c and ab > c (P = 0.05) (Kruskal-Wallis Test).

The relationship between iodine intake from iodine rich food sources and UIC, independent of dietary group, was assessed (**Table 5.7**). In 2016-17, UIC increased with greater intake of cow's milk and dairy products (r = 0.512, P = 0.030, r = 0.530, P = 0.013). This was not apparent in 2019 (r = -0.173, P = 0.612, r = – 0.056, P = 0.863)

Consumption of milk alternatives and milk alternative products had no relationship with UIC in both years (2016-17, r = 0.093, P = 0.722, r = 0.454, P = 0.160, 2019, r = -0.575, P = 0.136, r -0.400, P = 0.600). Many varieties of alternative milk were fortified with vitamins and minerals; however, fewer than 12% (2/17) of varieties were fortified with iodine. Iodine-fortified alternative milks provided an average of 47.6 μg per 200 ml portion of iodine (compared to 85 μg per 200 ml cow's milk) (Bath *et al*., 2017).

Table 5.7. Correlation coefficients between urinary iodine concentration (UIC) and sources of dietary iodine provided by Food Diary (FD) estimates, thyroid related micronutrients, and iodine knowledge.

	UIC (μg L^{-1})			
	2016-17 (n = 52)	**P**	**2019** (n = 35)	**P**
Food Group (g day^{-1})				
Cow's milk	0.512	0.030*	-0.173	0.612
Dairy products	0.530	0.013*	0.056	0.863
Fish and seafood	-0.025	0.936	0.100	0.797
Eggs	-0.246	0.258	-0.357	0.385
Alternative milk	0.093	0.722	-0.575	0.136
Alternative milk products	0.454	0.160	-0.400	0.600
Thyroid Related Micronutrients				
Iron	-0.311	0.025*	-0.024	0.888
Selenium	-0.136	0.335	0.192	0.262
Vitamin A	-0.318	0.022*	-0.078	0.653
Iodine Knowledge				
No. correct symptoms identified associated with deficiency	-0.037	0.814	-0.292	0.084
No. of correctly identified iodine rich food sources	-0.129	0.423	0.060	0.727
Total incorrect answers to iodine knowledge questions	-0.037	0.816	0.216	0.206
Total iodine knowledge score	-0.050	0.751	0.230	0.178

*Significant between dietary groups assessed by Spearman's correlation (P = < 0.05).

5.4.5 Iodine knowledge

Iodine knowledge was poor in both years, with median knowledge scores of 3 (2016-17) and 5 (2019) reported out of a total of 17. There was no difference in total iodine knowledge scores between dietary groups (2016-17; P = 0.219, 2019; P = 0.532).

Most participants stated awareness of the importance of adequate dietary iodine intake. However, more than half of participants 'did not know' or were unable to correctly identify a health condition related to iodine deficiency. The most common symptom identified was goitre or enlargement of the thyroid gland, followed by cretinism. Other symptoms recognised included: tiredness, being sensitive to cold or weight gain.

A considerable selection of participants could not recognise the main food sources of iodine in the UK diet (dairy and white fish). Many participants perceived foods such as leafy green vegetables and oily fish to be iodine rich. Overall, there was no significant difference in knowledge of iodine rich foods between different dietary groups. However, vegetarians in 2016-17 had significantly better knowledge of the role of cow's milk as a good source of iodine (P = 0.007).

Other demographics such as age were assessed as predictors of iodine knowledge. Younger participants tended to have lower iodine knowledge scores in 2016-17 (r = 0.409, P = 0.004). However, no relationship existed between age and iodine knowledge in 2019 (r = 0.409, P = 0.529).

5.5 Discussion

To the best of our knowledge, this is the first study to monitor iodine in different dietary groups at two time points. In support of our hypothesis and conclusions from previous research (Eveleigh *et al*., 2020), we show that achievement of adequate iodine intake and status remains problematic for those following vegan and vegetarian diets. Our research also indicates that many university students may be vulnerable to iodine deficiency regardless of dietary practice.

In 2014, the Scientific Advisory Committee on Nutrition (SACN) reported on the current state of iodine nutrition in the UK, identifying vegans and vegetarians as a sub-group with increased risk of iodine deficiency (Public Health England, 2014). Since publication, only one study has specifically addressed iodine in these diets in the UK (Fallon and Dillon, 2020).

5.5.1 Dietary intake

Our results confirm that those not consuming animal-derived foods continue to have lower dietary iodine intake. Although our study contains a relatively small, unbalanced sample of vegans and vegetarians in both years of study and may be subject to a high prevalence of underreporting, estimated average dietary intake for vegans and vegetarians were below the LRNI of 70 µg day^{-1} using FD data. This was consistent with current data comparing iodine between dietary groups in the UK (Davey *et al*., n.d.; Draper *et al*., 1993; Fallon and Dillon, 2020; Lightowler and Davies, 2002, 1998), Europe (Allès *et al*., 2017; Elorinne *et al*., 2016; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Henjum *et al*., 2018a; Krajcovicová-Kudlácková *et al*., 2003; Kristensen *et al*., 2015; Menzel *et al*., 2021; Nebl *et al*., 2019; Rauma *et al*., 1994; Remer *et al*., 1999; Schüpbach *et al*., 2017; Waldmann *et al*., 2003; Weikert *et al*., 2020), and the US (Leung *et al*., 2011). When iodine requirements are not met, thyroid hormone synthesis is disrupted (Ahad and Ganie, 2010). Persistent mild-moderate deficiency may put strain on the thyroid gland, stimulating TSH-independent growth and thyroid autonomy (Chung, 2014). Individuals experiencing thyroid autonomy at a young age may continue to have altered thyroid function in later life, even if adequate iodine intake is resumed (Chung, 2014). Vegans and vegetarian diets that do not provide adequate iodine are a concern given that meat-free diets are often frequented by women of childbearing age (18-34 y) (Statista, 2019c). Although there is limited recent evidence amongst UK vegans for the presence of low iodine compromised pregnancies (Dineva *et al*., 2020b), the rapidly expanding population comprising an increasing proportion of those less attentive to dietary requirements increases the number of individuals at greater risk of iodine deficiency in pregnancy and associated consequences for the developing foetus (Dineva *et al*., 2020b).

Adequate iodine intake is essential for those considering future pregnancy, as intra-thyroidal stores must be maximised before conception to facilitate foetal growth and neurological development (Zimmermann, 2011a, 2011b, 2009). Removing the possibility of pregnancy, those with increased risk should be shielded from the consequences of poor iodine nutrition. In both years of study, individuals following vegan diets had very low iodine intake (2016-17; 47.6 µg day^{-1}, 17.3 µg day^{-1}). This is of significant concern as dietary intake <50 µg day^{-1} can potentiate the development of endemic goitre and hypothyroidism (Kapil, 2007). Although, clinical manifestations are rare in Western nations experiencing mild-to-moderate iodine deficiency (UK), studies have observed meat-free diets be associated with the occurrence of IDDs (Brooks and Post, 2014; Shaikh *et al*., 2003; Yeliosof and Silverman, 2018). In both years of study, all dietary groups had median iodine intake below the current RNI (140 µg day^{-1}), highlighting the difficulty in achieving adequate iodine intake on any diet (Krela-Kaźmierczak *et al*., 2021).

Various challenges are associated with dietary assessment methods including accurate recall, memory retrieval, and recording duration (Shim *et al*., 2014; Thornton and Villamor, 2016). We selected two dietary methods to measure iodine intake, a 3-day FD and iodine specific FFQ. FDs typically underestimate usual dietary intake, whereas FFQs frequently overestimate (Næss *et al*., 2019; Y *et al*., 2018). In both years, the FFQ indicated that median dietary intake was above the RNI for vegetarians and omnivores, while FD estimates were below the RNI. The disparity in estimates may be due to different periods of recording (6 months vs. 3 days). Additionally, the FFQ covered the top food sources of iodine in the UK (cow's milk, dairy, eggs, fish, and seafood), possible non-animal sources applicable for vegans, and foods that are rarely consumed such as seaweed. The FFQ did not include other possible sources of iodine e.g. fruits, vegetables, grains etc. that did contribute to dietary intake for all groups. Shortening the FFQ to provide limited food choices may have resulted in an overestimation of items that are not frequently consumed or perhaps iodine rich food items were not covered in the time covered by FDs (Næss *et al*., 2019). Due to methodological challenges associated with FFQ we are unable to establish if iodine intake over time (6 months) is indeed adequate in our cohort.

We have focused on FD estimates for our analysis as these records reflect recent iodine intake and are likely to correspond more closely to UIC (WHO, 2007).

In Western diets, iodine is incorporated from adventitious sources such as iodine feed supplements and iodophors used in the dairy industry along with differing food practices between producers (Bath *et al*., 2012). Hence, cow's milk and milk products are good sources of iodine. One portion of cow's milk (200 ml) may provide an average iodine concentration up to around 85.4 μg, although this is subject to seasonal variation (Bath *et al*., 2012). In the current study, cow's milk and dairy products were positively associated with UIC in 2016-17, suggesting their importance as sources of dietary iodine. Contrary to recent findings (Dineva *et al*., 2020b; O'Kane *et al*., 2018b), consumption of cow's milk exhibited no relationship with UIC in 2019. This finding may be explained by lower cow's milk intake in our cohort paralleling recent UK data which shows that national dairy product consumption has reduced, particularly amongst younger people (Mintel, 2019a). Much of our study cohort comprised young adult females, a group in whom milk reduction is particularly noticeable (Mintel, 2019a).

In the UK, there has been a sizable increase in the availability and popularity of non-dairy alternative milks (e.g. soya, oat etc.). Research by Mintel identified that adult household consumption of alternative milks increased from 14% in 2017 to 23% in 2019 (Mintel, 2019a). Displacement of iodine containing cow's milk may increase the risk of deficiency. Label-based analysis conducted in 2015 revealed that alternative milks available in the UK had an average iodine content that is 1% to 5% of that of cow's milk, unless fortified (Bath *et al*., 2017). We found that milk alternative and milk alternative product consumption had no relationship with UIC in 2016-17 or 2019. Our findings did not match those observed in UK woman of childbearing age who were consumers of soya milk and a recent analysis of the NDNS (2014–17) which indicated that iodine nutrition was significantly lower in those who regularly consumed milk alternatives (Bath *et al*., 2014a; Dineva *et al*., 2020b). This study also showed intake of alternative milks to be significantly greater in vegans than vegetarians and omnivores. In our study, milk alternative consumption was not limited to vegan participants and were consumed by all dietary groups.

Iodine fortified milks were not greatly consumed, in either cohort, perhaps due to cost or low availability in the UK or lack of iodine awareness at the time of study. In 2016-17, the iodine contribution of alternative milks appeared to be significant in the diets of vegans and vegetarians despite having a low iodine content. The iodine intake of vegans and vegetarians in our study was so low that the proportion contributed by foods that are not considered good sources of iodine (alternative milks, alternative meats, fruit, vegetables, breads, grains, pulses and drinks) appeared significant even though the absolute quantity was small. Given that it is likely that vegan and vegetarian influence on the food sector will continue to grow, individuals relying on alternative milk products to meet iodine requirements must be advised to select fortified varieties or to consume iodine from other food sources or supplements.

Milk is often consumed daily, whereas fish and seafood are not consumed as frequently and may not always be included in dietary records. Apparent elevated consumption of fish amongst vegetarians in 2016-17 was due to the inclusion of a number of pescatarians in this group. In both years, average consumption of fish (for consumers) was greater than average fish consumption among adults in the UK of between 30-60 g per week (Public Health England and the Food Standards Agency, 2019). However, we did not see the expected positive relationship between UIC and fish and seafood consumption, presumably due to the low number of consumers across all groups. Fish intake in the UK is low, and thus may not serve as a good source of iodine for the general population. Barriers to fish intake include cost, availability, cooking knowledge and palatability (Kranz *et al*., 2017).

The UK currently does not have a universal iodised salt programme (Bath *et al*., 2014b). Only one omnivore in 2016-17 recorded consuming iodised salt in 3-days of records, contributing largely to iodine intake (61%). Despite using iodised salt, the intake of this individual was below recommended intake of 150 µg day^{-1} (119.3 µg day^{-1}). Vegan and vegetarian dietary choices are often linked with engagement in healthier behaviours and have been found to have lower salt intake compared to other groups (Clarys *et al*., 2014). Iodised salt is not routinely available from supermarkets for public purchasing, and varieties that are offered tend to be expensive compared to regular table salt (Bath *et al*., 2014b).

Participants were not specifically asked to record salt added to meals and consequently, as suggested by previous work (Condo *et al*., 2015), estimates of salt intake are likely to be low.

None of our participants indicated suffering from celiac disease, however we cannot rule out the presence of undiagnosed disease. Iodine absorption in those with celiac disease is impaired compared with a healthy population and so those with disease coupled with restriction of iodine rich foods may further exacerbate deficiency (M *et al*., 2021). Specific diagnoses of celiac disease were beyond the scope of this study, but the likelihood of a significant impact of undiagnosed disease on our findings is low.

5.5.2 Supplements

In regions where no universal iodised salt coverage exists, iodine supplementation is particularly useful for prevention of deficiency (Bath *et al*., 2014b; Untoro *et al*., 2010). Supplement use was widely adopted in vegan groups in our study, yet most consumed supplements were non-iodine containing. The most frequently used supplement for all groups was B12 (27%), followed by, non-iodine-containing multivitamin formulations (17%). Since restrictive diets increase the risk of nutritional deficiencies (B12, Vitamin D, Zinc, Fatty acids etc.) (Davey *et al*., 2002; Medawar *et al*., 2019), individuals may consume micronutrient complexes over concerns for dietary adequacy. One participant, an omnivorous male in 2019, had dietary intake above the criteria for iodine excess (>300 µg day^{-1}) according to food diary data (WHO, 2007), likely owing to consumption of a diet rich in cow's milk, dairy products, eggs and fish alongside daily use of iodine-containing micronutrient supplements. Improved awareness of iodine containing supplements to populations not consuming iodine rich foods is required.

Seaweed is a very rich and sustainable source of iodine. The iodine content of seaweed species can vary between 60 µg 100 g^{-1} to 624500 µg 100 g^{-1} (dry weight) (Cherry *et al*., 2019). Currently, seaweed is not recommended to improve iodine due to potential adverse effects relating to over-consumption (Zimmermann and Andersson, 2012), with regular intake of seaweeds providing >45 µg g^{-1} of iodine shown to compromise thyroid function (Desideri *et al*., 2016).

Despite this, research has shown low-level seaweed supplementation to improve status of iodine-insufficient individuals in the UK and Europe (Draper *et al*., 1993; Kristensen *et al*., 2015; Lightowler and Davies, 2002, 1998; Waldmann *et al*., 2003). Seaweed has been suggested as a possible source of iodine for vegans (Cherry *et al*., 2019), but has been shown to frequently contribute to excessive iodine intake (Eveleigh *et al*., 2020). In the present study, seaweed supplements did provide an additional 1541 µg day^{-1} to the dietary intake of two omnivores. Values at this level would exceed the upper tolerable limits of iodine and could lead to the development of alternative thyroid disorders (Sá Monteiro *et al*., 2019). Seaweed products are becoming more widely accepted in the UK (Bouga and Combet, 2015). To prevent excess associated with seaweed consumption products should be routinely monitored and their iodine content disclosed. Additionally, the risks involved with supplementing seaweeds should be communicated.

5.5.3 Iodine status

Despite low sample sizes, the present study aligns with existing studies signifying that UK adults, particularly those following vegan and vegetarian diets, are at risk of iodine deficiency (Davey *et al*., 2002; Draper *et al*., 1993; Fallon and Dillon, 2020; Lightowler and Davies, 2002, 1998). The iodine status of omnivores was significantly greater than vegans in both years and vegetarians in 2019. The UIC values for all dietary groups in our study were lower than those of the UK population. Nationally representative data collected in accordance with years of our study (2016-17 - 2018-19) recorded median UIC of 98 µg L^{-1} for women of childbearing age (19 - 49 y) and 106 µg L^{-1} for adults (Public Health England, 2016). However, omnivorous participants presented values signifying mild deficiency and both vegans and vegetarians had values within the criteria for moderate deficiency in 2016-17, and severe in 2019. Worryingly, this result is indicative of a time related decline in iodine status. Aligning with national trends, whereby, UIC averages fell between years 2014-2019 in both adults (3%), and women of childbearing age (9%) (Public Health England, 2016).

UIC is the internationally recognised criteria for measuring population iodine status (WHO, 2007). Spot samples are criticised for their inability to precisely detect mild to moderate iodine deficiency (Median UIC >50 μg L^{-1}) due to diurnal variation in UIC (Als *et al*., 2000; Andersen *et al*., 2001), which are lowest between 08.00-11.00 am and slowly increase after 12.00 pm, before peaking 4-5 hours after feeding. Our study was strengthened by concurrent collection of spot samples. By noon most participants would have consumed a meal, hence, UIC values would be above baseline. UIC has been found to be significantly lower in non-breakfast consuming individuals (Als *et al*., 2000). Given that numerous studies have concluded that breakfast skipping is widespread among young adults at universities (Sprake *et al*., 2018), this may have contributed to lower UIC in our study.

5.5.4 Iodine knowledge

Sufficient iodine knowledge is positively correlated with iodine nutrition with iodine intake and status (Garnweidner-Holme *et al*., 2017; O'Kane *et al*., 2016). Our study was populated by university students and staff; therefore, most participants were of a high education level. We found no difference in total iodine scores between the dietary groups, suggesting that dietary practice was not a predictor of iodine knowledge in this cohort. Limited research exists investigating the difference in dietary knowledge between vegans, vegetarians and omnivores. Iodine knowledge scores were lower than that recorded for UK females (2.1 (sd 0.8) out of a possible 8) (O'Kane *et al*., 2016), and was lower in younger participants in 2016-17. This may reflect the stage of education, such that first year undergraduate students may be less aware of the role of iodine in the diet, but this was not addressed in our study. Iodine awareness in general was low, with most participants being unable to identify a health condition related to iodine deficiency. Our findings also indicated that misconceptions exist in our population regarding which foods are iodine rich. Many selected leafy green vegetables and oily fish as good sources of iodine. Awareness of foods contribution to iodine varied by dietary group. A larger proportion of vegetarians in our study were able to correctly identify cow's milk as a useful iodine source, which did not translate to greater dietary intake. Understanding the role of cow's milk in iodine provision varies across studies.

In the UK, 16% of respondents showed good understanding and Australia 9%, whilst this rose to 47% in a Norwegian cohort (Charlton *et al*., 2010; Henjum *et al*., 2018b; O'Kane *et al*., 2016). Other foods rich in iodine (such as white fish and yogurt) had variable responses between dietary groups. Iodine knowledge may not translate to behaviour change in more restrictive dietary groups, for example, it is unlikely that strict vegans will decide to consume animal-products products based on iodine content. Our results suggest that public health strategies are needed to improve public awareness of iodine and good sources of iodine for those not consuming cow's milk, dairy, white fish or eggs need to be communicated, in addition to choosing foods that are fortified with iodine.

5.5.5 Energy Intake

We found no significant association between energy and iodine intake, however, in both years of study, average daily energy intake was below the current UK recommendations for weight maintenance (female; 2000 kcal, male; 2500 kcal) despite most participants recording BMIs within the healthy range (Statista, 2018b). In 2016-17, vegetarians had BMI values that were significantly lower than omnivores. However, in our current study average energy intake (kcal) did not differ between dietary groups (2016-17; $P = 0.438$, 2019; $P = 0.802$). Lowered energy intake may be attributed to high prevalence of underreporting in our study. The incidence of underreporting ranges between 18-54% in dietary studies (Macdiarmid and Blundell, 1998). In our study, the rate of underreporting was much greater (73%). This finding could be attributed to common determinants of misreporting. Our sample was largely female, and women tend to report energy intake to be significantly lower than daily recommendations (Macdiarmid and Blundell, 1998). We did not record physical activity levels as part of our study therefore EI:EE cut offs are likely to be inaccurate. Misreporting of iodine containing foods may have impacted our collected results. Healthy foods (fruit and vegetables) are often over reported, and females classed as under-reporters have been shown to consume significantly lower levels of foods rich in iodine, including cow's milk, dairy products, eggs and fats (Bingham *et al*., 1995).

5.5.6 Study limitations

There are few validated FFQs specifically assessing iodine intake in western or UK populations, of which none are tailored for vegans (Combet and Lean, 2014; Condo *et al*., 2015; Rasmussen *et al*., 2001). Despite our FFQ being based on that used in the EPIC study, which has been extensively validated (European Prospective Investigation into Cancer and Nutrition (EPIC) Oxford, 2020). The FFQ used in our study was not validated following modifications and so inaccuracies may occur due to difficulties distinguishing between categories. The Nutritics software, used to analyse FDs, uses food-tables to estimate average intake and cannot account for variability in iodine content within food (Bath *et al*., 2012). The iodine content of foods is not adjusted per season to constitute changes in content throughout the year (Bath *et al*., 2012). Cow's milk iodine concentration is highest in winter and since our data was collected in different seasons, winter 2016-17 and summer 2019, the data may be subject to seasonal variation (Bath *et al*., 2012). The seasonal variation in cow's milk iodine intake does not affect individuals who select non-dairy milks or are non-consumers of milks in general. Additionally, many manufacturers of vegan products cannot accurately provide measures of iodine (Lightowler and Davies, 2002).

Median UIC is the principal method for assessing population iodine status, as up to 90% of absorbed iodine is excreted in the urine. Several factors may influence UIC measured by spot samples, including daily variation in the iodine content of recently consumed foods and circadian rhythms (Als *et al*., 2000). Moreover, UIC varies by recent fluid intake as UIC is expressed per volume of urine (Vejbjerg *et al*., 2009). We were unable to account for fluid intake as creatinine was not measured and many participants did not record fluid intake within FDs.

Finally, inclusion of pescatarians and individuals who had recently transitioned onto a vegan diet as part of the "vegetarians" dietary group may not be reflective of the restrictions included in these groups. To retain sample size even vegans and vegetarians with low dietary adherence (i.e. occasional consumption of cow's milk/ dairy) were included into analysis. Lastly, most participants were students and so our cohort is therefore likely to be highly motivated and well-educated.

5.5.7 Conclusion

Vegans and vegetarians are a subgroup at increased risk of iodine deficiency. Regardless of dietary choice, the exclusion or substitution of iodine rich animal-products appears to act as a barrier to achieving iodine recommendations. Individuals following restricted diets should be encouraged to select iodine containing supplements or fortified foods. At policy level, mandatory fortification of products mimicking cow's milk may be beneficial given the popularity of these foods and potential for them to be a useful vehicle to improve iodine intake. Formal education focusing on providing accurate and reliable information to vulnerable groups (vegans, vegetarians, and young women) should be considered at national level. Further monitoring and assessment of the consequences of lowered iodine intake in individuals implementing strict dietary choices is required.

6. MANUSCRIPT 3

Eveleigh, ER, Coneyworth, L, Craigon, J, & Welham, SJM. (2023). Adoption of a short-term (4-week) vegan diet as part of 'Veganuary' significantly reduces saturated fatty acid (SFA), B12, and iodine intake in omnivorous individuals. *Suitable for submission in the European Journal of Nutrition.*

Author contributions can be found in **APPENDIX A.**

6.1 Abstract

Global campaigns promoting veganism are becoming popular. We aimed to evaluate the effect of a short-term (4-week) vegan diet, as part of 'Veganuary', on nutrient intake and status. Motivation for voluntary vegan diets and micronutrient knowledge was also addressed. Data were collected at baseline and post-intervention. Dietary intake were estimated by food frequency questionnaires (FFQs). Urinary iodine concentration (UIC), analysed by ICP-MS, measured iodine status by World Health Organisation (WHO) criteria. Free T4 (fT4) and Thyroglobulin (Tg) were measured by enzyme-linked immunosorbent assay (ELISA). Micronutrient knowledge and motivation were scored by questionnaires. IBM SPSS and Genstat were used for statistical analysis. One hundred and fifty-four UK adults (18-60 y) participated (2019, n = 81; 2020, n = 73). Intervention groups included vegetarians (VegV) and omnivores (OV) pledging to Veganuary. Controls were vegans (VV) and omnivores (OO) continuing their usual diet. Short-term (4-week) vegan diets significantly decreased the intake of saturated fatty acids (SFA), B12, and iodine in omnivorous participants, whereas thiamine increased from baseline to end in VegV and OV groups. UIC and age- and sex-adjusted I/Creat did not differ from baseline to post-intervention in samples provided in the morning, afternoon, or evening. Micronutrient knowledge was low and motivation to follow a vegan diet varied. Short-term vegan diets significantly decrease nutrient intake in omnivores. Individuals pledging to Veganuary would benefit from nutritional advice and/or supplementation. Micronutrient intake and knowledge in the UK need to be addressed urgently.

Motivations to vegan pledges may influence nutrient intake. Further investigation into the impact of following short-term vegan diets is needed.

6.2 Introduction

Vegan diets are typically defined by the absence of animal products and are predominantly plant-based (Phillips, 2005). Their popularity has increased in recent years and in 2022, 2,016,600 people in the UK reported their dietary preference to be vegan (YouGov, 2022). Motivations to implement vegan diets have been widely studied and include religious, ethical, environmental, or social reasons, along with improvement of health or animal welfare (De Backer and Hudders, 2014; Fox and Ward, 2008; Kerschke-Risch, 2015; MacInnis and Hodson, 2021; Mathieu and Dorard, 2016; North *et al*., 2021; Rosenfeld and Burrow, 2017). Health improvement is the top reason for reducing animal intake for those who do not consider themselves full-time vegans, whereas full-time vegans tend to have ethical motivations (De Backer and Hudders, 2014; MacInnis and Hodson, 2021; Rosenfeld and Burrow, 2017).

Short-term vegan diets may be more appealing and potentially more realistic than full-time veganism due to the flexible nature of dietary intake and focus on food inclusion rather than restriction (De Backer and Hudders, 2014). Worldwide, there is increasing interest in campaigns that promote temporary or short-term removal of animal products from the diet such as 'Meat-free Mondays' or 'Veganuary' (De Backer and Hudders, 2014; Veganuary, 2022). In 2021, more than 500,000 people worldwide signed up for the 'Veganuary' campaign and pledged to follow a vegan diet for one month (Veganuary, 2022).

Well-planned vegan diets can be useful to improve health and minimise the progression of chronic disease states and are now accepted by the British Dietetic Association (BDA) and other societies worldwide to provide an adequate nutrient supply (BDA, 2017; Dietitians Association of Australia, 2019). However, any diet that excludes certain food groups may pose a greater risk for micronutrient deficiencies (Derbyshire, 2018; Engel *et al*., 2018; García-Morant *et al*., 2020; Kristensen e*t al*., 2015; Malik *et al*., 2020; Schüpbach *et al*., 2017).

Those excluding animal-derived foods (meat, fish, milk, and eggs), which are rich sources of essential micronutrients such as vitamin B12, calcium, zinc, iron, and vitamin D (Damayanti *et al*., 2018; Gilsing *et al*., 2010; Pawlak *et al*., 2013; Rizzo *et al*., 2016; Selinger *et al*., 2019), and including those vital for thyroid hormone synthesis such as iodine, selenium, and vitamin A (Eveleigh *et al*., 2022; Fallon and Dillon, 2020; Groufh-Jacobsen *et al*., 2020; Krajcovicová-Kudlácková *et al*., 2003; Leung *et al*., 2011; Rauma *et al*., 1994; Yeliosof and Silverman, 2018), may significantly compromise their intake. The bioavailability of micronutrients from plant-derived foods is often lower than for animal products due to the presence of anti-nutritional factors that reduce or inhibit absorption (Platel and Srinivasan, 2016), thereby further compromising status. In addition, vegan food products imitating animal products may not yet offer comparable micronutrient profiles, are not regularly fortified, and may not provide the food matrix permitting nutrients to easily be absorbed (Alcorta *et al*., 2021; Bath *et al*., 2017.; Sethi *et al*., 2016; Nicol *et al*., 2022; Tso and Forde, 2021; Vanga and Raghavan, 2018).

Poorly planned long-term vegan diets that do not replace critical nutrients sourced from animal products may lead to deficiencies in essential micronutrients. Clinical deficiency states resulting in end-stage diseases are relatively infrequent in the UK, however, “subclinical deficiency” can occur when intakes are less than the dietary reference values (DRV) (The Nutrition Society *et al*., 2019). The severity of deficiency depends upon the micronutrient that is diminished and the availability of bodily stores (The Nutrition Society., 2019). Potential micronutrient deficiencies can be recognised using dietary data provided by methods such as food diaries (FD), food frequency questionnaires (FFQ), weighed food records, and 24h diet recalls (Bingham *et al*., 1995; Román-Viñas *et al*., 2017; Serra-Majem *et al*., 2009; Shim *et al*., 2014), along with biomarkers of status within the blood, breast milk, and/or urine (Als *et al*., 2000; Demers and Spencer, 2002; Dold *et al*., 2017; Karcz and Królak-Olejnik, 2021; Koulouri *et al*., 2013; Pearce and Caldwell, 2016; Tanaka *et al*., 2002).

Research into the effects of short-term vegan diets on micronutrient nutrition is limited and mostly focused on temporary vegan diets for weight loss (Brown *et al*., 2022; Rogerson *et al*., 2018). One intervention study assessed the influence of a 4-week vegan diet on cardiovascular disease (CVD) outcomes and micronutrient intake in sedentary young adults (Rogerson *et al*., 2018). This study noted that those following a vegan diet for the month had significant reductions in essential micronutrients including iodine and vitamin B12 despite having the support of trained nutritional professionals. This raises the question as to whether individuals can adequately plan a short or longer-term vegan diet to meet micronutrient requirements without specific nutritional guidance, particularly when nutrition knowledge of micronutrients, such as iodine, in the UK, is low (Eveleigh *et al*., 2022; O'Kane *et al*., 2016).

Similarly, data modelling studies have demonstrated that individuals exchanging animal foods for alternative plant substitutes are likely to have a lower intake of vitamin B12, riboflavin, zinc, iron, iodine, and calcium (Salomé *et al*., 2021; Tso and Forde, 2021). Hypothetical reference diets created using population data to compare changes in micronutrients when moving from an omnivorous diet to either a flexitarian, vegetarian or vegan diet, show that diets reliant on plant foods (vegan diets for example) provide significantly lower quantities of vitamin B12 and zinc (Tso and Forde, 2021). These studies additionally found that micronutrient intakes differ considerably within diets (e.g. vegan) simply due to variations in dietary patterns (Gallagher *et al*., 2022). Dietary patterns describe the amounts, proportions, frequency, and diversity of foods, drinks, and nutrients consumed as part of an individual's habitual diet (Gallagher *et al*., 2022). Therefore, it would be useful to assess the variability in nutritional choice in individuals who choose to follow a temporary vegan diet and make use of plant-based meat and dairy substitutes.

There is yet to be an intervention study investigating the influence of short-term vegan diets on micronutrient nutrition in individuals who choose to change their diet voluntarily. In this study, we evaluated the effect of following a short-term (4 weeks) vegan diet on micronutrient intake and status in UK adults.

We review the change in food consumption between dietary groups before and after pledging to a vegan diet as part of 'Veganuary'. We address the motivations, attitudes, and perceptions that may influence the decision to adhere to vegan diets in the short-term. We hypothesised that those following short-term vegan diets would have lowered micronutrient intake, attributed to changing dietary composition and exclusion of animal products when compared to dietary groups not changing their diet. We additionally hypothesised that the decline in micronutrient intake would be less severe for individuals who were already vegetarian compared with omnivores on the basis that vegetarians may have a better understanding of nutritional requirements as they already have some experience of dietary transition. Moreover, we predicted that biomarkers of status (in the blood and urine) would not significantly change throughout the study.

6.3 Subjects and Methods

UK-wide recruitment was conducted in November-December 2019 and 2020. Flyers and email advertisements were used for those living in Nottinghamshire in 2019. In both years, social and traditional media were used to publicise the study nationally. In 2020, due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/COVID-19) pandemic, all recruitment was conducted online. Criteria for inclusion were adults aged 18–60 years living in the UK. Those recruited either were changing their current diet to follow a vegan diet for 4 weeks as part of the 'Veganuary' pledge or were continuing their current diet (e.g. vegetarian, omnivore, etc.). Individuals who were already following a vegan diet were recruited to act as a control.

The exclusion criteria included those who did not provide consent, pregnant or lactating women, presence of a thyroid disorder, taking thyroid medication or a history of thyroid problems. All participants gave informed consent online before the study. Consent and applicability were assessed by researchers according to study criteria. The study was conducted per the Declaration of Helsinki and recent amendments. Ethical approval was obtained from the faculty of medicine and health sciences research ethics committee (FMHS REC ref no 391-1909). Following acceptance, participants were provided with a unique participant identification number for further correspondence to prevent bias.

A flow diagram of the study methodology is depicted in **Figure 6.1**. The study protocol was adapted from that used for the 2019 cohort to allow online participation during the COVID-19 pandemic. Changes to data collection will be further outlined in the sections below.

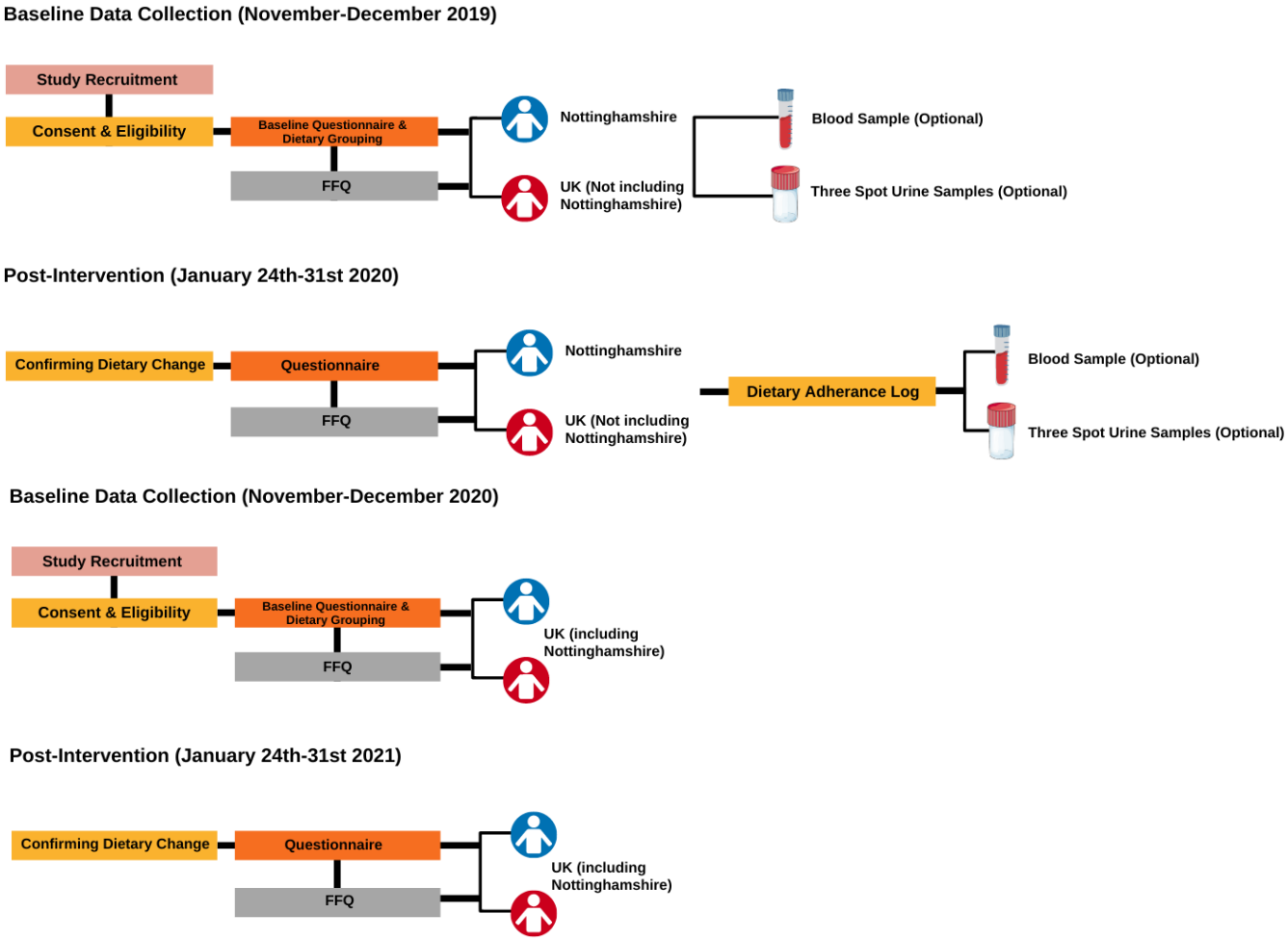


Figure 6.1. Schematic diagram of the Veganuary study protocol in years 2019 and 2020. FFQ, Food Frequency Questionnaire.

6.3.1 Sample Size

The sample size was calculated from our previous data (UIC values) which showed that for those who were already established vegans, the degree of difference in iodine status compared to omnivorous was approximately 16 µg L^{-1} (78 µg L^{-1} vs 62 µg L^{-1}) with a standard deviation of approximately 30 µg L^{-1} (Eveleigh *et al*., 2022). With these values, we would expect to require a sample size of ~56 participants in total to see a statistically significant difference (P = < 0.05). Since individuals in the present study were only expected to become vegan for a short term, we anticipated that this would increase the necessary total population size up to ~100.

6.3.2 Baseline Questionnaire

An online baseline questionnaire, designed using Online Surveys (Online Surveys, 2021), was completed by eligible participants. Demographic questions addressed age, sex, weight, height, current education, and nationality. In 2020, individuals were also asked about their job circumstances due to the COVID-19 pandemic e.g. furloughed, working from home, etc. Both surveys (2019 and 2020) asked about health habits and behaviours such as supplement intake, smoking status, and alcohol consumption. Physical activity levels were assessed using questions taken from the self-administered Short International Physical Activity Questionnaire (IPAQ-SF) (Lee *et al*., 2011). Knowledge of the role of micronutrients in the diet was also examined in 2019. In 2020, micronutrient questions were adapted to specifically address iodine knowledge. The iodine knowledge questionnaire was revised from a previously developed and validated version, which provided a total knowledge score ranging from 0 to 8 (Combet and Lean, 2014). Two additional questions were added addressing if individuals planned their diet to include sources of iodine and asked if any information on iodine was currently being received. The questions asked to assess micronutrient and iodine knowledge are shown in **Supplementary Table 6** and **Supplementary Table 7.**

6.3.1 Dietary Grouping

Participants were self-allocated into dietary groups according to responses to two questions in the online questionnaire. The first, addressed exclusion of specific food items from the diet e.g. cow's milk, poultry, etc. Next, participants selected the dietary group that best described their current diet from a list of possible classifications outlined by Phillips (2005), as definitions of vegan and vegetarian dietary preferences are often inconsistent (Phillips, 2005), we additionally asked participants to state their frequency of consumption of animal products in an FFQ. This methodology could not account for recent changes in dietary preference (<6 months) and were therefore asked how long they had been following their current dietary preference for clarification. Another category was included to outline requirements if not listed. Participants were also asked to define any food intolerances or allergies and were asked if these were professionally diagnosed.

Individuals were asked if they were pledging to follow a short-term vegan diet for January as part of "Veganuary" or were intending to follow their regular dietary preference.

The intervention groups included vegans who were remaining vegan (VV), vegetarian-vegans (VegV; vegetarians pledging to follow a short-term vegan diet), omnivores who were remaining omnivorous (OO), and omnivore-vegans (OV; omnivores pledging to follow a short-term vegan diet). We were unable to establish a solely vegetarian group due to a lack of participation.

6.3.2 Motivations Survey

The baseline attitudes questionnaire comprised 23 items to assess motivation for following a vegan diet. For each category, (e.g. “health”) respondents were asked to decide how much influence it evoked on a scale of 1 to 5 (1: “no influence at all”, to 5: “very strong influence”). Open-ended questions were used to identify additional factors that may have influenced their decision to follow a vegan diet but were not included in the traits listed. This survey was in accordance with published work used to assess motivations for following a vegan diet (Kerschke-Risch, 2015). Higher mean scores relate to greater motivation for each trait.

6.3.3 Food Choice Survey

A food choice survey assessed the importance of factors influencing food selection and the perceived difference between diets followed at baseline and at the end of January. Questions were designed based on the ‘The Food Choice Questionnaire (FCQ)’ (Steptoe *et al.*, 1995), with items categorised into groups including health, mood, convenience, sensory appeal, natural content, price, weight control, familiarity, and ethical concern. In 2019 the survey contained 28 items. In 2020, the survey contained 24 items. For both years, a five-point Likert scale was used to score responses ranging from 1 (“Strongly Disagree”) to 5 (“Strongly Agree”). Higher mean scores indicate greater importance of a particular factor in influencing food choice.

6.3.4 Dietary Adherence Log

To track the contribution of animal product consumption (accidental or deliberate) to micronutrient intake in VegV and OV groups during the intervention, we developed an online dietary adherence log called “whoops”. Participants were asked to record the date of consumption, the amount of food consumed, and a brief description of the circumstance.

Drop boxes were provided to allow individuals to select the item that was consumed. If participants did not want to fill in the log, they were asked to contact researchers in the event of animal consumption. Individuals who consumed non-significant quantities of animal products were not excluded. This was determined by individuals consuming less than 5% of a portion of specific foods and was to reflect food items that may contain small quantities of milk/diary.

6.3.5 Food Frequency Questionnaire (FFQ)

We used an online FFQ survey which included a 139-item semi-quantitative FFQ adapted from the European Prospective Investigation into Cancer and Nutrition Norfolk FFQ (EPIC-Norfolk FFQ) (Bingham *et al.*, 2001). Modifications were made to improve applicability to the population of interest, including the addition of food groups and imitation products regularly consumed by individuals avoiding animal products, accounting for foods such as dairy-free alternative milk, cheeses, creams, dressings, spreads, and alternative meats. The FFQ additionally addressed the brand and type of dairy-free milk consumed, including fortification status and storage of the product, to improve the estimation of the relative contribution to micronutrient intake. The FFQ administered at baseline was designed to assess dietary intake over the past 6-months. The FFQ provided at the end of the intervention in January was modified to record a month of dietary intake. The duration of the recording was selected to benefit those who only recently changed their dietary preference, to improve recall, and account for new food product launches in UK supermarkets. To minimize portion size as a source of error, images and portion size guides of average portions of foods regularly consumed in the UK diet were included. We did not ask about the consumption of sauces or preserves and did not differentiate between homemade and retail cakes and pies.

The FETA software was used to calculate nutrient values (Mulligan *et al*., 2014). The contribution of select vegan and vegetarian food products are not included in the FETA software. The original FETA software only contains 9 milk codes, of which, only one is dairy-free (soya) and this generic soya code does not contain fortification details.

We modified the FETA look-up files to account for 16 new food groups added to our FFQ along with 7 new non-dairy alternative milk. Nutrition values and portion sizes for these additions were generated from food items listed on Nutritics software (www.nutritics.com/en/) or were set to match similar foods already present in FETA look-up files (Nutritics, 2019).

The program allows only one type of milk, therefore only the dominant milk choice was used if participants consumed semi-skimmed cow's milk and soya milk, the relative consumption of each milk was calculated, and the milk consumed in the greatest quantity was coded. For participants who did specify the brand and type of dairy-free alternative milk consumed the generic food code for 'soya milk' was selected. Milk frequency was quantified according to measures listed within FETA e.g. Quarter of a pint, half a pint, etc. calculated from FFQ outputs. Our FFQ did not include specific questions about cereal consumption, therefore, a non-specific cereal code 'a1362' was selected. Additionally, we did not record the type of frying or baking fat used. The default fat code '17046' and '17018 were selected. Nor did we ask about visible fat, the code '-9' was used. Foods that were not considered in the FFQ, as mentioned above, were automatically coded as 'Never as or less than once a month'.

6.3.6 Iodine-specific Food Frequency Questionnaire (FFQ)

In 2020, an online iodine-specific FFQ was used to assess iodine intake only. The FFQ was developed using "Online surveys" (previously "Bristol Online Surveys"; (Online Surveys, 2022) as part of a previous research project assessing habitual iodine intake, over the past 6 months, in vegans, vegetarians, and omnivores in Nottinghamshire (Eveleigh *et al*., 2022). The iodine-specific FFQ was created based on the validated FFQ used in the Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC Oxford) study (EPIC Oxford, 2020), and contained 45 different food items (**Table 2.5**). The EPIC FFQ was modified to also include vegan appropriate sources of iodine, for example, alternative milk and dairy products. Images from the National Diet and Nutrition Survey (NDNS) (Lennox et al., 2008; **Supplementary Figure 3**) were used to demonstrate a medium serving size for items.

Questions were associated with frequency categories e.g. “two to four times per week” which were converted to daily iodine intake (μg day^{-1}) using values from an in-house food iodine database (Eveleigh *et al*., 2022).

6.3.7 Urinary Iodine Concentration (UIC)

Participants were asked to collect three midstream urine samples over one day using sterile 20 ml universal tubes (Thermo Scientific™). The first-morning void was discarded, and samples were subsequently collected in the morning (08.30 to 12.30), afternoon (12.31 to 17.30), and evening (17.31 to 23.59). The time of sample collection was recorded.

Urine specimens were centrifuged (Beckman GS-6R Refrigerated Centrifuge, Beckman, California, USA) for 10 minutes at 1500-2000 rpm (252 g) at room temperature to render them acellular and stored at -80ºC. If collected outside of laboratory working hours, samples were placed were stored at 4°C for next-day processing. UIC was measured by inductively coupled plasma mass spectrometry (ICP-MS; Thermo-Fisher Scientific Xseries II, Loughborough UK), using PlasmaLab software (version 2.5.1.276). All samples were analysed in duplicate with an internal standard (Seronorm).

Urinary creatinine (UCr) levels were measured using a modified version of the Jaffe principle (colorimetric assay) on a FluoStar Omega Microplate Reader (Ortenberg, Germany) (Moore and Sharer, 2017). The urinary iodine to creatinine ratio (I/Creat) was then calculated. I/Creat values were further corrected for age- and sex using data from published research (Knudsen *et al*., 2000).

Iodine status was determined from median UIC value according to the WHO cut-off for iodine adequacy for adults. Values of UIC > 100 μg L^{-1} were classified as “sufficient” and < 100 μg L^{-1} as “deficient”. The severity of deficiency was categorised as 50-99 μg L^{-1} mild, 20-49 μg L^{-1} moderate, < 20 μg L^{-1} severe, and ≥ 300 μg L^{-1} as excessive (WHO *et al*., 2007).

6.3.8 Thyroid Function

Blood plasma samples were used to determine free thyroxine (fT4) and thyroglobulin (Tg) as markers of thyroid function and iodine sufficiency (British Thyroid Foundation, 2021; Demers and Spencer, 2002).

Blood was taken from participants by a trained phlebotomist at Nottingham University Hospitals NHS Trust Queen's Medical Centre (QMC).

Blood samples (10 ml) were collected in an Ethylenediaminetetraacetic acid (EDTA) coated vacutainers (BD Vacutainer 10 ml EDTA Purple Blood Collection Tubes). To prevent haemolysis, the tourniquet was removed before sample collection. After collection, vacutainers were gently inverted 8 to 10 times. Blood samples were centrifuged (Heraeus Multifuge 3SR Plus, Thermo Scientific, Loughborough, UK) for 15 minutes at 1100 - 1300 g at room temperature. After centrifugation, 1.5 ml of plasma layer was transferred into labelled Eppendorf tubes ensuring that the buffy coat layer was not disturbed.

Samples were stored at -80ºC All samples were spun and stored for analysis within 30 minutes of collection. Due to the onset of the COVID-19 pandemic, samples remained in storage until September 2022.

fT4 and total Tg were measured using enzyme-linked immunosorbent assay (ELISA; Abcam Ltd. - ab108662 fT4; Abcam ab155441 thyroglobulin). Both assays were conducted according to the manufacturer's instructions. All measurements were made in duplicate.

6.3.9 Statistical Analysis

Analyses were conducted using Genstat (20th edition) and SPSS with a significance level set at $P \leq 0.05$. Data were checked for normality; where data was not normally distributed non-parametric tests were conducted and values were presented as median (75th percentiles). Non-skewed data were analysed using parametric tests and expressed as mean ± SD.

Two-way general ANOVA unbalanced design with factors "time" and "treatment" were used to assess the effect of short-term vegan diets on all measures of micronutrient intake and status. "Time" describes the point at which data was collected, either before or after January, and "treatment" describes the dietary group (VV, VegV, OO, and OV). The Fisher-Freeman-Halton Exact Test was used to assess the significance of micronutrient and iodine knowledge. The 2019 and 2020 cohorts were analysed and considered separately, this is because the study design and outcomes measures were not comparable.

Additionally, variations in food intake may have occurred between the cohorts due to food availability and personal circumstances experienced during the COVID-19 pandemic. Participants with incomplete (missing data) at either baseline or post-intervention data were excluded from analysis where two sets of data were required (e.g. food intake). Individuals who were lost before the end of the intervention were still able to provide data for outcomes that were only recorded at baseline (e.g. motivation).

6.4 Results

6.4.1 Participant Demographics

Following screening and confirmation of eligibility, 154 UK adults participated in the study at baseline (2019; n = 81, 2020; n = 73). In both years, the attrition rate was high, with 40% failing to provide data at the end of January (post-intervention/follow-up) in 2019 and 49% in 2020. The formal dropout rate was 2% in 2019, reasons for not continuing were newly diagnosed anaemia and time constraints. In 2020, this rate increased to 4%. The main reasons for dropping out of the study in 2020 were difficulties recording food intake along with challenges with participation caused by the COVID-19 pandemic lockdown restrictions (**Figure 6.2**). Participant demographics are presented in **Table 6.1**.

6.4.2 Motivations to follow a Vegan Diet

For those already following a vegan or vegetarian diet, their dietary choice in both years was strongly driven by issues with factory farming and animal welfare (P = < 0.01; **Supplementary Table 8** & **Supplementary Table 9**). This was also true for omnivores choosing to try a vegan diet but to a lesser extent. Sustainability and climate protection were more important for vegans and vegetarians compared with omnivores in 2019 (P = < 0.001), but these were more even across dietary groups in the 2020 cohort (P = 0.500 & P = 0.301 respectively). For both omnivore groups, health was the top motivational factor in 2019, but this changed to climate and sustainability in 2020.

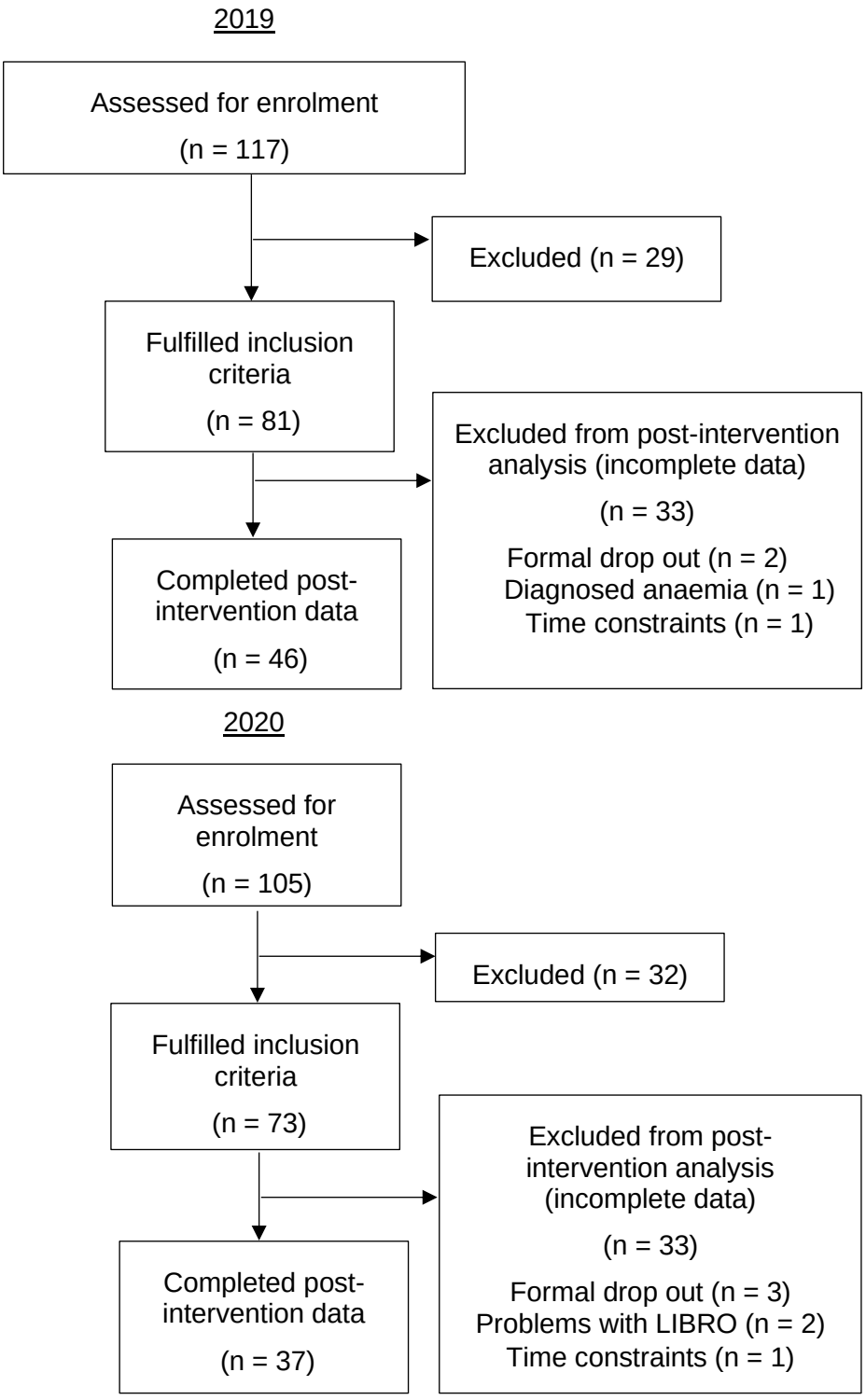


Figure 6.2. The Veganuary study flowchart in 2019 and 2020.

Table 6.1. Participant characteristics at baseline data collection for 2019 and 2020 Veganuary cohorts.

	2019				2020			
	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 14)	Omnivore (OO) (n = 21)	Omnivore-vegan (OV) (n = 22)	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)
Sex *(%)*								
Female	75.0	85.7	76.2	81.8	73.3	100.0	83.3	75.0
Age (Years), Mean ± SD	31.2 ± 0.4	35.2 ± 11.6	30.10 ± 9.5	39.1 ± 13.8	26.7 ± 8.4	23.3 ± 3.2	24.8 ± 2.0	34.7 ± 15.3
Highest education level (%)								
Secondary (GCSE equivalent)	0.0	7.1	0.0	9.1	2.2	0.0	0.0	0.0
College (A-level equivalent)	16.7	21.4	9.5	0.0	31.1	33.3	16.7	6.2
Undergraduate degree	62.5	35.7	42.9	59.1	46.7	50.0	50.0	31.2
Postgraduate degree (MSc, PhD)	8.3	35.7	42.8	27.2	20.0	16.7	33.3	37.5
Other	12.5	0.0	4.8	4.5	0.0	0.0	0.0	6.2
Employment status (%)								
Employed	50.0	92.9	33.3	59.1	53.4	33.3	33.3	62.4
Furloughed*	-	-	-	-	4.4	0.0	0.0	0.0
Student	25.0	0.0	38.1	18.2	28.9	16.7	66.7	25.0
Employed student	16.7	7.1	28.6	22.7	13.3	33.3	0.0	12.5
Unemployed	8.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Nationality (%)								
United Kingdom	95.8	92.9	85.7	81.9	-	-	-	-
Europe	0.0	0.0	4.8	9.0	-	-	-	-
East and Southeast Asia	4.2	0.0	4.8	9.0	-	-	-	-
United States	0.0	7.1	4.8	0.0	-	-	-	-
Mexico	0.0	0.0	0.0	0.0	-	-	-	-
Oceania	0.0	0.0	0.0	0.0	-	-	-	-

Table continued…

	2019				2020			
	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 14)	Omnivore (OO) (n = 21)	Omnivore-vegan (OV) (n = 22)	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)
Ethnicity (%)								
White - British/Irish	-	-	-	-	86.7	100.0	100.0	87.5
White - Other	-	-	-	-	11.1	0.0	0.0	6.2
Other	-	-	-	-	2.2	0.0	0.0	6.2
Weight status (BMI)	22.6 ± 3.4	24.1 ± 7.5	23.6 ± 4.3	26.2 ± 6.9	23.8 ± 4.8	23.4 ± 2.0	21.3 ± 2.5	23.6 ± 3.3
Minutes per week of moderate physical activity								
<30	4.2	14.3	15.0	18.2	2.2	0.0	0.0	6.2
30-90	20.8	7.1	5.0	27.3	31.1	33.3	16.7	37.5
90-150	12.5	14.3	30.0	27.3	20.0	0.0	16.7	31.2
150-300	25.0	35.7	30.0	13.6	31.1	16.7	50.0	18.8
>300	37.5	28.6	20.0	13.6	15.6	50.0	16.7	6.2
Smoking status, (%)								
Non-smoker	70.8	64.3	95.2	54.5	80.0	100.0	83.3	68.8
Smoker	8.3	28.6	0.0	22.7	6.7	0.0	0.0	6.2
Vapour	-	-	-	-	4.4	0.0	0.0	6.2
Ex-smoker	20.8	7.1	0.0	22.7	8.9	0.0	16.7	18.8
Did not disclose	0.0	0.0	4.8	0.0	0.0	0.0	0.0	0.0
Weekly alcohol consumption (%)								
None	12.5	0.0	14.3	22.7	33.3	33.3	50.0	18.8
<5 Units	41.7	42.9	38.1	31.8	37.8	66.7	33.3	18.8
5-10 units	29.2	28.6	23.8	13.6	13.3	0.0	16.7	31.2
10-15 units	12.5	21.4	19.0	22.7	11.1	0.0	0.0	18.8
15+	0.0	7.1	0.0	9.1	4.4	0.0	0.0	12.5

Table continued…

	2019				2020			
	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 14)	Omnivore (OO) (n = 21)	Omnivore-vegan (OV) (n = 22)	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)
Prefer not to disclose	4.2	0.0	4.8	0.0	0.0	0.0	0.0	0.0
Frequent salt usage (%)								
No	50.0	38.5	33.3	47.6	26.7	83.3	66.7	18.8
Yes, table salt	33.3	46.2	33.3	42.9	44.4	16.7	33.3	43.8
Yes, iodised salt	0.0	0.0	14.3	4.8	6.7	0.0	0.0	6.2
Yes, other salt	16.7	15.4	19.0	4.8	22.2	0.0	0.0	31.2
Length of diet (%)								
0-3 Months	16.7	14.3	9.5	9.1	2.2	0.0	0.0	0.0
3-6 Months	16.7	0.0	0.0	4.5	0.0	0.0	0.0	6.2
6-12 Months	12.5	7.1	4.8	22.7	22.2	16.7	0.0	12.5
12+ Months	41.7	57.1	9.5	9.1	37.8	50.0	0.0	31.2
5+ Years	12.5	21.4	76.2	54.5	37.8	33.3	0.0	12.5
Prefer not to disclose	-	-	-	-	0.0	0.0	100.0	37.5
Dietary intolerance (%)								
None	87.5	85.7	90.5	86.4	68.9	50.0	83.3	100.0
Yes, not professionally diagnosed	12.5	7.1	0.0	13.6	20.0	33.3	0.0	0.0
Yes, professionally diagnosed	0.0	7.1	9.5	0.0	11.1	16.7	16.7	0.0

-, Not applicable.

6.4.1 Dietary intake by Food Frequency Questionnaire in 2019

FFQ data clearly showed both positive and negative effects of the transition to a vegan diet (**Table 6.2** & **Table 6.3**). Saturated fat intake was lower in vegans compared with other groups (P = < 0.001) and was shown to be reduced by 31% and 53% in vegetarians and omnivores respectively when transitioning to a vegan diet (P = 0.005). Cholesterol intakes exhibited considerable reductions with diet and time-point. Vegans consumed roughly $1/10^{th}$ of that consumed by omnivores who themselves showed a 10-fold reduction in intake when adopting a vegan diet (P = 0.001). Vegetarians transitioning to a vegan diet similarly reduced their cholesterol intake by more than 80%. Before the addition of supplements to the analysis (**Figure 6.3**), consumption of vitamin B12 was significantly lower in vegans and vegetarians (P = < 0.001) and was reduced by 65% in omnivores changing to a vegan diet (P = < 0.001). For vegetarians whose intake was already considerably lower than omnivores, the transition to a vegan diet further reduced intake by 36%. After the inclusion of supplements (Figure 5), B12 intake substantially improved in the VV group at post-intervention (4570% increase). Additionally, there were improvements in B12 for the OV group post-intervention, such that changing to a vegan diet no longer presented a significant reduction in intake over time (P = 0.422; **Figure 6.4**). Iodine intake (non-inclusive of supplements) decreased in all groups between December and January but was considerably reduced in omnivores transitioning to a vegan diet (69%; P < 0.001; **Figure 6.3**). There remained a significant reduction in iodine intake in omnivores transitioning to a vegan diet once supplements were added to the analysis (P = 0.005; **Figure 6.4**). At both time points, iodine intake also improved with the addition of supplements in VV and VegV groups, but average intake remained below the RNI (140 µg day^{-1}). Interestingly, thiamine consumption was significantly increased by the transition to a vegan diet (P = 0.02; **Figure 6.4**).

Table 6.2. Average daily macronutrient intake non-inclusive of supplements of individuals in the 2019 cohort at baseline and post-intervention (End) provided Food Frequency Questionnaire (FFQ) estimates[1].

	Baseline	End	Baseline	End	Baseline	End	Baseline	End	Standard Errors of Difference of Means (max-min)			*P* Value (Baseline-to-end)		
	Vegan (VV) (n = 12)	Vegan (VV) (n = 12)	Vegetarian-vegan (VegV) (n = 10)	Vegetarian-vegan (VegV) (n = 10)	Omnivore-vegan (OV) (n = 12)	Omnivore-vegan (OV) (n = 12)	Omnivore (OO) (n = 12)	Omnivore (OO) (n = 12)	Time	Diet	Time x Diet	Time	Diet	Time x Diet
Energy (kcal)	1275.9	1073.2	1645.4	1516.4	1720.3	1422.7	1656.3	1514.7	72.8	193.1	149.5	0.010*	0.083	0.840
Protein (g)	50.4	37.4	56.1	56.8	72.5	47.0	76.3	69.4	3.6	8.3	7.3	0.002*	0.008*	0.087
COH (g)	158.2	141.5	193.7	171.5	203.6	204.3	183.2	162.9	8.7	22.3	17.9	0.109	0.109	0.778
Fat (g)	50.1	40.7	66.7	65.3	69.5	48.3	70.5	63.6	3.5	9.2	7.2	0.006*	0.071	0.253
SFA (g)	12.0	8.6	19.2	13.2	26.4	12.4	24.9	21.9	1.2	2.8	2.4	<.001*	<.001*	0.005*
MUFA (g)	17.8	16.2	22.6	23.8	25.3	17.3	26.9	24.4	1.3	3.4	2.7	0.032*	0.071	0.112
PUFA (g)	12.6	10.3	14.4	14.7	11.0	10.6	11.8	11.0	0.8	2.0	1.6	0.274	0.242	0.696
Cholesterol (mg)	22.1	3.8	124.1	20.0	273.3	24.5	295.5	254.9	21.4	35.6	44.0	<.001*	<.001*	0.001*
Sugar (g)	59.0	58.3	77.4	69.0	94.3	85.2	83.2	77.8	5.0	13.6	10.2	0.254	0.124	0.928
Fibre (g)	20.9	18.2	20.3	25.0	17.9	21.1	16.2	14.6	1.1	2.5	2.2	0.486	0.044*	0.059

[1]Data includes consumers and non-consumers of food sources; *Significance between dietary groups assessed by two-way general ANOVA (P = < 0.05).

Table 6.3. Average daily micronutrient intake non-inclusive of supplements of individuals in the 2019 cohort at baseline and post-intervention (End) provided Food Frequency Questionnaire (FFQ) estimates[1].

	Baseline	End	Baseline	End	Baseline	End	Baseline	End		Standard Errors of Difference of Means (max-min)		*P* Value (Baseline-to-end)		
	Vegan (VV) (n = 12)	Vegan (VV) (n = 12)	Vegetarian-vegan (VegV) (n = 10)	Vegetarian-vegan (VegV) (n = 10)	Omnivore-vegan (OV) (n = 12)	Omnivore-vegan (OV) (n = 12)	Omnivore (OO) (n = 12)	Omnivore (OO) (n = 12)	Time	Diet	Time x Diet	Time	Diet	Time x Diet
Vitamin A (µg)	918.5	649.1	952.4	1122.3	1193.1	839.8	1147.0	906.3	97.9	247.6	201.0	0.1	0.670	0.287
Vitamin C (mg)	111.3	105.2	103.6	140.4	99.3	107.0	113.0	97.9	9.4	19.5	19.3	0.6	0.780	0.270
Thiamine (mg)	3.0	2.0	2.5	3.6	1.9	3.3	1.6	1.5	0.3	0.7	0.6	0.291	0.176	0.020*
Riboflavin (mg)	1.1	1.0	1.5	1.5	1.6	1.3	1.7	1.4	0.1	0.3	0.2	0.021*	0.221	0.730
Niacin (mg)	13.8	11.4	14.8	16.1	17.2	14.2	18.7	17.8	1.0	2.1	2.1	0.196	0.062	0.499
Vitamin B6 (mg)	1.6	1.4	1.7	1.8	2.0	1.7	2.0	1.8	0.1	0.2	0.2	0.203	0.270	0.588
Vitamin B12 (µg)	1.4	1.0	2.5	1.6	5.1	1.8	6.4	5.0	0.4	0.8	0.7	<.001*	<.001*	0.020*
Folate (µg)	281.0	239.3	299.8	360.0	273.0	264.3	265.6	232.0	18.8	41.6	38.6	0.642	0.238	0.257

Table continued…

	Baseline	End	Baseline	End	Baseline	End	Baseline	End	Standard Errors of Difference of Means (max-min)			*P* Value (Baseline-to-end)		
	Vegan (VV) (n = 12)	Vegan (VV) (n = 12)	Vegetarian-vegan (VegV) (n = 10)	Vegetarian-vegan (VegV) (n = 10)	Omnivore-vegan (OV) (n = 12)	Omnivore-vegan (OV) (n = 12)	Omnivore (OO) (n = 12)	Omnivore (OO) (n = 12)	Time	Diet	Time x Diet	Time	Diet	Time x Diet
Calcium (mg)	651.3	535.9	825.1	802.7	879.7	609.8	852.6	657.2	48.7	133.4	99.9	0.003*	0.387	0.344
Iron (mg)	10.6	9.0	11.3	12.0	10.7	10.1	9.9	9.2	0.5	1.4	1.1	0.287	0.448	0.580
Magnesium (mg)	307.8	267.2	323.4	359.1	314.3	309.9	276.7	253.4	15.2	42.4	31.3	0.513	0.320	0.368
Potassium (mg)	2680.3	2386.1	3021.5	3329.0	3392.8	2956.7	3043.6	2709.2	157.4	400.6	323.1	0.187	0.309	0.384
Sodium (mg)	1799.0	1407.9	2173.3	2146.9	2193.2	1853.5	2112.0	1987.5	94.2	308.0	193.3	0.019*	0.277	0.490
Zinc (mg)	7.7	5.5	7.2	8.3	8.6	7.0	8.7	7.8	0.4	1.1	0.9	0.022*	0.287	0.238
Selenium (µg)	35.6	25.3	41.3	34.0	52.0	29.9	56.0	49.4	2.3	5.9	4.7	<.001*	0.003*	0.070
Iodine (µg)	28.3	18.7	61.4	39.2	125.2	38.2	125.7	105.1	7.0	14.9	14.3	<.001*	<.001*	<.001*
Vitamin D (µg)	1.8	1.6	2.4	1.5	2.7	1.7	3.5	2.7	0.2	0.6	0.4	<.001*	0.135	0.423

[1]Data includes consumers and non-consumers of food sources; *Significance between dietary groups assessed by two-way general ANOVA (P = < 0.05).

For the 2020 cohort, we felt that the emotional burden of the continued COVID-19 lockdown, particularly with the swift Christmas shutdown, might reduce the level of participation and increase attrition, so the FFQ was truncated to measure iodine intake only. Similar to 2019, iodine intake (non-inclusive of supplements) showed a significant decrease (87%) over time for the OV group (P = <0.001; **Table 6.4**; **Figure 6.5**). The greatest reduction in iodine came because of the loss of milk from the diet (28% of pre-vegan January intake) followed by white fish (14%) and yoghurt (12%). Dietary supplements boosted the iodine intake of individuals transitioning to a vegan diet in January (VegV; 272%, OV; 375%), such that changing to a vegan diet no longer presented a significant reduction in intake over time (P = 0.359; **Figure 6.5**).

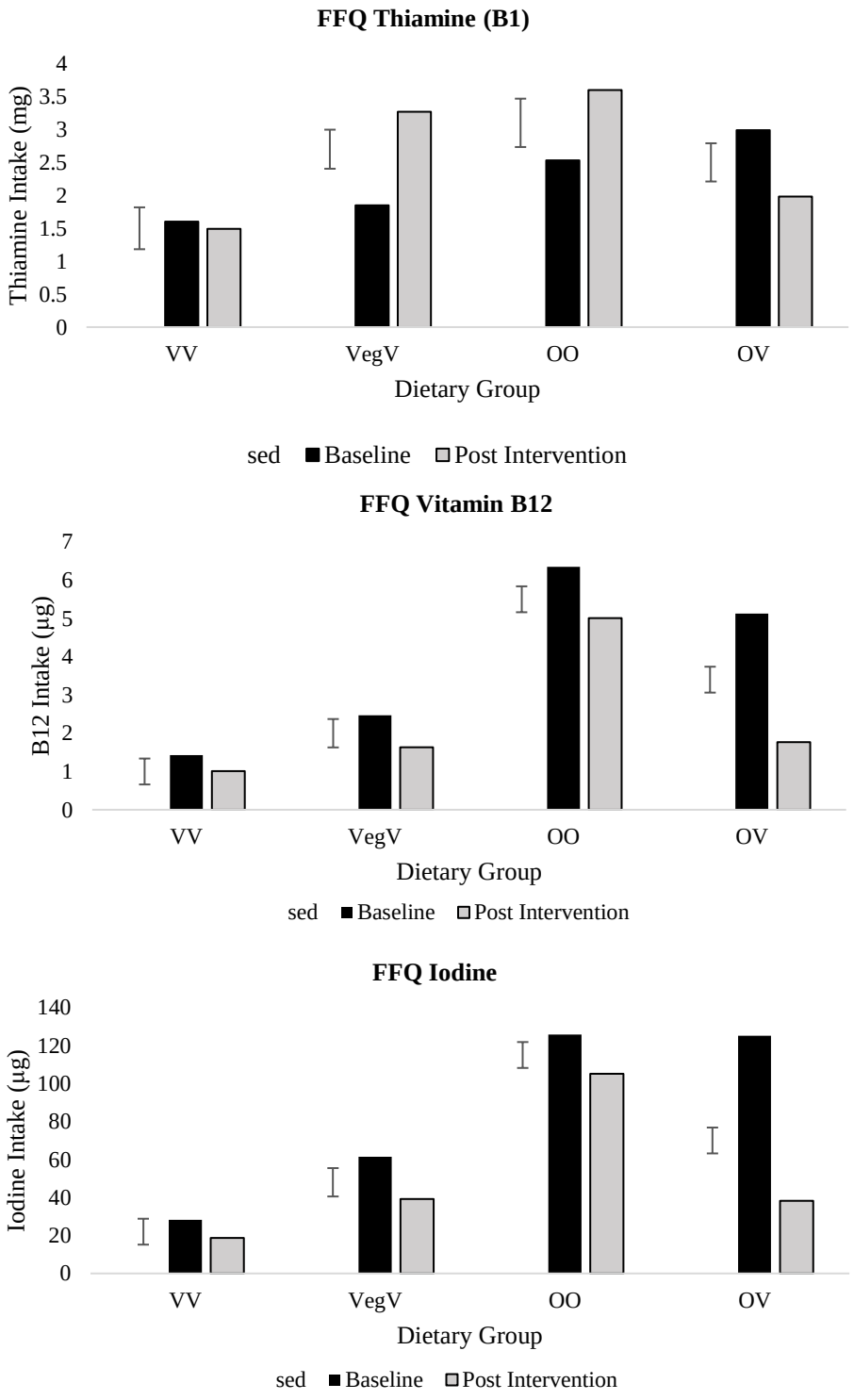


Figure 6.3. Average daily micronutrient intake non-inclusive of supplements of individuals in the 2019 cohort at baseline and post-intervention (End) provided Food Frequency Questionnaire (FFQ) estimates.
Mean and Standard Error of the Difference presented (sed). Only significant effects are presented and assessed by two-way general ANOVA (P = < 0.05). Groups are VV, vegan; VegV, vegetarian-vegan; OO, omnivore-omnivore; and OV, omnivore-vegan.

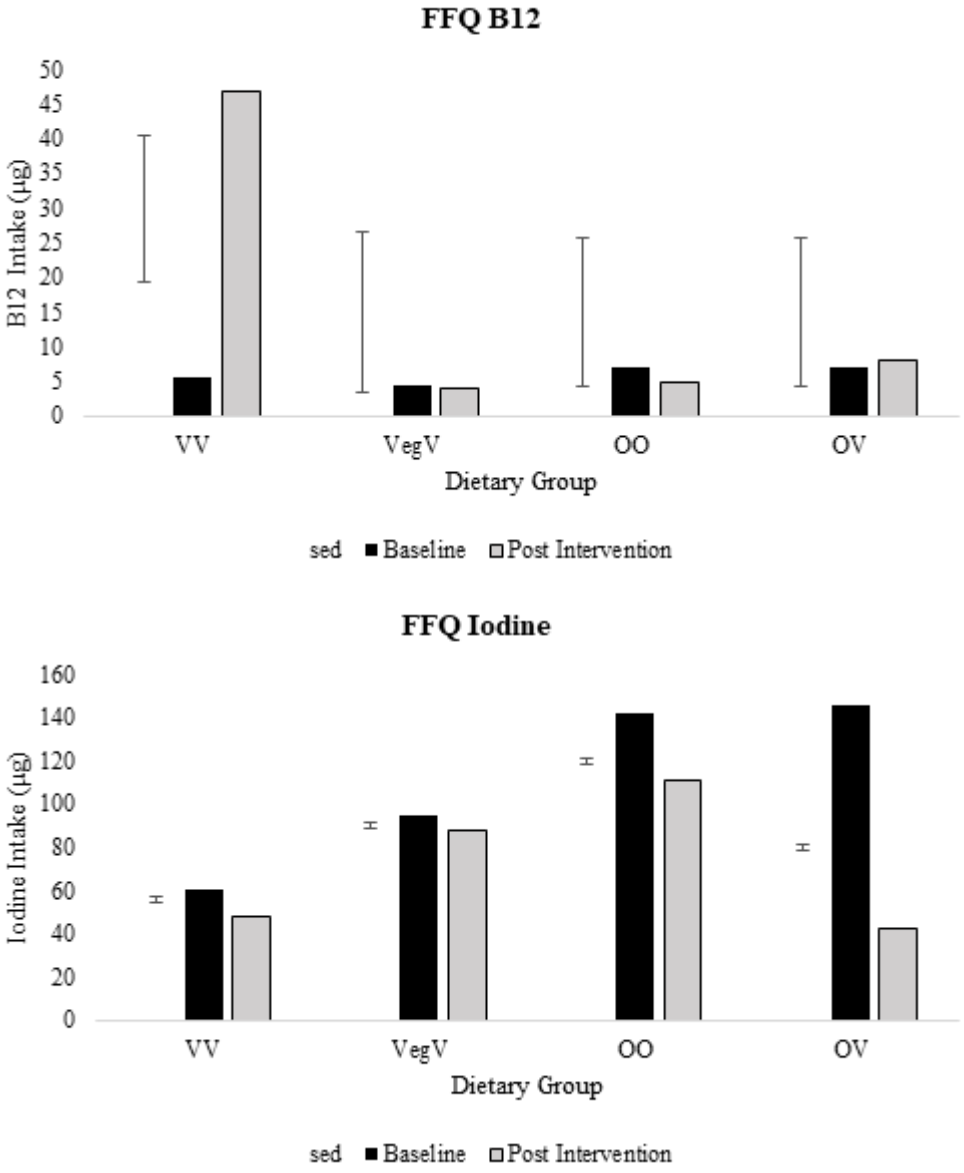


Figure 6.4. Average daily micronutrient intake inclusive of supplements of individuals in the 2019 cohort at baseline and post-intervention (End) provided Food Frequency Questionnaire (FFQ) estimates.
Mean and Standard Error of the Difference presented (sed). Significant effects are presented and assessed by two-way general ANOVA (P = < 0.05) for iodine estimates. Groups are VV, vegan; VegV, vegetarian-vegan; OO, omnivore-omnivore; and OV, omnivore-vegan.

6.4.2 Supplement intake

For participants in 2019, consumption of supplements at baseline was high with > 80% in the VV group, ~ 50% in the VegV and OO groups, and ~ 60% in the OV group (**Supplementary Table 10**). Vitamin B12 was most frequently supplemented in VV (50% of supplements) and VegV groups (60%). Individuals in the VV group also often consumed multivitamin supplement complexes (50%). Vitamin D was the most recorded supplement by OO (50%) and OV groups at baseline (27%). By the end of the intervention, fewer VV individuals recorded consuming supplements (66% down from 83%), while the proportion of VegV taking supplements increased by 80%, OV by 16%, and OO declined by 77%. Vitamins B12 and D remained the most consumed supplement for participants in the VV and OO groups (~ 75%). For the VegV group, the number of people consuming multivitamin supplement complexes increased from 20% to 90% at the end of the intervention. The number of people taking Vitamin B12 supplements also increased in the group from 10% to 60%.

Participants from the 2020 cohort showed broadly similar levels of supplement usage as seen in 2019 (**Supplementary Table 11**) although none of the OO group in 2020 recorded any supplement intake, numbers in this group were low (n = 5). Reasons for taking supplements were predominantly due to following a diet that does not contain animal products amongst vegans and vegetarians, whilst the principal reasons for supplementation in the OV group were to improve health and due to a lack of sunlight exposure in the UK winter.

Table 6.4. Average daily iodine intake non-inclusive of supplements of individuals in the 2020 cohort at baseline and post-intervention (End) provided by Iodine Specific Food Frequency Questionnaire (FFQ) estimates[1]

	Baseline	End	Baseline	End	Baseline	End	Baseline	End	Standard Errors of Difference of Means (max-min)			*P* Value (Baseline-to-end)		
	Vegan (VV) (n = 16)	Vegan (VV) (n = 16)	Vegetarian-vegan (VegV) (n = 3)	Vegetarian-vegan (VegV) (n = 3)	Omnivore-vegan (OV) (n = 13)	Omnivore-vegan (OV) (n = 16)	Omnivore (OO) (n = 5)	Omnivore (OO) (n = 5)	Time	Diet	Time x Diet	Time	Diet	Time x Diet
Iodine (µg)	16.7	19.0	49.8	31.7	109.6	13.8	115.0	153.0	6.8	19.1	18.3	<.001*	<.001	<.001*
Foods Contributing to Iodine Intake from FFQ Output (µg day^{-1})														
Cow's milk (total)	-	-	3.6	0.0	30.6	0.4	38.7	51.9	7.2	12.2	14.9	0.038*	0.009	0.056
Alternative milk (total)	8.8	7.5	12.9	11.6	9.4	2.7	0.2	0.2	2.4	8.5	6.6	0.222	0.607	0.739
Dairy yogurts	-	-	5.5	0.0	13.5	0.4	21.9	46.3	3.5	6.3	7.2	0.383	<.001*	0.001*
Non-dairy yogurts	3.1	2.4	4.7	6.8	2.8	1.8	0.1	1.1	1.1	2.2	2.9	0.725	0.254	0.834
Dairy cheese	-	-	2.3	0.0	5.5	0.1	7.5	7.0	0.8	1.7	1.7	<.001*	0.005*	0.059
Dairy-based Puddings	-	-	0.1	0.0	0.3	0.0	1.1	1.1	0.1	0.3	0.3	0.070	0.002*	0.625
Non-dairy Puddings	1.8	2.1	2.9	3.6	5.0	1.4	0.1	0.1	1.5	2.9	3.9	0.725	0.254	0.834
Eggs	-	-	4.8	0.0	7.7	0.1	20.8	19.3	2.4	6.2	5.0	0.029*	0.014*	0.581
Omelette	-	-	1.8	0.0	1.1	0.1	3.4	2.2	0.4	0.6	0.8	0.006*	0.001*	0.747
Egg-based deserts	-	-	1.2	0.0	3.0	0.1	1.5	5.8	1.3	1.9	2.6	0.468	0.310	0.091
White fish	-	-	3.9	0.0	16.2	0.5	10.8	6.1	3.5	5.3	7.3	0.005*	0.475	0.314
Oily fish	-	-	3.0	0.0	7.5	0.6	7.9	8.3	1.7	4.0	3.6	0.017*	0.317	0.233
Other seafood	-	-	1.0	0.0	1.0	0.1	0.2	0.7	0.1	0.3	0.2	<.001*	0.159	0.033*
Seaweed	2.6	7.1	0.0	9.7	5.8	5.4	2.9	2.9	1.4	5.2	3.7	0.050	0.793	0.357

[1]Non-dairy cheese was not included in the FFQ analysis because it provided little/no iodine to total intake; *Significance between dietary groups assessed by two-way general ANOVA (P = < 0.05); -, Not applicable.

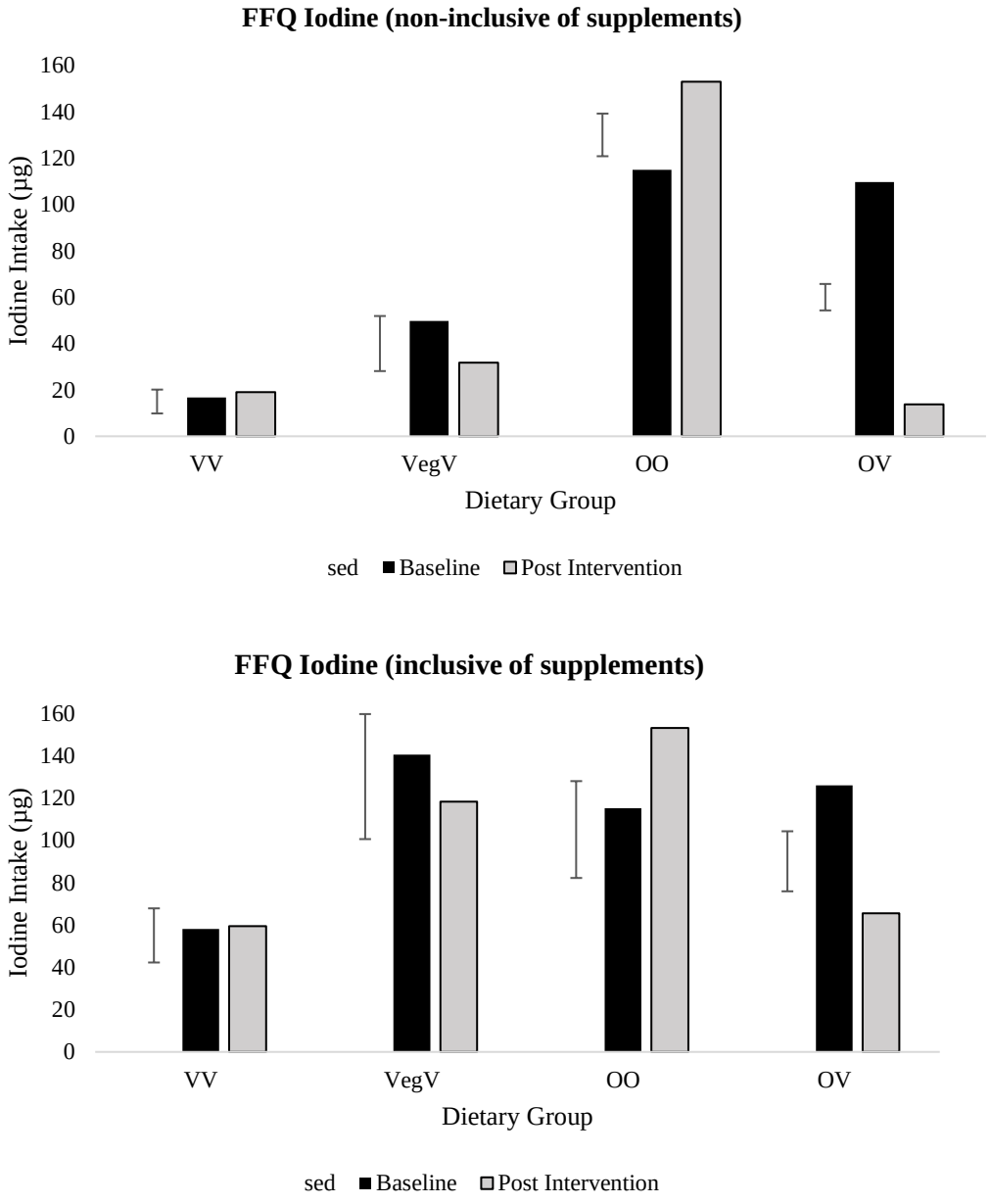


Figure 6.5. Average daily iodine intake non-inclusive and inclusive of supplements of individuals in the 2020 cohort at baseline and post-intervention (End) provided Iodine Specific Food Frequency Questionnaire (FFQ) estimates.
Mean and Standard Error of the Difference presented (sed). Significant effects are presented and assessed by two-way general ANOVA (P = < 0.05) for values inclusive of supplements). Groups are VV, vegan; VegV, vegetarian-vegan; OO, omnivore-omnivore; and OV, omnivore-vegan.

6.4.1 Food Choice Survey

Factors of food choice post-intervention varied by the dietary group in 2019 (**Supplementary Figure 4**). The strongest determinant of food choice for omnivores and vegetarians was the sensory appeal, with price also being similarly important for vegetarians specifically. For vegans, familiarity was the strongest driver of choice. Weight control was the lowest-scored factor of food choice for all omnivores and vegans, whilst for vegetarians, convenience was the least important. Vegans placed health, mood, and familiarity significantly higher than did omnivores transitioning to vegan, for whom price, weight control, and ethical reasons were significantly lower than for vegetarians ($P = 0.001$). We were unable to include an assessment of food choice for those in the VegV group due to low numbers ($n = 2$) in 2020. The OO group ranked mood as the strongest determinant of food choice, whereas, natural was the strongest determinant for the OV group and price for the VV group. The OO group had significantly higher scores than the OV group for determinants of mood, price, and "ethical", at a significance level of $P = 0.05$.

6.4.2 Micronutrient Knowledge

Overall, micronutrient knowledge at baseline was low (**Supplementary Table 12**). Fewer than 30% of respondents from each dietary group were aware of micronutrients in general. Awareness was lowest for micronutrients niacin and vitamin B6. Iron (VV; 54%, VegV; 53%, OO; 35%, OV; 43%) and vitamin D (VV; 46%, VegV; 33%, OO; 50%, OV; 48%) were most frequently recognised by participants. Individuals in the VV group had significantly greater awareness of vitamin B12 than those in the OV group. Over half of the participants were able to describe a symptom of micronutrient deficiency (VV; 58%, VegV; 67%, OO; 55%, OV; 65%). Symptoms of iron deficiency (anaemia, fatigue, etc.) and vitamin D (bone health, rickets, etc.) were most described. Participants had low awareness of symptoms of deficiencies in folate, calcium, magnesium, and zinc. Awareness of symptoms of vitamin B12 deficiency was significantly higher in the VV group (25%) than in the OV group (0%).

6.4.3 Iodine Knowledge

Iodine knowledge was poor in the 2020 cohort, with an average knowledge score of 2 out of a possible total of 8 (**Supplementary Table 13**). At baseline, the omnivore group had significantly greater iodine knowledge compared to the VV group with a score of 3.0 vs 1.4 (P = 0.004). There were significant differences in the knowledge of iodine deficiency being a problem in the UK, of dietary planning to achieve adequate iodine intake and receipt of iodine information between dietary groups

6.4.4 Urinary Iodine Concentration (UIC)

Several participants in 2019 provided urine samples for analysis at baseline and post-intervention, but the numbers were low (VV; n = 6, VegV; n = 3, OV; n = 6). Only one participant from the OO group provided a urine sample at both time points and hence was not included in the analysis. UIC and age- and sex-adjusted I/Creat did not differ from baseline to post-intervention in samples provided in the morning (P = 0.416, P = 0.397), afternoon (P = 0.056, P = 0.100), or evening (P = 0.426, P = 0.485) (**Supplementary Table 14**). Before creatinine adjustment, median UIC for the morning, afternoon, and evening samples, at baseline and post-intervention, were below the WHO criteria for iodine sufficiency (>100 μg L^{-1}) for all dietary groups. One participant in the VV group had one very high baseline UIC (morning; 117.9 μg L^{-1}, afternoon; 374.1 μg L^{-1}, evening; 24.3 μg L^{-1}) and at all post-intervention time-points (morning; 350.4 μg L^{-1}, afternoon; 234.9 μg L^{-1}, evening; 288.0 μg L^{-1}. At baseline and post-intervention, the highest median UIC was recorded in morning samples provided by the VV group (46.7 μg L^{-1}, 57 μg L^{-1}), and the lowest values were found in afternoon samples given by the VegV group (23.8 μg L^{-1}, 21.7 μg L^{-1}). After age- and sex-adjusted creatinine for fluid intake, median UIC improved for all groups. Median UIC for participants in the OV group raised above the WHO criteria for iodine sufficiency (>100 μg L^{-1}) at all urine collection time points (baseline and post-intervention). However, evening samples provided by individuals in the VV group at baseline (98.2 μg L^{-1}) and morning samples by individuals in the VegV group post-intervention (44.5 μg L^{-1}) were not above the iodine sufficiency cut-off.

6.4.5 Thyroid Function

Due to the limited number providing blood samples, we could only assess fT4 and Tg in omnivores taking part in Veganuary (OV group; n = 5) and vegans staying vegan (VV group; n = 4; Figure 7). For both groups, fT4 reduced numerically from baseline to post-intervention (OV; 12.8 to 7.3 ppmol L^{-1}, VV; 10.9 to 4.3 ppmol L^{-1}) but no significant differences were detected (P = 0.841). The reference value for fT4 in normal euthyroid subjects is 9.0 – 25.0 ppmol L^{-1} (British Thyroid Foundation, 2021), indicating that in January (post-intervention) fT4 declined below the normal range in both groups. There was also no significant change in plasma Tg with time or diet (P = 0.582).

6.5 Discussion

In recent years, there has been growing interest in part-time or short-term veganism. The 'Veganuary' challenge is one example of this shift to temporary dietary change and may be adopted for health reasons, as a challenge, or for a more manageable way of reducing animal products in the diet (Veganuary, 2023). A well-planned vegan diet can meet dietary recommendations (BDA, 2017), however, studies have found that certain micronutrients may be of concern in those following a vegan diet (Bakaloudi *et al*., 2021; Dinu *et al*., 2017; García-Morant *et al*., 2020; Kristensen *et al*., 2015; Schüpbach *et al*., 2017; Weder *et al*., 2022). To our knowledge, this study is the first to investigate the change in micronutrient intake and status in those choosing to follow a short-term (4 weeks) vegan diet as part of 'Veganuary'.

Our study shows that the adoption of a short-term (4-week) vegan diet has a significant effect on the nutrient intake of individuals following an omnivorous diet, particularly in those who were not consuming dietary supplements. However, we found no significant difference in micronutrient intake in vegetarians pledging to a vegan diet. This is likely to be due to our vegetarian participants recording a very low micronutrient intake at baseline and consuming dietary patterns that are more like vegans than omnivores before the intervention.

This finding agrees with research from other studies that have recorded comparable micronutrient intake in vegetarians and vegans (Clarys *et al*., 2014; Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Krajcovicová-Kudlácková *et al*., 2003; Schüpbach *et al*., 2017)

SFA and cholesterol intake significantly decreased in omnivores pledging to a short-term vegan diet during Veganuary. Fat reduction observed in omnivores in our study was similar to differences reported in previous studies (Benatar and Stewart, 2018; Kahleova *et al*., 2019; Turner-McGrievy *et al*., 2008). Vegans typically have a lower intake of SFA, and cholesterol compared to omnivores due to the absence of meat, dairy, fish, and eggs from the diet (Kristensen *et al*., 2015). However, SFA and cholesterol can also be found in plant foods such as alternative products, vegetable oils, coconut, nuts, and chocolate (Govindji, 2020). We did not assess the top sources of SFA and cholesterol in the diet at baseline or post-intervention, however, the replacement of animal products with plant-based foods has likely contributed to lower intake in the OV group (Clarys *et al*., 2014; Kuchta *et al*., 2016). Reduced intake of SFA and cholesterol have been shown to decrease cardio metabolic risk and body weight (Kuchta *et al*., 2016). Short-term vegan diets may therefore be appropriate for people aiming to reduce their SFA and cholesterol intake.

Thiamine intake significantly increased with time for omnivores following a short-term vegan diet. This result does agree with other studies (Bakaloudi *et al*., 2021). Thiamine intake is not usually a problem in vegan diets, as plant foods such as fortified cereals, whole grains, beans, and pulses are rich sources (Shim *et al*., 2014).

Lower vitamin B12 intake has been frequently recorded in vegan and vegetarian populations (Damayanti *et al*., 2018; Gilsing *et al*., 2010; Pawlak *et al*., 2013; Rizzo *et al*., 2016; Selinger *et al*., 2019). Vitamin B12 is synthesised by bacteria colonising the gastrointestinal (GI) system of animals and once produced, is stored in the tissue of the host. For this reason, vitamin B12 can only be obtained from animal foods (Pawlak *et al*., 2018). We found a significant reduction in B12 intake in non-supplementing omnivores following a short-term vegan diet, matching the results of other studies (Lederer *et al*., 2019).

Many plant foods are now fortified with vitamin B12 including alternative milk, dairy products, and meats, along with, some breakfast cereals and yeast products (Damayanti *et al*., 2018). Values for vegan diets may potentially be lower because some fortified sources of vitamin B12 may not have been captured by our FFQ, but the majority are present and therefore we feel the values provide a good estimate. Supplements have proven to be a useful way to improve vitamin B12 intake in those following vegan and vegetarian diets (Rizzo *et al*., 2016). Supplements may be consumed daily, episodically, or only during particular circumstances, hence, creating huge variability in estimates (Bailey *et al*., 2019). The number of people in the omnivore-vegan group who consumed vitamin B12 supplements in the FFQs increased from 10% at baseline to 60% at the end of the intervention.

There was a strong association between nutritional knowledge and nutrient intake. Knowledge and awareness of vitamin B12 were significantly lower in the OV group compared to the VV group. Consequently, individuals in the OV group may be less careful selecting fortified foods or supplements containing vitamin B12. Vitamin B12 can be stored internally (mainly in the liver) and is depleted slowly. Bodily stores of vitamin B12 take 3-4 years to deplete (Ankar and Bhimji, 2022), thus, 4 weeks of reduced intake during Veganuary is unlikely to have a negative influence on vitamin B12 status, unless individuals had low stores before pledging to change their diet. If the dietary transition persists, however, then those who were previously omnivorous may be at greater risk of future B12 deficiency due to a lack of prior knowledge.

Iodine intake also significantly decreased over time in the OV group. The WHO criteria for adequate iodine intake indicate people should consume 150 μg day^{-1} to achieve adequacy (WHO, 2007). As reported in other studies, we found iodine provision for UK adults was inadequate regardless of dietary choice (Eveleigh *et al*., 2022; Fallon and Dillon, 2020). Vegans and vegetarians are frequently recognised as a subgroup at risk of iodine deficiency, since foods typically rich in iodine are mostly of animal origin (cow's milk, dairy products, eggs, white fish, and seafood) (Eveleigh *et al*., 2020; Public Health England, 2014).

Many vegan alternatives to these foods sold in the UK are not fortified with iodine (Bath *et al*., 2017; Nicol *et al*., 2022), hence, transitioning to these foods could compromise iodine consumption (Dineva *et al*., 2020b). In 2020, a cross-sectional study assessed the iodine fortification status of vegan plant-based alternative products (e.g. plant-based milk, dairy, cheese, and seafood) and the impact that substitution with these products could have on dietary iodine (Nicol *et al*., 2022). The investigators found that the replacement of three servings of dairy products with non-fortified alternative products reduced iodine delivery by 97.9% (Dineva *et al*., 2020b). Individuals transitioning to vegan diets in the short term must be aware of the need to select iodine-fortified alternative milk drinks. The FFQs in both years of our study were modified to include information on the fortification status of different alternative milk.

Similarly, in 2020, iodine intake for the OVs group significantly decreased with time (109.6 to 13.9 µg day^{-1}, 87.3% reduction). In this cohort, it was apparent that loss of yogurt and seafood placed a further burden to iodine intakes on top of that from cessation of milk consumption. Our iodine-specific FFQ had a limited number of items and did not contain foods providing very small quantities of iodine to the diet e.g. fruit, vegetables, snacks, and/or drinks, therefore actual dietary iodine may be slightly greater, but this will be very limited. Iodine supplementation was greatest in the OV group post-intervention with 23% taking a supplement providing iodine quantities above the RNI for iodine (150 µg day^{-1}) which boosted intake in this group (WHO, 2007).

Approximately 90% of ingested iodine is excreted (within 24-48 hours), therefore, median spot UIC is a useful and sensitive biomarker that can be used to predict recent dietary iodine intake (Als *et al*., 2000). However, we did not observe significant changes in median UIC with time or diet.

Additionally, our findings show that there are differences in dietary motivations of different groups tracked in our study that could influence food choice and micronutrient intake. Motivation to follow a vegan diet has been widely studied (De Backer and Hudders, 2014; Fox and Ward, 2008; Mathieu and Dorard, 2016; North *et al*., 2021; Rosenfeld and Burrow, 2017), with the majority studying those who have already transitioned and have relatively stable beliefs.

In line with other studies (Miki *et al*., 2020), we found that environmental motives such as sustainability and climate protection along with ethical and animal related motives (factory farming and animal welfare) were most important to those following a vegan or vegetarian diet at baseline (VV or VegV groups). Individuals following an omnivorous (OO and OV groups) diet listed health as the biggest motivator. Health motives have been suggested to be adopted by individuals agreeing to immediate self-interest (Miki *et al*., 2020). In terms of our study, omnivores may follow vegan diets for personal gain, for example, to provide personal health benefits e.g. weight loss, improved immunity, etc. (Medawar *et al*., 2019). Omnivorous individuals may be less interested in motives that do not directly influence them e.g. animal and planetary health-related motives (Miki *et al*., 2020). There are differences in motivations to follow a vegan diet according to age, with younger individuals being significantly more likely to be driven by animal and environmental motives, in our study individuals in the OV group tended to be older which may account for the difference in motives between groups (Miki *et al*., 2020).

In the 2020 cohort, motivation scores for disease outbreaks for the omnivore-vegan group, and scores for COVID-19 infection for vegetarian-vegans were significantly greater than in other dietary groups. During the COVID-19 pandemic, many consumers shifted their consumption from meat products to plant foods (DEMOS and Food Standards Agency, 2021). Generally, omnivorous individuals had the lowest motivation scores; this result was to be expected, as motivation to transition to a vegan diet must be low given that these individuals eat animal products.

6.5.1 Limitations

A major limitation of our study was the low participant numbers and high attrition rate amongst those who began the study. Whilst we observed nutritional differences, further differences would likely have been seen with a larger study population. Future studies will likely require a more thorough advertising approach as well as reducing participant burden to diminish attrition.

Additionally, we cannot eliminate the possible seasonal implications of this research in the context of food intake, the study was conducted in November-January, it is likely that food intake was not representative of the habitual diet over the holiday period and that individuals may be implementing weight loss regimes in January, thus lowering micronutrient intake (Díaz-Zavala *et al*., 2017). A further challenge faced was that the COVID-19 pandemic influenced UK dietary habits significantly in both the initial months of the pandemic and throughout 2020-21 (DEMOS and Food Standards Agency, 2021). Our study did not assess food availability, food security, or other changes in food habits during the COVID-19 pandemic, which may have influenced our results (DEMOS and Food Standards Agency, 2021). Iodine excretion typically exhibits large intra-day variation and so samples may have recorded peaks in iodine excretion that are not reflective of actual iodine intake (Als *et al*., 2000; Soldin, 2002). Using 24h urine collections would have allowed for a more precise recording of UIC, but this method can be burdensome for participants (Bingham *et al*., 1995; Chen *et al*., 2016; König *et al*., 2011). However, given the novelty of this study, the observation of significant reduction in certain micronutrients, and the increased uptake of individuals pledging to the Veganuary campaign worldwide, we see scope for this investigation to be completed on a larger number of participants in the future to improve generalisability.

6.5.2 Conclusion

Our study shows that short-term vegan diets have a significant effect on the intake of vitamin B12, iodine, SFA and thiamine for individuals who typically follow omnivorous diets. Following a vegan diet in the short-term may benefit omnivores wishing to reduce their SFA intake. However, omnivores without experience of consuming a vegan diet may not be able to plan their diet sufficiently well to meet micronutrient requirements. Participants who lack micronutrient knowledge and/or experience in making vegan meals may select unfortified convenience food items and further limit micronutrient intake. Omnivores pledging to vegan campaigns may wish to seek nutritional advice before switching diets to ensure their nutrient intake is adequate. As this is unlikely for many, in the absence of dietary consultation, there is a need for clear guidance which is visible to all those considering such a dietary change. If vegan diets are continued after a short-term trial such as Veganuary, individuals must ensure they are supplementing appropriately or selecting fortified alternative foods to prevent clinical deficiency symptoms. There is a broader need to improve micronutrient knowledge and intake throughout the UK population regardless of dietary preference and this, alongside a more large-scale assessment of the impact of short-term dietary transition is warranted.

7. MANUSCRIPT 4

Eveleigh, ER, Coneyworth, L, & Welham, SJM. (2023). Iodine-fortified soya milk as a 'nutrient bridge' to improve iodine intake in vegan diets: A clinical trial protocol. *Suitable for submission in Nutrition and Health (Sage).*

Author contributions can be found in **APPENDIX A.**

7.1 Abstract

Iodine deficiency has been detected individuals who do not consume milk, dairy, or substitute cow's milk for non-iodine fortified alternative milks (soya, oat, rice, pea etc.). Recently, iodine-fortified alternative milks have been identified and promoted as a 'nutrient bridge' to improve dietary iodine intake, specifically in vegan populations. However, the effectiveness of iodine fortified alternative milks as an iodine fortification vehicle has yet to be investigated. In this study, we will ask UK adults (>18 – 30y) who follow a vegan diet and regularly consume alternative milk instead of cow's milk to join a 4-week randomized, blind, placebo-controlled study with two parallel groups (control and intervention group). The two groups will be asked to consume 200 ml per day of either an iodine-fortified milk alternative or a similar energy and micronutrient matched placebo unfortified drink. We will assess the difference in iodine intake and status of participants in each group at baseline and at weeks 2 and 4 of the intervention using food diaries, urinary iodine concentration (UIC), salivary iodine, and blood serum measures of thyroid function. This research will be the first study to provide proof-of-concept evidence that iodine fortified alternative milks could improve the iodine intake of those following a vegan diet. If improvements in iodine are observed from baseline to follow-up, this will provide important evidence that could support policy efforts to introduce a mandatory fortification of alternative milks with iodine in the UK.

7.2 Introduction

Iodine is an essential micronutrient required for thyroid hormone synthesis. If iodine requirements (150 $\mu g\ day^{-1}$) are not achieved by dietary intake, iodine deficiency and the development of Iodine Deficiency Disorders (IDDs) can occur (WHO, 2007). IDDs are currently one of the biggest public health problems worldwide (Zimmermann and Andersson, 2021). Iodine sufficiency can be achieved in most circumstances by consumption of iodine rich foods (Bath and Rayman, 2016). Milk and dairy products are predominant sources of iodine in the UK diet, the content of which was improved by farming practices in the 1930s (Bath *et al*., 2012; Bath and Rayman, 2016). White fish, seafood, eggs, and seaweed are other useful sources of iodine (Bath and Rayman, 2016).

The UK has been considered iodine replete for many years. However, current research has revealed that some populations, including pregnant women and women of childbearing age are now considered mild to moderately iodine deficient according to WHO criteria (WHO, 2007). Iodine deficiency has also recently has been detected individuals who do not consume milk, dairy, and other animal derived foods rich in iodine (Eveleigh *et al*., 2020), along with those who substitute cow's milk for non-iodine fortified milk alternatives (soya, oat, rice, pea etc.) (Dineva *et al*., 2020b). Vegans abstain from the use of animal products in the diet and are also recorded to have greater consumption of alternative milks compared to non-vegans (Whitbread *et al*., 2021; Eveleigh *et al*., 2022). For this reason, vegans have been identified to have increased risk of iodine deficiency (Public Health England, 2014). This is of concern as these dietary regimens are frequently being adopted by young women, where the impacts of deficiency would be detrimental to future generations (YouGov, 2022; Sebastiani and Barbero, 2019; Bath and Rayman, 2015). Given the popularity of these diets worldwide and the risk of iodine deficiency dietary restriction could pose, it is important to consider methods of improving iodine intake in those following vegan diets.

Many countries have adopted strategies to improve iodine nutrition, the most common being, universal salt iodisation (USI) (Zimmermann and Andersson, 2021). USI describes the addition of potassium iodate or iodide added to table salt to improve its iodine content (Zimmermann and Andersson, 2021). USI programmes are a successful and cost-effective approach to improve the burden of iodine deficiency worldwide (Zimmermann and Andersson, 2021). The UK has not established an USI initiative (Bath *et al*., 2014b). The reason for this is not clear but may be due to low household salt usage and possible conflicts to successful public health messages encouraging lowered salt intake (Bath *et al*., 2014b). At present, the availability of iodised salt in the UK is poor and products are costly compared to regular salt (Bath *et al*., 2014b). Worldwide, other foods have been fortified with iodine or have had iodised salt added into processing for example, refined water, tea, cereals such as wheat, rice and maize, sugar, seasonings, milk-powders, and sugar (Santos *et al.,* 2019). For iodine fortification to be a successful public health intervention, the selected food items must be appropriate and suitable for the target population (Santos *et al.,* 2019; WHO, 2022). For example, fortification of pork sausages with iodine would not be fitting for those avoiding animal-products for cultural, religious, and/or ethical reasons. Moreover, the selected food must be routinely consumed throughout the year (WHO, 2022). Again, these approaches are yet to be widely adopted in the UK (Bath *et al*., 2014b).

Iodine-fortified alternative milks (containing potassium iodide or iodate) have been identified as a 'nutrient bridge' to improve dietary iodine intake in individual's not consuming milk and those following a vegan diet (Govindji, 2020). The British Dietetic Association (BDA) England Board and the Maternal & Fertility Nutrition Specialist Group completed a project in May 2021 to consider the case for wider iodine fortification of alternative milk drinks in the UK (BDA, 2022b). The BDA has since developed a campaign to improve public awareness of iodine and are working with market leaders to implement iodine fortification strategies targeting alternative milk drinks and other products to ensure products contain an iodine content of at least 25-50 µg per 100 ml to match that of cow's milk (BDA, 2022b).

Additionally, the UK Vegan Society Eatwell Guide recommends daily consumption of 500 ml of fortified alternative milk to meet iodine requirements (Vegan Society, 2020a). Despite this approach being publicised broadly there is yet to be any research investigating the effectiveness of iodine fortified alternative milks to increase dietary iodine. It may be that the iodine fortificant added is not sufficiently absorbed from the food vehicle (alternative milk). Similarly, there may be potential interactions between the iodine fortificant and other nutrients (or goitrogens) present in alternative milks which may interfere with the metabolic uptake of iodine. If bioavailability and possible nutrient-nutrient interactions are not considered, the food vehicle may not improve the iodine status of the target population.

In this project we aim to assess the role of iodine fortified alternative milks as a method to improve iodine intake in those following vegan diets. To investigate the usefulness and applicability of using commercially available iodine fortified alternative milks as a vehicle to achieve optimal iodine status. To explore duration of metabolism/transport of iodine from consumption to excretion using blood and urine samples in iodine deplete individual or 'dose' of iodine fortified alternative milks required to improve iodine nutrition. We also hope that this study will add to our current evidence outlining that vegan are indeed a subgroup with increased risk of deficiency. We propose a hypothesis that states that iodine fortified alternative milks is more effective than non-fortified alternative milks at improving iodine nutrition by $P = < 0.05$.

7.3 Contribution to the field

This will be the first study to assess iodine fortified alternative milks as a 'nutrient bridge'. This research will provide proof-of-concept evidence that iodine fortified alternative milks could improve the iodine intake of those following a vegan diet. This idea has yet to be investigated, and is timely given the efforts of the BDA, the increased popularity of alternative milks, and the move to more sustainable diets globally. Identifying that alternative milks containing iodine can improve iodine intake would reduce the occurrence and mitigate the consequences of IDD to individuals living in the UK.

7.4 Methods

This study protocol was developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist guidelines (SPIRIT, 2022).

7.4.1 Proposed study

In this study, we will ask participants to join a randomized, blind, placebo-controlled study with two parallel groups (control and intervention group). The two groups will receive either an iodine-fortified milk alternative or a similar energy and micronutrient matched placebo unfortified drink. A block randomisation sequence will be used to ensure that numbers in both groups are equal. All the data collection points are compulsory for participants. The study will be conducted at the University of Nottingham, Division of Nutritional Sciences, the Clinical Skills Facility at the Queens Medical Centre (QMC) Nottingham University Hospitals and participant's homes.

7.4.2 Outcomes

Primary outcome will be iodine status by concentrations of iodine in the urine (UIC), with age- and sex-adjusted I:creat ratio, and saliva, in addition to blood (serum) thyroglobulin (Tg) and dietary iodine intake (Als *et al.*, 2000; Pearce and Caldwell, 2016). Secondary outcomes will be an evaluation of the effectiveness of using commercially available iodine fortified alternative milks as a vehicle to achieve optimal iodine status using supermarket cost data.

7.4.3 Ethical approval

The Faculty of Medicine & Health Sciences Research Ethics Committee Nottingham University Hospitals (FMHS) accepted approval for this study involving human participants (Ethics Reference: 317-0821). The Declaration of Helsinki will be followed and informed consent will be received for all participants.

7.4.1 Study population

Participants must meet the following inclusion and exclusion criteria (**Table 7.1**).

Table 7.1. Eligibility criteria for study recruitment.

Inclusion criteria	Exclusion criteria
Participant is willing and able to give informed consent for participation in the study.	History or currently diagnosed thyroid disorders.
Healthy adult females (18-30y) living in Nottingham (UK).	Currently taking any medications (except the contraceptive pill) including thyroid medication or medications containing iodine.
Follow a vegan diet > 3 months.	
Non-pregnant or lactating.	Regular consumption of iodine containing supplements, iodised salt or seaweeds.
Non- consumption of iodine containing supplements, salt or seaweeds.	Pregnant or lactating.
Not currently taking any medications.	Food allergies or intolerance to ingredients in test drinks (e.g. soya).
No history or current thyroid disorders.	Diagnosed blood-borne illnesses e.g. Hep B, HIV etc.
No known concurrent micronutrient deficiencies (e.g. iron).	Having taken part in a research study in the last 3 months involving invasive procedures or an inconvenience allowance
Have access to a fridge in their home.	
Must agree to provide a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2/COVID-19) rapid test result before interacting with researchers.	

7.4.1 Interventions

Participants will be supplied a months' worth of food grade, commercially available iodine-fortified or non-iodine-fortified non-dairy alternative milks (200 ml per day). The test drink will be easy to include in normal everyday diet without worsening dietary intake e.g. sodium, fat, sugar, for alternative milks are naturally lower in all these nutrients (Clegg *et al.,* 2021). The purpose of the test drink is to act as a vehicle to improve daily iodine intake and the placebo drink will be used for comparison. Soya milk was selected as the variety of non-dairy alternative used for test and placebo drinks. Soya remains to be a steady product in the UK (Vegan Society, 2020b). According to the Vegan Society, in 2019 soya held approximately 20% of the alternative milk market and remains dominant in the UK market (Vegan Society, 2020b). A label-based analysis of soya milk available from UK supermarkets was conducted in February-March 2022 and iodine values were established by Inductively Coupled Plasma Mass Spectrometry (ICP-MS) analysis (**Table 7.2**).

Table 7.2. Nutrient content of available soya alternative milk drinks (and semi-skimmed cow's milk for reference) sold in supermarkets in Nottinghamshire between February and March 2022 established by ICP-MS and label-based analysis. Values are mean estimates given as per 200 ml portion.

Item name	Price (£)	Iodine ICP-MS (µg)	Iodine (µg)	Energy (g)	Fat (g)	Saturated (g)	Carbohydrate (g)	Sugar (g)	Fibre (g)	Protein (g)	Salt (g)	Vitamin B2 (mg)	Vitamin B12 (µg)	Vitamin D (µg)	Calcium (mg)
M&S Plant Kitchen Unsweetened Soya Drink[1]	1.00	53.3	45.0	43.0	1.8	0.3	3.2	2.3	0.4	3.3	0.1	-	0.8	1.5	120.0
Semi Skimmed Milk (Non-Organic)[2]	0.88	39.5	30.0	47.0	1.7	1.1	4.5	4.5	0.0	3.4	0.1	0.24	0.9	0.0	120.0
Alpro Soya Growing Up Long Life Drink[1]	1.60	28.3	24.5	64.0	2.1	0.3	8.3	2.5	0.4	2.5	0.0	0.2	0.4	1.5	120.0
Tesco Longlife Soya Drink Sweetened[1]	0.95	26.7	-	44.0	1.9	0.3	3.0	2.5	0.5	3.4	0.1	-	-	-	-
Morrisons Long Life Sweetened Soya Milk Alternative[1]	0.95	26.1	22.0	45.0	1.9	0.3	3.0	2.5	0.5	3.7	0.1	0.2	0.4	-	120.0
Alpro Soya Long Life Drink[1]	1.60	25.5	0.0	42.0	1.9	0.3	2.7	2.5	0.6	3.3	0.1	0.2	1.4	0.8	120.0
ASDA Free From Soya Sweetened[2]	0.85	25.1	25	30.0	1.2	0.2	2.8	2.6	0.5	2	0.13	0.2	0.39	0.77	123
Alpro Soya Chilled Drink[2]	1.55	24.5	22.5	39.0	1.8	0.3	2.5	2.5	0.5	3.0	0.1	0.2	0.4	0.8	120.0

Table continued…

Item name	Price (£)	Iodine ICP-MS (µg)	Iodine (µg)	Energy (g)	Fat (g)	Saturated (g)	Carbohydrate (g)	Sugar (g)	Fibre (g)	Protein (g)	Salt (g)	Vitamin B2 (mg)	Vitamin B12 (µg)	Vitamin D (µg)	Calcium (mg)
Sainsbury's Sweetened Soya Drink[2]	0.95	24.4	-	42.0	1.6	0.3	3.1	2.7	0.5	3.5	0.2	0.2	0.4	0.8	120.0
Morrisons Unsweetened Soya Milk[2]	0.85	22.7	35.0	30.0	1.2	0.2	2.8	2.6	0.5	2.0	0.1	0.2	0.4	-	123.0
ASDA Free From Long Life Soya Drink Sweetened[1]	0.62	14.2	35	30.0	1.2	0.2	2.8	2.6	0.5	2	0.13	0.2	0.39	0.77	123
Alpro No Sugars Organic Soya Long Life Drink[1]	1.60	1.4	0.0	32.0	1.9	0.3	0.0	0.0	0.6	3.3	0.0	0.0	0.0	0.0	0.0
Actileaf Soya Original[1]	0.55	1.3	-	44.0	2.2	0.4	2.8	2.3	0.5	3.2	0.19	0.21	0.38	0.75	120
Morrisons Savers UHT Sweetened Soya Milk Alternative[1]	0.55	1.3	-	44.0	2.1	0.4	3.0	3.0	0.5	3.0	0.1	0.2	0.4	0.8	120.0
Alpro Soya Light Long Life Drink[1]	1.60	1.3	-	28.0	1.2	0.2	1.7	1.5	0.9	2.1	0.1	0.2	0.4	0.8	120.0
Alpro Soya Light Chilled Drink[2]	1.55	1.3	-	22.0	1.2	0.2	0.0	0.0	1.2	2.0	0.1	-	0.2	0.8	120.0

Table continued…

Item name	Price (£)	Iodine ICP-MS (µg)	Iodine (µg)	Energy (g)	Fat (g)	Saturated (g)	Carbohydrate (g)	Sugar (g)	Fibre (g)	Protein (g)	Salt (g)	Vitamin B2 (mg)	Vitamin B12 (µg)	Vitamin D (µg)	Calcium (mg)
Actileaf Soya Unsweetened[1]	0.55	1.2	-	34.0	2.1	0.4	0.5	0.5	0.5	3.4	0.03	0.21	0.38	0.75	120
Morrisons Savers UHT Unsweetened Soya Milk Alternative[1]	0.55	1.2	-	33.0	1.9	0.6	0.7	0.3	0.5	2.9	-	0.2	0.4	0.8	120.0
Alpro Soya No Sugars Chilled Drink[2]	1.55	1.2	-	33.0	1.8	0.3	0.0	0.0	0.6	3.3	0.1	0.2	0.4	0.8	120.0
Sainsbury's Unsweetened Soya Drink[1]	0.85	1.2	-	33.0	1.9	0.3	0.5	0.5	0.6	3.4	0.1	0.2	0.4	0.8	120.0
Sainsbury's Unsweetened Soya Drink[2]	0.95	1.2	-	82.0	4.0	0.5	3.0	0.5	0.5	8.5	0.4	0.2	0.4	0.8	120.0
Tesco Longlife Soya Drink Unsweetened[1]	0.95	1.2	-	38.0	2.1	0.3	1.1	0.5	0.5	3.4	0.1	-	-	-	-
Tesco Organic Longlife Soya Drink Sweetened[1]	1.05	1.2	-	41.0	1.9	0.3	2.4	2.4	0.5	3.4	0.2	-	-	-	-

Table continued…

Item name	Price (£)	Iodine ICP-MS (µg)	Iodine (µg)	Energy (g)	Fat (g)	Saturated (g)	Carbohydrate (g)	Sugar (g)	Fibre (g)	Protein (g)	Salt (g)	Vitamin B2 (mg)	Vitamin B12 (µg)	Vitamin D (µg)	Calcium (mg)
Tesco Organic Longlife Soya Drink Unsweetened[1]	1.05	1.2	-	33.0	1.7	0.3	0.9	0.0	0.0	3.4	0.1	-	-	-	-
Growers Harvest Unsweetened Soya Drink[1]	0.60	1.2	-	28.0	1.3	0.2	0.7	0.3	0.5	3.0	0.1	-	-	-	-
Morrisons Long Life Unsweetened Soya Milk Alternative[1]	0.95	1.1	-	36.0	2.1	0.4	0.5	0.3	0.5	3.4	0.0	0.2	0.4	0.8	120.0
Provamel Organic Soya No Sugars Drink[1]	1.60	1.1	-	35.0	2.1	0.4	0.0	0.0	0.6	3.7	0.0	-	-	-	-
Sainsbury's Sweetened Soya Drink[1]	0.85	1.1	-	42.0	1.9	0.3	2.6	2.5	0.6	3.4	0.1	0.2	0.4	0.8	120.0
Alpro Soya No Sugars Long Life Drink[1]	1.60	1.0	0.0	33.0	1.8	0.3	0.0	0.0	0.6	3.3	0.1	0.2	0.4	0.8	120.0
Alpro Plant Protein Original Soya Drink[1]	1.65	1.0	-	57.0	2.8	0.5	2.5	2.5	0.9	5.0	0.1	0.2	0.4	0.8	120.0
Lidl Just Free Soya Sweetened Milk Alternative[1]	0.59	0.7	-	42.0	1.9	0.3	2.6	2.4	0.6	3.4	0.14	0.21	0.38	0.75	120

Table continued…

Item name	Price (£)	Iodine ICP-MS (µg)	Iodine (µg)	Energ-y (g)	Fat (g)	Satur-ated (g)	Carb-ohydrate (g)	Sugar (g)	Fibre (g)	Prote-in (g)	Salt (g)	Vita-min B2 (mg)	Vita-min B12 (µg)	Vita-min D (µg)	Calci-um (mg)
Lidl Just Free Soya Unsweetened Milk Alternative[1]	0.59	0.6	-	34.0	1.9	0.3	0.5	0.5	0.6	3.4	0.03	0.21	0.38	0.75	120
Morrisons Sweetened Soya Milk[2]	0.85	0.4	-	42.0	1.9	0.3	2.7	2.6	0.3	3.3	0.1	0.2	0.4	0.8	120.0
Linda McCartney's Organic Soya Drink[1]	1.50	0.4	-	41.0	2.1	0.6	2.0	0.8	0.2	3.5	0.1	-	-	-	-
ASDA Unsweetened Soya Drink[1]	0.62	0.2	-	19.0	1.1	0.2	0.5	0.5	0.5	2	0.13	-	-	-	-

[1]Ultra-high temperature processing (UHT); [2]Chilled.

The following milks were selected as intervention and control substances (**Table 7.3**).

Table 7.3. Nutritional composition per 100 ml of test milk to be used as intervention and control products.

Test milks	Iodine-fortified (intervention)	Un-fortified (control)
Brand	Alpro	Morrisons
Type	Soya (Chilled)	Soya (UHT)
Cost (£)	0.14	0.09
Iodine (µg)	22.50	0.00
Energy (kcal)	39.00	42.00
Fat (g)	1.80	1.90
Saturated (g)	0.30	0.30
Carbohydrate (g)	2.50	2.70
Sugars (g)	2.50	2.60
Fibre (g)	0.50	0.30
Protein (g)	3.00	3.30
Salt (g)	0.08	0.13
Vitamin B2 (µg)	0.21	0.20
Vitamin B12 (µg)	0.38	0.40
Vitamin D (µg)	0.75	0.80
Calcium (mg)	120.00	120.00
Ingredients	Soya Base (Water, Hulled Soya Beans (8%)), Sugar, Acidity Regulators (Potassium Phosphates), Calcium (Calcium Carbonate), Flavouring, Sea Salt, Stabiliser (Gellan Gum), Potassium Iodide, Vitamins (B2, B12, D2)	Water, Soybean (12%), Sugar, Calcium Phosphates, Salt, Stabiliser (Gellan Gum), Vitamin B12, Vitamin D, Vitamin B2
Allergens	Soya	Soya

7.4.1 Study procedures and timeline

This study is a two-armed, randomized, single blind, placebo-controlled supplementation pilot trial to be conducted in Nottingham, UK. Participants will be randomly allocated into a test or placebo groups for the duration of the study (4 weeks). Individuals in the test group will receive an iodine-fortified non-dairy alternative milk and the placebo group will be provided an un-iodine-fortified non-dairy alternative milk. The study protocol is outlined in **Figure 7.1**.

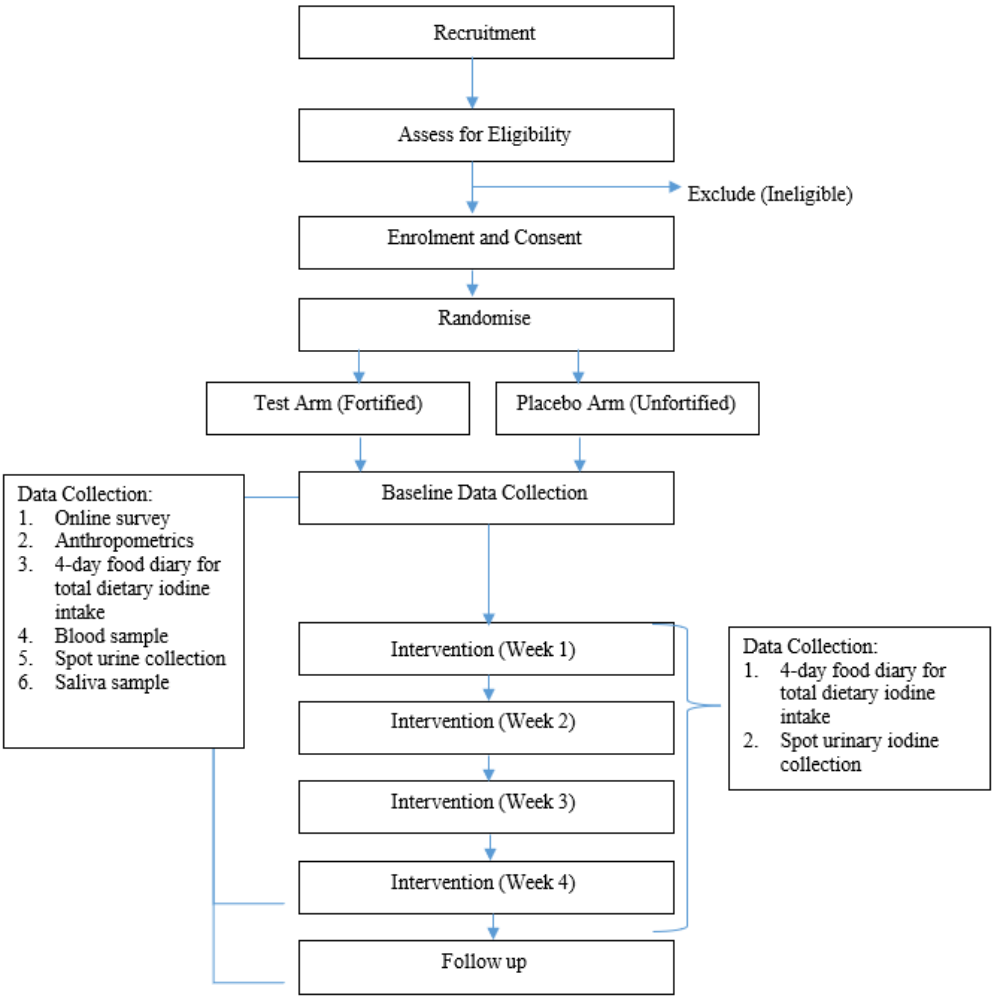


Figure 7.1. Flow diagram of study arms and protocol.

7.4.1.1 Recruitment

This research project aims to recruit adults (>18 – 30 y) from UK households who follow a vegan diet and regularly consume alternative milk instead of cow's milk. The opportunity to take part in the study will be advertised via several methods including social media (Facebook, Twitter, and Instagram), community groups. Particularly those related to vegan diets and nutrition, University of Nottingham newsletters and press releases. All participants will be assessed for eligibility by researchers prior to study enrolment as previously described (see **Table 7.1**).

7.4.1.2 Sample size

Power calculations were conducted using basis of x1 control group x1 intervention group. The effect size was recorded from previous studies investigating consumption of non-iodine-fortified alternative milks in adults following a vegan diet. A mean iodine intake of 43 µg day^{-1} with a population standard deviation of 41 µg day^{-1} and a recruitment bias of 1 was used. The test drink will provide an additional 45 µg day^{-1} of iodine to dietary intake. For group 2, a mean of 88 µg day^{-1}. For a power of 80% and α-error of 5% the sample size was calculated as a minimum of 13 per group using the "ClinCalc" online calculator (Clincalc, 2021).

7.4.1.3 Randomisation

MinimPy will be used for randomisation, this software is a free, open-source, desktop minimization program, which allocates subjects to treatment groups (Saghaei, and Saghaei, 2011). This method will prevent inconstant group sizes. Participants will be allocated to intervention arm (iodine- fortified alternative milk) or control arm (unfortified alternative milk).

7.4.1.4 Baseline data collection

Individuals who are interested and eligible for the study will be invited to attend a baseline data collection session at the Clinical Skills Facility at the QMC Nottingham University Hospitals.

Study researchers will explain the research methodology to participants and ask for written confirmed consent before collection of baseline data. Firstly, researchers will ask to take participants anthropometric data (height in cm and weight in kg). Next, participants will be asked to complete a baseline survey where clinical and sociodemographic characteristics will be collected including sex, date of birth (DOB), postcode of current address, education, household income, alcohol intake, smoking status, physical activity status, use of dietary supplements or medications, and presence of chronic diseases. The online questionnaire will also contain questions relating to alternative milk preference and usage, along with, iodine knowledge (as used by Eveleigh *et al*., 2022). The final section of the survey will contain an iodine specific food frequency questionnaire (FFQ) previously designed by researchers at the University of Nottingham (Eveleigh *et al.,* 2022). Online survey results will be printed and filed in the Case Report Form (CRF). Participants will then be asked to collect a 50 ml mid-stream spot urine sample, in a universal sterile (ThermoFisher Scientific™), in the bathrooms provided. All participants will be verbally explained how to collect urine samples by researchers. Individuals will be given a waterproof opaque envelope to conceal completed samples. Urine samples will be stored in a labelled biological specimen box at -80°C and defrosted before analysis. Additionally, participants will be asked to provide a 5 ml saliva sample. Two 5 ml venous blood samples will then be collected by a trained phlebotomist. Samples will be stored on ice to be centrifuged and stored within 30 minutes. The procedure of blood plasma processing has been described previously. Participants will be asked to wait for 10 minutes following blood samples and will be given the opportunity to ask any further questions. Participants will be given a participant pack containing: a personal copy of the participant information sheet, paper copied 4-day food and fluid diaries (ensuring at least one weekend day of records) to complete in the days following baseline sessions, and throughout the intervention (weeks 2 and 3), universal sterile tubes (ThermoFisher Scientific™) to collect mid-stream spot urine samples at week 2 and week 4 of the intervention. Participants will be given a supply of the control or test drink (dependant on group allocation) that will last throughout the intervention and instructions for consumption over the intervention period.

Individuals will also be verbally explained the intervention timeline to ensure accurate data collection at each time-point.

7.4.1.5 Intervention period

The intervention period will begin after 4-days after the attendance of the baseline data collection session, following the completion of the baseline 4-day food diary. During the intervention period (4 weeks), participants will be asked to consume 200 ml per day of the test or control drink, which was provided at baseline, throughout the duration of the intervention. Individuals will be blinded as to what milk they will be consuming. The drinks packaging will be covered with plastic wrap designed for ultra discreet packaging. Participants will be asked not to consume any other alternative milk in this time unless it is unfortified with iodine. Participants will be asked to complete a mid-stream spot urine sample and 4-day food and fluid diary at weeks 2 and 4. Researchers will pick up urine samples from participant's home address. Safeguarding and lone working procedures will be followed when collecting samples along with the use of personal protective equipment (PPE) and sample collection materials to prevent spillage or contamination e.g. labelling of biological fluids.

7.4.1.6 Follow-up data collection

Participants will be asked to attend a follow-up session on the final day of the intervention period (week 4) at the Clinical Skills Facility at the QMC Nottingham University Hospitals. The follow-up session follows a similar regime as the baseline sessions. Anthropometric data (height in cm and weight in kg) will be recorded. Participants will be asked to complete an online follow-up survey where clinical and sociodemographic characteristics that may have changed since baseline will be addressed for example: postcode of current address, education, household income, alcohol intake, etc. The final section of the survey will contain an iodine specific FFQ as before to be completed. Online survey results will be printed and filed in the Case Report Form (CRF). Participants will be asked to collect a 50 ml mid-stream spot urine sample and saliva sample as described at baseline.

Two 5 ml venous blood samples will then be collected by a trained phlebotomist as before. Participants will be asked to wait for 10 minutes following blood sample collection.

Participants will be asked if they would like to take part in a 15-minute feedback interview to evaluate the clinical trial procedure from a non-researcher's perspective and to assess feasibility of alternative milks as a vehicle for iodine fortification. Participants will be asked if they would like to be followed up in 3-months' time to assess their iodine intake post-study and will be given the opportunity to ask any further questions before the trial is considered complete.

7.4.1.7 Data collection, management, and analysis

All data collected will be handled by trained researchers and will be stored in paper and/or online CRF. The paper CRF will be stored in a locked locker in office at the University of Nottingham and will only be accessible by research involved in the project. All paper-copied information (e.g. consent forms, food diaries, etc.) will be filed in the CRF, other information such as Nutritics reports, and survey responses will be printed before storage. Online Case Report Forms will be created in Microsoft OneDrive to store any electronic data (e.g. excel spreadsheets of participant data). Biological data will be collected and stored in locked fridges and freezers prior to analysis. Following analysis coded data will be transcribed onto excel format for storage. Data will be archived following study completion and data publication. All data will be archived in accordance with Biotechnology and Biological Sciences Research Council (BBSRC) funding requirements. Our data involves people-based data and therefore should be retained and preserved for the future to allow others to re-evaluate. We will not archive sensitive information or information regarding to participant addressees, emails etc. Metadata which is not relevant to future study and are not vital for data findings will be removed and deleted. We will deposit our data with the University of Nottingham data repository. This is because there is no specific database used for our research field. If the data is submitted for publication, the publishers recommended disciplinary data repository will be used. This will allow the data to be formally cited using a site DOI. A license will be selected according to funding requirements.

7.4.1.1 Laboratory methods

Biological samples will be transported upright packaged in zip plastic zip lock bags in a leak-proof lined specimen container labelled with biological hazard symbols and description of samples inside by researchers to North Laboratory at the University of Nottingham Sutton Bonington Campus for storage and analysis. Urine samples will be centrifuged (Beckman GS-6R Refrigerated Centrifuge, Beckman, California, USA) for 10 minutes at 1500-2000 rpm (252 g). Saliva samples will be briefly span (Beckman GS-6R Refrigerated Centrifuge, Beckman, California, USA) at 1500-2000 rpm. Whole blood samples will be centrifuged (Heraeus Multifuge 3SR Plus, Thermo Scientific, Loughborough, UK) for 15 minutes (room temperature) at 1100 g. The resulting supernatant will be removed (serum). Aliquots of all biological samples will be pipetted into Eppendorf tubes and will be stored upright at -80ºC.

UIC and saliva iodine content will be measured by inductively coupled plasma mass spectrometry (ICP-MS; Thermo-Fisher Scientific Xseries II, Loughborough UK), using PlasmaLab software (version 2.5.1.276). All samples will be analysed in duplicate with an internal standard CRM (Seronorm). Saliva samples will be processed according to the protocol outlined by Dekker et al (2021). Iodine status will be estimated according to median UIC value by the WHO cut-off for iodine adequacy for adults. Values of UIC > 100 μg L^{-1} will be classified as "sufficient" and < 100 μg L^{-1} as "deficient". The severity of deficiency will be categorised as 50-99 μg L^{-1} mild, 20-49 μg L^{-1} moderate, < 20 μg L^{-1} severe, and ≥ 300 μg L^{-1} as excessive (WHO *et al*., 2007). Iodine deficiency will also be determined using the EAR cut-off method described by Zimmermann and Andersson (2012). Serum Tg will be assessed using Abcam Ltd. Human Thyroglobulin Enzyme-Linked Immunosorbent Assay (ELISA) Kit (ab155441) according to the manufacturer's instructions.

7.4.1.2 Statistical methods

Genstat and SPSS will be used for analysis. Data will be assessed for normality. Normally distributed data will be analysed by ANOVA with treatment structure Timepoint*Treatment, where Timepoint refers to baseline or end data points and treatment refers to the two groups. A block for ID will be added. Non-normally distributed will be analysed using Mann Whitney U.

7.4.1.3 Study monitoring

7.4.1.3.1 Adverse events

The risk of participating in the study are very low as participants will be consuming a safe food product that is commercially available and allergens/intolerances will be screened for during eligibility checks. It is possible that an abrupt increase in iodine may result in a temporary 'stunning' effect of the thyroid in those with very low stores of iodine. Hence, dietary iodine intake and iodine status will be assessed closely at baseline and throughout the study period.

However, we accept that adverse reactions are possible. All adverse events will be recorded in the CRF and Adverse Event Form. All Adverse events will be discussed with the research team to assess the severity, in the meantime, participants will be asked to discontinue consumption of the study drink.

A serious adverse event (SAE) occurring to a participant will be reported to UoN FMHS where, in the opinion of the Principal Investigator (PI), the event was 'related' (resulted from administration of any of the research procedures) and 'unexpected' (the type of event is not listed on this form as an expected occurrence). Reports of related and unexpected SAE's will be submitted by the PI within 7 days of the event. For fatal and life-threatening Suspected Unexpected Serious Adverse Reaction (SUSARs), this will be done no later than 3 calendar days after the PI is first aware of the reaction. Any additional relevant information will be reported within 7 calendar days of the initial report. Adverse events occurring as a response to this study will be communicated to relevant regulatory authorities.

7.4.1.4 Ethics

7.4.1.4.1 Amendments to study protocol

Any significant changes to study protocol will require a formal amendment via FMHS before implementation.

7.4.1.4.2 Confidentiality

Nutrition and food can be a sensitive subject for some individuals and the data that we are collecting does contain personal data.

Consent procedures will be tailored for the specific research context, methods and sample, the nature of the data (personal, sensitive, level of detail), the format of the data (surveys, written, recordings) and the planned data uses and handling. We will be providing participants with a participant number; this number will be randomly selected and will be anonymous.

The participant number will be used for all data collection. This ensures that the participants cannot be identified from the data. We plan to keep raw/source data and any pseudonymisation key-file containing personal information separate from the de-identified data. We will use different folder on Microsoft Office to complete this.

Individuals will have a copy of the participant information sheet, which will outline in detail how their data will be used throughout the study and will be linked to documents written by the University about privacy and General Data Protection Regulation (GDPR).

7.4.1.4.3 Dissemination

As mentioned previously, we will deposit our data with the University of Nottingham data repository to allow our data to be accessed by other researchers in the future. The results of this study will be presented at seminars and conferences. Data will also be published in peer-reviewed research journals following authorship eligibility guidelines. Participants taking part in the study will be informed of the results by email.

7.4.2 Summary

Research has demonstrated that vegans have increased risk of iodine deficiency. To improve the iodine intake of individuals following vegan diets, iodine fortified alternative milks have been proposed as a ‘nutrient bridge’.

The BDA England Board, the Maternal & Fertility Nutrition Specialist Group (BDA, 2022b), and the Vegan Society have advocated and promoted the use of fortified alternative milks as a good source of iodine (Vegan Society, 2020a). However, our understanding of these products as an appropriate and feasible way to access iodine for vegan individuals remains limited and has not been demonstrated in human participants.

The results of this study will provide novel evidence of the use of iodine fortified alternative milks as a method to improve iodine intake in groups that do not consume cow's milk. If improvements in iodine are observed from baseline to follow-up, this will provide important evidence that could support policy efforts to introduce a mandatory fortification of alternative milks with iodine in the UK.

If our study results show that iodine fortified alternative milks are feasible and can substantially improve the iodine intake of the UK population, this will lead to improved iodine intake and health outcomes across the nation. Further, this project is one of the first of its kind investigating methods to improve the iodine nutrition in vegan groups.

8. MANUSCRIPT 5

Eveleigh, ER, Coneyworth, L, & Welham, SJM. (2023). Systematic review and meta-analysis of iodine nutrition in modern vegan and vegetarian diets. *Br. J. Nutr*, 1-15.

Author contributions can be found in **APPENDIX A**.

8.1 Abstract

Vegan and vegetarian diets are widely supported and adopted, but individuals following such diets remain at greater risk of iodine deficiency. This systematic review and meta-analysis were conducted to assess the iodine intake and status in adults following a vegan or vegetarian diet in the modern day. A systematic review and quality assessment were conducted from October 2020-December 2022 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidance. Studies were identified in Ovid MEDLINE, Web of Science, PubMed, and Scopus. Eleven articles were eligible for review containing 4,421 adults (aged ≥ 18 years). Vegan groups had the lowest median urinary iodine concentration (mUIC) (12.2 L^{-1}). None of the dietary groups had mUIC within the optimal range for iodine status (100-299 µg L^{-1}) (World Health Organisation). Vegan diets had the poorest iodine intake (17.3 µg day^{-1}) and were strongly associated with lower iodine intake (P = < 0.001) compared to omnivorous diets. Lower intake in vegan diets were influenced by gender (P = 0.007), the presence of voluntary or absence of Universal Salt Iodisation (USI) programmes (P = 0.01 & P = < 0.001) and living in a country with adequate iodine nutrition (P = < 0.001). Vegetarians and particularly vegans, living in countries with no current USI programme continue to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake. Further research into the usefulness of mandatory fortification of vegan appropriate foods is required.

8.2 Introduction

Environmentally sustainable diets, that are rich in plant foods, are advocated as a solution to feeding the growing human population and reducing the impact of our food systems on the planet (The EAT-Lancet Commission, 2022). Today, vegetarian and vegan diets are widely supported and adopted throughout the population, particularly among young people and women (Allès *et al*., 2017; Martinelli and Berkmanienė, 2018; YouGov, 2022). Vegans do not consume any animal products, whereas vegetarians exclude only meat and fish (Phillips, 2005). The inclusion of fish in a vegetarian diet is often called a pescatarian diet (Phillips, 2005). There are also growing numbers of people in Western countries reducing their animal product consumption who define as flexitarian (Phillips, 2005; YouGov, 2022).

The rising interest in plant-based eating has increased demand for a diversity of commercially available alternative products (e.g. plant-based milk) suitable for vegetarians, vegans, or those wishing to reduce their intake of animal products (Mintel, 2018, 2019). Fast food chains have similarly designed animal-free products targeting consumers (Dunn *et al*., 2021; Mintel, 2018, 2019) and restaurants have expanded menu options to suit all dietary requirements (Dunn *et al*., 2021; Mintel, 2018, 2019). Individuals now have a more diverse pool of foods suitable for their dietary preferences than before, permitting huge variations in food and nutrient intake. However, although the breadth of choice is beneficial for diet diversity, there continue to be difficulties in achieving adequate quantities of some micronutrients, most notably iodine (Gallagher *et al*., 2022).

Iodine is essential for the synthesis of the thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) and is dependent on adequate supply via the diet (Ahad and Ganie, 2010). The World Health Organisation (WHO) recommends a daily intake of 150 µg day^{-1} for adults (18+ y) and 250 µg day^{-1} for pregnant and lactating women to maintain thyroid synthesis and prevent the development of associated 'iodine deficiency disorders' (IDDs) (Ahad and Ganie, 2010; WHO, 2007). However, iodine recommendations are often country-specific, in the UK a Reference Nutrient Intake (RNI) of 140 µg day^{-1} is advised for adults (19-50 y) (British Nutrition Foundation, 2021a).

The UK currently has no RNI set for pregnant/lactating women (British Nutrition Foundation, 2021a). The thyroid hormones have a vital role in the regulation of metabolism, growth, and foetal neurological development (Hess and Zimmermann, 2013; Zimmermann, 2011, 2009). IDDs include hypothyroidism, goitre, the formation of thyroid nodules, and cretinism (as a consequence of gestational exposure) (Ahad and Ganie, 2010; Eastman and Zimmermann, 2018; Zimmermann, 2009a). Iodine excess (consumption of >1000 μg day^{-1} iodine) can also have health repercussions, including hypo- and hyperthyroidism (Bürgi, 2010; Leung and Braverman, 2014).

Iodine deficiency remains a public health issue worldwide (Zimmermann and Andersson, 2021), although the number of countries with adequate iodine intake has nearly doubled over the past 20 years (Iodine Global Network, 2021). Improvements in global iodine intake and status have largely been due to the effective implementation of universal salt iodisation (USI) (Iodine Global Network, 2021; Zimmermann and Andersson, 2021). However, not all countries currently facilitate USI programmes, and other factors (e.g. low household coverage, low usage, low or no accessibility, and inadequate quality) may limit its effectiveness (Zimmermann and Andersson, 2021). Currently in industrialised countries, the predominant dietary iodine sources are iodised salt, cow′s milk, dairy products, fish and seafood, eggs and fortified foods (e.g. bread) (Zimmermann, 2011). Plant foods are generally low in iodine, unless bio-fortified, with seaweed being an exception (Bath and Rayman, 2016; Golubkina *et al*., 2021). The iodine content of seaweed is highly variable and can be linked to iodine excess in certain populations (Bouga and Combet, 2015; Smyth and Karger, 2021; Yeh *et al*., 2014).

Individuals who restrict iodine-rich foods from their diet or are solely dependent on iodine provision from plant foods are at risk of iodine deficiency (Eveleigh *et al*., 2020). The increased risk of iodine deficiency in vegans and vegetarians was highlighted by the Scientific Advisory Committee on Nutrition (SACN) in 2014 (Public Health England, 2014). Since its publication, several studies have assessed iodine nutrition to be poorer in these groups (Allès *et al*., 2017; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; Kristensen *et al*., 2015; Nebl *et al*., 2019; Sobiecki *et al*., 2016).

Innovation in the vegan and vegetarian food sector has resulted in a rapid proliferation of products. Many items, such as meat alternatives are not often fortified with iodine (Pointke and Pawelzik, 2022; Nicol *et al*., 2022). Alternative dairy products such as alternative "milks" and "yogurts" are now regularly fortified with vitamin B12, D, and calcium (Bath *et al.*, 2017; Clegg *et al*., 2021; Dineva *et al*., 2020b; Nicol *et al*., 2022), but rarely with iodine (Nicol *et al*., 2022; Bath *et al*., 2017). Additionally, iodine supplements are still not universally consumed by individuals following vegan and vegetarian diets (Eveleigh *et al*., 2022).

We previously reviewed the literature on iodine intake and the status of vegans and vegetarians living in industrialised countries in 2020 (Eveleigh *et al*., 2020). Our study concluded that those individuals' not consuming seaweed or iodine-containing supplements were at risk of poor iodine nutrition. However, half of the studies included in our review were published before meat-free diets entered the mainstream in many countries (2010) and therefore, may not represent the diversity of 'modern-day' vegan and vegetarian diets observed in today's society (Eveleigh *et al*., 2020). Following the publication of our review many new studies have examined iodine in the diet of vegans and vegetarians. Iodine deficiency is still a major public health issue and given that sustainable diets are being promoted in many countries worldwide, a re-evaluation of the literature is needed to monitor iodine nutrition and deficiency in those who select to follow a vegan or vegetarian diet in the modern day.

This review aims to assess the iodine intake and status in adults following a vegan or vegetarian diet in the modern day. The objectives included (1) determination of the iodine intake and food consumption in vegan and vegetarian adults; (2) assessment of the iodine status and prevalence of iodine deficiency using urinary iodine concentration (UIC); (3) comparison of the iodine intake, status, and prevalence of deficiency between modern day vegans, vegetarians, and omnivores; (4) completion of a meta-analysis to provide a more precise estimate of the effect size results of individual studies.

We hypothesise that vegans and vegetarians will continue to be a sub-group at risk of iodine deficiency, however, given the increase in the availability of iodine fortified foods suitable for individuals following these diets, iodine deficiency may be less severe.

8.3 Methods

8.3.1 Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses of Observational Studies (MOOSE) checklist were used to complete this systematic review (Moher *et al*., 2009; Stroup *et al*., 2000). A systematic search of the literature was performed from 5 October 2020 to 16 December 2022. Electronic databases (Ovid MEDLINE, Web of Science, PubMed, and Scopus) were explored. Searches were completed with appropriate text terms with truncation, and medical subject headings. Our search strategy is the same as that described in our previous systematic review (Eveleigh *et al*., 2020). All database searches were refined by 'humans, adults (aged > 18 years), English language, full-papers, and publications between January 2020-December 2022'. Search lists were exported into EndNoteTM before the removal of duplicates. Additional studies were identified via reference lists of relevant published materials and citation searching. A review protocol has not been published prior to our literature search.

8.3.2 Population and outcomes

The population–intervention–comparison–outcome (PICOS) formulation was used to assess study eligibility (**Table 8.1**) (Eriksen and Frandsen, 2018).

Table 8.1. Population–intervention–comparison–outcome (PICOS) criteria for study inclusion and exclusion (Eriksen and Frandsen, 2018).

Criteria Category	Inclusion	Exclusion
Population	Adults (aged ≥ 18 y)	Individuals (aged < 18 y), unless results display separate data; adults residing in developing countries; populations with a high prevalence of thyroid disorders.
Intervention/exposure	Participants with any type of dietary preference or restriction. Voluntary or otherwise.	Use of a dietary grouping without defining diet characteristics.
Comparators	Differing dietary preference or restriction.	None.
Outcome measure	Iodine intake or status measured by urinary iodine concentration (UIC) or analysis of dietary records.	No analysis of iodine intake or status; use of thyroid measures alone for iodine intake and status.
Study design	Any study design with relevant outcomes.	None.

8.3.3 Data extraction

Extraction forms identified study information including author name, journal, publication date, study location, participant characteristics, dietary groups addressed and grouping method, relevant outcome measures (length of diet, iodine intake, status, and supplement use), and any key findings or study considerations (limitations, etc.). Where possible, gendered data were considered separately. Data extraction was completed by the first author.

8.3.4 Classification of outcomes

The nomenclature defining dietary preferences can vary, therefore, dietary groups were compared according to the following classifications (**Table 8.2**). We also recorded the method of dietary grouping used and the length of dietary adherence for each study. For articles where individuals are following vegan/vegetarian/etc. diets as part of an intervention, post-intervention data was used.

Table 8.2. Definition of common vegetarian and vegan diet types.

Type[1]	Definition
Flexitarian	Occasionally excludes meat and poultry but remains consumption of fish, eggs, and dairy
Pescatarian	Excludes meat and poultry but remains consumption of fish, eggs, and dairy
Lacto-ovo vegetarian	Excludes meat, poultry, and fish but remains consumption of dairy and eggs
Lacto vegetarian	Excludes meat, poultry, fish, and eggs but remains consumption of dairy
Ovo vegetarian	Excludes meat, poultry, fish, and dairy but remains consumption of eggs
Vegan	Excludes all animal products (meat, poultry, fish, eggs, and dairy)

[1]Diet definitions from Phillips 2005.

The WHO criteria were used to assess iodine status using UIC (WHO, 2017). Therefore, a median UIC >100 μg L^{-1} was considered "sufficient" and a median UIC <100 μg L^{-1} was considered "deficient", with severity of IDD based on UIC being: 50-99 μg L^{-1} mild, 20-49 μg L^{-1} moderate, and <20 μg L^{-1} severe (WHO, 2007). Recommended adequate iodine intake varies across countries, so the WHO recommended dietary allowance (RDA) for adults and adolescents of 150 μg day^{-1} was used to assess iodine intake between studies (WHO, 2007).

8.3.5 Quality assessment

The quality of observational cohort, cross-sectional, and case-control (matched-pairs) studies was assessed using the Newcastle-Ottawa scale (good, fair, or poor) (Wells *et al*., 2022). The quality of modelling studies was not assessed (n = 1). Quality assessment was completed by the first author and was reviewed by the study team (**Supplementary Table 15**).

8.3.6 Statistical analysis

We performed meta-analysis and subgroup analysis to compare iodine intake and status in vegan and vegetarian diets compared to omnivores using the software RevMan designed by Cochrane (Cochrane Training, 2022).

We assumed that the studies are heterogenous, therefore we selected a random effects mode. For studies reporting data as medians (IQR), we estimated the sample mean and standard deviation using calculations as described by Wan *et al* (Wan *et al*., 2014). We separated comparisons of vegan and vegetarian diets into different forest plots to avoid arbitrary omission of relevant groups and double counting of participants. If the test for overall effect were P = < 0.05, the following covariables for subgroup analysis for both meta-analyses were used: gender (female v. mixed gender), USI status, and iodine status by country. Countries were categorised into iodine deficient or sufficient according to the Iodine Global Network (IGN) Scorecard (Iodine Global Network, 2021).

8.4 Results

The initial literature search yielded 1208 articles. Following screening and exclusion, 28 reports were assessed for eligibility. The PRISMA 2020 flow diagram outlines the study selection process for this review (**Figure 8.1**) (Page *et al.*, 2020). A total of 11 articles were identified as eligible for review inclusion (**Table 8.3**).

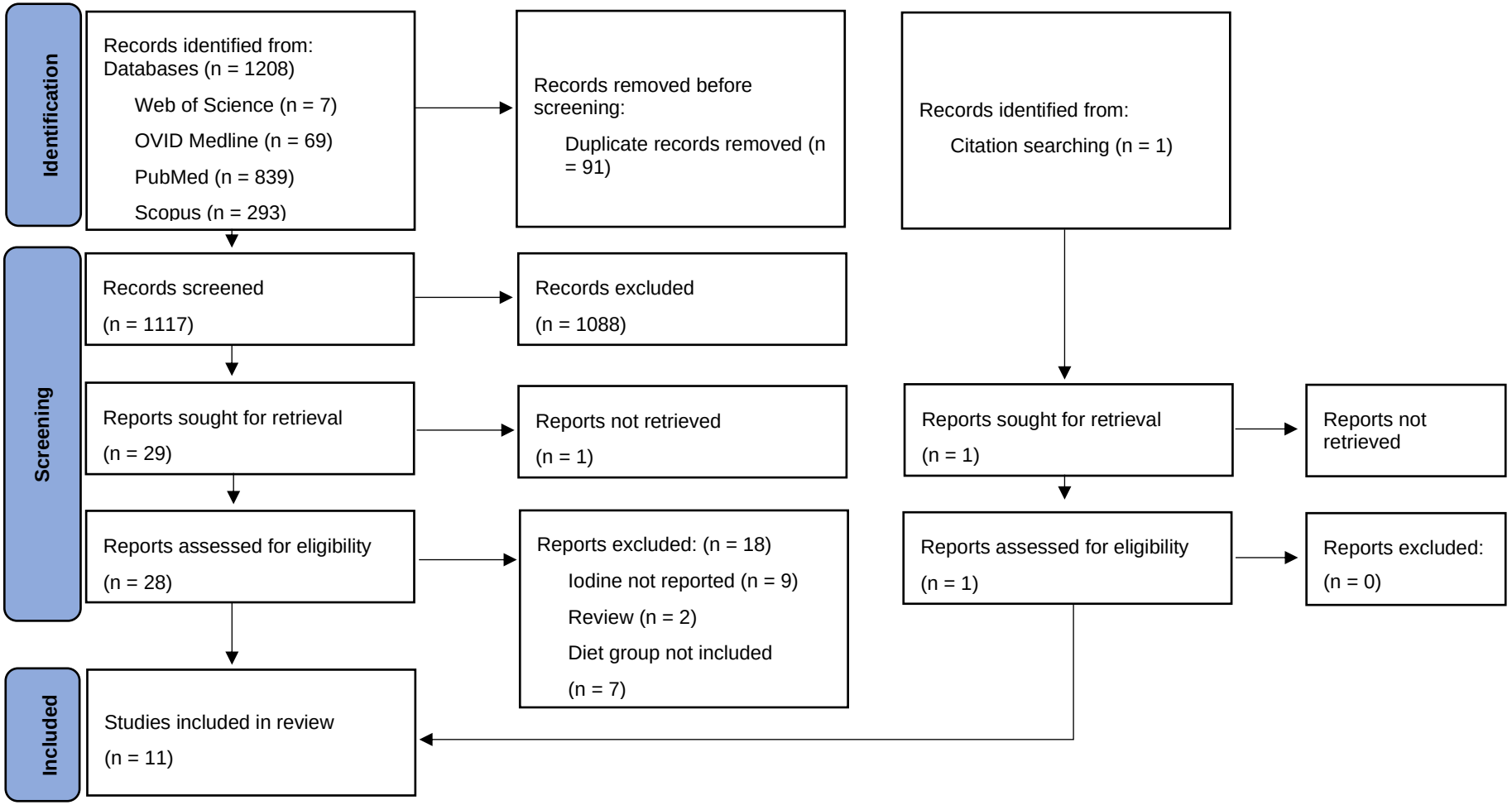


Figure 8.1. PRISMA 2020 flow diagram of the study selection process (Page *et al.*, 2021).

Table 8.3. Studies investigating iodine among vegans, vegetarians, and omnivores published after January 2020.

Study, Year	Study Design	Location	Dietary Groups	Sample (n) (Female, Male)	Method of Dietary Classification	Grouping adherence length
Abraham *et al.*, 2022	Cross-Sectional	Berlin, Germany	Strict raw	16 (5, 11)	Classified according to RBVD study criteria. (Not self-selected)	Diet for at least four months (raw food diet) or at least one year
			Vegan	32 (18, 14)		
			Omnivore	27 (14, 13)		
Blaurock *et al.*, 2021	Cross-Sectional	Munich, Germany	Vegetarian	31 (31, 0)	Self-assessed	NA
			Omnivore	30 (30, 0)		
Dawczynski *et al.*, 2022	Cross-sectional	Jena, Halle, and Leipzig, Germany	Vegan	58 (41, 17)	Self-assessed. Food intake data were also checked by researchers for discrepancies in diet selection	3.0 (3.0)[1] 6.0 (10.)[1] 8.0 (17.8)[1] 32.0 (20.0)[1]
			Vegetarian (lacto-ovo)	65 (47, 18)		
			Flexitarian	70 (56, 14)		
			Omnivore	65 (40, 25)		
Eveleigh *et al.*, 2022	Cross-sectional	Nottingham, UK	Vegan (2016-17)	12 (12, 0)	Self-assessed. Food intake data were also checked by researchers for discrepancies in diet selection	>6 months
			Vegan (2019)	7 (4,3)		
			Vegetarian (including pescatarians) (2016-17)	5 (5, 0)		
			Vegetarian (including pescatarians) (2019)	10 (9, 1)		
			Omnivore (2016-17)	43 (36, 7)		
			Omnivore (2019)	19 (14, 5)		

Table continued…

Study, Year	Study Design	Location	Dietary Groups	Sample (n) (Female, Male)	Method of Dietary Classification	Grouping adherence length
Fallon and Dillon, 2020	Cross-Sectional	Lancashire, UK	Vegan	20 (20, 0)	The diaries were cross-checked to ensure they had correctly identified themselves	NA
			Vegetarian	16 (16, 0)		
			Omnivore	26 (26, 0)		
García-Morant *et al.*, 2020	Cross-Sectional	Spain	Vegan	102 (67, 35)	NA	NA
			Omnivore	3323 (1732, 1587)		
Groufh-Jacobsen *et al.*, 2020	Cross-Sectional	Oslo, Norway	Vegan	115 (74, 41)	Classified by researchers according to questions addressing animal product consumption	≥6 months
			Vegetarian	55 (43, 12)		
			Pescatarian	35 (31, 4)		
Jakše *et al.*, 2021	Cross-Sectional	Slovenia	Vegan	51 (34, 17)	Self-assessed. Food intake data was also checked by researchers for discrepancies in diet	Participants should have had the same (current) dietary pattern for ≥1 year
			Omnivore (non-vegan)	29 (16, 13)		

Table continued…

Study, Year	Study Design	Location	Dietary Groups	Sample (n) (Female, Male)	Method of Dietary Classification	Grouping adherence length
Kowalska *et al.*, 2020	Data Modelling	Poland	Vegan	Participants were only used for creation of the Omnivore (regular) diet. The other diets were generated by analysis of 70 menus prepared by dieticians	NA	NA
			Vegetarian (lacto-ovo)			
			Pescatarian			
			Omnivore (fish free)			
			Omnivore (milk free)			
			Omnivore (basic)			
			Omnivore (regular)	30 (12, 18)		
Menzel *et al.*, 2021	Matched Pairs (Age and Sex)	Germany	Vegan	36 (18,18)	Self-assessed	4.8 (3.1–8.7)[1]
			Omnivore	36 (18,18)		
Whitbread *et al.*, 2021	Cross-Sectional	South Australia	Vegan	31 (31, 0)	Self-assessed	NA
			Omnivore	26 (26, 0)		

NA, not assessed; [1]Median and IQR.

8.4.1 Urinary iodine status

Iodine status by UIC was investigated in 5 studies with a total of 700 participants (vegan; 271, vegetarian; 135, pescatarian; 35, omnivore; 189, flexitarian; 70)(Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021) (**Figure 8.2**). Three studies assessed UIC using single spot urine samples (Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021); the remaining 2 studies used 24h urinary samples (Dawczynski *et al*., 2022; Menzel *et al*., 2021). We were unable to separate UIC estimates by gender, as all included studies provided either mixed gender estimates or estimates in females alone.

Vegan participants had the lowest median UIC in all 5 studies (12.2 – 44.0 µg L^{-1}) (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021), with the lowest value recorded by Eveleigh *et al* in UK vegans (12.2 µg L^{-1}) (Eveleigh *et al*., 2022). In all studies, vegans had significantly lower median UIC compared to omnivores ($P < 0.05$) (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021). Vegetarians in the included studies tended to have median UIC values greater than vegans but lower than omnivores, flexitarians, and pescatarians (Dawczynski *et al*., 2022; Groufh-Jacobsen *et al*., 2020). Only one study reported the median UIC of vegetarians to be significantly lower than omnivores ($P < 0.05$) (Eveleigh *et al*., 2022). Pescatarians in Norway experienced the greatest median UIC of 96.0 µg L^{-1} (Groufh-Jacobsen *et al*., 2020). The median UIC of flexitarians was reported in one study (52.0 µg L^{-1}) and was slightly lower than the omnivores in the same study (53.0 µg L^{-1}) (Dawczynski *et al*., 2022). The included studies showed considerable variation in UIC recorded within dietary groups, for example, the upper range for median UIC for vegans in Dawcynski *et al* study was 509 µg L^{-1} (Dawczynski *et al*., 2022).

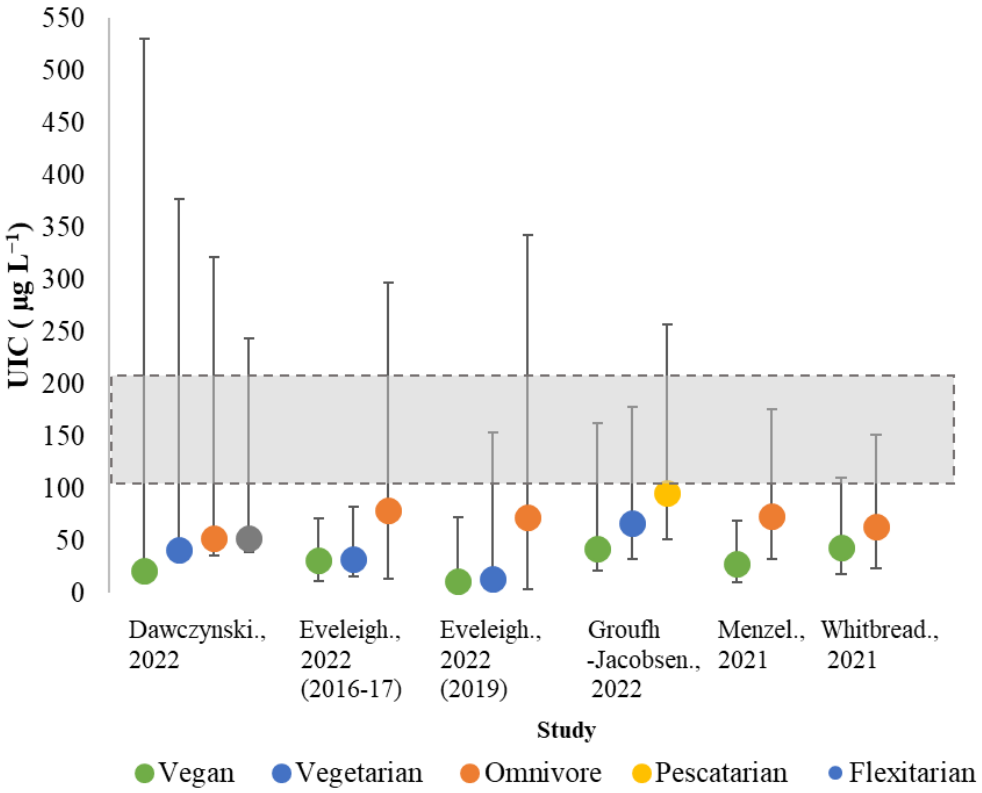


Figure 8.2. Iodine status measurements of included studies by median urinary iodine concentration (UIC). Shaded grey areas illustrate the World Health Organisation (WHO) criteria for optimal iodine status (100-200 µg L^{-1}).

None of the dietary groups included in this review had median UIC values within the optimal range for iodine status (100-299 µg L^{-1}) according to WHO criteria (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021). Severe iodine deficiency (>20 µg L^{-1}) was observed in one study of vegans living in the UK (Eveleigh *et al*., 2022). Moderate deficiency (20–49 µg L^{-1}) was observed in all vegan diets and 75% (3/4) of vegetarian diets (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021). Omnivores, flexitarians, and pescatarians had median UIC values within the range of mild iodine deficiency (50–99 µg L^{-1}) (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021). None of the dietary groups in our current review had median UIC values relating to excessive iodine intake (>300 µg L^{-1}) (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021).

None of the studies investigating iodine status used creatinine correction (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021).

8.4.2 Dietary iodine intake

Dietary iodine intakes were recorded in 9 studies and included 678 participants (strict raw; 16, vegan; 280, vegetarian; 117, pescatarian; 35, omnivore; 230) (**Table 8.4**; **Figure 8.3**; **Figure 8.4**) (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). All studies evaluated iodine intake between vegans and one or more dietary groups (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). Most studies reported mixed gender estimates of dietary iodine. Only 2 studies separated dietary iodine intake by gender (Abraham *et al*., 2022; García-Morant *et al*., 2020), and 3 studies only recruited females to study (Blaurock *et al*., 2021; Fallon and Dillon, 2020; Whitbread *et al*., 2021).

Sixty-seven percent of studies (6/9) were conducted in countries considered ‘adequate’ according to national data from the Global scorecard of iodine nutrition (2021) (Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Iodine Global Network, 2021; Whitbread *et al.*, 2021).

Food diaries >3 days (44%, 4/9) and FFQs (44%, 4/9) were the most commonly used dietary method to measure iodine intake (Abraham *et al*., 2022; Blaurock *et al.*, 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; Jakše *et al*., 2021). Other dietary methods included 24h food recalls (33%, 3/9) (García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021). Three studies addressed iodine intake using two dietary methods to assess both short-term and longer-term dietary intake (Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021).

Vegan participants living in the UK in 2019 had the lowest average iodine intake of 17.3 µg day^{-1} (17.2-21.4 µg day^{-1}; mixed gender estimates) (Eveleigh *et al*., 2022). The greatest iodine intake was recorded in vegetarians in Oslo, Norway at 843.0 µg day^{-1} (705.0-1590.0 µg day^{-1}; mixed gender estimates) (Groufh-Jacobsen *et al*., 2020). Omnivores had the greatest dietary iodine intake in 70% (7/10) of included cohorts (Abraham *et al*., 2022; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Kowalska *et al*., 2020; Whitbread *et al*., 2021), whereas, vegans had the lowest iodine intake in 73% of cohorts (8/11) (Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Kowalska *et al*., 2020; Whitbread *et al*., 2021). There was substantial variation in iodine intake within dietary groups with the greatest variation being observed by Groufh-Jacobsen *et al* in FFQ estimates of pescatarians (705.0-1590.0 µg day^{-1}) (Groufh-Jacobsen *et al*., 2020).

Seven studies recorded a significant difference in iodine intake between one or more dietary group ($P = < 0.05$) (Abraham *et al*., 2022; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Whitbread *et al*., 2021). Four studies found the iodine intake of vegans to be significantly lower than omnivores ($P = < 0.001$) (Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Whitbread *et al*., 2021). Vegans and vegetarians had significantly lower habitual

iodine intake compared to pescatarians in one study (Groufh-Jacobsen *et al*., 2020). Raw food eaters were recorded to have significantly lower iodine intake than vegans and omnivores (Abraham *et al*., 2022). The study conducted by Kowalska *et al* (2020) did not statistically evaluate the difference in iodine intake between groups. There were differences in significance between groups according to methods of assessing iodine intake. In the study by Groufh-Jacobsen *et al* (2020) a significant difference in iodine intake between vegans, vegetarians, and pescatarians was only observed in FFQ estimates and not 24h recalls. However, Eveleigh *et al* did not observe a significant difference in iodine intake by FFQ in their 2019 cohort but did see differences when measured using food diaries (Eveleigh *et al*., 2022).

The WHO recommended iodine intake of 150 µg day^{-1} was used for the assessment of adequate dietary intake (WHO, 2007). None of the included studies recorded estimates above the adequate range for all dietary groups. Iodine inadequacy was reported in all dietary groups in 75% (9/12) of the cohorts assessed (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). Only two studies reported at least one dietary group to have adequate average iodine intake (Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020).

Five studies addressed the types of foods consumed by different dietary groups (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Jakše *et al*., 2021; Whitbread *et al*., 2021), of which, 3 estimated the possible contribution of specific food groups to total iodine intake (Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021). Overall, the vegan and vegetarian groups consumed greater quantities of plant-based food groups (fruit, vegetables, legumes, tubers, cereals, and grains (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Jakše *et al*., 2021; Whitbread *et al*., 2021)). Two studies recorded alternative milk intake to be significantly greater in vegan and vegetarian groups (Eveleigh *et al*., 2022; Whitbread *et al*., 2021). Within these two studies, dairy products and eggs were the greatest source of iodine for individuals not restricting these foods.

Kowalska *et al* (2020) created model diets for each dietary group and used foods that were typically consumed according to dieticians' advice and current research (Kowalska *et al*., 2020). Foods present in the models of vegan diets included: cereal, fruit, vegetables, nuts, mushrooms, legumes, oils, and alternative milk.

Mandatory or voluntary USI was present in 7 of the included studies, investigations conducted in the UK had no USI programme (Eveleigh *et al*., 2022; Fallon and Dillon, 2020). Only 2 studies addressed the relative consumption of iodised salt to total iodine intake (Eveleigh *et al*., 2022; Whitbread *et al*., 2021). Iodised salt was only consumed by vegan (n = 4; 4/31) (Whitbread *et al*., 2021), and omnivorous participants (n = 5; 1/34 & 4/26) (Eveleigh *et al*., 2022; Whitbread *et al*., 2021). Whitbread *et al* (2021), was the only study to monitor the intake of bread fortified with iodine, an average quantity of 28 g day^{-1} and 36 g day^{-1} for vegans and omnivores consumed (Whitbread *et al*., 2021). Consumption of iodised bread was similar between dietary groups and was acknowledged as a good source of iodine. The consumption of iodine-containing supplements to total iodine intake was recorded in 5 studies (Blaurock *et al*., 2021; Eveleigh *et al*., 2022; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021). Two of the studies that reported supplement use did not provide data on the actual contribution of iodine-containing supplements to total intake (Abraham *et al*., 2022; Blaurock *et al*., 2021). One study prevented supplement intake during the study (Whitbread *et al*., 2021). Four studies addressed the consumption of seaweed and microalgae in different dietary groups (Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021), however, in two of these studies the relative contribution of seaweed to iodine was not discussed (Abraham *et al*., 2022; Whitbread *et al*., 2021). Vegans (n = 29) were most likely to consume seaweed as part of their diet. Seaweed intake was also reported in strict raw food eaters (n = 1), vegetarians (n = 8), pescatarians (n = 4), and omnivores (n = 2) (Abraham *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021).

Table 8.4. Assessment of dietary iodine intake for vegans, vegetarians, and omnivores in included studies.

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake (Iodine Global Network, 2021)
Abraham *et al.*, 2022	3-day weighed food diaries	D-A-CH reference values F;150 µg day^{-1}, M;180 µg day^{-1}	Strict raw 16 (5, 11)	F; 49.6 (37.4-64.6)[1] M; 78.9 (51.7-106.0)[1]	Twelve participants (75%) recorded intake of dietary supplements (B12 and Vitamin D). The consumption of iodine-containing supplements and iodised salt was not stated. Only individuals in the strict raw diet group consumed seaweed, but the contribution to iodine was not discussed.	N	Voluntary	Insufficient
			Vegan 32 (18, 14)	F; 74.8 (48.9-124.6)[1] M; 88.0 (41.6-104.5)[1]		N		
			Omnivore 27 (14, 13)	F; 100.5 (76.5-142.6)[1] M; 165.9 (106.2-181.5)[1]		N		

Table continued…

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake
Blaurock *et al.*, 2021	Self-administered, online 157 – item FFQ as part of the eNutri2019-DE web application.	Dietary reference values (DRV) Germany 200 µg day^{-1} (18–51 y)	Vegetarian 31 (31, 0)	F; 116.7 (92-164)[1]	Seventy-four percent of vegetarians and 63% of omnivores reported consuming dietary supplements. The consumption of iodine-containing supplements, iodised salt, and seaweed was not stated.	N	None	Adequate
			Omnivore 30 (30, 0)	F; 108.6 (75-144)[1]		N		
Eveleigh *et al*., 2022)	Online iodine-specific 45-item FFQ and 3-day food diaries analysed by a dietary software program, Nutritics	Reference Nutrient Intake (RNI) for UK 140 µg day^{-1}	Vegan (2016-17) FFQ; 12 FD; 10	FFQ; 107.0 (88.0-131.5)[1] Food diaries: 47.6 (29.6-61.8)[1]	Multivitamins containing iodine were consumed by 12% of participants providing an average of 140 µg day^{-1} to dietary iodine. Multivitamin supplements provided significantly greater iodine to the diets of vegans compared to omnivores and vegetarians (P = < 0.001 & P = 0.033 respectively).	FFQ; N Food diaries; N	None	Adequate
			Vegetarian (2016-17) FFQ; 5 FD; 4	FFQ; 202.9 (176.5-291.7)[1] Food diaries: 68.8 (55.8-90.4)[1]		FFQ; Y Food diaries; N		

Table continued…

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake
			Omnivore (2016-17) FFQ; 34 FD; 27	FFQ; 299.6 (147.2-291.7)[1] Food diaries: 111.9 (85.4-145.6)[1]	Seaweed supplements kelp and/or kombu were consumed by two omnivores in 2019, providing an average iodine intake estimate of 1541 µg day^{-1}. Seaweed supplied a significantly greater iodine contribution to the diets of vegans compared to omnivores (P = 0.040). One omnivore in 2016-17 recorded consuming iodised salt contributing 61% of dietary iodine.	FFQ; Y Food diaries; N	None	Adequate
Fallon and Dillon, 2020	4-day food diaries analysed by Nutritics	RNI for UK 140 µg day^{-1} and DRV 150 µg day^{-1}.	Vegan 20 (20, 0)	F; 24.4 ± 12.7[2]	Seaweed, salt, or supplements not measured.	N	None	Adequate
			Vegetarian 16 (16, 0)	F; 90.8 ± 55.9[2]		N		
			Omnivore 26 (26, 0)	F; 112.6 ± 62.1[2]		N		

Table continued…

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake
García-Morant *et al.*, 2020	Online 24h food recalls analysed by DIAL and data from the Spanish National Dietary Intake Survey	None provided	Vegan 102 (67, 35)	F; 79.0 ± 76.0[2] M; 64.0 ± 42.0[2]	Dietary supplements were recorded and combined with dietary intake data. Seaweed and iodised salt not measured.	N	Voluntary	Adequate
			Omnivore 3,321 (1,589, 1,732)	F; 100.0 ± 50.0[2] M; 85.0 ± 47.0[2]		N		
Groufh-Jacobsen *et al.*, 2020	24h food recalls and 32-item FFQ updated from the Norwegian Food Composition Table 2019	Estimated Average Requirement (EAR) of 100 µg day^{-1}	Vegan 115 (74, 41)	24h recall; 92.0 (19.0, 171.0)[1] FFQ; 315.0 (19.0, 361.0)[1]	The median contribution of supplements to iodine intake of 24h recalls were 150 µg day^{-1} for vegans (n = 57), vegetarians (n = 25), and pescatarians (n =18). For FFQ estimates supplements also contributed a median average of 150 µg day^{-1} to dietary iodine intake of intake of vegans (n = 69), vegetarians (n = 26), and pescatarians (n = 10).	24h recall; N FFQ; Y	Voluntary	Insufficient
			Vegetarian 55 (43, 12)	24h recall; 70.0 (17.0, 165.0)[1] FFQ; 843.0 (705.0, 1590.0)[1]		24h recall; N FFQ; Y		

Table continued…

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (µg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake
			Pescatarian 35 (31, 4)	24h; 123.0 (16.0, 176.0)[1] FFQ; 39.0 (16.0, 324.0)[1]	Seaweed (microalgae) provided 865 µg day^{-1} (364, 1978) to vegans (n = 23), 843 µg day^{-1} (705, 1590) to vegetarians (n = 8) and 375 µg day^{-1} (110, 610) to pescatarians (n = 4). Iodised salt not measured.	24h recall; Y FFQ; Y	Voluntary	Insufficient
Jakše *et al.*, 2021	52-item FFQ analysed by a dietary software program, Open Platform for Clinical Nutrition (OPEN)	D-A-CH reference values F;150 µg day-1, M;180 µg day-	Vegan 51 (34, 17)	112.0 ± 60.02	Dietary supplements were recorded and combined with dietary intake data. Dietary supplements provided >25% of total iodine intake for vegans and omnivores (non-vegans) Seaweed and iodised salt not measured.	N	Mandatory	Adequate
			Omnivore (non-vegan) 29 (16, 13)	96.0 ± 58.0[2]		N		
Kowalska *et al.*, 2020	Modelled diets were created by trained dieticians	EAR for Poland 95 ug day^{-1}	Vegan	29.4 ± 10.3[2]	Seaweed, salt, or supplements not measured.	N	Mandatory	Adequate
			Vegetarian (lacto-ovo)	37.6 ± 9.2[2]		N		
			Pescatarian	39.2 ± 11.1[2]		N		

Table continued…

Study, year	Assessment of Dietary Iodine	Criteria for Iodine Intake	Dietary Group (n) (Female, Male)	Dietary Iodine Intake (μg day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)[3]	National salt fortification status	National iodine intake
			Omnivore (fish free)	46.9 ± 20.3[2]		N		
			Omnivore (milk free)	62.8 ± 46.4[2]		N		
Whitbread *et al.*, 2021	24h diet food recalls by a smartphone app and food diaries analysed by a dietary software program, FoodWorks Dietary Analysis package	Recommended daily intake (RDI) 150 ug day^{-1}, EAR 100 ug day^{-1} and Nutrient Reference Values (NRV) for Australia and New Zealand (NHMRC)	Vegan 31 (31, 0)	78.0 (62.0–91.0)[1]	Participants who frequently consumed iodine-containing supplements were excluded. Six vegans reported ingesting seaweed (2.7 g day^{-1}), but iodine intake from seaweed was recorded as 0.0 ug day^{-1}. Iodised bread was the main iodised food source in vegans. Iodised salt was consumed by 4 vegan and 4 omnivore participants.	N	Mandatory	Adequate
			Omnivore 26 (26, 0)	125.0 (86.0–175.0)[1]		N		

[1]Median (Q1 –Q3); [2]Mean ± SD; [3]According to WHO criteria of 150 ug day^{-1}.

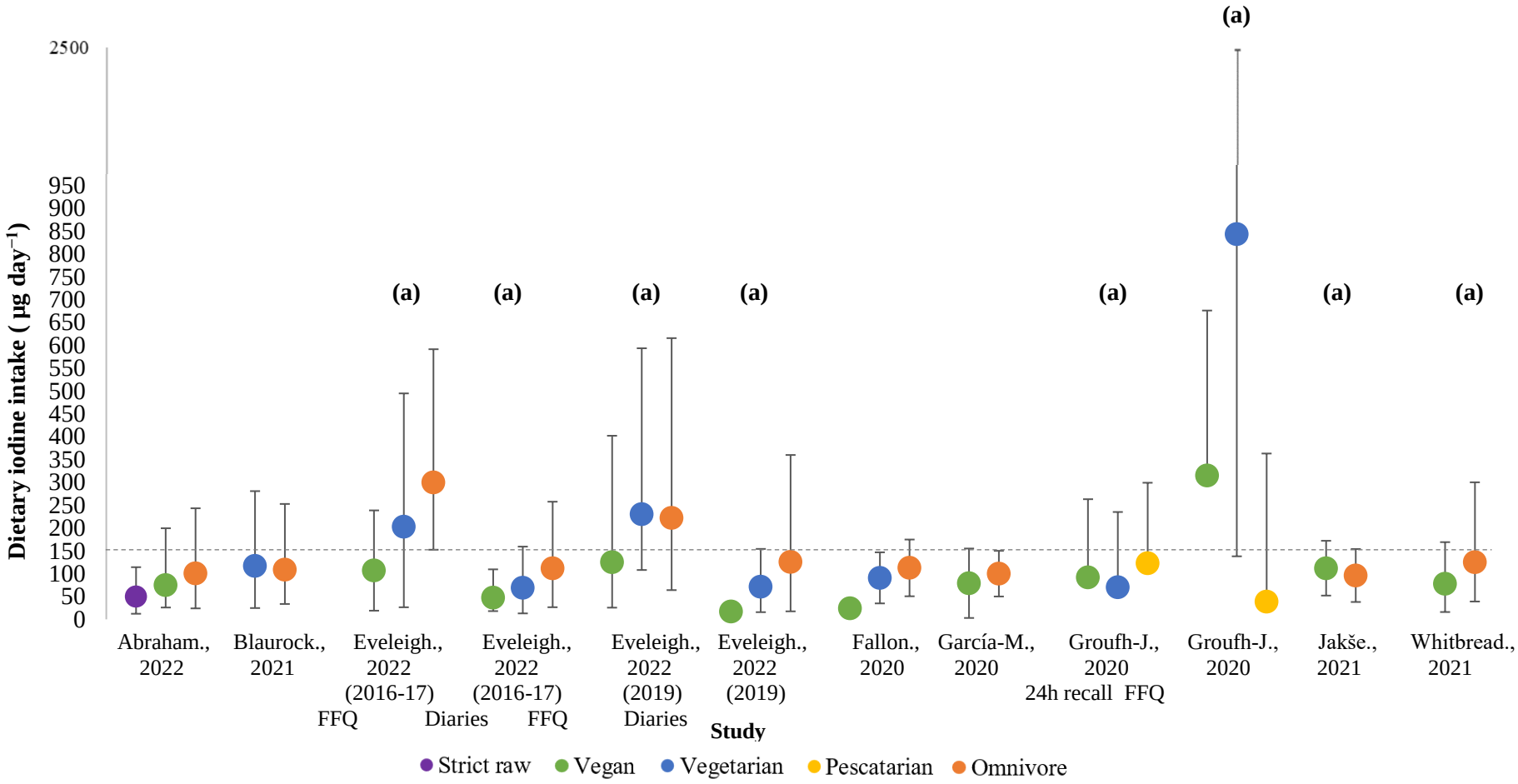


Figure 8.3. Visual representation of estimated average iodine intake (µg day^{-1}) for females in included studies. The grey dashed line represents the adequate intake recommended by the World Health Organisation (WHO) of 150 µg day^{-1} (WHO, 2007); (a), mixed gender values. This graph does not present data from the modelling study conducted at Kowalska *et al* (2020) to permit comparison between dietary studies.

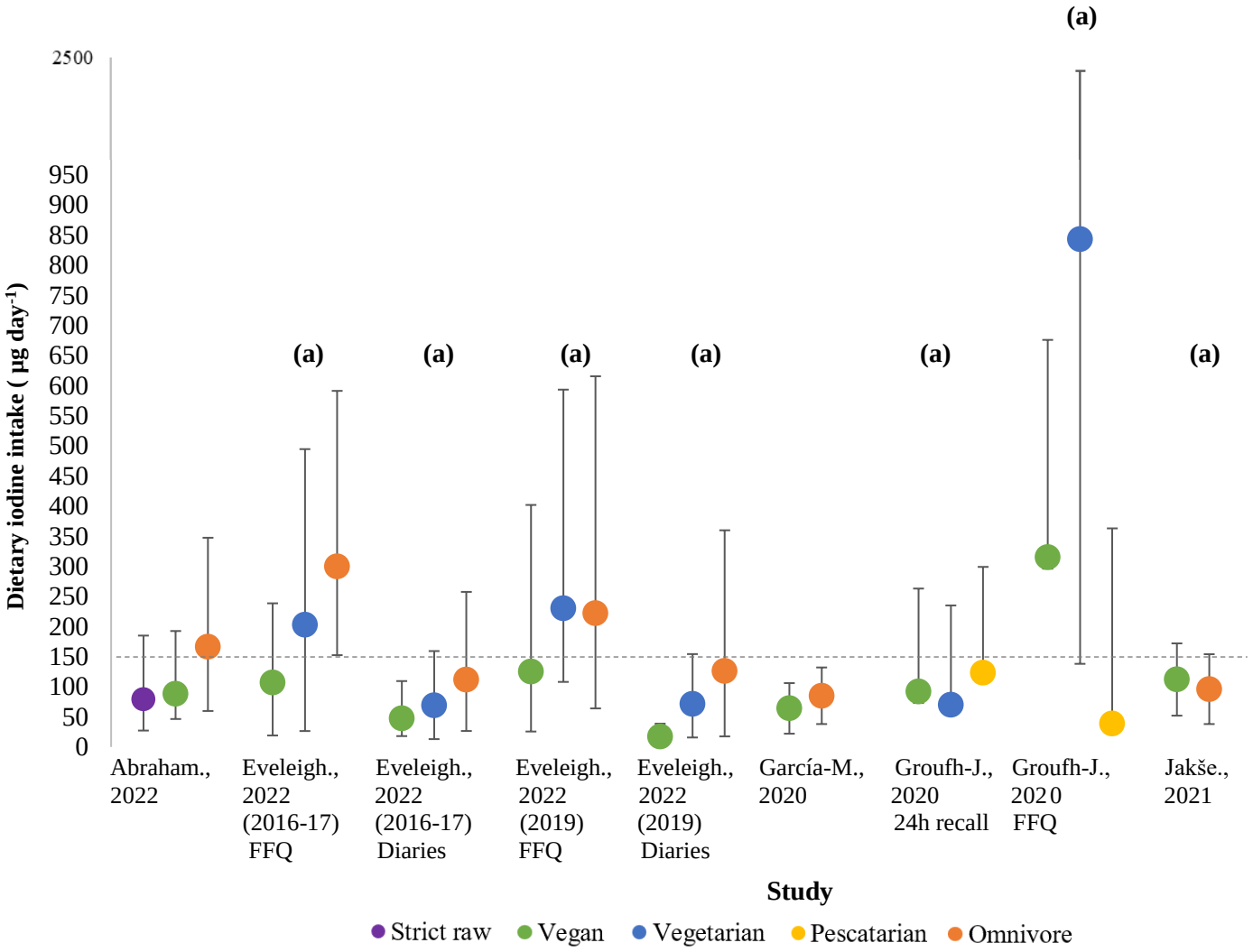


Figure 8.4. Visual representation of estimated average iodine intake (µg day^{-1}) for males in included studies. The grey dashed line represents the adequate intake recommended by the World Health Organisation (WHO) of 150 µg day^{-1} (WHO, 2007); (a), mixed gender values**.** This graph does not present data from the modelling study conducted at Kowalska *et al* (2020) to permit comparison between dietary studies.

8.4.1 Meta-analysis of iodine status and intake in vegans and vegetarians compared to omnivores

There was a strong trend for vegan or vegetarian diets to be associated with reduced iodine status as measured by UIC, but this did not quite reach significance (**Figure 8.5** & **Figure 8.6**; P = 0.06 & P = 0.18), so no subgroup analysis was completed. There was, however, an overall significant negative effect of vegan diets on iodine intake (P = < 0.001; **Figure 8.7**), with no effect observed for vegetarian diets (P = 0.12; **Figure 8.8)**. Subgroup analysis for iodine intake vegan vs omnivore is shown in **Supplementary Figure 5.** Significant effects were shown for female only intake (P = 0.007), mixed gender intake (P = 0.01), living in a country with voluntary (P = 0.01) or no USI programme (P = < 0.00001), and living in a country with national iodine intake considered as adequate (P = <0.000001). In countries with mandatory salt iodisation, there was no effect of vegan diet on iodine intake (P = 0.60).

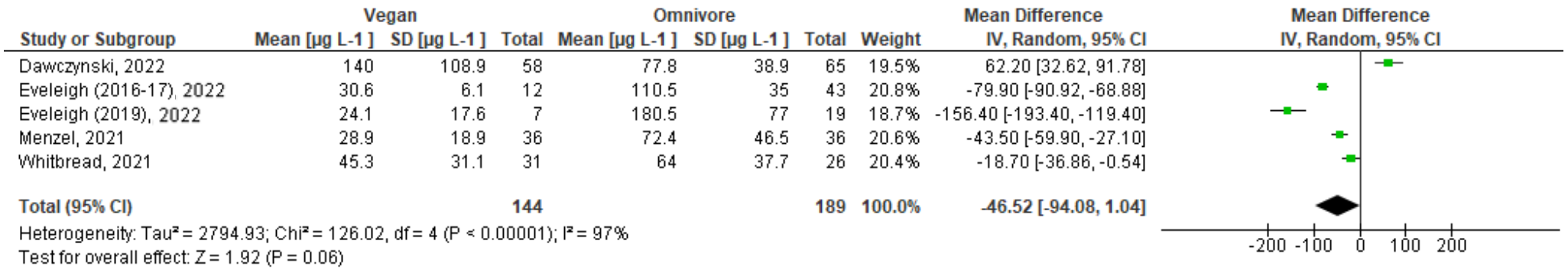


Figure 8.5. Meta-analysis forest plot comparing the effect of a vegan v. omnivorous diet on iodine status.
Data presented is female and mixed gender estimates only. 95% CI, confidence interval.

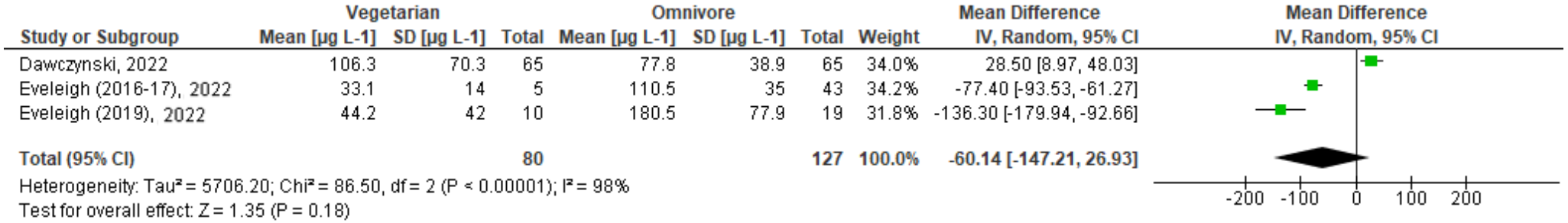


Figure 8.6. Meta-analysis forest plot comparing the effect of a vegetarian v. omnivorous diet on iodine status.
Data presented is female and mixed gender estimates only. 95% CI, confidence interval.

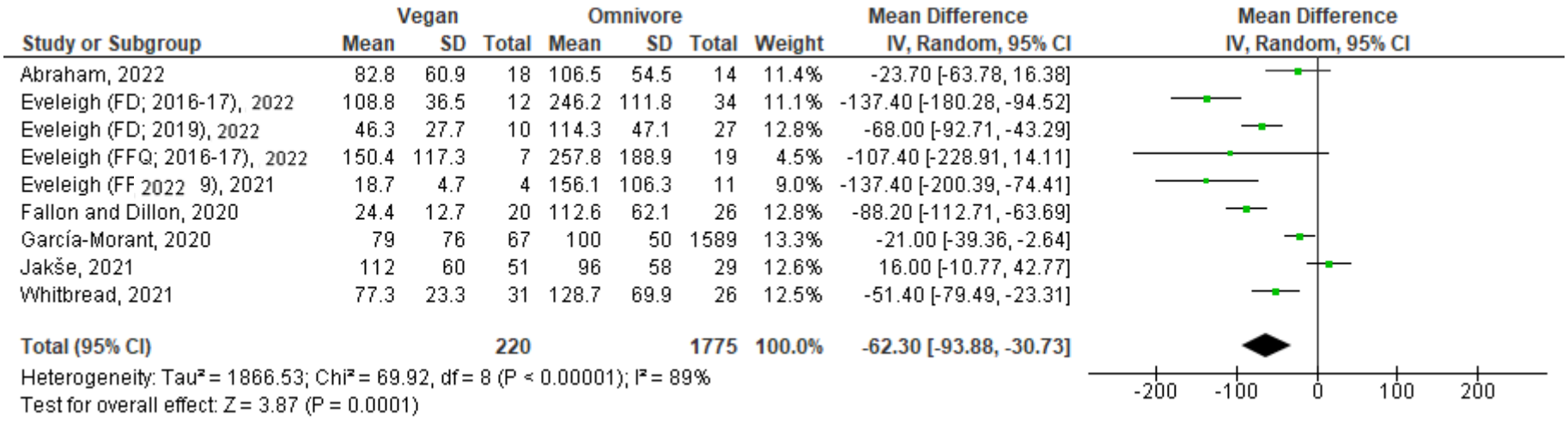


Figure 8.7. Meta-analysis forest plot comparing the effect of vegan v. omnivorous diet on iodine intake.
Data presented is female and mixed gender estimates only. 95% CI, confidence interval.

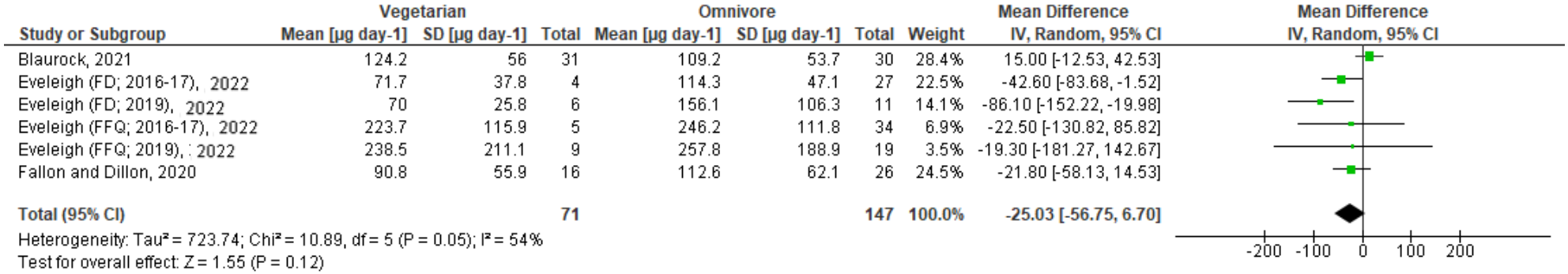


Figure 8.8. Meta-analysis forest plot comparing the effect of vegetarian v. omnivorous diet on iodine intake.
Data presented is female and mixed gender estimates only. 95% CI, confidence interval.

8.5 Discussion

This systematic review is an update of our previous work, investigating the evidence for iodine intake and status among adults following vegan and vegetarian diets, to reflect dietary consumption in the modern day. The publication of 11 studies eligible for inclusion in the past two years since our previous review demonstrates that there is an increased interest and awareness in this area. Our systematic review confirms that individuals following vegan and vegetarian diets, living in countries without mandatory salt iodisation, and not consuming seaweed or iodine-containing supplements, still have an increased risk of low iodine status, iodine deficiency, and inadequate iodine intake compared to less restrictive dietary groups (Eveleigh *et al*., 2020). Our review also highlights that iodine nutrition is poor in many sub-groups of the global population and that difficulties achieving iodine recommendations are not unique to those following restrictive diets.

In our previous review (Eveleigh *et al*., 2020), we found that the degree of vulnerability in all dietary groups appeared to be impacted by the standing of national iodine estimates, whereby the median UIC of omnivorous participants studied tended to reflect a country's national data. In our present review, we found that on average urine samples provided by omnivorous participants were lower in iodine than national estimates (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021). Only in studies conducted in Germany were omnivores within the same bracket of the WHO criteria as national data (89 μg L^{-1}; 50-99 μg L^{-1} Mild) (Dawczynski *et al*., 2022; Menzel *et al*., 2021; Iodine Global Network, 2021; WHO, 2007). However, there is still a general trend in which vegans are likely to have median UIC corresponding to a lower bracket of the WHO criteria than omnivores recruited in the same study (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021) . Although the median UIC of all dietary groups studied in this review fell below the WHO criteria for optimal iodine status (100-299 μg L^{-1}) (Dawczynski *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Menzel *et al*., 2021; Whitbread *et al*., 2021; WHO, 2007).

We found that 67% (6/9) of studies investigating iodine intake were conducted in countries considered ‘adequate’ according to national data from the global scorecard of iodine nutrition (2021) (Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). But none of the included studies recorded estimates above the adequate range for all dietary groups (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). Equally, iodine inadequacy was reported in 75% (9/12) of the cohorts assessed (Abraham *et al*., 2022; Blaurock *et al*., 2021; Eveleigh *et al*., 2022; Fallon and Dillon, 2020; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). The global scorecard population monitoring uses the WHO recommendation of median UIC from school-aged children (SAC) or women of childbearing age as a proxy for assessing adequate iodine intake on a national level (Iodine Global Network, 2021). The use of median UIC from SAC as an indicator of iodine intake has been criticised for masking particular sub-groups with varying diets and/or iodine sources (Zimmermann and Andersson, 2021). Women are a sub-group more vulnerable to the consequences of iodine deficiency and are twice as likely as men to adopt a vegan or vegetarian diet (Modlinska *et al*., 2020). Three studies assessed iodine intake specifically in women of childbearing age (Blaurock *et al*., 2021; Fallon and Dillon, 2020; Whitbread *et al*., 2021). Iodine intake was found to be below the WHO recommendation of 150 µg day^{-1} in all studies of women in our review regardless of dietary choice (Blaurock *et al*., 2021; Fallon and Dillon, 2020; Whitbread *et al*., 2021). Moderate iodine deficiency pre-conception increases the risk of infant mortality by stillbirth and miscarriage (Zimmermann, 2012). Furthermore, iodine deficiency in utero may disrupt normal foetal neurodevelopment and cause irreversible neurological damage (Zimmermann, 2012). Our present review highlights that iodine intake must be assessed among different subsets of the population to identify groups at risk of deficiency.

Vegan participants living in the UK were recorded to have the lowest average iodine intake of 17.3 µg day^{-1} and 24.4 µg day^{-1} (Eveleigh *et al*., 2022; Fallon and Dillon, 2020). Dietary intake estimates recorded by Eveleigh *et al* (2022) and Fallon *et al* (2020) were much lower than past data collected on British vegans (Lightowler, 2009; Lightowler and Davies, 2002; Sobiecki *et al*., 2016), suggesting that iodine intake has reduced over time. Vegans living in the UK may find it more challenging to meet their iodine requirements because along with restricting rich sources of iodine from animal sources, individuals selecting these diets also live in a country with no current USI programme. Salt iodisation is an effective and sustainable way of improving iodine intake (Zimmermann and Andersson, 2021). Currently, 145 countries globally have enrolled in either mandatory (124/145) or voluntary (21/145) USI (Zimmermann and Andersson, 2021). Apart from the UK, all other included studies were conducted in a country with USI (Abraham *et al*., 2022; Blaurock *et al*., 2021; García-Morant *et al*., 2020; Groufh-Jacobsen *et al*., 2020; Jakše *et al*., 2021; Kowalska *et al*., 2020; Whitbread *et al*., 2021). Iodised salt can be purchased in the UK, but its availability is low and it tends to be more expensive than non-iodised household varieties (Bath *et al*., 2014a). Eveleigh., *et al* (2022) found that only one omnivorous participant recorded consuming iodised salt equating to 61% of their total dietary iodine. However, it is very difficult to quantify the amount of salt added to meals and used or lost during cooking (Zimmermann and Andersson, 2021). Additionally, the iodine content of fortified salt can vary considerably (Zimmermann and Andersson, 2021). Whitbread *et al* (2021) was the only study, conducted in a location with USI, to estimate the relative contribution of iodised salt and foods containing iodised salt such as bread (Whitbread *et al*., 2021). Hence, dietary iodine intake may be lower in many of the included studies because the involvement of iodised salt was not estimated.

Although mandatory USI measures are considered to be the optimal approach, most countries with voluntary fortification are iodine-sufficient (Zimmermann and Andersson, 2021). We identified that individuals following a vegan diet living in countries with no mandatory USI programme were significantly more likely to have lower iodine intake.

Our findings match the global experience, in that voluntary fortification may not benefit all sub-groups of the population (WHO, 2018). There is an urgent need to investigate the usefulness of mandatory iodine fortification to address the emergence of iodine-deficiency in those selecting vegan or vegetarian diets.

Bread has been selected as a vehicle for iodine fortification in countries including, Australia, New Zealand (NZ), and Denmark (Whitbread *et al*., 2021). In most countries, bread is a staple food product that can be consumed by nearly everyone in the population including those following vegan and/or vegetarian diets making it a practical method of iodine fortification. In the study by Whitbread *et al* (2021) iodised bread was the main iodised food source in the diets of Australian vegans and greater bread intake (g day^{-1}) correlated significantly with improved UIC (Whitbread *et al*., 2021). The mandatory fortification of bread in Australia is estimated to be around 53-70 μg per 100g (Food Standards Australia and New Zealand, 2016). The British Dietetics Association (BDA) denotes a portion of bread is equivalent to one slice or 34-36 g (BDA, 2021), if bread was fortified in the UK to the same level as in Australia, one portion would provide an average of 22 μg which could potentially boost iodine intake in all dietary groups.

Alternative milk has also been identified and promoted as a possible vehicle for iodine fortification for vegans and/or those who do not consume cow's milk (Govindji, 2020). A recent study investigating the iodine fortification status of plant-based dairy and fish alternatives in the UK found that only 28% of milk alternatives and 6% of yogurt alternatives were fortified with iodine (Nicol *et al*., 2022). Similarly, no cheese or fish alternatives were found to be currently fortified with iodine (Nicol *et al*., 2022). Other studies have identified that individuals who consume alternative milk exclusively tend to have significantly lower iodine intake than cow's milk consumers (94 v. 129 μg day^{-1}) (Dineva *et al*., 2020b). Two studies in our review recorded alternative milk intake to be significantly greater in vegan and vegetarian groups (Eveleigh *et al*., 2022; Whitbread *et al*., 2021), the displacement of cow's milk may have contributed to lower iodine intake.

In May 2021, the BDA's England Board and the Maternal & Fertility Nutrition Specialist Group completed a project to consider the case for the wider iodine fortification of alternative milk to improve iodine intake (BDA, 2022b). However, at present no UK policy has been implemented for the mandatory iodine fortification of any foods, therefore individuals following a vegan and/or vegetarian diet are responsible for planning their diet to include appropriate sources of iodine (e.g. iodine supplements, occasional seaweed consumption, and/or iodine fortified alternative milk).

The modelling study conducted by Kowalska *et al* (2020) in Poland demonstrates the difficulty in achieving adequate iodine intake in several different diet types if iodine fortified foods (including salt) or supplements are not available. In this study, modelled diet menus of vegan, vegetarian, pescatarian and variations of the omnivorous diet (fish free, milk free, basic, and regular), were prepared by qualified dieticians with the use of methods avoiding nutritional deficiencies. Even though these diets had been appropriately planned by dieticians, all the diets were characterised by insufficient iodine intake. In Poland, the main sources of dietary iodine are iodised salt and white fish including cod and Pollock (Kowalska *et al*., 2020). Therefore, it is unsurprising that iodine intake was observed to be lowest in individuals following diets that exclude fish (vegans, vegetarians, and fish-free omnivores) when contribution of iodised salt was not added to intake estimates.

The greatest average iodine intake and status were recorded in Norwegian pescatarians (123.0 µg day^{-1} and UIC of 96.0 µg L^{-1}) (Groufh-Jacobsen *et al*., 2020). Pescatarians do not consume meat but may eat fish, milk, or eggs in varying quantities (Phillips, 2005). In a typical Norwegian diet, lean fish like cod, haddock, and saithe are the richest sources of iodine along with cow's milk and dairy products (Groufh-Jacobsen *et al*., 2020). However, the iodine content of fish can vary significantly between species and geographical locations (Nerhus *et al*., 2018). The Norwegian Directorate of Health recommends one portion of fish two or three times a week, however, annual fish intake has dropped in Norway across all age groups apart from the elderly, this decline is particularly noticeable in young people (18 – 34 y) (Eurofish, 2020).

The authors suggest that greater iodine intake in pescatarians in this study was more due to consumption of iodine-containing supplements rather than that of fish (Groufh-Jacobsen *et al*., 2020), as this significantly improves iodine status (Bath *et al*., 2014). A larger proportion of vegans and vegetarians consumed dietary supplements (inclusive of non-iodine-containing varieties) compared to omnivores and in two studies, iodine-containing supplements provided between 140 – 150 µg day^{-1} to total iodine (Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020). However, despite their consumption, most participants had inadequate UIC and below-recommended iodine intake. The WHO recommends a daily iodine supplement dose of 150 µg day^{-1} for women of childbearing age (15-19 y) living in areas with insufficient access to iodised salt or vulnerable groups (WHO, 2007). Considering the vulnerability of individuals in the included studies, the effect of iodine-containing supplements in vegan and vegetarian populations warrants further investigation.

We found previously that the greatest iodine intake was recorded for females following vegan diets, living in London (1448.0 ± 3879.0 µg day^{-1}), whose regular consumption of seaweed increased intakes to over six times the RNI (Lightowler and Davies, 2002). In our present review, four studies addressed the consumption of seaweed and microalgae in different dietary groups (Abraham *et al*., 2022; Eveleigh *et al*., 2022; Groufh-Jacobsen *et al*., 2020; Whitbread *et al*., 2021), however, not all studies considered their contribution to total iodine. Vegans were the most frequent consumers of seaweed which provided iodine intake close to the maximum tolerable level of 1,000 µg day^{-1}. The iodine content of seaweed is high and varies considerably according to the species consumed (Bouga and Combet, 2015; Yeh *et al*., 2014), with kombu having the greatest iodine content (2523.5 mg kg^{-1}) and so is not recommended to improve iodine intake due to the significant risk of excess (Bouga and Combet, 2015; Yeh *et al*., 2014).

In our previous review we discussed key issues with the methodology selected to record intake from vegan and vegetarian groups including accurately defining diets (Eveleigh *et al*., 2020), the use of outdated food tables or databases, and variation in techniques used to measure iodine in the diet (e.g. 24h food recalls v. FFQs).

These issues are still relevant to the present review and may reduce the accuracy of dietary intake estimates. Further limitations of this study include the relatively small number of included studies, oversimplifying of dietary practice to enable comparison of studies, and a lack of studies that were well populated or well represent the public.

8.6 Conclusions

This review agrees with findings from our previous systematic assessment on this topic (Eveleigh *et al.*, 2020). We found that vegans and vegetarians consuming seaweed or iodine-containing supplements continue to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared to adults following less restrictive diets living in countries lacking mandatory iodisation of salt. Similarly, to our previous review, there is a relationship between national iodine deficiency and the degree of vulnerability to vegans and vegetarians. However, we also conclude that iodine nutrition is inadequate in many sub-groups and that complications achieving iodine recommendations are universal. There is an urgent need to monitor iodine intake and status in at-risk populations including young women, and those following a vegan or vegetarian diet. In addition to research into safe routes of improving iodine intake in vegan and vegetarian populations living in regions where staple foods are not fortified or USI coverage is not present or is not mandatory. Further awareness of how to appropriately plan a vegan or vegetarian diet to achieve iodine recommendations is required.

9. General discussion

The research presented in this thesis contributes to a greater understanding of the relationship between micronutrient intake and status, and dietary choice. Worryingly, our research findings show that many individuals selecting vegan and vegetarian diets, particularly women of childbearing age, have poor iodine nutrition. Our research shows there is a clear and urgent need for policy approaches and future research to support individuals to achieve healthy and micronutrient rich diets.

9.1 Achieving adequate iodine intake and status in vegan and vegetarian diets

Vegans and vegetarians are a sub-group of the population with an increased risk of iodine deficiency. This is because individuals following these dietary patterns do not consume foods that are typically iodine-rich and are heavily reliant on plant-based foods to achieve micronutrient recommendations. The data presented throughout this thesis (**Manuscripts 1, 2, 3, and 5**) clearly shows that the level of restriction implemented at the dietary level greatly impacts iodine intake and subsequently iodine status. Vegans, who have the strictest dietary pattern, tend to have the lowest iodine intake, followed by vegetarians/pescatarians, and omnivores. However, we also acknowledge that all dietary groups within our cohort studies (**Manuscripts 2 and 3**) presented with low iodine intake and status, signifying that certain population groups in the UK (e.g. young women) are now at risk of iodine deficiency.

In **Manuscript 1**, we identify that adults following vegan and vegetarian diets living in countries with a higher prevalence of iodine deficiency at the national level may be more vulnerable. The global strategy to correct and prevent iodine deficiency is by fortification of salt with iodine (Zimmermann and Andersson, 2021). It is largely assumed that the iodine needs of all sub-groups within a population can be met by the implementation of voluntary and mandatory USI programmes (Zimmermann and Andersson, 2021).

In **Manuscript 5**, we show that individuals following a vegan diet living in a country without a USI programme, or with the presence of a voluntary programme, are significantly more likely to have inadequate iodine intake than omnivores living in the same population. There appears to be less difference in the iodine intake of vegans compared to omnivores in countries with mandatory USI. Our findings indicate that voluntary salt fortification is not sufficient to improve the iodine intake of individuals following restrictive diets.

In countries such as the UK, where no formal USI programme is present, individuals are solely reliant on individual food choices to achieve the recommended iodine intake. Country-specific dietary determinants and individual food choices can therefore have a major role in preventing and correcting iodine deficiency. Many countries have observed a shift from the habitual consumption of iodine-rich foods. For instance, countries such as Norway and the UK have recorded a population decline in dairy and cow's milk intake (Groufh-Jacobsen *et al*., 2020; Mintel, 2019a). This decline is likely to be problematic as research has consistently shown intake of these foods to be positively associated with iodine intake and status (O'Kane *et al*., 2018; Van Der Reijden *et al*., 2019; Dineva *et al*., 2020b; Ferreira *et al*., 2021). In **Manuscript 2**, we found that cow's milk and dairy products were positively associated with UIC in 2016-17, signifying their importance as sources of dietary iodine. However, due to a decline in cow's milk intake in our 2019 cohort, there was no longer a positive relationship with UIC. Although, cow's milk is still the dominant milk drink consumed in the UK, currently over one-third of the British population select non-dairy alternative milk (e.g. soya, oat etc.). We observed that although the intake of alternative milk was significantly greater in vegans, un-fortified variations were regularly consumed by individuals in all dietary groups. Non-dairy alternative milk, unless fortified (130-450 μg kg^{-1}), has a very low iodine content (7.3 μg kg^{-1}) compared to cow's milk (438 μg kg^{-1}) (Bath *et al*., 2017). The displacement of iodine-rich cow's milk with unfortified alternative milk has been shown to contribute to the reduction in iodine intake and status in the UK (Dineva *et al*., 2020b), and may be particularly problematic for those who select these drinks for consumption as well as vegans and vegetarians.

Ensuring that all alternative milk products are nutritionally similar to cow's milk and provide adequate nutritional value is a matter of public health concern. Our research supports the BDA's England Board and the Maternal & Fertility Nutrition Specialist Group's proposal to consider the case for the wider iodine fortification of alternative milk drinks in the UK (BDA, 2022b). Currently, our understanding of these products as an appropriate and feasible way to access iodine for vegan individuals remains limited and has not been demonstrated in human participants. We designed our clinical trial protocol described in **Manuscript 4** to fill the knowledge gap on this topic and to provide novel evidence of the use of iodine-fortified alternative milk as a method to improve iodine intake in groups that do not consume cow's milk. Given that vegans and vegetarians are a specific population group consistently presenting with low iodine intake and status, there is an opportunity to explore other methods of targeted fortification. For instance, the iodine fortification of vegan vegetable bouillon powder/cubes, bread, or other alternative vegan products (meats, fish etc.), which presently have a low iodine content (Nicol *et al*., 2022). When iodine is not added to foods during processing and manufacturing, the responsibility of selecting appropriate sources of iodine for consumption is borne by consumers at an individual level. Previous studies have identified that poor iodine awareness and knowledge are major risk factors for iodine deficiency (O'Kane *et al*., 2016; Heimberg *et al*., 2022; McMullan *et al*., 2019; Charlton *et al*., 2010; Henjum *et al*., 2018b). We found that iodine knowledge was very low in the UK population (**Manuscripts 2 and 3**) and that knowledge scores were considerably lower than reported in other global studies (Charlton *et al*., 2010; Henjum *et al*., 2018b; O'Kane *et al*., 2016). **Manuscripts 2 and 3** present the first exploration into the differences in iodine knowledge between vegans, vegetarians, and omnivores.

In **Manuscript 2**, we found that a significantly larger proportion of vegetarians in our study were able to correctly identify cow's milk as a useful iodine source, but this did not translate to greater dietary intake. However in **Manuscript 3,** omnivorous individuals tended to have better iodine knowledge and greater iodine intake than vegans and vegetarians.

Our results suggest that public health strategies are needed to improve public awareness of iodine and good sources of iodine, particularly for those not consuming cow's milk, dairy, white fish or eggs, in addition to choosing foods that are fortified with iodine or dietary supplements. Our evidence calls for further investigation into the difference in iodine knowledge between dietary groups.

Other opportunities for iodine improvement in vegan and vegetarian diets include 'point-of-use fortification', such as the use of seaweed/microalgae, iodine-containing supplements and iodised salt (if living in a country without mandatory USI). Seaweed is a very rich and sustainable source of iodine. The potential of commercially available seaweeds as a safe and acceptable method of improving iodine intake and status in individuals consuming diets low in seafood, cow's milk and dairy products is effective at low levels (Combet *et al*., 2014). In human studies, the seaweed test-material fed to participants is rigorously monitored to mitigate disparities in iodine content and to prevent iodine excess (Combet *et al*., 2014). However, the iodine content of seaweeds and seaweed-containing products available to UK consumers does vary substantially and accurate iodine estimates may not be present (Bouga and Combet, 2015). In our systematic review of iodine intake in industrialised countries (**Manuscript 1**), we found that seaweed use was frequently the cause of iodine excess in vegan individuals (Draper and Lewis, 1993; Lightowler and Davis, 1998; Lightowler and Davis, 2002; Waldmann *et al*., 2003; Kristensen *et al*., 2015). Similarly, in **Manuscript 2**, seaweed provided an additional 1541 µg day^{-1} to the dietary intake of two omnivores who were already accessing iodine from dietary sources such as cow's milk and dairy products. Unmonitored and frequent intake of seaweed (particularly kelp varieties) has the potential to expose individuals to excess iodine and may increase the risk of inducing thyroid disorders (Sá Monteiro *et al*., 2019). A benefit of point-of-use fortification is that it allows for flexibility in the delivery of iodine to achieve adequate intake. Consuming seaweed intermittently (once or twice a week) may have a role in improving iodine intake and is unlikely to be problematic for adults who do not have a pre-existing thyroid disorder and are not pregnant/lactating (Smith, 2021).

To prevent excess associated with seaweed consumption, products should be routinely monitored and their iodine content disclosed. Moreover, the risks involved with frequent seaweed consumption must be communicated.

In 2009, Fields and Borak stated that "Strict vegetarians and vegans are likely to use iodine supplements" (Fields and Borak, 2019). There is limited evidence of frequent usage of iodine-containing dietary supplements in the diets of individuals following vegan and vegetarian diets. In **Manuscript 2**, we found that supplement use was widely adopted in vegan groups in our study, yet most consumed supplements were non-iodine containing. The most frequently used supplement for all groups was B12 (27%), followed by, non-iodine-containing multivitamin formulations (17%). In **Manuscript 3**, we show that consumption of B12 supplements appears to mitigate the decline of B12 intake that is experienced by those transitioning from an omnivorous diet to a short-term vegan diet. Contrarily, for iodine intake, there remained a significant reduction even once supplements were added to the analysis and while iodine-containing supplements were consumed by 23% of individuals in the OV group. Our findings may suggest that individuals have a greater awareness of the requirement to consume B12 supplements when implementing a vegan diet. As discussed previously, our findings have consistently shown that iodine awareness and knowledge are low in British participants. Iodine supplements may be a useful tool for improving iodine nutrition and thyroid function in at-risk population's e.g. pregnant, lactating and postpartum women, along with iodine-deficient individuals (Næss *et al*., 2021; Delshad *et al*., 2021; Censi *et al*., 2019). Currently, there is insufficient evidence to support iodine supplementation use in individuals following vegan and vegetarian diets and it is an area that requires further exploration.

As mentioned previously, the UK does not have a monitored USI programme, and the availability of iodised salt varieties is poor. In 2014, a shelf survey was conducted to assess the obtainability of iodised salts from major UK supermarkets. It was found that less than half (41.6%) of supermarkets surveyed sold iodised salt and that the price of salts was 5.3-6.4 times more expensive than regular unfortified table salts.

Consumers able to locate iodised salt must also be willing and able to bear the additional cost of purchasing which may exclude certain population groups. Vegans and vegetarians typically consume low-sodium diets and may miss the benefits of adding iodised salt to meals at the table (Clarys *et al*., 2014). Correspondingly, we found that iodised salt usage in our studies was low and only contributed a relatively small percentage of total iodine intake (**Manuscripts 2 and 3).** In **Manuscript 5**, we discuss the potential for iodised salt to be used in staple foods such as bread, which has shown to be an effective method to improve iodine status in Australia and New Zealand. There are currently no plans to implement an iodised salt programme in the UK, however, any efforts must be balanced to salt reduction targets.

Iodine rich foods or supplements may need be added to the diet in increments to avoid an abrupt increase in dietary iodine, particularly in individuals who may already be experiencing iodine deficiency. In regions of mild to moderate iodine deficiency, rapid increases in iodine intake in pregnancy have been associated with temporary suppression of fT4 production and transient hypothyroidism thought to be caused by a thyroid 'stunning effect' (see Introduction, Section 1.1.6). This thesis does not evaluate how an abrupt increase in iodine intake may affect individuals following vegan and vegetarian diets with very low iodine intake and possibly diminished stores of iodine and is an opportunity for further study.

We have not yet discussed the role of goitrogenic foods in vegan and vegetarian diets. Currently, only one study has attempted to assess goitrogen consumption by dietary group (Leung *et al*., 2011). The study by Leung *et al* found that the average urinary thiocyanate concentration was significantly greater in vegans than vegetarians (576 μg L^{-1} vs. 321 μg L^{-1} retrospectively). The authors also concluded that the difference in urinary thiocyanate between the dietary groups was unlikely to have a significant clinical effect unless participants were experiencing severe iodine deficiency. We did develop an assay to quantify urinary thiocyanate (for **Manuscript 3**), however, due to the COVID-19 pandemic, we were unable to access stored urine due to risk of possible viral contamination. Further studies are needed to outline the role of goitrogens in the diets of modern vegan and vegetarian diets.

9.1.1 Monitoring

Routine monitoring of the iodine status of a population, including assessment of all at-risk sub-groups, is essential to develop effective public health policies to control and prevent iodine deficiency. In the absence of monitoring programmes, national iodine deficiency can often be left unnoticed. For example, the re-occurrence of iodine deficiency in the UK was not identified until 2009 when Vanderpump *et al*., investigated the prevalence of iodine deficiency in a cohort of 737 schoolgirls (14-15 y) (Vanderpump *et al*., 2011).

Before this evaluation, there had not been a national study assessing iodine status in the UK for over 60 years (Rayman and Bath, 2015). Since 2013, national iodine status has been assessed in the UK using the NDNS (Public Health England, 2016, 2019, 2020). In a recent secondary analysis of the NDNS surveys (years 7 to 9), it was determined that vegan participants had a significantly lower UIC (45 µg L^{-1}) compared to vegetarians (111 µg L^{-1}) and omnivores (125 µg L^{-1}) (Dineva *et al*., 2020b). The most recent NDNS data suggests that 4.5% of the UK population self-identify as vegan or vegetarian (Stewart *et al*., 2021), which is equivalent to more than 3 million people (World Bank, 2023). The number of individuals reporting adhering to a vegetarian or vegan diet in the NDNS has also significantly increased over time (3% point increase from 2008) (Stewart *et al*., 2021). However, the accrued sample of vegans and vegetarians in the NDNS is not large enough to permit results to be generalised to all individuals within the population sub-group.

Currently, the EPIC-Oxford cohort is the only large-scale national study in the UK to address the difference in iodine intake between dietary groups (Davey *et al*., 2002; Sobiecki *et al*., 2016). The study contained a sample of 1516 vegetarians and 269 vegans, which accounted for 24% and 4% of total participants. Vegans were found to have an average iodine intake of only 55.5 µg day^{-1} (Sobiecki *et al*., 2016), therefore agreeing with our findings that vegans generally have a very low iodine intake (**Manuscripts 1, 2, 3, and 5**). The upward trend favouring the acceptance of vegan and/or vegetarian diets in the UK and the large body of evidence indicating that iodine nutrition is poor warrants the implementation of large-scale dietary monitoring in these groups.

The recent NDNS survey also identified that the average UIC for females aged 16-49 y was 98 μg L^{-1} and that almost ¼ of individuals had values below 50 μg L^{-1} (Public Health England, 2020). According to the WHO criteria for iodine deficiency, a population with an average UIC of 50-99 μg L^{-1} would be classed as mildly iodine deficient (WHO, 2007). This finding is particularly worrying for two reasons, firstly women of childbearing age must achieve optimal intra-thyroidal iodine stores before conception to ensure that thyroid hormone production can increase during pregnancy to support foetal development (Ahad and Ganie, 2010; Kapil, 2007).

Secondly, women of childbearing age (18-34 y) are the demographic in the UK most likely to adhere to vegan and vegetarian diets (YouGov, 2022). Individuals transitioning to a vegan or vegetarian diet at this life stage may find it more challenging to consume the RNI for iodine of 140-150 μg day^{-1} and sustain the increased iodine requirements in pregnancy (250 μg day^{-1}) (British Nutrition Foundation, 2021a; WHO, 2007). There is yet to be a study investigating the influence of vegan and vegetarian diets on iodine intake and status during pregnancy. However, a small-scale study observed that BMIC was significantly lower in vegan and vegetarian mothers (Pawlak *et al*., 2022). This study also found that most breast milk samples from vegans and vegetarians were unable to provide adequate iodine consumption to infants (0-6 months). This finding may have significant negative consequences on the health and brain development of future generations (Ahad and Ganie, 2010; Kapil, 2007).

Most studies assessing iodine nutrition in vegan and vegetarian populations are dominated by female participants (**Manuscript 1 and 5**). While there may be a gendered difference in the decision to participate in nutritional research, the skew towards female participation is likely to reflect the greater uptake of vegan and vegetarian diets compared to males. In our first systematic review (**Manuscript 1)**, we identified that vegan males frequently did not achieve adequate iodine intake and tended to have poorer iodine consumption compared with females from the same cohort. Low dietary iodine intake and hypothyroidism in males can affect fertility by lowering semen quality, testicular function, and libido (Sun *et al*., 2020).

Along with producing other negative symptoms associated with hypothyroidism and altered thyroid hormone synthesis experienced by both genders (Ahad and Ganie, 2010; Kapil, 2007). There is a need for further studies observing iodine intake and status in vegan and vegetarian males.

9.1.1.1 Challenges associated with dietary monitoring of vegans and vegetarians in populations

Monitoring the dietary intake of vegans and vegetarians is not straightforward. An appropriate sampling technique must be selected to reach a sufficient number of vegan and vegetarian participants for monitoring programmes. Non-probability-based approaches (e.g. convenience sampling or snowball sampling) are commonly used to recruit individuals from minority populations (Raifman *et al*., 2022). However, sampling in this way may produce estimates that are biased or cannot be generalised (Raifman *et al*., 2022). To improve the generalisability of results, individuals must also be sampled from different geographic areas and include a range of demographics (Groufh-Jacobsen *et al*., 2020). Researchers must establish a robust approach to categorise and define dietary groups for monitoring. In **Manuscript 1**, we discussed that individuals following vegan and vegetarian diets may be misclassified in dietary studies due to differing dietary definitions, along with the possibility that vegans and vegetarians may occasionally consume food items that are usually restricted. We tried to improve the classification of individuals to dietary groups by inspecting FFQ responses relating to the consumption of animal products and comparing intake to definitions of vegan and vegetarian diets (Phillips, 2005) (**Manuscript 2**). Dietary preferences are not fixed and individuals are likely to transition between definitions over time (e.g. omnivore-vegetarian etc.), thus making dietary monitoring challenging (Waters, 2018).

Dietary methods for iodine estimation are reliant on the availability and use of food composition data. Most countries have national food composition tables, but data provided by these resources may differ in quality. In **Manuscript 1**, we identified that many food composition tables lack up-to-date and appropriate iodine values for foods commonly consumed by vegans and vegetarians such as plant-based alternatives.

The fortification status of these products can vary considerably across types and brands, for example the iodine content of iodine-fortified alternative milk drinks available in the UK can range between 130–450 μg per kg (Nicol *et al*., 2022). Inaccurate data can limit the accuracy of iodine intake estimates using food tables. There is a need for the creation of a comprehensive iodine food composition database to estimate dietary intake among adults adhering to vegan and vegetarian diets.

Precise evaluation of the iodine status within the population is necessary for monitoring and research efforts. While the most widely used method for population iodine status is spot UIC, this approach has several limitations. Spot UIC samples are subject to substantial diurnal and day-to-day variation due to circadian rhythms and changes in recent iodine intake (Als et al., 2000; Soldin, 2002, Hlucny *et al*., 2021). At the population level, variations can be mitigated with a sufficient quantity of samples (König et al., 2011). Hydration correction can be also completed using the age- and sex-adjusted I/Creat ratio. As demonstrated in **Manuscript 1 and 5**, this rectification is typically not applied in studies of iodine in vegans and vegetarians. To attempt to improve UIC estimates in **Manuscript 3**, we asked participants to collect x3 UIC samples over one day, and we corrected samples for fluid intake using the I/Creat ratio. Typically, the prevalence of iodine deficiency and excess is assessed in populations by comparing the distribution of UIC according to established cut-offs for median UIC in varying age/sex groups denoted by WHO (WHO, 2007; Zimmermann *et al*., 2013). Using the reference cut-offs for deficiency may carry the potential for inaccuracies. As discussed in **Manuscript 5**, cut-offs have been developed using median UIC from school-aged children (SAC) which may mask sub-groups with varying diets and/or iodine sources (Zimmermann and Andersson, 2021). Additionally, the WHO cut-offs for iodine deficiency do not correspond with the EAR for adults. Zimmermann and Andersson (2012), identified that the EAR cut-off method for identifying iodine deficiency according to the distribution of a population may be more appropriate. The thresholds for UIC according to the EAR method for an average female population, (18y and average weight of 64kg) would be 63 μg L^{-1} (Zimmermann and Andersson, 2012).

Given that multiple urine samples were provided in **Manuscript 3**, we could have considered applying the EAR cut-off as an additional indicator of the prevalence of iodine deficiency from the UIC population distribution. Additional studies of iodine nutrition in vegans and vegetarians should explore this approach.

In Manuscript 3, we used blood constituents (fT4 and Tg) as a measure of thyroid function. The thyroid gland can adapt its function in response to iodine deficiency, and typically serum TSH and Tg will increase, serum T4 will reduce, and T3 will remain normal or high-normal (Zimmermann, 2009a). Individuals experiencing overt hypothyroidism typically display elevated serum TSH and low fT4 (Zimmermann, 2009a). However individuals experiencing subclinical hypothyroidism may have increased serum TSH but normal serum free thyroxine (fT4) (Zimmermann, 2009a). The ability for the thyroid gland to adapt is subject to between-individual variation, hence thyroid function may not be a useful indicator of population iodine status (Pearce and Caldwell, 2016). **In Manuscript 3**, we found that there was no change in fT4 concentration over time or dietary group despite a significant reduction in dietary iodine intake, aligning with previous research of thyroid function of vegetarians and vegans in Boston (Leung *et al*., 2011). Unlike Leung *et al*, we did not measure TSH, the most sensitive early indicator of thyroid dysfunction, due to a lack of sample volume for analysis (Pearce and Caldwell, 2016). Similarly, we did not find any change in Tg concentration. A lack of significant change may be due to the monthly duration of our study as serum Tg tends to reflect iodine nutrition over a period of months. Much of the research concluding Tg as a useful biomarker for iodine deficiency has been conducted in SAC and pregnant women (Zimmermann *et al*., 2013; Dineva *et al*., 2023). It is possible that serum Tg may be a complementary biomarker of iodine status in adult populations, however further research is needed along with the development of international reference values for serum Tg in all age groups. To our knowledge this is the first study to address Tg concentration as a biomarker for iodine nutrition in adults following vegan and vegetarian diets.

Blood collection poses many challenges. For instance, a trained phlebotomist is needed to retrieve samples, equipment is required for drawing blood (e.g. needles, blood collection tubes, etc.), and laboratory facilities are needed for the processing and storage of biological samples to prevent contamination and degradation of the sample. Additionally, collecting blood intravenously is an invasive procedure which is burdensome for participants. The collection of blood spots on filter paper for the assessment of Tg circumvents many of the challenges associated with intravenous blood collection outlined above.

We considered the use of SIC as a possible biomarker for iodine status in our clinical trial protocol since the salivary glands express the NIS and other related iodine transporters (Dekker *et al*., 2021) (**Manuscript 4**). SIC in this study could be used as a reflection of the total body iodine pool (Dekker *et al*., 2021), which may have allowed us to assess if stores improve after the introduction of an iodine fortified alternative milk. Additionally, understanding of participants' total iodine stores prior to the intervention may identify participants with very low bodily stores who may be susceptible to 'iodine stunning' after the introduction of the test milk. SIC has yet to be investigated in adult individuals following vegan diets and could be of interest in future work.

Success in the implementation of a routine monitoring system targeting individuals following vegan and vegetarian diets to assess nutrient sufficiency could reduce the prevalence of iodine deficiency in the UK. However, monitoring programmes are a large financial commitment and require a clear financing strategy. The responsibility lies largely with nutrition researchers and government stakeholders to mobilise resources to fund a successful monitoring programme.

9.2 Future research

This thesis has identified several research gaps and potential areas for future research.

Firstly, the results of this thesis present a need for robust large-scale studies investigating the iodine intake and status of habitual vegans and vegetarians in the UK as well as individuals transitioning to a vegan diet in the short term. Particularly, there is still a limited number of studies investigating thyroid function and the role of dietary goitrogens in vegans and vegetarians (Leung *et al*., 2011).

We attempted to assess thyroid function using plasma fT4 and Tg, however, our work is restricted by the poor availability of biomarker data. Larger studies are needed to definitively assess the role of dietary choice on thyroid function in populations consistently presenting with low iodine intake. Additional studies also offer the opportunity to implement sampling techniques to improve the proportion of participating males. Moreover, there is a lack of studies assessing the prevalence and incidence of hypothyroidism in vegan and vegetarian populations. Along with the possible 'stunning' effect that may be related to abrupt intake of iodine in those with reduced iodine stores.

Secondly, the research presented in this thesis clearly shows that women of childbearing age following vegan and vegetarian diets are extremely vulnerable to iodine deficiency. Research has shown that diets selected at preconception are continued throughout pregnancy (Sebastiani *et al*., 2019). As the prevalence of vegan and vegetarian diets increases globally, more women are likely to enter pregnancy while implementing dietary restrictions (Sebastiani *et al*., 2019). However, the influence of vegan and vegetarian dietary practices on iodine intake and status during pregnancy has not been well researched. Similarly, the effect of strict dietary restrictions on pregnancy outcomes, BMIC, infant iodine intake, or infant development has not been established.

Thirdly, in **Manuscripts 2 and 3**, we add to the growing evidence which suggests that iodine knowledge is very poor among individuals living in the UK, particularly young women (Kayes *et al*., 2022; O'Kane *et al*., 2016).

In our research, low iodine knowledge also may correspond to low dietary iodine intake. Investigating educational interventions and public health campaigns to improve national iodine knowledge is crucial. Along with the consistent and continuous promotion of iodine-rich food sources to consumers that are appropriate for all dietary choices including vegan and vegetarian.

Lastly, our systematic reviews (**Manuscripts 1 and 5**) identify that the iodine intake of individuals following vegan and vegetarian diets does depend on national iodine deficiency prevention strategies. We also found that voluntary salt iodine fortification may not be a sufficient method to improve iodine intake in populations following restrictive diets. Therefore, there is an urgent need for studies to address new opportunities for food fortification (such as described in **Manuscript 4**), and/or iodine supplement provision to individuals following vegan and vegetarian diets. Our research also indicates that policy interventions improving the iodine content of certain foods (e.g. alternative milk and associated products) need to be considered. Along with engagement with manufacturers of vegan products mimicking iodine-rich foods to advertise the nutritional dis-similarities and to persuade companies to fortify new product lines with iodine.

9.3 Limitations

Several limitations must be considered when interpreting the findings from this thesis. The confines of specific studies are outlined in the corresponding manuscripts (**Manuscripts 1-5**) and will be discussed briefly in this section.

Manuscripts 1 and **5** aim to identify and synthesise all the evidence concerning the iodine intake and status of individuals following vegan and vegetarian diets. Systematic reviews are subject to potential limitations. To avoid bias during the selection process, three different researchers were responsible for establishing a robust eligibility criterion. Additionally, two researchers contributed to the screening process and selected papers were reviewed by the study team to confirm inclusion. Other limitations are related to the primary studies included in our review which tended to have a small sample size and low heterogeneity (e.g. sample populations, age, gender, reported outcomes, study design, etc.).

Additionally, some of the studies were of poor quality due to the nature of cohort studies (Ramirez-Santana, 2018).

In **Manuscript 1** we did not perform a meta-analysis or use any other statistical methods to summarise our findings. In **Manuscript 5**, although we did perform a meta-analysis, due to a low sample of males in the included studies, we only completed the analysis using mixed gender and female estimates.

Data presented in this thesis was collected from observational studies (**Manuscripts 2 and 3**). A cross-sectional study design was selected to monitor the iodine nutrition of vegan, vegetarian, and omnivorous populations at one specific point in time (**Manuscript 2**).

The data presented in this study were collected from a relatively small number of volunteers based in Nottinghamshire between 2016-17 and 2019. Our participants tended to be young, motivated, well-educated, and female. Therefore, data is likely subject to participation bias and our findings are not generalizable to the wider population. We cannot remove the possibility of research bias in this study as we did not compare the different characteristics of participants and non-participants. Another main limitation is that we are unable to generate a causal inference between variables and the outcome of interest using single time-point data.

In **Manuscript 3**, we conducted a study to assess the influence of "Veganuary" on micronutrient nutrition. Although we found a significant reduction in micronutrient intake in omnivorous participants, we cannot be certain that the implementation of a short-term vegan diet was the singular cause of the observed reductions. Our study outcomes are confounded by several factors, for example, seasonal changes in food consumption (whereby intake is generally higher over the Christmas period), the possibility that participants were implementing a vegan diet for weight loss, and the impact of food availability/security during the COVID-19 pandemic. Unfortunately, we did not adjust for these factors or others that may have influenced our outcomes. Individuals in this study volunteered to take part in "Veganuary" and therefore participation bias is likely present in our sample. Our study was subject to a large decline in study participation from baseline-follow-up, which is also related to selection bias.

Due to high levels of attrition, we received a low number of biological samples from participants that considerably reduces the power of the study. Blood samples were processed to permit plasma analysis of fT4 and Tg, however, serum measurements would have been a more useful and accurate measure of thyroid function. Additionally, we were unable to interpose for a sufficient length of time to investigate the occurrence of IDD or symptoms relating to iodine deficiency in our population. A limitation of using Tg as a marker for iodine status in adult populations is that reliability is reduced in individuals with detectable TgAb (Pearce and Caldwell, 2016), in our study we did not test for the presence of these antibodies.

The gold standard for human research studies is Randomised Control Trials (RCT). In **Manuscript 4**, we outline the protocol for a single-blind, randomized, placebo-controlled study with two parallel groups (control and intervention group) to assess the usefulness of iodine-fortified alternative milk as a method of improving iodine intake in vegan populations. Although we received ethical approval, we were unable to conduct the study due to a national shortage of blood testing tubes in England in September 2021. However, we acknowledge that use of a cross-over design, whereby the study participants change their respective arms halfway through the trial and experience consumption of both test and control drinks, would have been more appropriate. Similarly, our study design would have benefited from a wash-out period prior to study. We also could have considered a greater 'dose' of iodine given that individuals are likely to have very low intake of iodine. However, we also did not wish to induce 'iodine stunning'.

Both of our human studies (**Manuscripts 2 and 3**) relied on dietary surveys (FFQs) and FDs. Dietary methods are associated with various limitations (e.g. social desirability, underreporting, recall bias, etc.) (Bingham, 1991). We developed two new tools based on the EPIC FFQs to estimate habitual food and nutrient intake over a specified period (Bingham *et al*., 2001; EPIC-Oxford, 2020). We did not conduct a methodological study to assess the validity and reliability of our FFQs, which may lower the accuracy of our estimates.

However, in **Manuscript 2**, we did discuss the difference in iodine estimates between dietary methods and found that our iodine-specific FFQ tended to overestimate intake, a phenomenon that is commonly associated with FFQ methodology overestimate (Næss *et al*., 2019; Y *et al*., 2018). The EPIC FFQs have been validated in UK populations (Lietz *et al*., 2002), however, studies have not specifically certified the micronutrient iodine.

Future studies need to evaluate the validity and reliability of FFQs assessing iodine intake in populations with a high proportion of vegans and vegetarians. Our FFQ only provided a finite list of foods and beverages, foods contributing to iodine intake may have been excluded or missed. As mentioned above, dietary intake methods are reliant on up-to-date food tables and databases to provide accurate micronutrient values. Many of these tables do not provide values for new products designed for vegan and/or vegan consumers and are an unreliable method to accurately assess iodine contribution from foods such as seaweeds, iodised salts, and supplements. Finally, other limitations include the use of casual spot UIC samples to assess iodine status in **Manuscripts 2 and 3**.

9.4 Conclusion

The work presented in this thesis has identified several novel research findings which have substantially added to the current field of iodine in vegan and vegetarian diets. This thesis demonstrates that vegans and vegetarians are indeed a sub-group that is vulnerable to iodine deficiency, both in the short and longer term. Vegan and vegetarian individuals living in countries without mandatory iodised salt policies, or those with inadequate national iodine status have a heightened risk. Still, little is known about the influence of vegan and vegetarian diets on thyroid status, an area of research that requires further investigation.

We also highlight that iodine intake and status are low in the UK, regardless of dietary choice. In countries where individuals are responsible for planning their diet to include sources of iodine, public health campaigns stimulating iodine awareness and the promotion of iodine-rich food consumption are urgently required. Additionally, there is a need for researchers to identify vegan appropriate sources of iodine.

As the global proportion of vegans and vegetarians continues to grow, there is an increased need to regularly monitor and correct iodine deficiency in this vulnerable population.

SUPPLEMENTARY MATERIALS

Supplementary Table 1. Search terms used in the study (Manuscript 1).

1	exp Iodine/
2	Iodine*.mp
3	Iodine* Status*
4	Iodine* Intake*
5	Exp Deficiency
6	Exp Hypothyroidism
7	Vegetarian*.mp.
8	Exp Diet, Vegetarian/
9	Vegan*.mp.
10	Exp Diet, Vegan/
12	Fruitarian*.mp.
13	Flexatarian*.mp.
14	Pescatarian*.mp
15	Herbivore*.mp.
16	Plant?Based*.mp.
17	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15
18	16 AND 17

Limit all to ‘Humans’, ‘Adult (18 years)’ and ‘English Language’

Supplementary Table 2. Quality assessment questions (Manuscript 1).

Question	Observational Cohort and Cross-Sectional	Controlled Intervention	Quality Assessment of Case-Control
1	Was the research question or objective in this paper clearly stated?	Was the study described as randomised, a randomised trial, a randomised clinical trial, or an RCT?	Was the research question or objective in this paper clearly stated and appropriate?
2	Was the study population clearly specified and defined?	Was the method of randomisation adequate (i.e., use of randomly generated assignment)?	Was the study population clearly specified and defined?
3	Was the participation rate of eligible persons at least 50%?	Was the treatment allocation concealed (so that assignments could not be predicted)?	Did the authors include a sample size justification?
4	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	Were study participants and providers blinded to treatment group assignment?	Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
5	Was a sample size justification, power description, or variance and effect estimates provided?	Were the people assessing the outcomes blinded to the participants′ group assignments?	Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented

			consistently across all study participants?
6	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	Were the groups similar at baseline on important characteristics that could affect outcomes (e.g. demographics, risk factors, co-morbid conditions)?	Were the cases clearly defined and differentiated from controls?
7	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
8	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as continuous variable)?	Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Was there use of concurrent controls?
9	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was there high adherence to the intervention protocols for each treatment group?	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
10	Was the exposure(s) assessed more than once over time?	Were other interventions avoided or similar in the groups (e.g. similar background treatments)?	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across

			all study participants?
11	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Were the assessors of exposure/risk blinded to the case or control status of participants?
12	Were the outcome assessors blinded to the exposure status of participants?	Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?
13	Was loss to follow-up after baseline 20% or less?	Were outcomes reported or subgroups analysed pre-specified (i.e., identified before analyses were conducted)?	-
14	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Were all randomised participants analysed in the group to which they were originally assigned, i.e., did they use an intention-to- treat analysis?	-

Supplementary Table 3. Definitions and characteristics of dietary groups studied in included articles (Manuscript 1).

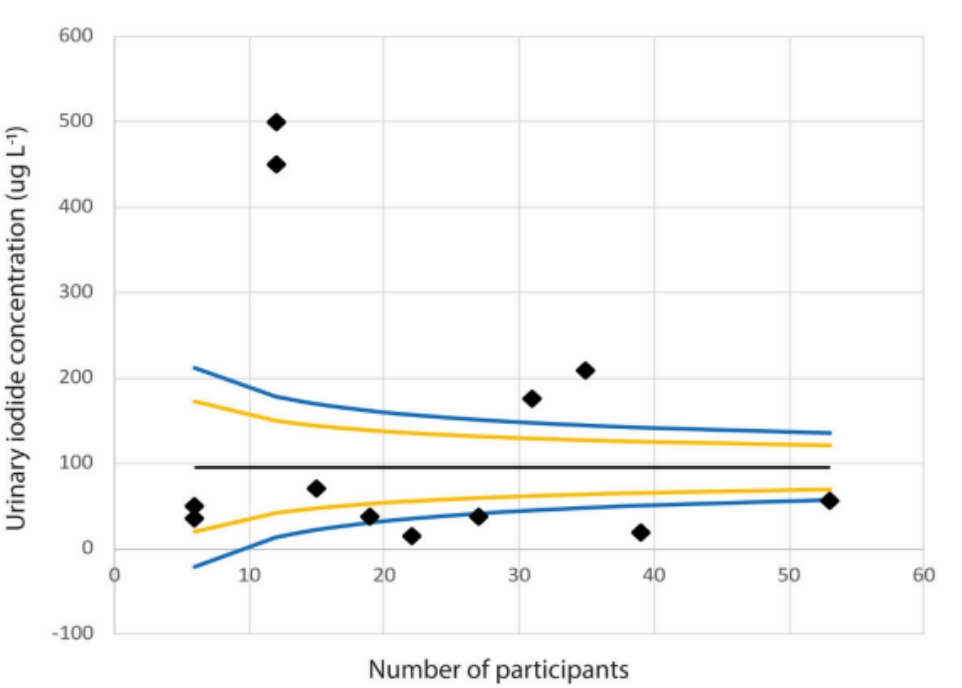
Dietary Group	Characteristics
Vegan	Avoids all products of animal origin.
Vegan (Living Food Diet)	Consumption of lactobacillus rich foods avoids products of animal origin.
Vegan (Strict)	Avoids all products of animal origin
Vegan (Moderate)	Aims to avoid all products of animal origin with occasional consumption of diary and/or eggs.
Vegetarian	Consumption of dairy and eggs but no meat or fish.
Lacto-Vegetarian	No consumption of meat or eggs.
Pescatarian	Consumption of dairy, eggs and fish but not meat.
Demi-vegetarian	Occasional consumption of products of animal origin.
Omnivore (Meat Eaters)	No dietary restrictions or avoidance.

Supplementary Table 4. National data corresponding to location of included studies (Manuscript 1).

Country	**Population**	**Year**	**MUIC* (µg L^{-1})**	**Adequacy**	**World Health Organisation (WHO) Iodine Deficiency Disorder (IDD) Criteria** (WHO, 2007)
Boston (U.S.)	National	2008	164	Adequate	Optimal
Denmark	Adults (16-65)	2012	145	Adequate	Optimal
France	National, Adults (18-74)	2006-7	136	Adequate	Optimal
Finland	National, Adults (25-64)	2013	83	Insufficient	Mild
Germany	National, Woman (18-79)	2008-2011	54	Insufficient	Mild
Norway	National, Adults (25-64)	2003-4	75	Insufficient	Mild
Slovakia	National, School Aged Children (6-12)	2002	183	Adequate	Optimal
Switzerland	National, Woman Reproductive Age	2015	86	Insufficient	Mild
UK	National, Woman Reproductive Age (16-49)	2013	177	Adequate	Optimal

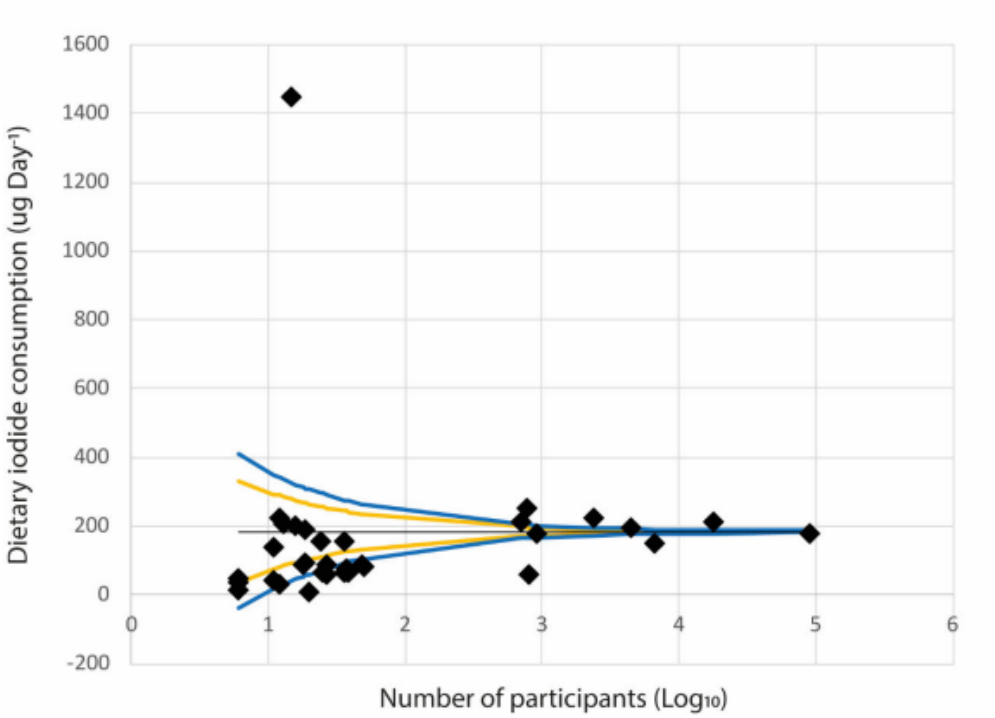
Supplementary Table 5. Common methods for assessing dietary iodine (Manuscript 1).

Method	Dietary Record or Food Dairy Diary	Weighed Food Diary	Duplicate Diet	Food Frequency Questionnaire (FFQ)	Semi quantitative FFQ	24-h Food Recalls
Description	Food and beverages are recorded at consumption. Iodine intake is determined by regional composition data considering seasonal variation.	Food and beverages are weighed and logged into a food record at consumption by the individual or investigator.	Duplicate portions of all food and beverages consumed during a set period are collected and chemically analysed.	A limited checklist of foods and beverages associated with frequency response. Individuals report item consumption over a specific duration.	A checklist of foods and beverages associated with frequency response using standardized portions.	A structured interview capturing detailed information about food and beverages consumed by an individual over the past 24 hours.



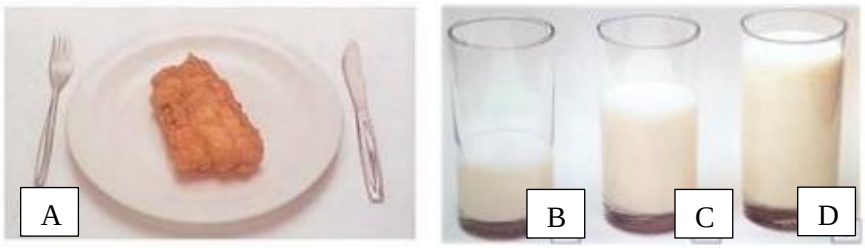
Supplementary Figure 1. Funnel plot showing iodide status for individual groups according to number of individuals in each group (Manuscript 1).

For each study, data for urinary iodide concentration (μg L^{-1}) was plotted for omnivores, vegetarians, and vegans where provided, against the number of participants in each group. Each data point represents a specific group rather than a specific study.



Supplementary Figure 2. Funnel plot showing iodide consumption for individual groups according to number of individuals in each group (Manuscript 1).

For each study, data for dietary iodide intake (μg day^{-1}) was plotted for omnivores, vegetarians, and vegans where provided, against the Log10 of the number of participants in each group. Each data point represents a specific group rather than a specific study.



Supplementary Figure 3. Example of photos provided within the Food Frequency Questionnaire (FFQ) to demonstrate medium portions of commonly consumed foods.

Example A: Fried fish in batter

Example B: Milk with tea or coffee

Example C: Milk with breakfast cereals

Example D: Milk in latte, hot chocolate or just on its own.

Supplementary Table 6. Questions assessing micronutrient knowledge in the 2019 cohort (Manuscript 3).

Question	Responses
1. Before you volunteered to take part in this study were you aware of any symptoms associated with micronutrient deficiencies?	Yes No
2. If yes, what deficiency symptoms are you aware of? Please list all of the symptoms you are aware of. Be as specific as possible.	Free text available
3. Are you confident that your current diet provides adequate micronutrients?	Yes No

Supplementary Table 7. Questions assessing iodine knowledge.

	Question	Responses
1.	Are you aware of the nutrient iodine?	Yes No
2.	Which of the following do you think is the richest food source of iodine in the UK?	Fruit Vegetables Eggs Meat and meat products Salt (table) Milk and Dairy Bread Dairy-alternative or milk substitute Fish and seafood Nuts and seeds Breakfast cereals Non-dairy yogurt and cheese Do not know
3.	What do you understand to be the main health problem/s associated with not having enough iodine in the diet? (select all that apply)	Weak bones and teeth Heart conditions Malformations in pregnancy (Birth defects) Impaired physical development during childhood Neural Tube Defects Allergy Do not know Blindness Goitre Weak immune system Mental Retardation Arthritis Other (free text available)
4.	Based on your understanding, at which stage of the life cycle do you think iodine is most important?	Babies and young children Teenagers Adults Elderly adults Pregnant and breastfeeding women Women of childbearing age Don't know
5.	Do you think iodine deficiency is a common health problem in the UK and Ireland now?[1]	Yes No
6.	Do you think that your present diet provides you with enough iodine?	Yes No Unsure
7.	Do you plan your diet to ensure you eat foods rich in iodine?	Yes No Unsure
8.	Have you ever received any information related to iodine and health?	Yes (free text available) No Unsure

[1]Question not addressed in the iodine knowledge survey (Manuscript 2).

Supplementary Table 8. Motivation towards following a vegan diet for individuals recruited in 2019 (Manuscript 3).
Higher mean ± SD scores relate to greater motivation for each trait (max score 5).

Motivation for a vegan diet Mean ± SD	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 15)	Omnivore (OO) (n = 20)	Omnivore-vegan (OV) (n = 23)	P
Health	3.8 ± 1.2	4.1 ± 0.9	3.5 ± 1.3	3.7 ± 1.2	0.539
Factory farming	4.2 ± 1.0	4.3 ± 1.0	2.6 ± 1.0	2.9 ± 1.4	<.001*
Sustainability	4.6 ± 0.7	4.4 ± 0.6	3.0 ± 1.4	3.6 ± 1.2	<.001*
Climate protection	4.4 ± 0.7	4.4 ± 0.6	3.2 ± 1.4	3.6 ± 1.2	<.001*
Vegan friends	2.0 ± 1.2	2.7 ± 1.4	1.4 ± 0.6	1.7 ± 0.9	0.005*
Food scandals	2.1 ± 1.2	2.5 ± 1.1	1.8 ± 0.6	1.6 ± 1.0	0.048*
Animal welfare	4.2 ± 1.0	4.3 ± 1.1	2.9 ± 1.0	3.0 ± 1.2	<.001*
Food safety	2.8 ± 1.2	3.5 ± 1.3	2.7 ± 1.2	2.2 ± 1.2	0.017*
Food availability	2.3 ± 1.3	3.1 ± 1.3	2.5 ± 1.1	2.2 ± 1.2	0.130
Food choice	2.3 ± 1.2	3.3 ± 1.2	2.4 ± 1.1	2.1 ± 1.2	0.016*
Food trends	1.7 ± 1.0	2.2 ± 1.6	1.7 ± 0.8	1.9 ± 1.3	0.462
Food taste	2.5 ± 1.4	3.8 ± 1.3	3.4 ± 1.3	2.4 ± 1.4	0.004*
Vegan family	1.6 ± 1.1	2.0 ± 1.5	1.3 ± 0.6	1.4 ± 0.9	0.177
Personal morals	4.1 ± 1.1	4.3 ± 1.0	2.3 ± 1.0	2.7 ± 1.4	<.001*
Rotten meat	2.0 ± 1.4	2.5 ± 1.4	2.3 ± 1.5	1.7 ± 1.3	0.360
Religion	1.3 ± 0.7	1.3 ± 1.0	1.2 ± 0.7	1.0 ± 0.2	0.618
New year resolution	1.6 ± 1.1	1.9 ± 1.5	1.3 ± 0.5	2.0 ± 1.1	0.193
Previous experience	1.5 ± 0.9	3.0 ± 1.7	2.5 ± 1.0	1.8 ± 1.3	0.001*
Vegan Society support	2.2 ± 1.3	2.9 ± 1.6	1.2 ± 0.4	1.6 ± 1.0	<.001*
Challenge	2.2 ± 1.4	3.3 ± 1.5	1.8 ± 0.9	3.2 ± 1.3	<.001*

Table continued…

Motivation for a vegan diet Mean ± SD	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 15)	Omnivore (OO) (n = 20)	Omnivore-vegan (OV) (n = 23)	P
Cost or expense	1.8 ± 1.0	2.0 ± 1.4	2.6 ± 1.3	2.0 ± 1.3	0.156
Food variety	2.1 ± 1.2	2.6 ± 1.5	2.5 ± 1.3	2.2 ± 1.4	0.648
Novelty	1.3 ± 0.7	1.9 ± 1.4	2.0 ± 1.3	2.3 ± 1.3	0.029*
Social media	1.9 ± 1.3	2.1 ± 1.3	1.4 ± 0.7	1.6 ± 1.2	0.197
Weight loss	1.4 ± 0.9	2.5 ± 1.2	1.9 ± 1.2	2.5 ± 1.5	0.011*
Media and TV	2.8 ± 1.4	2.7 ± 1.5	1.5 ± 0.7	2.0 ± 1.5	0.197

*Significance between dietary groups assessed by two-way general ANOVA (P = < 0.05).

Supplementary Table 9. Motivation towards following a vegan diet for individuals recruited in 2020 (Manuscript 3).
Higher mean ± SD scores relate to greater motivation for each trait (max score 5).

Motivation for a vegan diet Mean ± SD	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = *6*)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)	P
Health	3.1 ± 1.4	3.2 ± 1.5	3.2 ± 1.3	2.5 ± 1.3	0.584
Factory farming	4.4 ± 1.0	4.0 ± 0.9	3.5 ± 1.7	2.6 ± 1.4	0.002*
Sustainability	4.2 ± 1.0	4.5 ± 1.3	3.7 ± 1.5	3.8 ± 1.4	0.500
Climate protection	4.3 ± 1.1	3.8 ± 1.2	3.5 ± 1.4	3.8 ± 1.5	0.301
Vegan friends	1.8 ± 1.1	2.3 ± 1.4	1.3 ± 0.5	1.8 ± 1.0	0.523
Food scandals	2.5 ± 1.3	2.7 ± 1.0	2.8 ± 1.8	1.5 ± 0.9	0.063
Animal welfare	4.8 ± 0.7	4.0 ± 1.1	2.8 ± 1.2	3.3 ± 1.5	0.001*
Food safety	2.1 ± 1.4	2.5 ± 1.4	2.5 ± 1.5	2.0 ± 1.4	0.887
Food availability	2.0 ± 1.2	2.7 ± 1.5	2.3 ± 1.2	1.5 ± 1.2	0.596
Food choice	2.2 ± 1.3	2.3 ± 1.4	3.5 ± 1.3	2.0 ± 1.4	0.551
Food trends	1.4 ± 0.8	2.3 ± 1.0	1.8 ± 1.0	1.6 ± 0.7	0.055
Food taste	2.2 ± 1.3	2.8 ± 1.5	2.8 ± 1.8	2.4 ± 1.6	0.125
Vegan family	1.9 ± 1.3	2.7 ± 1.9	1.3 ± 0.5	1.6 ± 1.0	0.149
Personal morals	4.6 ± 0.9	3.8 ± 0.4	2.5 ± 1.4	3.5 ± 1.5	0.001*
Rotten meat	1.7 ± 1.0	2.2 ± 1.6	1.7 ± 1.2	1.5 ± 1.0	0.711
Religion	1.0 ± 0.0	1.2 ± 0.4	2.0 ± 0.0	1.0 ± 0.0	0.160
New year resolution	1.3 ± 0.8	2.0 ± 1.7	2.5 ± 0.8	1.6 ± 1.2	0.210
Previous experience	1.3 ± 0.8	2.5 ± 1.8	1.5 ± 0.8	1.5 ± 0.9	0.058
Vegan Society support	2.1 ± 1.5	2.3 ± 1.5	1.2 ± 0.4	1.4 ± 0.9	0.167
Challenge	1.6 ± 0.9	2.0 ± 1.1	2.5 ± 1.3	2.9 ± 1.5	0.005*
Cost or expense	1.4 ± 0.8	2.5 ± 1.4	3.2 ± 1.3	1.2 ± 0.5	0.001*
Social media	1.7 ± 1.0	2.2 ± 1.0	1.3 ± 0.5	1.4 ± 1.0	0.297
COVID-19 infection	1.2 ± 0.7	1.8 ± 1.3	1.8 ± 1.2	1.1 ± 0.5	0.001*
Disease outbreaks (in general)	1.4 ± 1.1	2.0 ± 1.6	2.2 ± 1.5	1.1 ± 03	0.007*

*Significance between dietary groups assessed by two-way general ANOVA (P = < 0.05).

Supplementary Table 10. Average micronutrient intake provided by dietary supplements recorded in Food Frequency Questionnaire (FFQ) in the 2019 cohort at baseline and end, compared with 10% of the Reference Nutrient Intake (RNI) (Manuscript 3).

	Baseline													
	Vegan (VV) (n = 12)			Vegetarian-vegan (VegV) (n = 10)			Omnivore (OO) (n = 12)			Omnivore-vegan (OV) (n = 12)			50% of RNI	
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Female	Male
Vitamin A (µg)	4	1000.0	400.0	2	800.0	0.0	3	633.3	288.7	2	600.0	282.8	300.0	350.0
Vitamin C (mg)	4	85.0	5.8	2	85.0	7.1	3	199.0	140.1	2	198.6	224.2	20.0	20.0
Thiamine (mg)	5	1.7	0.8	3	1.8	0.7	2	7.3	6.7	1	8.4	0.0	0.4	0.5
Riboflavin (mg)	5	2.0	0.8	3	2.1	0.7	2	3.8	1.4	1	10.7	0.0	0.6	0.7
Niacin (mg)	4	16.8	1.1	3	13.7	5.8	2	18.0	0.0	2	7.7	0.4	6.5	8.5
Vitamin B6 (mg)	6	2.9	2.4	3	2.9	2.7	2	8.0	2.8	3	18.9	27.1	0.6	0.7
Vitamin B12 (µg)	9	6.9	4.3	4	6.6	5.5	2	5.8	4.6	4	6.2	3.2	0.8	0.8
Folate (µg)	7	214.3	69.0	3	185.7	122.1	2	350.0	70.7	-	-	-	100.0	100.0
Calcium (mg)	4	300.0	200.0	3	138.1	107.2	1	200.0	0.0	-	-	-	400.0	350.0
Iron (mg)	5	25.0	24.6	3	14.0	0.0	2	20.0	5.7	-	-	-	7.4	4.4
Magnesium (mg)	1	100.0	0.0	3	71.4	49.5	2	214.3	69.0	-	-	-	135.0	150.0
Zinc (mg)	3	13.3	2.9	3	8.8	6.9	2	15.0	0.0	1	5.0	0.0	3.5	4.8
Selenium (µg)	2	42.5	17.7	1	55.0	0.0	1	150.0	0.0	-	-	-	30.0	37.5
Iodine (µg)	3	125.0	43.3	1	150.0	0.0	1	100.0	0.0	1	75.0	0.0	70.0	70.0
Vitamin D (µg)	8	8.4	3.5	4	8.8	2.5	6	7.9	4.6	4	25.0	33.4	5.0	5.0
	End													
Vitamin A (µg)	2	800.0	0.0	6	685.7	279.9	2	800.0	0.0	3	833.3	57.7	300.0	350.0
Vitamin C (mg)	2	85.0	7.1	3	105.9	90.1	1	90.0	0.0	3	90.0	0.0	20.0	20.0
Thiamine (mg)	2	1.8	1.0	8	3.7	5.8	1	2.5	0.0	4	4.1	4.0	0.4	0.5
Riboflavin (mg)	2	2.1	1.0	8	2.9	3.0	1	2.8	0.0	4	5.5	6.4	0.6	0.7
Niacin (mg)	2	17.0	1.4	8	18.2	14.1	1	18.0	0.0	4	19.3	3.9	6.5	8.5
Vitamin B6 (mg)	3	2.8	2.8	8	3.4	2.6	1	6.0	0.0	5	24.7	42.2	0.6	0.7
Vitamin B12 (µg)	8	173.8	70.0	9	3.8	3.6	1	2.5	0.0	5	17.6	19.3	0.8	0.8
Folate (µg)	3	200.0	100.0	8	223.2	128.4	1	300.0	0.0	4	416.8	173.4	100.0	100.0
Calcium (mg)	2	200.0	0.0	7	149.0	87.2	1	200.0	0.0	4	232.5	116.4	400.0	350.0

Table continued…

	Vegan (VV) (n = 12)			Vegetarian-vegan (VegV) (n = 10)			Omnivore (OO) (n = 12)			Omnivore-vegan (OV) (n = 12)			50% of RNI	
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Female	Male
Iron (mg)	3	14.0	0.0	6	12.0	4.9	1	14.0	0.0	3	15.33	2.3	7.4	4.4
Magnesium (mg)	1	100.0	0.0	5	65.7	46.9	-	-	-	1	42.0	0.0	135.0	150.0
Zinc (mg)	2	12.5	3.5	7	9.7	6.1	1	15.0	0.0	3	13.7	2.3	3.5	4.8
Selenium (μg)	2	42.5	17.7	3	39.3	27.2	-	-	-	1	55.0	0.0	30.0	37.5
Iodine (μg)	3	125.0	43.3	4	117.9	64.3	-	-	-	1	150.0	0.0	70.0	70.0
Vitamin D (μg)	6	8.8	2.1	7	6.6	3.4	4	12.5	2.9	6	19.6	27.9	5.0	5.0

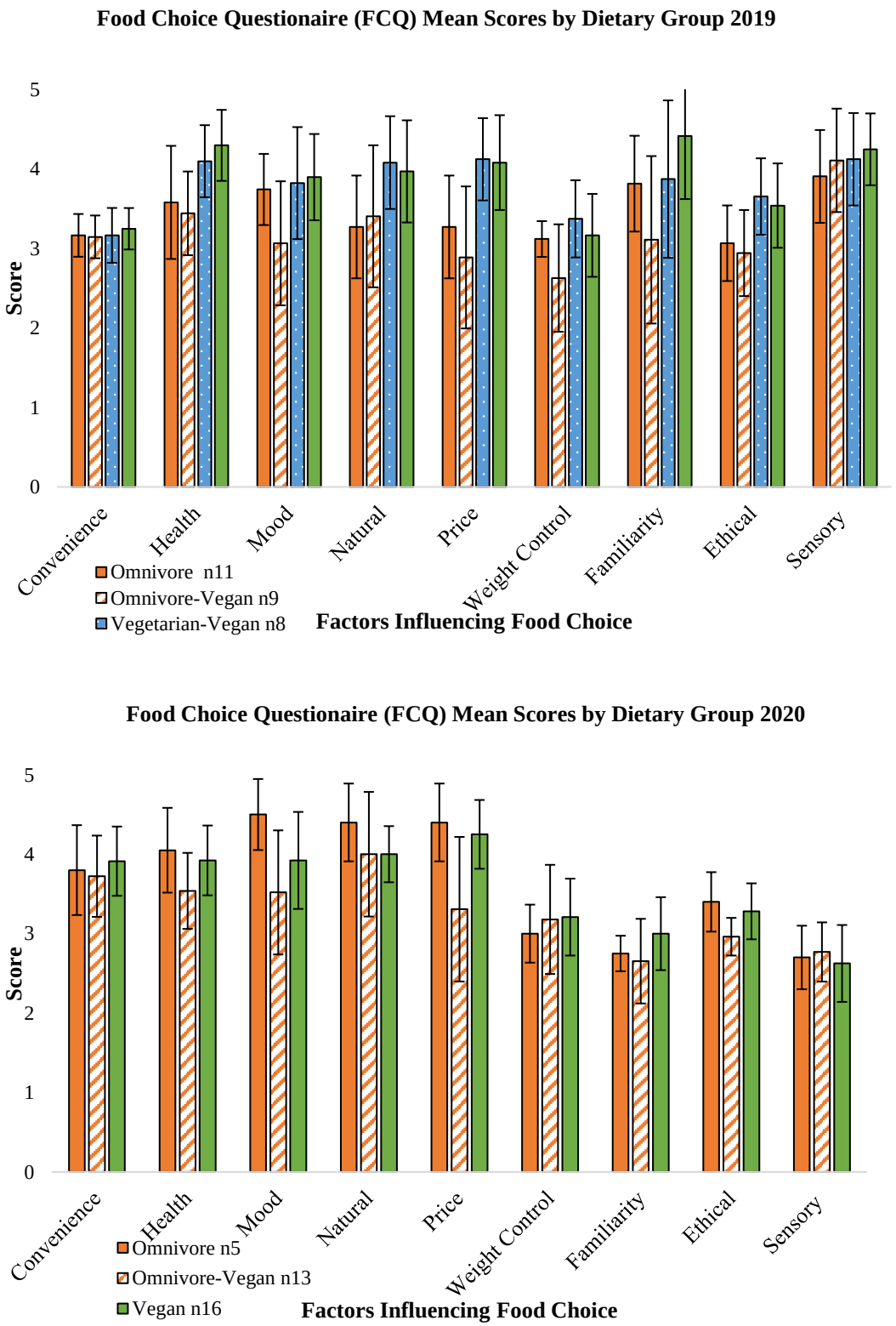
-, Not applicable.

Supplementary Table 11. Average micronutrient intake provided by dietary supplements recorded in Food Frequency Questionnaire (FFQ) in the 2020 cohort at baseline and end, compared with 10% of the Reference Nutrient Intake (RNI) (Manuscript 3).

	Baseline										
	Vegan (VV) (n = 16)			Vegetarian-vegan (VegV) (n = 3)			Omnivore-vegan (OV) (n = 13)			50% of RNI	
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Female	Male
Vitamin A (µg)	3	633.3	288.7	1	800.0	0.0	2	600.0	282.8	300.0	350.0
Vitamin C (mg)	4	65.0	19.2	1	80.0	0.0	2	46.0	48.1	20.0	20.0
Thiamine (mg)	3	4.1	5.1	1	1.1	0.0	2	6.1	6.3	0.4	0.5
Riboflavin (mg)	3	2.6	2.1	1	5.0	0.0	2	7.8	8.1	0.6	0.7
Niacin (mg)	3	22.7	11.6	1	16.0	0.0	2	30.5	20.5	6.5	8.5
Vitamin B6 (mg)	4	3.3	4.5	1	2.0	0.0	2	4.8	3.8	0.6	0.7
Vitamin B12 (µg)	12	120.8	295.3	1	30.0	0.0	5	17.7	21.0	0.8	0.8
Folate (µg)	3	240.0	144.2	1	200.0	0.0	2	380.0	28.3	100.0	100.0
Calcium (mg)	1	200.0	0.0	1	200.0	0.0	2	260.0	198.0	400.0	350.0
Iron (mg)	3	14.0	0.0	1	14.0	0.0	1	14.0	0.0	7.4	4.4
Magnesium (mg)	2	63.5	51.6	1	60.0	0.0	3	102.6	53.0	135.0	150.0
Zinc (mg)	2	12.5	3.5	1	10.0	0.0	2	9.5	0.7	3.5	4.8
Selenium (µg)	2	77.5	31.8	1	100.0	0.0	1	55.0	0.0	30.0	37.5
Iodine (µg)	2	150.0	0.0	1	150.0	0.0	1	150.0	0.0	70.0	70.0
Vitamin D (µg)	8	20.9	22.1	1	20.0	0.0	8	12.5	6.6	5.0	5.0
	End										
Vitamin A (µg)	3	800.0	0.0	2	800.0	0.0	5	800.0	0.0	300.0	350.0
Vitamin C (mg)	4	75.0	10.0	2	85.0	7.1	5	82.0	2.5	20.0	20.0
Thiamine (mg)	4	3.3	4.5	2	1.8	1.0	5	1.5	0.6	0.4	0.5
Riboflavin (mg)	4	2.3	1.8	2	2.1	1.0	5	1.8	0.6	0.6	0.7
Niacin (mg)	4	21.0	0.0	2	17.0	1.4	5	16.4	0.9	6.5	8.5
Vitamin B6 (mg)	4	3.6	4.3	2	3.7	3.3	4	2.7	2.2	0.6	0.7
Vitamin B12 (µg)	11	85.9	172.6	2	10.0	10.6	9	11.2	18.6	0.8	0.8

Table continued…

	Vegan (VV) (n = 16)			Vegetarian-vegan (VegV) (n = 3)			Omnivore-vegan (OV) (n = 13)			50% of RNI	
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD	Female	Male
Folate (μg)	4	250.0	100.0	2	250.0	70.7	5	260.0	89.4	100.0	100.0
Calcium (mg)	1	200.0	0.0	2	200.0	0.0	5	184.0	35.8	400.0	350.0
Iron (mg)	3	14.0	0.0	2	14.0	0.0	5	14.0	0.0	7.4	4.4
Magnesium (mg)	2	63.5	51.6	1	27.0	0.0	3	37.0	17.3	135.0	150.0
Zinc (mg)	2	20.0	7.1	2	12.5	3.5	4	11.3	2.5	3.5	4.8
Selenium (μg)	2	77.5	31.8	2	55.0	0.0	3	55.0	0.0	30.0	37.5
Iodine (μg)	2	150.0	0.0	1	150.0	0.0	3	150.0	0.0	70.0	70.0
Vitamin D (μg)	8	17.5	15.6	2	7.5	3.5	10	18.1	29.2	5.0	5.0



Supplementary Figure 4. Factors influencing food choice; results from the Food Choice Questionnaire (FCQ) in 2019 and 2020 (Manuscript 3).

Supplementary Table 12. Baseline micronutrient knowledge in the 2019 cohort (Manuscript 3).

	Dietary group				
	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 15)	Omnivore (OO) (n = 20)	Omnivore-vegan (OV) (n = 23)	*P*
Self-assessed micronutrient Awareness					
Yes (%)	4.2	20.0	30.0	26.1	0.098
No (%)	95.8	80.0	70.0	73.9	
Awareness of Specific Micronutrients					
Vitamin A (%)	25.0	13.3	35.0	34.8	0.447
Vitamin C (%)	45.8	26.7	50.0	43.5	0.573
Niacin (%)	4.2	0.0	0.0	0.0	-
Vitamin B6 (%)	4.2	0.0	0.0	0.0	-
Vitamin B12 (%)	50.0	33.3	20.0	8.7	0.012*
Folate (%)	4.2	0.0	5.0	0.0	-
Calcium (%)	33.3	26.7	40.0	30.4	0.865
Iron (%)	54.2	53.3	35.0	43.5	0.587
Magnesium (%)	8.3	0.0	15.0	8.7	0.543
Potassium (%)	12.5	6.7	15.0	13	0.967
Sodium (%)	0.0	6.7	5.0	8.7	0.549
Zinc (%)	12.5	13.3	10.0	17.4	0.943
Selenium (%)	8.3	6.7	5.0	4.3	1.000
Iodine (%)	20.8	6.7	15.0	17.4	0.753
Vitamin D	45.8	33.3	50.0	47.8	0.796

Table continued…

	Vegan (VV) (n = 24)	Vegetarian-vegan (VegV) (n = 15)	Omnivore (OO) (n = 20)	Omnivore-vegan (OV) (n = 23)	*P*
Awareness of Micronutrient Deficiencies					
Yes (%)	58.3	66.7	55.0	65.2	0.216
No (%)	41.7	33.3	45.0	34.8	
Non-Specific Deficiency Symptom (%)	16.7	12.3	4.2	4.3	0.882
Vitamin A (%)	10.0	13.3	4.2	4.3	0.650
Vitamin C (%)	20.8	13.3	25.0	21.7	0.873
B Vitamins (non-inclusive of B12) (%)	8.3	6.7	5.0	8.7	1.000
Vitamin B12 (%)	25	6.7	20.0	0.0	0.032*
Folate (%)	0.0	0.0	5.0	4.3	-
Calcium (%)	0.0	0.0	5.0	17.4	-
Iron (%)	33.3	33.3	20.0	8.7	0.148
Magnesium (%)	0.0	6.7	0.0	0.0	-
Zinc (%)	8.3	0.0	5.0	0.0	-
Iodine (%)	4.2	6.7	20.0	13	0.377
Vitamin D (%)	12.5	26.7	20.0	21.7	0.709

Fisher-Freeman-Halton Exact Test (P = < 0.05); -, Not applicable analysis for more than two groups had counts less than 1.

Supplementary Table 13. Baseline record of iodine knowledge (%) by dietary group in 2020 (Manuscript 3).

Responses	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)	*P*
Awareness of the importance of adequate dietary intake					
Yes	75.6	33.3	83.3	87.5	0.692
No	24.4	66.7	16.7	12.5	
Symptoms correctly identified					
Yes	33.3	33.3	66.7	62.5	<.001*
No	66.7	66.7	33.3	37.5	
Knowledge of iodine deficiency symptoms					
Mental Retardation	8.9	16.7	33.3	18.8	0.206
Malformations in pregnancy (Birth defects)	13.3	16.7	33.3	18.8	0.649
Goitre /enlargement of the thyroid gland	11.1	33.3	33.3	50.0	0.008*
Impaired physical development during childhood	15.6	16.7	16.7	25.0	0.751
Neural Tube Defects	6.7	0.0	16.7	0.0	0.371
Heart conditions	11.1	0.0	16.7	18.6	0.584
Weak immune system	20.0	66.7	16.7	37.5	0.062
Blindness	0.0	0.0	16.7	0.0	-
Weak bones and teeth	6.7	33.3	0.9	12.5	0.180
Arthritis	2.2	0.0	0.0	0.0	-
Other	8.9	0.0	0.0	0.0	-
Do not know/ no response	48.9	33.3	33.3	12.5	0.089

Table continued…

Responses	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)	*P*
Understanding of iodine in the life cycle					
Elderly adults	2.2	0.0	0.0	0.0	-
Adults	0.0	0.0	0.0	25.0	-
Pregnant and breastfeeding women	9.0	0.0	2.0	7.0	0.116
Women of childbearing age	0.0	0.0	33.3	0.0	-
Teenagers	15.6	0.0	0.0	0.0	-
Babies and young children	15.6	33.3	16.7	12.5	0.614
Don’t know	46.7	66.7	16.7	18.8	0.065
Perceptions of the main food sources of iodine in the UK diet					
Cow’s milk and dairy	2.2	0.0	33.3	18.8	0.021*
Fish and seafood	35.6	66.7	66.7	43.8	0.292
Eggs	2.2	0.0	0.0	6.2	0.623
Meat and meat products	4.4	0.0	0.0	0.0	-
Nuts and seeds	0.0	0.0	0.0	12.5	-
Table salt	0.0	0.0	0.0	6.2	-
Vegetables	17.8	0.0	0.0	6.2	0.499
Don’t know	26.7	33.3	0.0	6.2	0.133
Knowledge of iodine deficiency being a problem in the UK					
Yes	33.3	0.0	50.0	81.2	<.001*
No	15.6	33.3	16.7	6.2	
Don’t know	51.1	66.7	33.3	12.5	

Table continued…

Responses	Vegan (VV) (n = 45)	Vegetarian-vegan (VegV) (n = 6)	Omnivore (OO) (n = 6)	Omnivore-vegan (OV) (n = 16)	*P*
Reported planning their diet to include sources of iodine					
Yes	6.7	0.0	100.0	81.2	<.001*
No	75.6	66.7	0.0	6.2	
Unsure or don't know	17.8	33.3	0.0	12.5	
Currently receiving iodine information					
Yes	6.7	0.0	16.7	18.8	<.001*
No	88.9	100.0	83.3	81.2	
Unsure or don't know	4.4	0.0	0.0	0.0	
Total iodine knowledge score (mean)					
Total score	1.4	1.5	3.0	2.8	0.004*

Fisher-Freeman-Halton Exact Test (P = < 0.05); -, Not applicable analysis for more than two groups had counts less than 1.

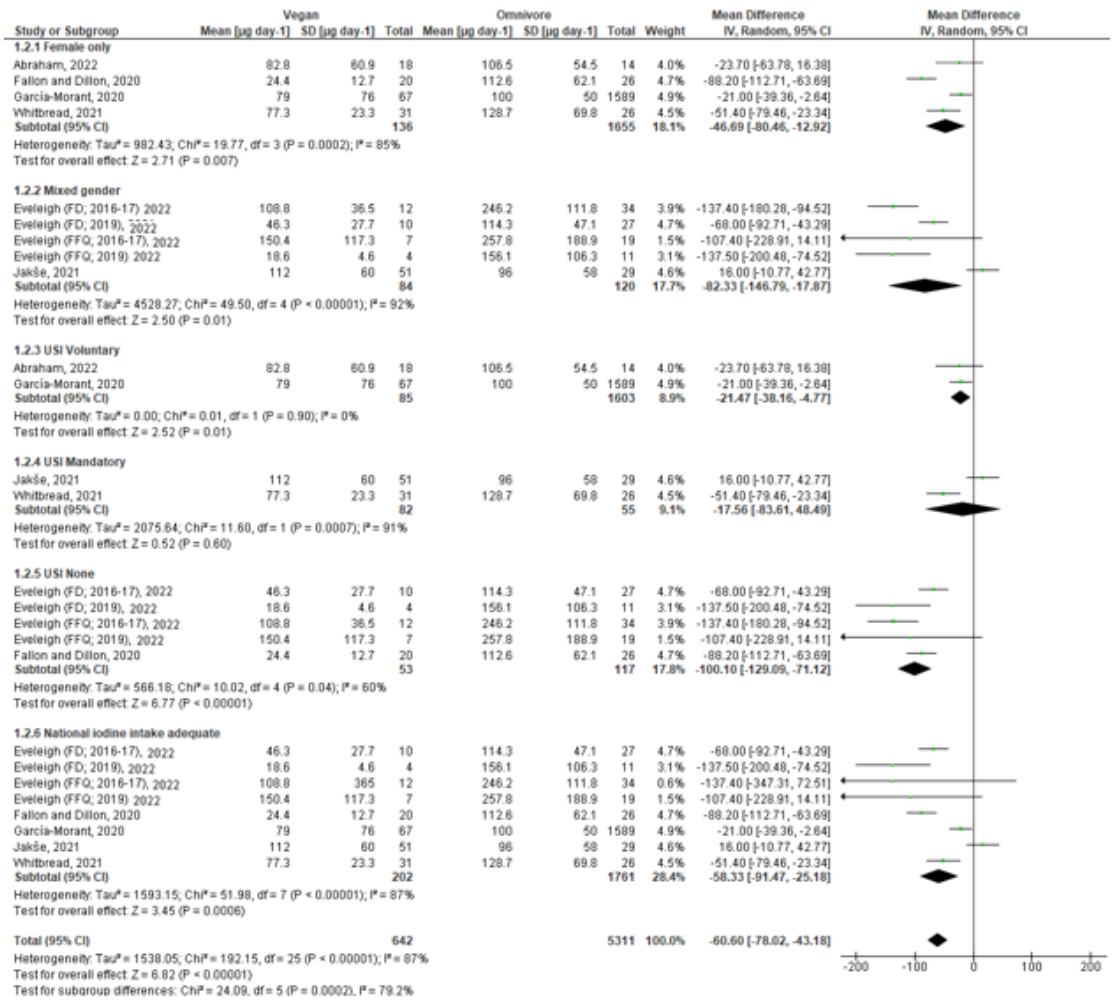
Supplementary Table 14. Urinary iodine concentration (UIC) and urinary age- and sex-adjusted iodine-to-creatinine ratio (I:Cr) in the 2019 cohort at baseline and post-intervention (End). Data is presented as median (interquartile range (IQR)) (Manuscript 3).

		Baseline (median (IQR))			End (median (IQR))		
	Time of urine collection	Vegan (VV) (n = 6)	Vegetarian-vegan (VegV) (n = 3)	Omnivore-Vegan (OV) (n = 6)	Vegan (VV) (n = 6)	Vegetarian-Vegan (VegV) (n = 3)	Omnivore-vegan (OV) (n = 6)
UIC ($\mu g\ L^{-1}$)	Morning	46.7 (32.2)	28.9 (26.9)	34.1 (41.0)	57.4 (71.8)	36.7 (14.4)	22.5 (23.4)
	Afternoon	24.0 (32.2)	23.8 (12.7)	30.3 (24.9)	32.7 (26.7)	21.7 (11.1)	44.2 (68.6)
	Evening	25.0 (30.9)	24.6 (17.6)	36.6 (38.8)	45.1 (21.2)	24.8 (9.5)	52.4 (21.0)
Age- and sex-adjusted I:Cr ($\mu g\ L^{-1}$)	Morning	131.1 (160.4)	104.2 (64.7)	132.8 (46.7)	162.1 (661.6)	44.5 (129.1)	147.4 (12.5.4)
	Afternoon	203.8 (384.8)	229.7 (170.4)	117.7 (123.1)	133.8 (160.8)	111.2 (64.3)	436.4 (651.9)
	Evening	98.2 (401.0)	199.7 (67.1)	124.0 (32.0)	486.8 (508.9)	169.8 (32.7)	104.5 (229.2)

Supplementary Table 15. Quality assessment of included Observational Cohort, Cross-Sectional, and Case-Control studies using the Newcastle-Ottawa scale (Manuscript 5).

Study, year	Selection (max 5 stars)	Comparability (max 2 stars)	Outcome Assessment (or Exposure for Case-Control studies) (max 3 stars)	Quality score[1]
Abraham *et al*, 2022	★★★	★	★★	Good
Blaurock *et al*, 2021	★★	★	★★	Fair
Dawczynski *et al*, 2022	★★★★	★	★★	Good
Eveleigh *et al*, 2022	★★★	★	★★	Good
Fallon and Dillon, 2020	★★★	★	★★	Good
García-Morant *et al*, 2020	★★	★	★★	Fair
Groufh-Jacobsen *et al*, 2020	★★★★	★	★★	Good
Jakše *et al*, 2021	★★★	★	★★	Good
Menzel *et al*, 2021[2]	★★★	★★	★★	Good
Whitbread *et al*, 2021	★★★	★	★★	Good

[1]Quality score, Good = 3 or 4 stars in 'selection' and 1 or 2 stars in 'comparability' and 2 or 3 stars in 'outcome/exposure'; Fair = 2 stars in 'selection' and 1 or 2 stars in' comparability' and 2 or 3 stars in 'outcome/exposure'; Poor = 0 or 1 star in 'selection' OR 0 stars in 'comparability' OR 0 or 1 stars in 'outcome/exposure; [2]Quality assessment has been conducted by the Newcastle-Ottawa scale for Case-Control studies.



Supplementary Figure 5. Meta-analysis sub-group analysis forest plot comparing the effect of vegetarian v. omnivorous diet on iodine intake (Manuscript 5).
Data presented is female and mixed gender estimates only; USI, Universal salt iodisation; 95% CI, confidence interval.

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APPENDIX A

STATEMENT OF AUTHORSHIP OF PUBLICATIONS

This statement confirms the contribution made by Elizabeth Eveleigh to jointly authored work included within this thesis.

I confirm that Elizabeth Eveleigh contributed 80% to the publication:

Eveleigh, ER, Coneyworth, L, Avery, A, & Welham, S. (2020). Vegans, vegetarians, and omnivores: How does dietary choice influence iodine intake? A systematic review. *Nutrients*, 12(6), 1606.

I confirm that Elizabeth Eveleigh contributed 70% to the publication:

Eveleigh, ER, Zhou, M, Burdett, H, Hoang Nguyen, V, & Welham, SJM. (2022). Vegans and vegetarians living in Nottingham (UK) continue to be at risk of iodine deficiency. *Br. J. Nutr*, 1–46.

I confirm that Elizabeth Eveleigh contributed 80% to the publication:

Eveleigh, ER, Coneyworth, L, Craigon, J, & Welham, SJM. (2023). Adoption of a short-term (4-week) vegan diet as part of 'Veganuary' significantly reduces saturated fatty acid (SFA), B12, and iodine intake in omnivorous individuals. *Suitable for submission in the European Journal of Nutrition.*

I confirm that Elizabeth Eveleigh contributed 80% to the publication:

Eveleigh, ER, Coneyworth, L, & Welham, SJM. (2023). Iodine-fortified soya milk as a 'nutrient bridge' to improve iodine intake in vegan diets: A clinical trial protocol. *Suitable for submission in Nutrition and Health (Sage).*

I confirm that Elizabeth Eveleigh contributed 80% to the publication:

Eveleigh, ER, Coneyworth, L, Craigon, J, & Welham, SJM. (2023). Systematic review and meta-analysis of iodine nutrition in modern vegan and vegetarian diets. *Submitted to the British Journal of Nutrition.*

Signature: 

Dr. Simon Welham

Date: 14/02/2023

APPENDIX B

Eveleigh, ER, Coneyworth, L, Avery, A, & Welham, S. (2020). Vegans, vegetarians, and omnivores: How does dietary choice influence iodine intake? A systematic review. *Nutrients*, 12(6), 1606.

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Article

Vegans, Vegetarians, and Omnivores: How Does Dietary Choice Influence Iodine Intake? A Systematic Review

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Abstract: Vegan and vegetarian diets are becoming increasingly popular. Dietary restrictions may increase the risk of iodine deficiency. This systematic review aims to assess iodine intake and status in adults following a vegan or vegetarian diet in industrialised countries. A systematic review and quality assessment were conducted in the period May 2019–April 2020 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Studies were identified in Ovid MEDLINE, Embase, Web of Science, PubMed, Scopus, and secondary sources. Fifteen articles met inclusion criteria. Participants included 127,094 adults (aged ≥ 18 years). Vegan groups presented the lowest median urinary iodine concentrations, followed by vegetarians, and did not achieve optimal status. The highest iodine intakes were recorded in female vegans (1448.0 ± 3879.0 μg day^{-1}) and the lowest in vegetarians (15.6 ± 21.0 μg day^{-1}). Omnivores recorded the greatest intake in 83% of studies. Seaweed contributed largely to diets of vegans with excessive iodine intake. Vegans appear to have increased risk of low iodine status, deficiency and inadequate intake compared with adults following less restrictive diets. Adults following vegan and vegetarian diets living in countries with a high prevalence of deficiency may be more vulnerable. Therefore, further monitoring of iodine status in industrialised countries and research into improving the iodine intake and status of adults following vegan and vegetarian diets is required.

Keywords: iodine status; iodine intake; iodine deficiency; vegan; vegetarian

1. Introduction

Vegan and vegetarian diets have gained popularity over the past decade. Characteristically, vegans do not consume any animal-derived products including eggs, dairy, meat, and fish. Vegetarians exclude meat and fish but may consume milk and eggs. A subclass of the vegetarian diet may consume fish but not meat, termed pescatarians. Despite these definitions, varying levels of strictness and adherence to dietary restriction exist at the level of the individual [1].

The prevalence of vegetarian and vegan diets differs globally. In developing regions, meat-free diets are traditionally adopted owing to religious, social, ecological, or economic constraints as opposed to personal choice [2]. In industrialised countries, most individuals are afforded the choice of food consumption and level of dietary restriction. Populations in developed countries may adopt these diets for environmental, ethical, religious, health beliefs or social reasons. Presently, well-planned vegan and vegetarian diets have been regarded by the British Dietetic Association and other organizations in industrialised countries to be suitable throughout the lifespan, inclusive of infancy and pregnancy [3–5]. However, concerns have been raised regarding the ability of these diets to adequately provide essential micronutrients, such as iodine [6].

Iodine is an essential micronutrient, required in trace quantities, which is vital for the synthesis of thyroid hormones—triiodothyronine (T3) and thyroxine (T4) [7]. The thyroid hormones are crucial for the regulation of metabolism, growth, and neurological development [8]. Iodine deficiency presents as a spectrum of clinical disorders termed 'iodine deficiency disorders' (IDD's) which occur when recommended intakes are not achieved (150 μg day^{-1}) [8]. These include hypothyroidism, goitre abnormal thyroid nodular pathology, and cretininism in infants born to mothers with a low iodine status during pregnancy and lactation [7,9]. Low iodine intake may be a risk factor for thyroid nodule formation, particularly in females [10,11]. Most nodules are harmless; however, some may result in thyroid dysfunction or malignancy [11]. Excessive iodine intake (>1000 μg day^{-1}) may lead to hyperthyroidism in individuals with preexisting thyroid disease or iodine deficiency [12]. Iodine deficiency is not limited to developing countries—mild–moderate deficiency exists in industrialised nations including Europe, UK, Australia and select populations in the USA [9]. In 2011, iodine nutrition was highlighted as a significant public health concern following estimates indicating that 2 billion people globally were deficient [13]. Recent data collected by the WHO show a global decline in iodine deficiency between 1993 and 2019, suggesting that less than 8.5% of the world's population are affected [14]. However, subgroups of European populations are still at increased risk of iodine deficiency [6].

Iodine deficiency traditionally was assessed by monitoring the prevalence of visible goitre in populations [7]. After the development of newer methods for measuring iodine status, it was recognized that low-level deficiency may be present in industrialised populations not displaying obvious thyroid enlargement [15]. Various biomarkers can be used to estimate population iodine status and intake [15]. Urinary iodine concentration (UIC) is the most common and practical marker [16]. This is because >90% of the iodine ingested from dietary sources is readily excreted in the urine [17]. Spot UIC and 24 h measures can be used to detect and monitor iodine adequacy and deficiency. However, these estimates only correspond to recent intake [16]. Additionally, thyroid function tests are required routinely to detect iodine adequacy in vulnerable populations such as pregnant and/or lactating women and infants [16]. Dietary iodine can be estimated indirectly by UIC or by common dietary assessment methods [15]. Limitations of the methods used must be considered. Biomarkers of status and dietary intake methods are not always the same between studies which adds to the challenge of reliably comparing iodine amid populations [18].

Individuals residing in developing countries, who are reliant on plant-based foods in their diet, have a higher prevalence of iodine deficiency [19]. The bioavailability of iodine from plant sources has been suggested to be determined by rainfall and water collection on crop leaves with much of the iodine within plants not being bioavailable [20]. In industrialised countries where people consume a 'Western diet', the key dietary sources of iodine are bread fortified by iodised salt, cow's milk, and dairy products [21]. Seafood, eggs, and seaweed are also iodine rich but are not regularly consumed [22]. Water and salt iodination strategies are present in most states in the US and select countries in Europe [23,24]. Countries such as the UK have yet to establish a mandatory salt fortification program and despite regular manufacturing of iodised salt, it is not widely available for public purchase [25].

For this reason, individuals who consume diets excluding iodine-rich food, principally dairy, eggs, and/or fish, have increased risk of iodine deficiency [26]. Further complicating this issue is the growing availability and acceptance of plant-based food 'alternatives', regularly consumed by vegans and vegetarians, that naturally have negligible iodine content and are not regularly fortified [27,28]. The size of the plant-based 'alternatives' food market has been reported to have almost doubled between 2014 and 2017 in the UK [29].

Currently, two reviews exist investigating iodine in the diets of vegans and vegetarians, one in 2005, which was updated in 2009 by the same authors [30,31]. The most recent review included eight studies, covering a period between 1981 and 2003, with the conclusion that strict vegans and vegetarians living in Europe have iodine values below recommended levels and are at risk of deficiency. In the years since publication, these diets have become more widely accepted and it is likely that food consumption practices have changed considerably since this last assessment of iodine intake in adults

following vegan and vegetarian diets. Given the potential health consequences of iodine deficiency, it is important to re-examine whether adults following either a vegan or vegetarian diet are still at risk of iodine deficiency.

Thus, the aim of this review is to assess the iodine intake and status in adults following a vegan or vegetarian diet in industrialised countries across time. The objectives included (1) evaluation of the methods used to assess iodine; (2) determination of the iodine intake and food consumption in vegan and vegetarian adults; (3) assessment of the iodine status and prevalence of iodine deficiency using urinary iodine concentration (UIC); (4) comparison of the iodine intake, status and prevalence of deficiency between vegans, vegetarians and omnivores; and (5) consideration of gender differences in estimates of iodine nutrition.

2. Materials and Methods

This systematic review was according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [32].

A systematic search of literature was performed from 20 May 2019 to April 2020. Electronic databases (Ovid MEDLINE, Embase, Web of Science, PubMed, and Scopus) were searched using text terms with appropriate truncation, and Medical Subject Headings. Search term sensitivity and relevance of article identification was tested using preliminary searches in Ovid MEDLINE (Supplementary Table S1). All database searches were refined by 'Humans, Adults (aged < 18 years) and English Language'. Identified relevant studies were saved onto EndNoteTM online and duplicates were removed. To limit bias, relevance was confirmed by two investigators. Additional relevant articles were sourced from reference lists of included studies.

The current systematic review addressed study eligibility using the population–intervention–comparison–outcome (PICOS) formulation (Table 1) [33]. Additionally, only articles with full paper availability published in/after 1990 were considered for inclusion.

Table 1. Population–intervention–comparison–outcome (PICOS) criteria for study inclusion and exclusion.

Criteria Category	Inclusion	Exclusion
Population	Adults (aged ≥ 18 y) residing in industrialised nations.	Individuals (aged < 18 y), unless results display separate data; adults residing in developing countries; populations with a high prevalence of thyroid disorders.
Intervention/exposure	Participants with any type of dietary preference or restriction. Voluntary or otherwise.	Use of a dietary grouping without defining diet characteristics.
Comparators	Differing dietary preference or restriction.	None.
Outcome measure	Iodine intake or status measured by UIC or analysis of dietary records.	No analysis of iodine intake or status; use of thyroid measures alone for iodine intake and status.
Study design	Any study design with relevant outcomes.	None.

Data extraction was completed independently. The terms used for data extraction were discussed and finalised by two secondary researchers. A modified version of "Data collection form for intervention review—RCTs and non-RCTs" by The Cochrane Collaboration was used for data extraction [34]. Adaptions considered the characteristics of interest and study design. To permit comparison between groups, 'moderate vegans' were considered as vegetarians. 'Mixed diet' and 'meat eaters' as omnivores and 'living food dieters' as vegans. Due to variation in nomenclature, demi vegetarians will be considered separately. To make comparisons between genders, where possible, data on males and females were extracted separately.

Following data extraction, study quality was critically appraised by one author. Quality was assessed using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [35].

According to Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies provided by NHLBI, fixed response was selected for three questions to account for the nature of cross-sectional studies. Exposures and outcomes are measured and assessed during the same timeframe excluding time to see an effect and often lack a follow up, hence questions 6 and 7 would automatically receive a "NO" response. Additionally, question 13 was given a fixed response of "NA" (Supplementary Table S2). Quality of matched-pair interventions was assessed using the Quality Assessment of Controlled Intervention Studies, and Matched-Pairs (Case-Control) by The Quality Assessment of Case-Control Studies NHLBI [35]. Assessment was completed by one author and reviewed by another independent assessor prior to agreement (Table 2).

Table 2. NHLBI tool for quality assessment of included studies.

	Question														
Study, Year	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Rating**
Observational Cohort Cross-Sectional Studies															
Alles, 2017 [36]	+	+	+	+	−	−	−	−	+	+	+	−	a	+	Fair
Draper, 1993 [37]	+	−	r	+	−	−	−	+	+	+	+	−	a	−	Fair
Henjum, 2018 [38]	+	+	r	+	−	−	−	+	+	+	+	−	a	+	Good
Krajcovicová-Kudlácková, 2003 [39]	+	−	r	+	−	−	−	+	+	+	+	−	a	−	Fair
Leung, 2011 [40]	+	−	r	+	−	−	−	+	+	+	+	−	a	+	Good
Lightowler, 1998 [41]	+	+	+	+	−	−	−	+	+	+	+	−	a	+	Fair
Lightowler, 2002 [42]	+	+	+	+	−	−	−	+	+	+	+	−	a	+	Good
Nebl, 2019 [43]	+	+	+	+	−	−	−	−	+	+	+	r	a	−	Good
Schűpbach, 2017 [44]	+	−	+	+	−	−	−	+	+	+	+	−	a	+	Good
Sobiecki, 2016 [45]	+	+	+	+	+	−	−	+	+	+	+	−	a	+	Good
Waldmann, 2003 [46]	+	−	+	+	−	−	−	+	+	+	+	−	a	+	Good
Controlled Intervention Studies															
Remer, 1999 [47]	−	?	−	-	−	+	+	+	+	+	+	+	+	+	Good
Case-Control Studies															
Elorinne, 2016 [48]	+	−	+	+	r	+	?	?	−	+	−	+	a	a	Fair
Kristensen, 2015 [49]	+	+	−	−	+	+	?	?	−	+	−	+	a	a	Fair
Rauma, 1994 [50]	+	−	−	+	−	+	?	?	−	+	−	−	a	a	Poor

+, yes; −, no; ?, cannot determine; a, not applicable; r, not reported; ○(outlined), fixed answers according to NHLBI recommendations.

The WHO criteria for assessing the severity of IDD (1994) stratified by median urinary iodine concentration (UIC) was used to assess the relative level of deficiency in each dietary group. According to this classification, the rate of deficiency is described as the percentage of individuals in each group with UIC below <100 or <50 µg L^{-1}, in severe deficiency [6].

Funnel plots were generated for both UIC and dietary iodine intake data. For urinary iodine status, summary values and *number of participants* for each dietary group (Table 3) were used to generate an overall *population mean* value (μ).

$$Population\ mean\ (\mu) = \frac{\sum \text{UIC } values}{total\ number\ of\ participants}$$

Table 3. Iodine status and deficiency in vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Assessment Method	Dietary Group (n) (Male, Female)	Iodine Status by UIC (μg day^{-1})	Criteria for Iodine Deficiency Disorders
Elorinne, 2016 [48]	Spot UIC Sandell–Kolthoff method.	Vegan (21) Omnivore (18)	15.0 (4.6, 21.8) [1,**] 37.4 (17.7, 86.5) [1]	Severe Moderate
Henjum, 2018 [38]	Spot UIC.	Vegan (9) Vegetarian (27) Omnivore (367)	38.0 [1,**] 80.0 [1]	Moderate Mild
Krajcovicová-Kudlácková, 2003 [39]	24 h UIC Sandell–Kolthoff method.	Vegan (15) (6,9) Vegetarian (31) (12,19) Omnivore (Mixed Diet) (35) (15,20)	71.0 (9.0–204.0) [2,**] 177.0 (44.0–273.0) [2,**] 210.0 (76.0–423.0) [2]	Mild Optimal Optimal with risk of health consequences
Leung, 2011 [40]	Spot UIC spectrophotometry.	Vegan (62) (19,43) Vegetarian (78) (26,52)	78.5 (6.8–964.7) [2,*] 147.0 (9.3–778.6) [2]	Mild Optimal
Lightowler, 1998 [41]	Four 24 h UIC Sandell–Kolthoff method reaction.	Vegan (30) (11,19)	Total, 20.2 [1], M, 16.8 [1], F, 20.5 [1]	Severe-Moderate
Rauma, 1994 [50]	24 h UIC.	Vegan (Living Food Diet) (10) Omnivore (12)	<450.0 (<200.0–1700.0) [2] <500.0 (300.0–1200.0) [2]	Optimal with risk of health consequences
Remer, 1999 [47]	Two 24 h UIC.	Vegetarian (6) (3,3) Omnivore (6) (3,3) Omnivore (High Protein) (6) (3,3)	36.6 ± 8.8 [3,*] 50.2 ± 14.0 [3] 61.0 ± 8 [3]	Moderate Mild Mild
Schüpbach, 2017 [44]	Four fasted spot UIC.	Vegan (53) (20,33) Vegetarian (53) (17,36) Omnivore (100) (37,63)	56.0 (27.0–586.0) [2,*] 75.0 (1.0–610.0) [2] 83.0 (22.0–228.0) [2]	Mild Mild Mild

M, male; F, female; [1], median (25th–75th percentile); [2], median (range); [3], mean ± SD; * significantly different between dietary group comparison; $p < 0.05$, ** $p < 0.001$; criteria for iodine deficiency disorders (WHO); severe < 20 μg day^{-1}, moderate 20–49 μg day^{-1}, mild 50–99 μg day^{-1}, adequate 100–199 μg day^{-1}, excessive risk of adverse health consequences ≥ 300 μg day^{-1}.

The standard error for each observation group was generated according to the equation:

$$SE = SQRT(SQRT\left(\mu \times \frac{1-\mu}{number\ of\ subjects}\right)^2)$$

Confidence limits were generated as indicated below.

$$95\%\ CI = \mu \pm (1.96 \times SE)$$
$$99.7\%\ CI = \mu \pm (3 \times SE)$$

Confidence limits were generated for each population studied and used to generate funnel plots of UIC or iodine intake shown against study size (Supplementary Figures S1 and S2).

3. Results

The following exclusion of studies qualitative synthesis was completed for fifteen studies. The technique of study selection along with the number of included and excluded studies recorded for this systematic review is shown in the PRISMA 2009 flow diagram (Figure 1) [32].

Fifteen relevant studies were identified examining the iodine intake or status by dietary group Table 4. Consistent with scientific literature, different descriptors and nomenclature were used to define vegetarian diet types (Supplementary Table S3). Three studies used objective assessments to group individuals [43,45,46].

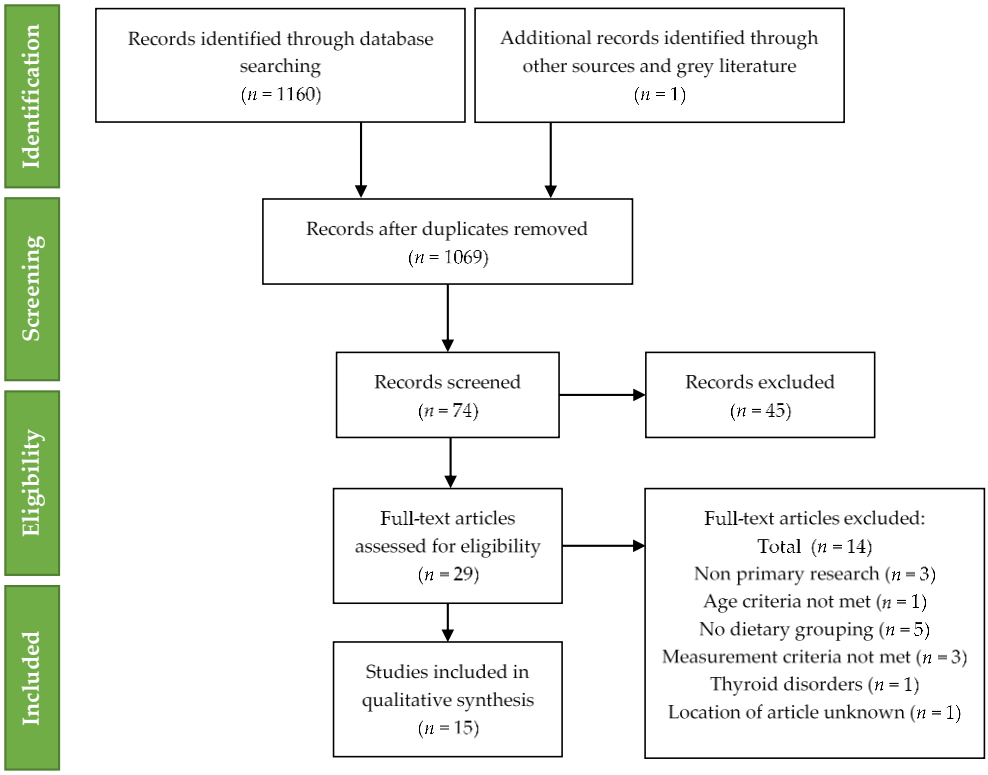


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for included studies.

3.1. Urinary Iodine Status

Eight studies investigated iodine status by urinary iodine concentration (UIC) (Table 3; Figure 2). Four studies measured UIC using spot samples [38,40,44,48]—of which, one study collected multiple fasted samples to determine average values [44].

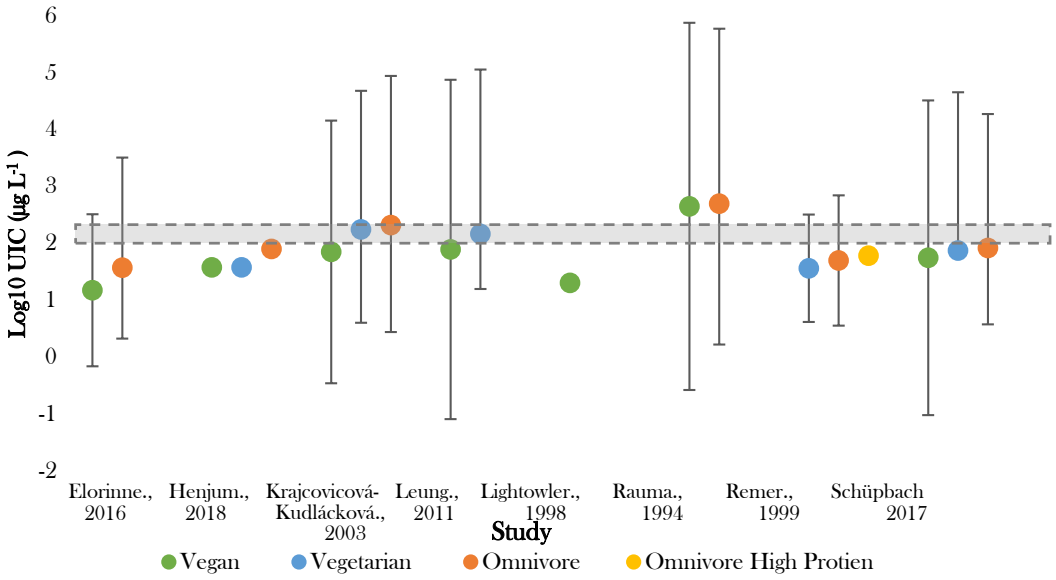


Figure 2. Visual representation of iodine status by median urinary iodine concentration (UIC) for included studies. The shaded grey bar represents the optimal range for iodine status (100–299 µg L^{-1}). Significance values are not presented within this figure. See Table 3.

Table 4. Studies investigating iodine among vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Study Design	Location	Dietary Groups	Sample (*n*) (Male, Female)	Method of Dietary Classification	Average Diet Adherence (Years)
Alles, 2017 [36]	Cross-Sectional	France	Vegan	789	Assessed by investigators pre-study	NA
			Vegetarian	2370		
			Omnivore	90,664		
Draper, 1993 [37]	Cross-sectional	London, UK	Vegan	38 (18,20)	Self-reported	1.0
			Lacto-Vegetarian	52 (16,36)		2.0
			Demi-vegetarian	37 (13,24)		5.0–9.0
Elorinne, 2016 [48]	Matched pairs by age and sex	Kuopio, Finland	Vegan	22 (16,6)	Self-reported	8.6
			Omnivore	19 (11,8)		NA
Henjum, 2018 [38]	Cross-Sectional	Norway, eastern and western geographical regions	Vegan	27	Self-reported	NA
			Vegetarian	9		
			Omnivore	367		
Kristensen, 2015 [49]	Matched pairs by age	Denmark	Vegan	75 (36,39)	Self-reported	≤1.0
			Omnivore	1627 (716, 911)		NA
Krajcovicová-Kudlácková, 2003 [39]	Cross-sectional	Slovakia	Vegan	15 (6,9)	Self-reported	9.7
			Vegetarian	31 (12,19)		9.0
			Omnivore (Mixed Diet)	35 (15,20)		NA
Leung, 2011 [40]	Cross-sectional	Boston, Massachusetts	Vegan	63	Self-reported	11.3 ± 11.7 [1]
			Vegetarian	78		5.6 ± 5.7 [1]
Lightowler, 1998 [41]	Cross-sectional	London and surrounding counties, UK	Vegan	30 (11,19)	Self-reported	M, 10.0, F, 9.2
Lightowler, 2002 [42]	Cross-sectional	London and the south-east of England, UK	Vegan	26 (11, 15)	Self-reported	M, 9.9, F, 11.7
Nebl, 2019 [43]	Cross-sectional	Hanover, Germany	Vegan	27 (11,16)	Assessed by investigators pre-study	>2.0
			Vegetarian	25 (10, 15)		>2.0
			Omnivore	27 (10,17)		>3.0
Rauma, 1994 [50]	Matched pairs	Kuopio, Finland.	Vegan (Living Food Diet)	12	Self-reported	6.7 ± 3.8 [1]
			Omnivore	12		NA
Remer, 1999 [47]	Repeated-measures	Germany	Vegetarian (Lacto)	6 (3,3)	Allocated by investigators	0.0
			Omnivore	6 (3,3)		
			Omnivore (High protein)	6 (3,3)		
Schüpbach, 2017 [44]	Cross-sectional	Lausanne and Zurich, Switzerland	Vegan	53 (20,33)	Self-reported	≤1.0
			Vegetarian	53 (17,36)		≤1.0
			Omnivore	100 (37,63)		≤1.0
Sobiecki, 2016 [45]	Cross-sectional	Oxford, UK	Vegan	803	Assessed by investigators pre-study	≤1.0
			Vegetarian	6673		≤1.0
			Pescatarian	4531		≤1.0
			Omnivore (Meat-eaters)	18,244		≤1.0
Waldmann, 2003 [46]	Cross-sectional	Hanover, Germany	Vegan (Strict)	98	Assessed by investigators pre-study	4.3
			Vegan (Moderate)	56		3.4

NA, not assessed; M, male; F, female; [1], mean ± SD.

The lowest median UIC (16.8 μg L^{-1}) was recorded by Lightowler in UK male adults following vegan diets [41]. Rauma [50] reported the highest median UIC (<500.0 μg L^{-1}) in Finish omnivores. Large variation in UIC existed in several studies [40,44,50], with one study showing variation in those following vegan diets between <200 and 1700 μg L^{-1} [50]. The majority (75%) of the recorded values for UIC fell below the expected population mean of 95.6 μg L^{-1} (Supplementary Figure S1) and half of the values fell either on or outside of the 99.7% confidence limit.

In all studies giving intergroup comparisons, the lowest median UIC was recorded for those following vegan diets and the highest for omnivores [38–40,44,47,48,50]. Five out of eight studies recorded median UIC in vegans to be significantly lower than omnivores ($p < 0.005$) [38–40,44,47]. All studies observed UIC in those following vegetarian diets to be higher than vegan diets, yet lower than omnivorous diets [38–40,44,47]. The difference between vegetarian and omnivorous diets was significant in three studies ($p < 0.05$) [38,39,47].

IDD assessment according to the WHO criteria ranged from severe (inadequate) to at 'risk' of adverse health consequences (excess) across studies [51]. Supplementary Table S4 presents national data corresponding to countries of included studies.

Optimal status (100–200 μg L^{-1}) was achieved in vegetarian groups in Slovakia and Boston [39,40]. No adults following vegan diet had median UIC within the optimal range [38–41,44,48,50]. Seven studies observed one or more dietary group below the cut off for optimal population UIC [38–40,42,44,47,48]. Iodine deficiency (mild–severe) (50–99 μg L^{-1}–>20 μg L^{-1}) was recorded in adults following vegan diets in six studies [38–40,42,44,48], vegetarian diets in two studies [44,47], and omnivorous diets in four studies [38,44,47,48].

Those following vegan diets were most frequently seen to exhibit either mild (50–99 μg L^{-1}) or moderate deficiency (20–49 μg L^{-1}) [12,38,39,41,44,48], and in two studies were found to be severely deficient (<20 μg L^{-1}) [40,47]. In one of these studies, >75% of those following vegan diets fell into the severely deficient category [48]. Both those following vegan and vegetarian diets were more commonly observed to be moderately deficient, whilst, conversely, omnivores were found in two studies to exhibit excessive iodine status [39,50]. This was also noted for those following vegan diets in one Finnish study [50].

3.2. Dietary Iodine Intake

Methods for assessing dietary intake are listed in Supplementary Table S5. Ten studies reported estimates for daily iodine intake [36,37,41–43,45–47,49,50]—of which, four studies were investigating iodine specifically [41,42,47,50]. The additional studies investigated other macro- and micronutrient intakes besides iodine (Table 5; Figure 3) [36,37,43,45,46,49].

Table 5. Assessment of dietary iodine intake for vegans, vegetarians, and omnivores in industrialised countries.

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (μG Day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Allès, 2017 [36]	Three repeated 24 h dietary records.	150 μg day^{-1} RDI for the French population (2001) [52].	Vegan (789) Vegetarian (2370) Omnivore (90,664)	248.3 ± 9.8 (a) [1] 222.6 ± 5.7 (a) [1] 180.1 ± 1.1 (a) [1,**]	Seaweed, salt, or supplements not measured.	Y Y Y
Draper, 1993 [37]	Three-day weighted food diaries. Analysed using UK Ministry of Agriculture, Fisheries and Food data.	DRV of 140 μg day^{-1} Department of Health (1991) [53].	Vegan (38) (18,20)	M, 98.0 ± 42.0 [2,**] F, 66.0 ± 22.0 [2,**]	95% used sea salt or seaweed. 30%–40% consumed food supplements containing seaweed 1–2 days a month. 15.6 μg day^{-1} provided by dietary supplements.	N
			Lacto-Vegetarian (52) (16,36)	M, 216.0 ± 73.0 [2,**] F, 167.0 ± 59.0 [2,**]	No iodine provided by salt, seaweed or supplements.	Y
			Demi-Vegetarian (35) (13,24)	M, 253.0 ± 164.0 [2,**] F, 172.0 ± 91.0 [2,**]	No iodine provided by salt, seaweed or supplements.	Y
Kristensen, 2015 [49]	Four-day weighed food diary.	150 μg day^{-1} NNR (2012) [54].	Vegan (70) (33,37)	M, 64.0 (43.0–91.0) [3,**] F, 65.0 (54.0–86.0) [3,**]	Salt not measured. Three vegans consumed seaweed. 9.0 μg day^{-1} (M) and 6.0 μg day^{-1} (F) was provided by dietary supplements.	N
			Omnivore (1257) (566,691)	M, 213.0 (180.0–269.0) [3] F, 178.0 (146.0–215.0) [3]	Salt not measured. No iodine provided by seaweed. 107 μg day^{-1} (M) and 78.9 μg day^{-1} (F) was provided by dietary supplements.	Y
Lightowler, 1998 [41]	Four-day weighed food diary with duplicate portion technique.	140 mg day^{-1} RNI Department of Health (1991) [53].	Vegan (30) (11,19)	M, 138.0 ± 149.0 [2] F, 187.0 ± 246.0 [2]	Salt not measured. Three vegans consumed seaweed, resulting in significantly higher iodine intake ($p < 0.001$) Seaweed consumers were over six times the RNI. Iodine-containing supplements were consumed by five (45%) males and seven females (37%). Providing 54.0 mg day^{-1} on average to the diet.	M, N F, Y
Lightowler, 2002 [42]	Four -day food diaries with duplicate portion technique. Analysed using CompEat 4 software.	140 mg day^{-1} RNI Department of Health (1991) [53].	Vegan (26) (11,15)	Diet Diary M, 42.0 ± 46.0 [2] F, 1448.0 ± 3879.0 [2] Duplicate Diary M, 137.0 ± 147.0 [2] F, 216.0 ± 386.0 [2]	Salt not measured. Two vegans consumed seaweed, resulting in iodine intake to exceed the RNI. Dietary supplement intake was recorded but not included to dietary intake.	Diet Diary M, N F, Y Duplicate DiaryM, N F, Y

Table 5. *Cont.*

Study, Year	Assessment of Dietary Iodine	Criteria for Iodine Intake Used in Study	Dietary Group (N) (Male, Female)	Dietary Iodine Intake (μG Day^{-1})	Contribution of Iodised Salt, Seaweed, and Iodine-Containing Supplements	Meeting Criteria (Y/N)
Nebl, 2019 [43]	Three-day food diaries analysed by PROD16.4®.	200 μg day^{-1} RV German, Austrian and Swiss Nutrition Societies (2019) [55]	Vegan (27) (10,17)	57.7 (48.4, 67.0) [4,*]	Salt or seaweed not measured. No iodine provided by supplements.	N
			Vegetarian (25) (10,15)	61.6 (49.4, 73.7) [4,*]		N
			Omnivore (27) (11,16)	88.8 (64.1, 114.0) [4,**]		N
Rauma, 1994 [50]	Seven-day food diaries analysed by NUTRICA Finland.	0.1–0.2 mg day^{-1} RDA (120–200 μg day^{-1}) Committee on Dietary Allowances, Food and Nutrition Board, National Research Council (1989) [56].	Vegan (Living Food Diet) (9)	29.0 ± 18.0 [2]	One participant did not use iodised salt. 25% of daily iodine in vegans was provided by seaweed (estimated >8.0 μg day^{-1}). Four vegans consumed seaweed, resulting in higher intake.	N
			Omnivore (8)	222.0 ± 93.0 [2]		Y
Remer, 1999 [47]	Five-day dietary intervention of pre-selected food items representing each diet. Calculated using food tables.	NA	Vegetarian (Ovo-Vegetarian)(6)	15.6 ± 21.0 [2]	No iodized salt, seaweed or supplements were permitted during the study. All drinks including water were low in iodine and other minerals.	N
			Omnivore (6)	35.2 ± 15.0 [2]		N
			Omnivore (High Protein) (6)	44.5 ± 16.5 [2]		N
Waldmann, 2003 [46]	Pre-study questionnaire identifying regularly consumed foods. Two estimated nine-day FFQs using 7 days of records.	200 mg day^{-1} RI, German Society of Nutrition (2000) [57]	Vegan (Strict) (98) (48,50)	M, 87.7 ± 30.6 [2] F, 82.1 ± 34.4 [2]	Salt not measured. Seaweed intake not measured. 46% of participants used some form of nutritional supplement. Iodine-specific supplements were not recorded.	N
			Vegan (Moderate) (56) (19,37)	M, 93.7 ± 27.8 [2] F, 78.1 ± 25.6 [2]		N
Sobiecki, 2016 [45]	112-item semi-quantitative FFQ. Analysed based on UK Ministry of Agriculture, Fisheries and Food data.	150 μg day^{-1} RDA, dietary reference intakes for iodine (2001) [58]	Vegan (803) (269,534)	M, 55.5 ± 40.0 [2] F, 54.1 ± 40.0 [2] Total, 58.5 (a) [2]	Salt not measured. Two participants who consumed seaweed had values close to the maximum tolerable daily intake for iodine. Supplement intakes recorded did not specify iodine content.	M, N F, Y (a), N
			Vegetarian (6673) (1516,5157)	M, 141.0 ± 77.4 [2] F, 146.1 ± 78.8 [2] Total, 148.1 (a) [2]		M, N F, N (a), N
			Pescatarian (4431) (782,3749)	M, 197.4 ± 84.7 [2] F, 194.8 ± 85.9 [2] Total, 196.8 (a) [2]		Y (a), Y
			Omnivore (Meat-Eaters) (18,244) (3798,14446)	M, 214.3 ± 85.6 [2] F, 213.8 ± 85.2 [2] Total, 212.2 (a) [2]		Y (a), Y

Abbreviations; RDI, Recommended Daily Intake; DRV, Daily Recommended Value; NNR, Nordic Nutrition Recommendations; RNI, Recommended Nutrient Intake; RV, Recommended Value; RDA, Recommended Daily Allowance; RI, Recommended Intake; (a), adjusted by age and sex; [1], mean ± SEM; [2] mean ± SD; [3], median (25th–75th percentile); [4], mean (95% CI); * significant difference with other dietary groups; $p < 0.005$ ** significant difference with other dietary groups; $p < 0.001$.

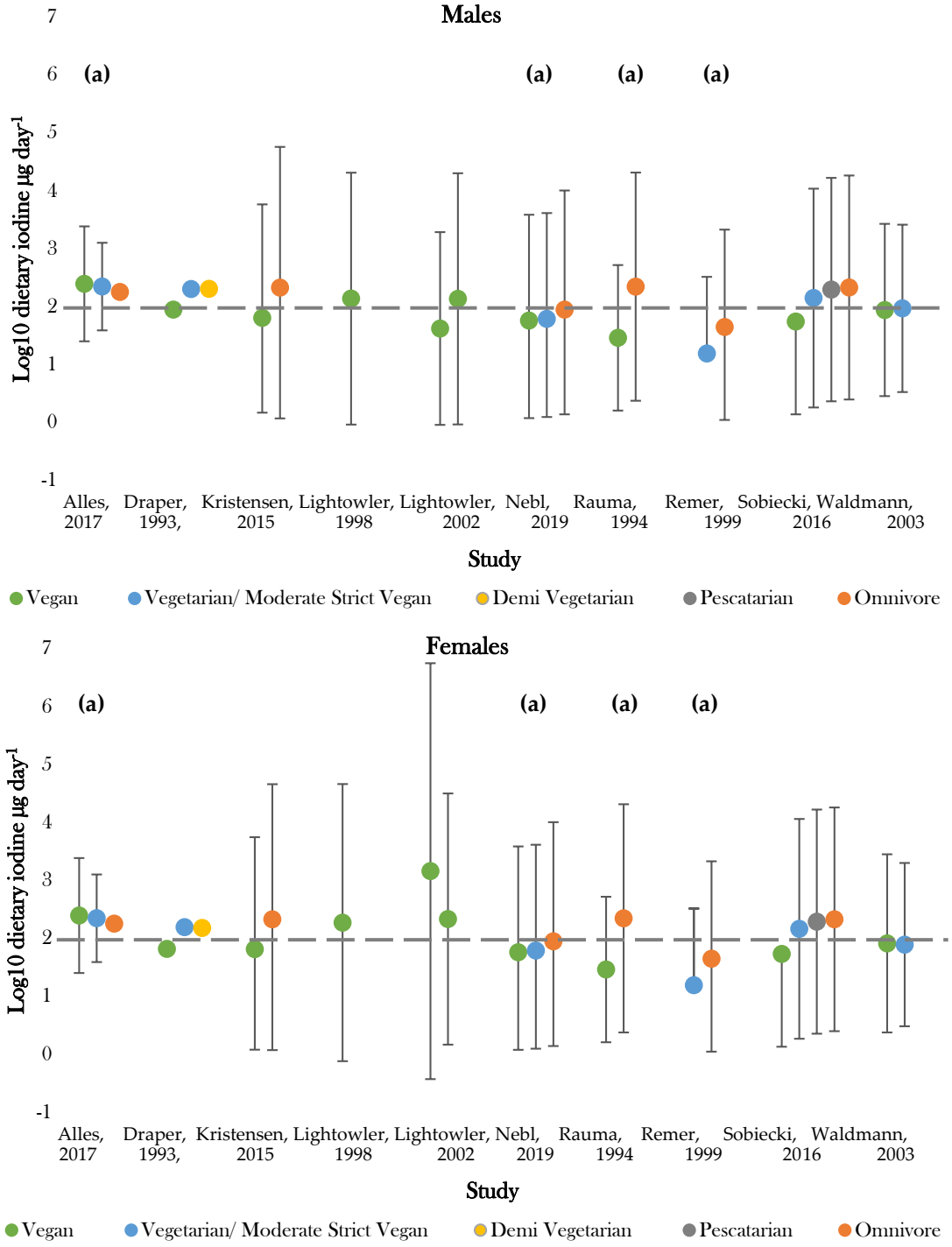


Figure 3. Visual representation of estimated average iodine intake (µg day^{-1}) for included studies. The grey dashed line represents the adequate intake recommended by the WHO of 150 µg day^{-1}. (**a**), mixed gender values. Significance values are not presented within this figure. See Table 5.

The highest daily iodine intake was recorded in females following vegan diets of 1448.0 ± 3879.0; 29.0 ± 18.0 µg day^{-1} [42,50]. The lowest dietary intake was found in those following vegetarian diets of 15.6 ± 21.0 µg day^{-1} [47]. Seven studies assessed iodine intake between vegans and one or more dietary group [36,37,43,45,46,49,50]. Omnivores (male and female) had the highest estimated average intake in 85% of studies [43,45–47,49,50]. Vegan groups tended to have the lowest iodine intake. Males following vegan diets had average intakes lower than all comparative dietary groups in all studies, apart from that conducted by Allès (2017) [36]. Females following vegan diets presented

the lowest iodine intake in 75% of studies [37,45,49]. Varied intakes were recorded for moderate vegans, vegetarians, and pescatarians across studies, with estimates ranging between 222.6 ± 1.1 and 15.6 ± 21.0 μg day^{-1} [36,43,47]. The majority of values fell around the expected population mean (184.1 μg day^{-1}), although there was a general tendency for values to be slightly below this level (Supplementary Figure S2).

Recommended criteria for iodine intake varied according to country of study. Comparisons were, therefore, drawn according to recommended intake values denoted by the WHO, with values above 150 μg day^{-1} being classed as adequate [51]. One study recorded estimates above the adequate range for all dietary groups [36]. Omnivores most frequently achieved adequate intake, with only two studies recording intakes below 150 μg day^{-1} for both genders [43,47]. Those following vegan diets most frequently showed dietary iodine inadequacy. Adequate intake was recorded for 44% of female and 66% of mixed gender estimates [36,37,41–43,45,46,49,50]. No groups of males only had intakes above the adequate cut off values [37,41,42,49,50]. Intakes for moderate vegans (vegetarians), vegetarians, and pescatarians were similar between genders and were above adequate in half of studies [36,37,43].

Only four studies investigated the relative consumption of different food groups [36,37,43,46]. None reported the actual contribution of each food group to dietary iodine independent of iodised salt and supplements. However, adults following vegan and vegetarian diets tended to report significantly higher consumption of plant-based food groups (fruit, vegetables, legumes, tubers cereals and grains) [43,46], along with tofu and soya-based products which naturally have a low iodine content. One study reported the consumption of milk alternatives in each dietary group, and vegans had the largest consumption of plant-based milk alternatives [36]. As expected, milk and dairy, egg, and fish consumption was significantly higher ($p < 0.0001$) in vegetarians and omnivores compared to vegans [36,43].

Six studies measured seaweed consumption [37,41,42,45,49,50]. Adults following vegan diets had the greatest seaweed intake, with four studies stating that consumption significantly increased dietary intake such that iodine intake would be considered 'excessive' [37,41,42,49]. Seaweed was not regularly consumed by omnivores and moderate vegans (vegetarians), vegetarians, demi vegetarians or pescatarians [37,45–47,49,50].

Mandatory salt fortification programs were present in three countries of included studies (Table 6) [39,40,49]. Eight studies did not record the contribution of iodised salt to dietary iodine [36,37,41–43,45,46,49].

Table 6. Summary of salt fortification programs present in included studies [59].

Country	Year	Iodate and/or Iodide	Iodine Amount (ppm)	State of Legislation
Boston (U.S.)	1920	Iodide	43	Mandatory
Denmark	1999	Iodide	13	Mandatory
France	1997	Iodide	10–15	Voluntary
Finland	1963	Iodide	25	Voluntary
Germany	1981	Iodate	15–20	Voluntary
Norway	NA	Iodide	5	Voluntary
Slovakia	1966	Iodide	25 ± 10	Mandatory
Switzerland	1922	Both	20–30	Voluntary
UK	NA	Iodide	10–22	Voluntary

Supplement intake was recorded in seven studies [37,41–43,45,46,49]. Two studies did not record iodine-specific supplementation [45,46]. One study prevented supplement intake during the study and another excluded supplement contribution in dietary analysis [42,47].

Three studies recorded supplement intake in adults following vegan diets, contributing between 9.0 and 54.0 μg day^{-1} to dietary intake [37,41,49]. Supplements contributed greater iodine to diets of omnivores (78.9 μg day^{-1}–107.0 μg day^{-1}) [37,49]. No supplement consumption was recorded for moderate vegans (vegetarians), vegetarians, demi vegetarians or pescatarians [37,43,45–47].

4. Discussion

The popularity of vegan and vegetarian diets has increased considerably in the past decade. The prospect of these diets acting as a barrier to adequate iodine nutrition could increase the risk of developing preventable health consequences associated with deficiency and furthering the worldwide public health issue of iodine [60]. Given that these diets are commonly followed by females of childbearing age (16–24 years), lowered dietary iodine intake in these groups could significantly impact future generations and reduce societal productivity [6,61,62].

The present systematic review is the most recent review to evaluate the evidence for iodine intake and status among adults following vegan and vegetarian diets [30]. Our review showed that the discourse has not changed and that adults following a vegan diet, living in industrialised countries, not consuming seaweed or iodine-containing supplements, appear to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared to less restrictive dietary groups. Comparison of dietary estimates supports the possibility of a gender difference within vegan groups, as no vegan males achieved adequate intake. Vegetarians or pescatarians are more at risk of low iodine status and intake compared to omnivores but not vegans.

These results are in accordance with the previous review by Fields, Dourson and Borak in 2009 [30], whereby it was concluded that iodine adequacy decreased with increased dietary restriction [30]. However, the previous review did not highlight that some study populations following omnivorous diets also had low iodine status and mild–moderate deficiency [30]. The degree of vulnerability in all dietary groups appears to be impacted by not only individual dietary choices, practices, and restrictions, but country-specific dietary determinants and national food fortification strategies. For this reason, vegans and vegetarians living in industrialised regions where national population iodine measures are below adequate or where dietary intake is insufficient are more susceptible to iodine deficiency. This trend can be observed by comparing median UIC (MUIC) of included studies with the corresponding national data from the country of origin. MUIC tends to closely represent that of omnivorous diets, owing to these practices being the dominant in most industrialised countries.

Vegan and vegetarian MUIC in all studies, apart from that conducted by Rauma (1994), fell below national values [50]. In half of studies, the extent was substantial enough for adults following vegan and vegetarian diets to be classified in a lower deficiency category, according to the WHO criteria, than omnivores and national data—for example, mild (omnivores)–moderate (Vegans and vegetarians) [38–40,48]. This trend can be explained by exploring values determined by Henjum (2018) of non-pregnant young women in Norway [38]. Omnivores in this study presented UIC values concordant with current Norwegian national data (80.0, 75.0 μg day^{-1}), which could be due to efficient data collection of northern, western and eastern regions of Norway [14,38]. As omnivorous diets are the most dominant in industrialised countries, this sample is likely to be representative of the Norwegian population. Omnivorous MUIC and national data are indicative of mild deficiency, whereas for those following vegan and vegetarian diets, MUIC is suggestive of moderate deficiency, therefore indicating that the susceptibility of vegan and vegetarian populations to deficiency is in part dependent on national iodine status.

This trend is not apparent in woman of reproductive age in Switzerland, despite lower observed values in those following vegan diets, as all groups and national data would be classified as mildly deficient [44]. This could be explained by regular consumption of iodized salt in Swiss households, which is greater than 80% [63]. Fortified bread is a significant contributor to dietary iodine and can be consumed by all dietary groups [63]. A reduction or restricted legislation in iodine fortification could increase the risk of iodine deficiency. In Germany, Remer (1999) induced deficiency in vegetarian and omnivorous diets when preventing consumption of fortified and iodinated foods under controlled conditions [47]. In this study, daily iodine intake dropped below requirements required for optimal thyroidal function (50.0–80.0 μg day^{-1}). Disuse or lack of availability of iodine-fortified foods could produce similar consequences.

Shifting legislation reflects changes in iodine status by dietary group over time in Finland from a risk of excess to moderate–severe deficiency in 2016 [48,50]. This is following a reduction in iodised salt consumption possibly influenced by efforts to reduce salt consumption in the general public and replacement of the traditional diet rich in fish and dairy for diets providing improved fruit and vegetable intake [64]. The Finnish Vegan Society was founded in October 1993 [65], a year before Rauma's study was conducted, and food consumption is likely to have changed in this time, as these diets have become widely accepted. Papers published prior to 1990 were excluded, as meat-free diets did not appear in the mainstream until the 1980s, and it is likely that food choices and landscape have changed substantially since this period [66]. Recent studies published after 2010 represent almost half of the included studies which could account for the 'second-wave' vegetarian movement supported today [12,38,43–45,48,49].

Despite the popularity of vegan and vegetarian diets, there is no homogenous term to define these dietary groups, thus questioning the accuracy of group estimates in included studies. Three studies used objective assessments to group individuals by dietary preference [43,45,46]. Self-reported measures are frequently inaccurate at determining dietary preference [30]. Misreporting may additionally be a consequence of misinterpretation of the term "vegetarian" and its associated dietary restrictions or, additionally, over exaggeration of restrictive practices to align with vegetarian ideology [30,67]. Juan, Yamini and Britten (2015) observed errors with adherence to vegetarian diets when investigating food consumption patterns of the U.S. population in the period 2007–2010 [67]. The authors determined that half of those identifying themselves as vegetarian consumed meat, poultry, or seafood and, therefore, would not be described as vegetarian using typical definitions. This issue was discussed previously in the systematic review conducted by Fields, Dourson and Borak, indicating that individual dietary intake based on the description of typical "vegetarian" regimes from self-reports may be inaccurate and indicates that consistent strict dietary adherence in the included studies is likely to be low [30].

The duration of practicing a specific dietary preference must be considered when examining the diets of vegan and vegetarians. Most studies (apart from that conducted in experimental conditions and studies of recreational runners) included participants with 1-year minimum dietary adherence [43,47]. Draper (1993) only recruited participants who had elected to adopt their diets in adulthood and had not grown up as vegetarian [37]. This raises the question as to whether the length of dietary adherence affects iodine measures. Long-term vegetarians could be better at planning their diet adequately if receiving guidance from their parents from a young age or iodine intake could reflect reduced diet diversity and long-term dietary compliance.

Reduced dietary intake for those following vegan diets may reflect difficulties in accurately measuring dietary intake. Intake can be measured using various methods. The "gold standard" for estimating iodine intake is a dietary record or food diary inclusive of one weekend day [17]. Seven included studies followed this methodology, additionally pairing food diaries with weighed or duplicate records [36,37,41–43,47,49]. Food diary measurements reflect recent intake; therefore, 10 days are recommended for iodine to account for food items that are rich in iodine but not regularly consumed [68]. Only two studies collected records exceeding this duration [46,50]. The most frequent length of estimates was 4 days, which is acknowledged as an adequate length to record dietary intake [69]. Duplicate dairies are suitable for valuation of minerals such as iodine [70]. This technique is useful for foods with iodine values not contained within food tables or composition data. For this reason, this technique is useful to assess the dietary iodine of those following vegan diets who may consume foods that are novel or not frequently eaten by the general public.

Two studies used validated FFQs to estimate iodine intake [45,46]. FFQs are often designed to be specific to a nutrient of interest and aim to include food items contributing to intake. Both studies had developed FFQs to address intake of multiple micronutrients and were not iodine specific. As FFQs are a comprehensive list and not all foods can be contained, they are, therefore, limited to the listed items. It is unlikely that these studies addressed foods that largely contribute to iodine intake but are not

regularly consumed such as seaweed or novel foods consumed by vegans. In addition, FFQs have been recognised to frequently overestimate iodine intake as supported by previous validation studies [71].

For all studies, estimations of iodine intake were calculated using mean iodine concentration of foods and beverages provided by regional food composition tables or databases and are, therefore, country specific [36,37,41–43,45–47,50]. Estimates based on one summary statistic cannot account for variation in iodine content between food items across time, season, and geographic location—for example, the iodine content of milk, which also varies according to processing and product origin [72]. In vegan adults, the lowest intakes were recorded in Finland (29.0 ± 18.0 μg day^{-1}) [50]. Krajcovicová-Kudlácková (2003) discussed that Finish food tables tended to estimate lower iodine intake compared to British food tables [39], and variation in this case probably represents geographical diversity between countries and food availability. Waldmann (2003) [46] created a database accounting for vegan food items regularly consumed in Germany, thus improving estimates. Four studies were conducted in the 1990s [37,41,47,50]. It is likely that food tables and databases have improved availability of the iodine content of foods. However, these methods lack iodine values for newly consumed food and products, particularly those gaining in popularity such as plant-based alternatives.

Adults following vegan diets had the largest consumption of plant-based milk alternatives. Bath et al. investigated the iodine concentration of milk alternatives available in the UK in 2015 and determined the concentration of unfortified milk-alternative drinks (median 7.3 μg kg^{-1}) to be significantly lower than the dairy milks analysed (median 438.0 μg kg^{-1}) [28]. Those consuming alternative milks may not be aware of the lower contribution of plant-based milks to iodine and need to ensure intake from other sources.

The highest iodine intake was recorded for females following vegan diets, living in London (1448.0 ± 3879.0 μg day^{-1}), whose regular consumption of seaweed increased intakes to over six times the RNI [42]. Five studies recorded seaweed consumption in vegan diets only, observing intakes close to, or over, the maximum tolerant level [37,41,42,46,49]. Seaweed is a naturally rich source of iodine, but the relative content is highly variable and can provide excessive quantities and, therefore, regular consumption is not recommended [73]. Seaweed is not customarily consumed in the Western diet. However, it has recently become popular in UK food products as a whole food and functional ingredient [74]. For example, carrageenan is widely used in newly formulated vegan and vegetarian products. Manufacturers use it to replace gelatine, as it is derived from plant origin [74]. Draper (1993) observed low iodine intakes in adults following vegan diets in London despite 95% recording regular consumption of seaweed or foods containing seaweed powder [37]. While the iodine content of seaweeds is often high, it is not a food that is consumed in large quantities, hence the contribution towards dietary intakes is likely to be small and inconstant [75]. Moreover, iodine content significantly differs between seaweed species consumed [73].

Voluntary fortification is present in most countries [59], yet very few manufacturers add fortified salt to food items and iodinated salt is not easily available to consumers. This appears to be true in the study conducted by Rauma (1994), where only one Finish vegan reported consuming iodised salt regularly [50]. Furthermore, Bath et al. (2013) conducted a shelf survey of five major chain supermarkets in the UK and found that iodized salt was only sold in 42% (32 out of 77) of shops and that the iodine content of fortified salt sold was low (11.5 ± 4.2 μg g^{-1}) [25]. Draper (1993) noted the consumption of 'sea salt' in 95% of UK adults following vegan diets [37]. Although 'sea salt' and other 'specialty' salts such as Himalayan sea salt contain iodine, the concentration is relatively small compared to iodised salts [76]. Additionally, of two studies reporting iodised salt intake [37,50], neither identified having adjusted intakes to account for volatile iodine losses experienced during cooking [77]. Kristensen (2015) attempted to quantify the involvement of iodised salt by measuring reported sodium intake [49]. Despite, the routine uses of iodised salt in Danish households, 55 out of 70 vegans failed to meet dietary recommendations for iodine [49]. Low dietary intake in vegans in this study may be explained by reduced dietary sodium intake reported by vegan participants and

infrequent consumption of salt-rich processed food items. Moreover, vegan ready meals are not always readily available from retailers.

Limitations of the study. In addition to the limitations highlighted above, it should be noted that the values recorded in the included studies tended to be skewed below the mean estimated population levels for UIC (Supplementary Figure S1) and intake (Supplementary Figure S2). This would suggest that for most studies, the sample population was not wholly reflective of the general population. This is a challenge for such studies, as the cohort of individuals prepared to participate is often characterised by those with an interest either in their dietary choice or dietary control for health reasons. Accessing the wider public is much more difficult and a challenge that needs to be addressed in future studies. There was some overlap with the previous systematic review, and we found that recent studies investigating iodine nutrition were relatively scarce. Further, it was necessary to combine groups, thereby oversimplifying dietary practice to enable comparison of studies. Lastly, there was a lack of values for contribution of specific food groups (e.g., supplements) and iodised salt.

5. Conclusions

Iodine deficiency remains a public health problem worldwide and is of concern following the "re-emergence" of iodine deficiency, especially in industrialised countries [78]. This review agrees with findings from the previous systematic reviews exploring this topic [30,31], confirming that vegans and vegetarians, living in industrialised countries, not consuming seaweed or iodine-containing supplements, appear to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared to adults following less restrictive diets. The evidence suggests that the degree of vulnerability appears to be relative to the prevalence of deficiency at the national level. This review also highlights the variety of methodological issues associated with estimating iodine in unique dietary groups. In conclusion, further monitoring of iodine status in industrialised countries and research into improving the intake and status of vegan and vegetarian diets is required. Efforts need to be made to devise a means of safe iodine consumption whether by fortification of staple foods or iodised salt provision, in addition to information delivery intended for tolerable consumption of seaweed varieties. Lastly, nutrients frequently lacking in vegan and vegetarian diets should be routinely labelled on foods regularly consumed by these groups in order to highlight to those making these purchases that there is a need to consider the levels that are being consumed.

Supplementary Materials: The following are available online at http://www.mdpi.com/2072-6643/12/6/1606/s1. Figure S1: Funnel plot showing iodide status for individual groups according to number of individuals in each group. For each study, data for urinary iodide concentration (μg L^{-1}) was plotted for omnivores, vegetarians and vegans where provided, against the number of participants in each group. Each data point represents a specific group rather than a specific study. Figure S2 Funnel plot showing iodide consumption for individual groups according to number of individuals in each group. For each study, data for dietary iodide intake (μg Day^{-1}) was plotted for omnivores, vegetarians and vegans where provided, against the Log_{10} of the number of participants in each group. Each data point represents a specific group rather than a specific study. Table S1: Search terms used in the study, Table S2: Quality assessment questions, Table S3: Definitions and characteristics of dietary groups studied in included studies, Table S4: National data corresponding to location of included studies, Table S5:Common methods for assessing Dietary Iodine Intake in Population Studies.

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APPENDIX C

Eveleigh, ER, Zhou, M, Burdett, H, Hoang Nguyen, V, & Welham, SJM. (2022). Vegans and vegetarians living in Nottingham (UK) continue to be at risk of iodine deficiency. *Br. J. Nutr*, 1–46.

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Vegans and vegetarians living in Nottingham (UK) continue to be at risk of iodine deficiency

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Abstract

Iodine is essential for thyroid hormone synthesis. Individuals adhering to vegan and vegetarian diets have been found to be vulnerable to iodine deficiency. Yet, iodine has not been monitored in these groups across time. This study aims to investigate iodine status, intake and knowledge in vegans, vegetarians and omnivores and determine changes between 2016–2017 and 2019. Dietary intake (μg/d) was estimated by 3-d food diaries and iodine FFQ. Urinary iodine concentration, analysed by inductively coupled plasma mass spectrometry, assessed iodine status according to WHO criteria. Iodine knowledge was scored by an adapted questionnaire. IBM SPSS was used for statistical analysis. Ninety-six adults (18–60 years) were recruited in October 2016–2017 (vegans: 12; vegetarians: 5; omnivores: 43) and June 2019 (vegans: 7; vegetarians: 10;omnivores: 19). Median dietary iodine was below the Reference Nutrient Intake for all groups. Vegans and vegetarians had the lowest iodine intake. Vegans had significantly lower iodine intake than omnivores (2016–2017, $P = 0\ 032$; 2019, $P = 0\ 001$). Omnivores had the highest iodine status (2016–2017, 79 4 μg/l; 2019, 72 4 μg/l) and vegans the lowest (2016–2017, 31 2 μg/l; 2019, 12 2 μg/l). Iodine knowledge was poor but did not differ between dietary groups (2016–2017, $P = 0\ 219$; 2019, $P = 0\ 532$). Vegans and vegetarians continue to be at risk of iodine deficiency. Further, iodine intake in the UK is poor independent of dietary choice. Iodine education is needed along with research into improving iodine nutrition at national level.

Key words: **Iodine: Vegan: Vegetarian: Micronutrient deficiency**

Iodine is an essential micronutrient required to produce thyroid hormones, thyroxine (T4) and triiodothyronine (T3)[1]. Thyroid hormones are necessary for normal neuronal development, metabolic function and growth throughout the lifespan[1]. Iodine deficiency occurs when physiological requirements are not met, and thyroid hormone synthesis is low[2]. Deficiency can result in a series of clinical abnormalities termed 'iodine deficiency disorders' and is most obviously manifested with the appearance of a goitre, the enlargement of the thyroid gland[1–3]. In pregnancy, risk of stillbirth, spontaneous abortion and other birth defects are increased in iodine deficient states[3]. Infants exposed to deficiency *in utero* are at risk of impaired cognitive development resulting in irreversible neurological damage, leading to cretinism in its most severe form[1–3]. Coexisting deficiencies of micronutrients such as Fe, Se and vitamin A may further impair iodine absorption and thyroid hormone production[4]. Deficiency, attributed to insufficient dietary iodine intake, is recognised as a major public health problem[5].

The WHO recommends a Reference Intake of 150 μg/d for adults (>12 years), in order to optimise thyroid hormone production (typically requiring around 70 μg/d)[6,7]. In the UK, a lower Reference Nutrient Intake (RNI) of 140 μg/d has been selected to ensure that 97·5 % of the population meets iodine intake[8]. Historically, iodine deficiency was prevalent in the UK, with some regions experiencing endemic goitre[9]. Eradication began in the 1960s due to government campaigns encouraging milk consumption, and changes in farming practice resulting in production of milk with a higher iodine content[10]. For many years following intervention, intake was considered sufficient, but is now a recognised public health issue after mild iodine deficiency was detected in schoolgirls and pregnant women in 2014–2015[9,11]. More recently, iodine intake was recognised as of concern for UK adults following a secondary analysis of the UK National Diet and Nutrition Survey in 2018[12]. Iodine intake estimates for males and females (aged 20–59 years) were recorded to be significantly lower than the current RNI. Young adults (aged 20–29 years) were recognised to be substantially

Abbreviations EE, energy expenditure; FD, food diaries; PAL, physical activity level; RNI, Reference Nutrient Intake; UIC, urinary iodine concentration.

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more at risk than older adults (aged 30–59 years), with 15 % of males and 17 % of females falling below the Lower Reference Nutrient Intake for iodine. Recent studies suggest that lack of information and knowledge regarding iodine may be greater in individuals at risk of iodine deficiency[13–15]. Current trends in food avoidance and dietary restriction, particularly of meat and dairy, have been recognised as a factor contributing to lowered iodine intake[16]. Individuals who have low knowledge and are not aware of the importance of adequate iodine intake may be less well equipped to make dietary changes that permit them to meet their iodine requirements.

In the UK, the main sources of dietary iodine are cows' milk and dairy products[17]. Seafood, eggs, seaweed and iodine-containing supplements are also iodine rich[17]. The relative iodine content of foods commonly consumed in the UK is presented in Table 1. Despite being the primary source of iodine, milk consumption has reduced considerably over the last decade. Particularly in those aged 16–24 years, whose cows' milk consumption has declined rapidly in recent years[18]. The proportion of people in this age group consuming cows' milk decreased from 79 to 73 % between years 2018–2019[18]. This decrease could reflect the growth and appeal of the alternative milk market in the UK. Food purchasing data from average UK households indicated an upwards trend in purchasing of alternative milks since 2014 (Table 2)[19,20]. Alternative milks such as soya, oat and coconut are now regularly consumed, very

Table 1. Average iodine content of foods consumed regularly in the UK per food portion

Food	Serving size (ml/g)	Average iodine/portion (μg/g)	Contribution of food groups to average daily iodine intake by NDNS (2016–2017 to 2018–2019) (%)
Milk and dairy products			
Cows' milk (semi-skimmed)	200	50–100*,†	13‖
Organic cows' milk (semi-skimmed)	200	30–60*,†	NA
Yogurt	150	50–100*,†	6‖
Cheese	40	15†	3‖
Fish and seafood			
Whitefish (haddock and cod)	120	230–390†	8‖
Salmon	100	14†	NA
Tinned tuna	100	12†	NA
Prawns	60	6†	NA
Eggs, meat and poultry			
Eggs	50	25†	9‖
Meat and poultry	100	10†	9‖
Plant based			
Fortified alternative milk	200	53–57‡	NA
Unfortified alternative milk	200	1–4‡	NA
Nuts	25	5†	0
Bread	36	5†	3
Fruit and vegetables	80	3†	6
Nori seaweed	26	382§	NA

NA, not applicable.
* Actual iodine content subject to seasonal variation (winter = higher) and organic farming practices (organic = lower).
† Data from the British Dietetic Association (BDA) Iodine Fact Sheet[17].
‡ Data from Bath *et al.*[21].
§ Data from Nutritics database UK (2015 COFIDS including McCance and Widdowson 7th edition, 2015)[40,41].
‖ Data from NDNS Y9–11 Descriptive statistics tables (19–64 years used[42]).

Table 2. Purchasing data and trends from UK households: Family Food 2018–2019 Living Costs and Food Survey (LCFS)[19,20]

Food item (g/d)	2015–2016	2016–2017	2017–2018	2018–2019	Change from 2015–2016 to 2016–2017 (%)	Change from 2016–17 to 2017–2018 (%)	Trend between 2017–2018 and 2018–2019
Cows' milk and milk products†	258·09	259·78	255·17	262·80	+2	+3	–
Semi-skimmed cows' milk	134·99	135·78	132·05	128·98	−4	−2	–
Yogurt and fromage frais	27·55	28·52	26·88	28·41	−3	+6	–
Cheese	16·46	17·69	17·82	17·64	+7	−1	↑
Fish	20·64	19·86	19·79	20·81	+1	+5	–
Whitefish‡	2·51	1·95	2·21	2·10	−16	−5	–
Eggs	0·28	0·28	0·28	0·3	+9	+6	↑
Dairy milk alternatives	5·86	7·15	9·38	9·85	+71	→+5→	↑

† Excluding cheese.
‡ Fresh, chilled or frozen.Upward arrows show significant increases in UK purchasing between 2017–2018 and 2018–2019 ($P = < 0·05$).
No significant change in purchasing trends 2017–2018 and 2018–2019 ($P \leq 0·05$).

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low in iodine and not regularly iodine fortified[21]. Although iodine rich, the contribution of fish and seaweed to iodine intake in the UK is likely to be small reflecting low national consumption[22]. The iodine content of seaweed is highly variable and if not monitored in the diet, over-consumption could induce excess iodine intake[23–25]. Many countries implement mandatory or voluntary iodised salt legislation[26]. Fortified salt used at household level provides additional dietary iodine and has been shown to alleviate deficiency[27]. Routine salt iodisation is not present in the UK currently and access to iodised salt in supermarkets is low[28]. Even if table salt was fully iodised, it is unlikely to provide adequate dietary iodine as table salt only comprises a small proportion (15 %) of dietary sodium consumed in the UK diet, and over half of intake (>60 %) is provided by ready-made and processed foods[29,30].

Inadequate iodine intake has been observed in individuals who consume diets excluding iodine-rich foods, principally dairy and/or fish[31]. For this reason, vegans and vegetarians are recognised as a subgroup with increased risk of iodine deficiency[16], as confirmed by recent research conducted in European nations including the UK, Germany, Finland, Norway, Spain and Switzerland[32–39].

Despite the increasing acceptance of vegan and vegetarian diets in the UK and the emergence of iodine deficiency, there is a lack of data regarding the level of iodine knowledge and whether good understanding of the challenges allows individuals to account for iodine when dietary restrictions are implemented. The purpose of this study was to investigate iodine status, intake and knowledge in vegans, vegetarians and omnivores and determine if changes were observed with time (between 2016 and 2019). We hypothesised that iodine intake and status would be positively associated with knowledge and that deficiency would be greater in vegans and vegetarians lacking good understanding compared with omnivores. We additionally proposed that, since a greater array of specialist foods would be available in 2019 than in 2016, iodine intake and status would be improved in vegans and vegetarians in the more recent cohort.

Methods

Ethical approval

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Faculty of Medicine & Health Sciences Research Ethics Committee Nottingham University Hospitals (Ethics Reference No. BS02082016). Written informed consent was obtained from all subjects.

Design and recruitment

Students and staff of The University of Nottingham (*n* 96) were recruited to the study at two separate time points, 2016–2017 and 2019. The first phase of recruitment was conducted between 24 October 2016 and 01 January 2017 and the second 16 June and 13 November 2019. The study protocol is outlined in Fig. 1. The study was advertised using posters, leaflets and emails distributed throughout the university. Adults following vegan and vegetarian diets were recruited by social media advertisement circulated through university societies.

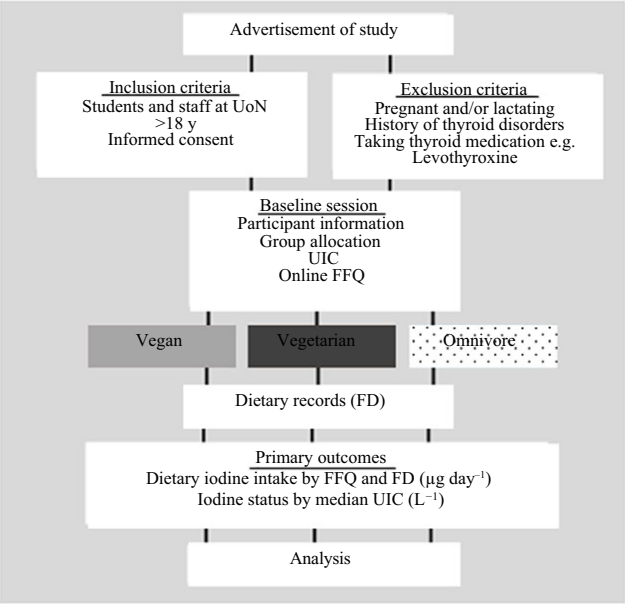


Fig. 1. Flow chart of study protocol. UIC, urinary iodine concentration. FD, food diary.

Participants matching the inclusion criteria were invited to attend a one-off session at 12.00 hours each day, whereby the experimental methodology was explained, and baseline data collected. To maintain anonymity, a unique participant number was randomly selected at baseline. During these sessions, individuals were provided with a participant information pack containing the study information sheet, 3-d food diary (FD), weblink to an online FFQ, a sterile universal urine tube and an ID number unknown to researchers. Participation was optional and written informed consent was obtained.

Dietary grouping

Participants were categorised into three dietary groups: vegan, vegetarian and omnivore, based on responses to the online FFQ addressing current dietary preference and consumption of animal products in the past 6 months. Participants who reported no dietary restrictions relating to animal products were classified as omnivores. Participants who did not consume animal products of any form were classified as vegans. Vegetarians encompassed all descriptions of vegetarian diets and were those who consume milk, eggs and possibly fish (pescatarians) but not meat. The vegetarian group also comprised individuals who had recently (< 3 months) transitioned from vegetarian to a vegan diet.

Assessing dietary iodine intake

Dietary iodine consumption was assessed using an online FFQ and 3-d FD introduced during baseline sessions. Adequate

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iodine intake was assessed using the current UK RNI of 140 μg/d and Lower Reference Nutrient Intake of 70 μg/d[8,16].

FFQ

The FFQ was developed using 'Online surveys' (previously 'Bristol Online Surveys'[43]) to assess habitual dietary intake over the past 6 months and was based on the validated FFQ used in the Oxford component of the European Prospective Investigation into Cancer and Nutrition (EPIC Oxford) study[44]. The FFQ addressed forty-five different food items including sources of dietary iodine and goitrogenic foods (online Supplementary Table S1). Prior to study, the FFQ was modified to address dietary preference and consumption of substitutes of specific foods that could be a potential source of iodine for those following vegan and vegetarian diets, such as alternative milk and dairy products. Frequently consumed food items, such as cows' milk, were listed in separate questions accounting for variations in serving sizes. Medium serving size was indicated using labelled food images employed by the National Diet and Nutrition Survey[45] (online Supplementary Fig. S1). For each food item, frequency categories were converted to daily iodine intake (μg/d). The category: '2 to 4 times/week' was adjusted to three per week or equivalent to 0·4 servings/d. It was assumed that those selecting the 'Less than once or never' option for rare foods such as samphire or animal products for vegans were not consumed within the past 6 months, thus generating a value of 0·0. Food items were assigned iodine values per portion from an in-house database created using data from Nutritics 4.3 software and McCance and Widdowson's composition of foods integrated dataset[40,41].

Three-day food diary

Iodine consumption was measured by a 3-d FD based on that used in the National Diet and Nutrition Survey[46]. Participants were asked to record estimated daily food and drink consumption, including descriptions of relative portion sizes, brand names of packaged items, home-cooked meal ingredients and supplement intake. Further questions addressed fluctuation from usual dietary patterns to establish if recorded intakes reflected that of a normal day. Participants were asked to complete the FD in the three consecutive days following recruitment sessions. To reduce disparity in diet patterns between the week and weekends, sessions were organised so that FD records contained at least one weekend day. If the consecutive days after recruitment did not contain a weekend, completion was postponed. Participants were asked to return completed FD to accessible drop-off points. Nutritics 4.3 was used to estimate dietary intakes. Databases used were limited to include food values of UK foods only. Average portion sizes for items designated by Nutritics were selected if not specified by participants. It was assumed that, unless stated, all milk was semi-skimmed non-organic cows' milk, alternative milks were unfortified unless brand information or fortification status was specified and salt added to meals was non-iodinated. Best estimates were made for vegan substitutes of food items not listed on Nutritics software using online information from retailers or back-of packet values. Recipes from the Vegan Society were used to calculate iodine values for vegan compound foods, such as cakes and biscuits, where there was no viable substitution in UK databases. All analysis considered edible portions for analysis and adjusted for cooking procedure when required. Where possible, Nutritics food codes with values for iodine were selected. Iodine values were added manually using data from Nutritics if the selected food code was established from label-based analysis. Nutritics outputs from FD were used to calculate the average quantity (g) of iodine-rich foods consumed and the contribution (%) of food groups to total iodine intake.

Assessing iodine status

Urinary iodine concentration. Optional spot urine samples were collected to determine median urinary iodine concentration (UIC). Participants were asked to complete a 50 ml single spot urine sample during information sessions to reduce diurnal variation associated with estimates. Samples were centrifuged immediately after collection at 914 relative centrifugal force for 5 min (Beckman GS-6R Refrigerated Centrifuge GS1M31) and supernatant frozen at −80 °C. Samples were defrosted overnight at 4 °C. UIC was determined using inductively coupled plasma mass spectrometry (Thermo Fisher Scientific). Known iodine concentrations were used as a control during analysis. Standards and samples were diluted 1:10 with Milli-Q H_20, transferred to analysis tubes and analysed in triplicate.

Classification of status. The WHO criteria were used to assess iodine status using UIC expressed as a median with inter-quartile range[6]. Groups with median with UIC > 100 μg/l were considered 'sufficient' and those with values <100 μg/l were considered 'deficient'. Relative levels of deficiency were classified as: 50–99 μg/l mild, 20–49 μg/l moderate and >20 μg/l severe.

Iodine knowledge and demographic data. The FFQ additionally collected demographic information which may contribute to iodine status, including ethnicity, educational level, degree classification, employment status, smoking status and alcohol consumption. Participants were also asked to complete seven questions addressing iodine knowledge and factors influencing iodine nutrition, generating a total possible score of 17 (online Supplementary Table S2). Questions were modified from studies previously investigating iodine knowledge in the UK[14]. Negative marking was used and a point was deducted for each incorrect answer, this was so that individuals were discouraged from selecting all listed responses. Iodine knowledge was considered 'poor' if scores were 5 or below, 'fair' if between 5 and 10 and 'good' if above 10.

Anthropometric data. All measurements of height (cm) and weight (kg) were self-recorded as part of the FFQ. BMI (weight/height^2, kg/m^2) was determined and classified according to the WHO assessment[47].

Assessing under-reporting. FD estimates were used to assess under-reporting. FFQ could not be used as energy intake was not estimated. Schofield equations were applied to determine the ratio between BMR or energy expenditure (EE) and actual

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reported intake (EIrep:EE) using age and weight (kg) as a reference[48]. To identify records of poor validity, participants were classified according to EIrep:EE into under-reporters, acceptable reporters and over-reporters using the Goldberg cut-off[48,49]. Activity levels were not assessed during this study; therefore, a lower activity factor was used to calculate the estimated energy requirement. A physical activity level (PAL) of 1·5 was used for adjustment[50]. This value describes a population with a low level of daily physical activity (not sick, disabled or elderly).

The calculations used to determine cut-offs were

$$95\,\%\,\text{Confidence limits} = \text{PAL} \times \exp(\pm 2 \times ((\text{S}/100)/\sqrt{\text{n}})$$

where, PAL is equal to 1·5; n is the participant no (45) and S is the factor accounting for variation in estimated intake (EI), BMR and PAL was estimated by:

$$\text{S} = \sqrt{(\text{CV2wEI/d} + \text{CV2wB} + \text{CV2tP})}$$

where, CVwEI is the within-subject variation in EI in our cohort (28 %); D is the number of days of dietary assessment (3 d); CVwB is the variation in repeat BMR measures (9 %) and CVtP is the total variation in PAL (15 %).

The CV for within-individual variation for our cohort was determined as 18 %. CV parameters (9 and 15 %) were taken from those generated by Black[48] and have been accepted as suitable for use in the Goldberg equation. CI at 95 % were applied; those with EIrep:EE of 1·41–1·71 were considered as acceptable reporters. Participants with values <1·41 were under-reporters and >1·71 as over-reporters.

Statistical analysis. Data analysis was performed using IBM SPSS Statistics V22.0. A significance of $P < 0{\cdot}05$ (two-tailed) was selected for all statistical analysis. Normality of the data was assessed using the Shapiro–Wilk test for normality. UIC and dietary iodine intake values were not normally distributed; therefore, medians are reported. Kruskal–Wallis H tests with Dunn's post hoc tests were performed to compare intake and status where groups were two or more. Spearman's rank correlation was used to determine relationships between continuous data. Pearson's χ^2 test was used for comparison between categorical variables. The Bonferroni test for adjustment was used for correction. Sample size estimates were calculated based upon data obtained from a previous report which provided mean and standard deviation measurements for vegans and omnivores[51]. The effect size was recorded as 106 µg/d with a population standard deviation of 91 µg/d and a recruitment bias of 1. For a power of 80 % and an α-error of 5 %, the sample size was calculated as a minimum of 24 (12 per group) for vegans and omnivores using the 'ClinCalc' online calculator[52].

Results

Study population

Descriptive characteristics of participants (n 96) are listed in Table 3. Two individuals in 2019 (one male and one female) had recently transitioned onto a vegan diet and were considered

Table 3. Participant characteristics (n 96). Values are n and median (range)

		2016–2017						2019					
		Vegans (n 12)		Vegetarians (n 5)		Omnivores (n 43)			Vegans (n 7)		Vegetarians (n 10)		Omnivores (n 19)		
		Median	Range	Median	Range	Median	Range	P	Median	Range	Median	Range	Median	Range	P
Sex (n)	Male	0		0		7			3		1		5		
	Female	12		5		36			4		9		14		
Age (years)		21·5	10·0	22·0	3·0	21·0	32·0	0·934	23·0	12·0	23·0	18·0	25·0	29·0	0·066
BMI (kg m^2)		21·0	6·0	19·4	5·6	22·0	18·8	0·019*	20·4	5·6	21·7	7·3	22·9	14·5	0·521
Birth region (n)	UK (UK)	11		5		24			4		7		9		
	Europe	1		0		2			3		1		2		
	East and Southeast Asia	0		0		8			0		2		6		
	Western Asia	0		0		1			0		0		0		
	West Africa	0		0		0			0		0		1		
	Caribbean	0		0		0			0		0		1		
	Did not disclose			0		8			0		0		0		
Education (n)	BSc BA or lower	9		4		20			2		5		4		
	PhD or MD	3		1		8			4		5		9		
	Staff	0		0		5			0		0		1		
	Did not disclose	0		0		10			1		0		5		

* Significance between dietary groups assessed by Kruskal–Wallis ($P \leq 0{\cdot}05$).
Normality was assessed by Shapiro–Wilk ($P = 0{\cdot}001$).

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as vegetarians. All dietary groups were predominantly composed of females (84 %). The average BMI for each dietary group was lower than the UK population[50], but within the healthy range (18·5–24·9) for most participants. Exceptions included six overweight female omnivores (BMI; overweight: 25·0–29·9), as well as two female vegetarians and one female vegan who were below the normal range of BMI (17·0, 16·6 and 18·2, respectively). BMI values were significantly lower in vegetarians than omnivores in 2016–2017 ($P = 0·019$). In 2019, there was no difference in BMI between dietary groups ($P = 0·066$). We were unable to assess differences in sex, nationality and qualifications by χ^2 as the minimum expected count was under 5 for these variables.

Dietary intake

Other specific diets were followed by three vegans in 2016–2017, two of which avoided starch and bread/flour products and one described having a lactose intolerance. Lactose intolerance was reported by one omnivore in 2019.

The prevalence of under-reporting was high in both years with 73 % of participants recording an EIrep:EE ratio < 1·41. All male participants were classified as under-reporters, but under-reporting did not differ between dietary groups with vegans, vegetarians and omnivores having similar occurrence (2016–2017; 75, 50 and 68 %, $P = 0·830$). In 2019, under-reporting was more prevalent, with 100 % of vegans being classed as under-reporters compared with 71 % of vegetarians and 86 % of omnivores ($P = 0·608$). In both years, vegetarians had the largest proportion of acceptable-reporters (2016–2017: 50 %; 2019, 28 %), while none of the vegan participants in 2019 had values within this range. Over-reporting was low in both years, with none recorded in 2019 compared with two omnivores and one vegan in 2016–2017.

Energy intake did not differ between dietary groups (2016–2017, $P = 0·438$; 2019, $P = 0·802$, Table 4). We were unable to stratify by sex due to low numbers of males in our cohort. However, with the inclusion of males, average energy intake was greater than current estimates of the UK population for females (1632 kcal) but not males (2313 kcal) for most dietary groups[53]. In both years, vegans had the greatest daily energy intake (2016–2017, 1755·3 kcal; 2019, 1656·0 kcal). There was no relationship between energy and iodine intake by FD or FFQ in 2016–2017 or 2019 (FD, r 0·085, $P = 0·610$; FFQ, r 0·044, $P = 0·796$ and FD, r 0·067, $P = 0·786$; FFQ, r 0·012, $P = 0·960$).

Average daily intake of macronutrients by dietary group is presented in Table 4. In both years, vegans consumed significantly greater quantities of fibre than omnivores (2016–2017, $P < 0·001$; 2019, $P = 0·030$). In 2016–2017, polyunsaturated fat intake was significantly higher in vegans compared with omnivores ($P = 0·011$).

Dietary iodine

Median iodine intake estimated by FFQ and FD is shown in Fig. 2. Intakes derived from the FFQ were higher ($P = 0·020$) and displayed larger variation than those provided by FD.

Table 4. Average daily macronutrient intake of vegans, vegetarians and omnivores by diet group in years 2016–17 and 2019 provided by food diary (FD) estimates. Data presented are median (range)

	2016–2017							2019						
	Vegans (*n* 10)		Vegetarians (*n* 4)		Omnivores (*n* 27)			Vegans (*n* 4)		Vegetarians (*n* 6)		Omnivores (*n* 11)		
	Median	Range	Median	Range	Median	Range	*P*	Median	Range	Median	Range	Median	Range	*P*
Energy (kJ)	7344·2	6168·9	6326·2	6446·7	6910·3	12821·9	0·438	6928·7	5757·2	6922·8	5014·9	6643·8	7096·1	0·802
Protein (g)	65·1	102·8	55·5	27·9	66·8	186·8	0·633	59·1	37·0	56·2	45·8	85·7	84·9	0·081
Fat total (g)	62·2	100·0	64·3	46·6	67·2	142·6	0·973	69·2	69·9	67·1614	62·2	64·1	66·3	0·806
Saturated (g)	14·6	30·4	20·3	15·7	23·3	45·7	0·139	22·3	36·0	20·3	19·9	21·0	33·5	0·995
Monosaturated (g)	23·3	37·3	19·9	11·3	21·0	56·0	0·747	18·8	6·4	22·7	24·6	20·6	19·4	0·739
Polyunsaturated (g)	18·6	32·6	9·1	17·3	10·2	27·4	0·012*	13·1	12·5	10·8	24·8	9·5	10·9	0·199
Carbohydrates (g)	237·4	246·2	184·0	160·9	198·3	332·7	0·268	202·5	239·7	206·9	141·7	176·1	267·4	0·525
Added sugars (g)	102·6	111·5	96·8	68·0	69·6	181·1	0·266	63·4	110·0	107·1	84·1	60·54	105·0	0·493
Fibres (g)	37·1	46·9	29·5	16·4	16·9	33·5	< 0·001	34·3	24·6	25·5	26·4	19·5	25·6	0·030*
Alcohol (ml)	2·4	29·6	4·1	69·5	0·0	64·0	0·128	0·3	47·3	0·0	13·4	0·0	6·1	0·528

* Significance between dietary groups assessed by Kruskal–Wallis ($P \leq 0·05$).
Normality was assessed by Shapiro–Wilk ($P = 0·001$).

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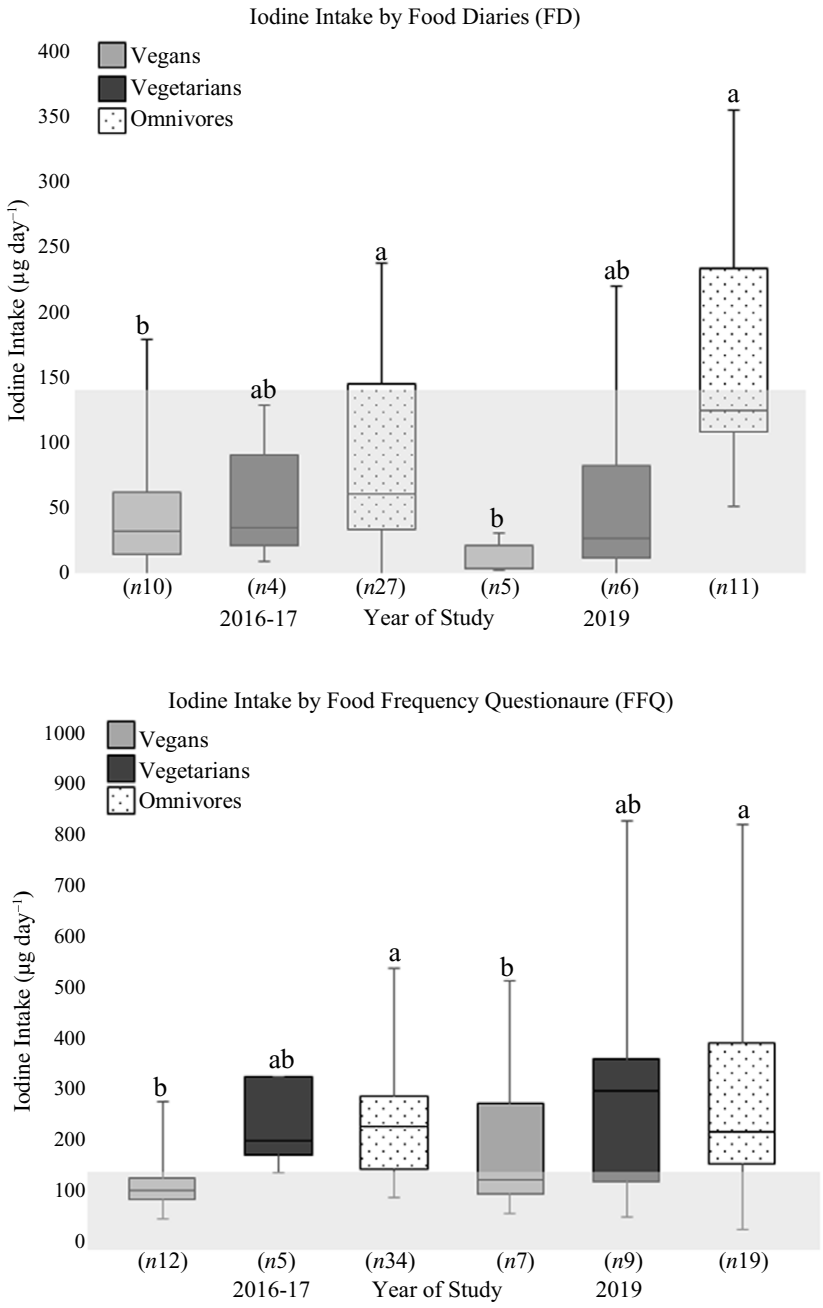


Fig. 2. Estimated dietary iodine intake by FFQ and food diaries (FD) for vegans, vegetarians and omnivores. Shaded areas represent intakes below the Reference Nutrient Intake (RNI) of 140 µg/d. Different letters (a and b) represent significant differences among dietary groups, whereby a > b, ab = a, ab = b, a > c, b > c and ab > c ($P \leq 0{\cdot}05$) (Kruskal–Wallis test).

Iodine intake by food diary

Median iodine intake was below the RNI (150 µg/d) for all dietary groups in 2016–2017 (vegans: 47·6 µg/d; vegetarians: 68·8 µg/d and omnivores: 111·9 µg/d) and 2019 (vegans: 17·3 µg/d; vegetarians: 71·4 µg/d and omnivores: 126·0 µg/d) (Fig. 2). The RNI was not achieved by any vegetarians in 2016–2017 or vegans in 2019. Median values for vegans and vegetarians in 2016–2017, and vegans in 2019, were below the Lower Reference Nutrient Intake of 70 µg/d. More than 75 % of participants had values associated with severe deficiency. Average iodine intake in vegans and vegetarians was lower than current estimates of the UK population of 98 µg/l for women of childbearing age (19–49 years) and 106 µg/l for adults (19–64 years).

Inadequate intake was more frequent in those following vegan and vegetarian diets than omnivorous diets. In both years, median intake was numerically lower in vegan and vegetarian groups and was significantly lower in vegans compared with omnivores both years (2016–2017, $P = 0{\cdot}032$; 2019, $P = 0{\cdot}001$).

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Iodine intake by FFQ

In both years, FFQ median dietary iodine intake for vegetarians and omnivores was above the RNI (2016–2017, 202·9 μg/d, 299·6 μg/d; 2019, 230·0 μg/d, 221·9 μg/d). Dietary iodine intake for vegans did not meet the RNI (2016–2017, 107·0 μg/d, 124·9 μg/d). Intakes between dietary groups displayed a similar trend as observed in FD. In 2016–2017, median values were significantly lower in vegans compared with omnivores ($P < 0·001$). This trend was not seen in vegetarians, whose intake in 2016–2017 was similar to those of omnivores ($P = 1·000$). In 2019, no significant differences in iodine intake were observed between dietary groups ($P = 0·356$).

Sources of iodine

We assessed the average daily consumption of foods potentially contributing to iodine intake using data from FD (Table 5). In both years, omnivores had the greatest consumption of cows' milk, dairy products and eggs. In 2019, fish and seafood were predominantly consumed by omnivores. Seaweed was only consumed as a supplement by two omnivores and is not considered a regular dietary source of iodine. In 2016–2017, alternative milk, alternative milk product and seaweed consumption were significantly greater in vegans than omnivores ($P = 0·001$, 0·016 and 0·040). No significant differences in iodine-rich food consumption were observed between dietary groups for either year when non-consumers were removed from analysis.

Food group contribution to iodine

The major sources of dietary iodine in each cohort are displayed in Table 6. In 2016–2017, the food groups contributing the largest proportion to iodine intake in omnivores were cows' milk (21 %) and eggs (10 %). In 2019, cows' milk (24 %) and fish and seafood (12 %) were major sources of dietary iodine. Cows' milk was a key source of iodine in the diets of vegetarians in both years rising from 10 % in 2016–2017 to 14 % in 2019. Eggs were also a good source of iodine in the diets of vegetarians in 2016–2017 but not 2019 (7 and 0 %, respectively).

Plant-based sources were the major providers of iodine for vegans. Fruit and vegetables being the predominant source (21 and 27 %), followed by breads, grains and pulses (5 and 22 %). Unlike cows' milk and dairy products, alternative milk (1 %) and alternative milk products (0 %) did not greatly contribute to dietary iodine, in any dietary groups, in either year.

In 2016–2017, the iodine contribution of alternative milks was significantly greater in vegans and vegetarians ($P \leq 0·001$, $P = 0·016$). Alternative meats provided significantly greater contribution to dietary iodine in vegans compared with omnivores ($P = 0·018$). Seaweed supplied a significantly greater iodine contribution to the diets of vegans compared with omnivores ($P = 0·040$). Multivitamin supplements provided significantly greater iodine to the diets of vegans compared with omnivores and vegetarians ($P \leq 0·001$, $P = 0·033$).

In both years, the contribution of fruit and vegetables to dietary iodine was greater for vegans than omnivores ($P = 0·001$ and 0·029). In 2019, breads, grains and pulses and

Table 5. Daily consumption (g) of possible sources of iodine in the diets of vegans, vegetarians and omnivores in years 2016–2017 and 2019 (Medians and ranges)

	Vegans				Vegetarians				Omnivores				*P*	
	2016–2017 (*n* 10)		2019 (*n* 4)		2016–2017 (*n* 4)		2019 (*n* 5)		2016–2017 (*n* 27)		2019 (*n* 10)			
	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	2016–2017	2019
Consumers														
Cows' milk	–		–		146·7	98·3–195·0	186·7	40·0–358·0	120·0	10·0–413·3	198·3	6·17–476	0·905	0·838
Dairy products	–		–		62·3	21·2 –103·3	36·84	4·67–89·7	56·3	1·7–201·7	87·3	10·0–199·0	0·913	0·174
Fish and seafood	–		–		50·0	33·3–66·7	66·7	40·0–93·3	37·3	3·3–100·0	40·0	18·3–206·7	0·734	0·303
Eggs	–		–		30·0	20·0–40·0	62·5	50·0–75·0	21·0	3·3–73·3	66·7	18·3–206·7	0·724	1·000
Alternative milks	170·0	46·7–471·7	268·7	120·7–306·7	136·7	11·7–270·0	116·7	66·7–116·7	125·0	11·6–350·0	199·5	161·7–237·3	0·613	0·074
Alternative milk products	22·5	14·0–120·0	51·7	50·0–53·3	98·3	90·0–106·7	467·5	41·7–93·3	41·7	13·3–166·7	–		0·614	1·000
Seaweed	2·2	1·7–2·7	–		–		–		–		0·7	0·0–0·67	NA	NA
Inclusive of non-consumers														
Cows' milk	–		–		49·2	0·0–195·0	40·0	0·0–358·0	60·0	0·0–413·3	161·8	0·0–476·0	0·549	0·458
Dairy products	–		–		10·6	0·0–103·3	30·0	0·0–89·7	41·6	0·0–201·7	56·5	0·0–199·0	0·405	0·325
Fish and seafood	–		–		16·7	0·0–66·7	0·0	0·0–93·3	0·0	0·0–100·0	21·6	0·0–71·7	0·849	0·613
Eggs	–		–		10·0	0·0–40·0	0·0	0·0–75·0	20·0	0·0–73·3	19·2	0·0 –206·7	0·358	0·519
Alternative milks	168·3	0·0–471·7	194·7	0·0 –306·7	74·2	0·0–270·0	66·7	0·0–116·7	0·0	0·0–350·0	0·0	0·0–237·3	0·001*	0·101
Alternative milk products	17·0	0·0–120·0	25·0	0·0–53·3	45·0	0·0–106·7	0·0	0·0–93·3	0·0	0·0–166·7	0·0	0·0–0·0	0·009*	0·068
Seaweed	0·0	0·0–2·67	0·0	0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·6	0·042*	0·638

NA, No measures of association were calculated as at least one variable was continuous.
* Significant between dietary groups for nominal data assessed by χ^2 and continuous by Kruskal–Wallis ($P \leq 0·05$).
No consumers included in group comparisons.
Normality was assessed by Shapiro–Wilk ($P = 0·001$).

Table 6. Percentage (%) iodine intake from different food groups in vegans, vegetarians and omnivores in years 2016–2017 and 2019. Inclusive of both consumers and non-consumers (Median percentages and ranges)

Percentage iodine intake (%)														
	Vegans				Vegetarians				Omnivores				*P*	
	2016–2017 (*n* 10)		2019 (*n* 4)		2016–2017 (*n* 4)		2019 (*n* 5)		2016–2017 (*n* 27)		2019 (*n* 10)			
	Median percentage	Range	Median percentage	Range	Median percentage	Range	Median percentage	Range	Median percentage	Range	Median percentage	Range	2016–2017	2019
Food group														
Cows' milk	–		–		9·5	0·0–65·0	14·0	0·0–74·9	21·0	0·0 - 65·0	23·5	0·0–51·6	0·697	0·704
Dairy products	–		–		0·0	0·0–0·0	3·3	0·0–58·0	0·0	0·0–41·0	1·8	0·0–43·8	0·130	0·708
Fish and seafood	–		–		0·9	0·0–2·2	0·0	0·0–15·8	0·0	0·4–85·0	12·0	0·0–47·5	0·573	0·184
Eggs	–		–		6·8	0·0–14·4	0·0	0·0–28·0	9·8	0·0–35·7	11·7	0·0–29·3	0·512	0·343
Alternative milks	0·6	0·0–16·7	0·6	0·0–3·6	0·3	0·1–38·3	0·0	0·0–1·4	0·0	0·0–60·4	0·0	0·0–1·9	0·001*	0·129
Alternative milk products	0·0	0·0–3·4	0·0	0·0–36·3	0·0	0·0–0·0	0·0	0·0–6·8	0·0	0·0–1·3	0·0	0·0–0·0	0·210	0·114
Meat and poultry	–		–		–		–		5·3	0·0–63·9	6·7	0·0–16·3	NA	NA
Alternative meat	1·6	0·0–51·6	4·3	0·0–24·8	4·4	0·0–16·6	0·0	0·0–0·9	0·0	0·0–11·3	0·0	0·0–0·0	0·007*	0·057
Fruit and vegetables	21·3	2·9–76·9	26·8	7·7–69·4	9·1	8·1–21·1	8·8	1·1– 93·6	5·9	0·5–33·6	2·7	1·0–8·0	0·001*	0·025*
Breads, grains, pulses, etc.	5·0	1·9–36·9	21·9	17·8–45·6	6·0	0·8–27·3	2·7	0·0–12·5	2·8	0·0–20·0	3·0	0·0–8·0	0·105	0·012*
Snacks, crisps, cakes and nuts/seeds	3·6	0·0–58·9	11·4	0·0–37·8	2·6	1·3–18·8	5·7	0·0–28·5	2·7	0·0–16·8	1·3	0·0–35·0	0·253	0·633
Drinks	0·3	0·0–58·9	0·3	0·0–26·1	0·0	0·0–36·4	0·0	0·0–0·4	0·0	0·0–2·0	0·0	0·0–0·0	0·172	0·009*
Salt and spices	0·0	0·0–2·7	0·1	0·0–0·5	0·3	0·0–0·5	0·0	0·0–0·8	0·0	0·0–5·5	0·0	0·0–2·6	0·371	0·869
Iodised salt	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–50·0	0·0	0·0–0·0	0·588	1·000
Seaweed	0·0	0·0–79·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–8·0	0·042*	0·638
Supplements	2·0	0·0–86·6	0·0	0·0 0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–0·0	0·0	0·0–42·0	0·001*	0·638

* Significant between dietary groups by Kruskal–Wallis ($P \leq 0.05$).
Normality was assessed by Shapiro–Wilk ($P = 0.001$).

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drinks contributed significantly greater iodine to the diet of vegans than omnivores ($P = 0{\cdot}011$ and $0{\cdot}007$).

Iodised salt was only consumed by one female participant in 2016–2017 following an omnivorous diet.

Supplement usage

Supplement usage was determined by FFQ. Overall, 42 % of participants recorded consumption of a dietary supplement, either daily, weekly or sporadically. The most frequently used supplement for all groups was B_{12} (27 %), followed by non-iodine-containing multivitamin formulations (17 %) and vitamin D (12 %). Multivitamins containing iodine were consumed by 12 % of participants providing an average of 140 μg/d to dietary iodine. Seaweed supplements kelp and/or kombu were consumed by two omnivores in 2019, providing an average iodine intake estimate of 1541 μg/d.

When comparing supplement use between years, the only significant difference observed was that vegans supplemented to a greater extent than omnivores in 2016–2017 ($P = 0{\cdot}001$). The iodine content provided by all consumed supplements differed according to dietary group in 2016–2017 ($P = 0{\cdot}013$) but not 2019 ($P = 0{\cdot}910$). The iodine content of supplements consumed by vegetarians in 2016–2017 was significantly lower than those consumed by omnivores ($P = 0{\cdot}022$). Pearson's χ^2 was used to assess iodine-containing supplement consumption (providing > 20 μg/d) by dietary group.

A significantly greater proportion of vegetarians consumed iodine-containing supplements in 2016–2017 ($P = 0{\cdot}009$) but not 2019 ($P = 0{\cdot}942$). While supplement usage was recorded by participants in FFQ, only four participants recorded consumption in their FD.

Iodine status

Iodine status assessed by UIC is presented in Fig. 3. Nine participants did not provide a urine sample (2016–2017, *n* 8; 2019, *n* 1). In both years, omnivores had the greatest UIC (2016–2017, 79·4 μg/l; 2019, 72·4 μg/l), followed by vegetarians 7·32 ,2017–2016) μg/l; 2019, 13·4 μg/l) and the lowest was recorded in vegans (2016–2017, 31·2 μg/l; 2019, 12·2 μg/l). In 2016–2017, omnivores had significantly greater median UIC than vegans ($P = 0{\cdot}003$) but not vegetarians ($P = 0{\cdot}083$). A similar trend was observed in 2019, where omnivores had significantly higher median UIC than vegans and vegetarians ($P = 0{\cdot}029$ and $0{\cdot}044$). The greatest variation in UIC (inter-quartile range) was observed for omnivores in 2016–2017 and 2019 (76·3–100·9), compared with vegans (30·5–36·5) and vegetarians (33·3–43·6).

None of the samples given by vegan participants in either years, or vegetarians in 2016–2017, was above the cut-off for iodine adequacy (100 μg/l). Vegans and vegetarians had median values signifying severe deficiency (20–49 μg/l) in both years studied.

The relationship between iodine intake from iodine-rich food sources and UIC, independent of dietary group, was assessed (Table 7). In 2016–2017, UIC increased with greater intake of cows' milk and dairy products (r 0·512, $P = 0{\cdot}030$, r 0·530, $P = 0{\cdot}013$). This was not apparent in 2019 (r −0·173, $P = 0{\cdot}612$, r – 0·056, $P = 0{\cdot}863$).

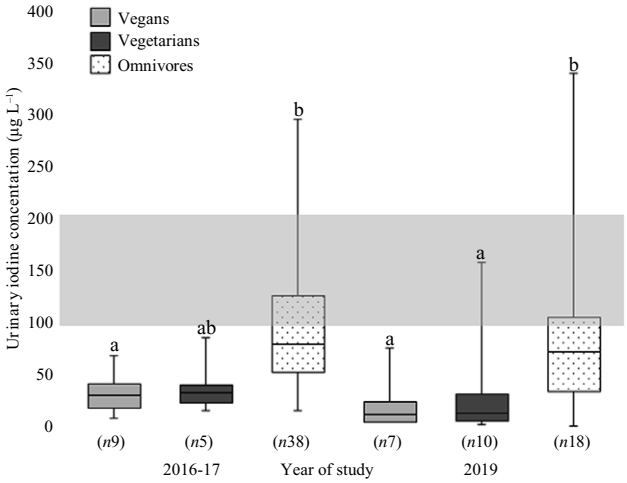


Fig. 3. Iodine status of vegans, vegetarians and omnivores by urinary iodine concentration (UIC). Shaded areas show the proportion of participants within the WHO adequate range for median UIC (100 μg/l). Bars show variation (minimum and maximum). Different letters (a, b and c) represent significant differences among dietary groups, whereby a > b, ab = a, ab = b, a > c, b > c and ab > c ($P = 0{\cdot}05$) (Kruskal–Wallis test).

Table 7. Correlation coefficients between urinary iodine concentration (UIC) and sources of dietary iodine provided by food diary (FD) estimates, thyroid related micronutrients and iodine knowledge

	UIC (μg/l)			
	2016–2017 (*n* 52)	*P*	2019 (*n* 35)	*P*
Food group (g/d)				
Cows' milk	0·512	0·030*	−0·173	0·612
Dairy products	0·530	0·013*	0·056	0·863
Fish and seafood	−0·025	0·936	0·100	0·797
Eggs	−0·246	0·258	−0·357	0·385
Alternative milk	0·093	0·722	−0·575	0·136
Alternative milk products	0·454	0·160	−0·400	0·600
Thyroid-related micronutrients				
Fe	−0·311*	0·025	−0·024	0·888
Se	−0·136	0·335	0·192	0·262
Vitamin A	−0·318*	0·022	−0·078	0·653
Iodine knowledge				
No. of correct symptoms identified associated with deficiency	−0·037	0·814	−0·292	0·084
No. of correctly identified iodine-rich food sources	−0·129	0·423	0·060	0·727
Total incorrect answers to iodine knowledge questions	−0·037	0·816	0·216	0·206
Total iodine knowledge score	−0·050	0·751	0·230	0·178

* Significant between dietary groups assessed by Spearman's correlation ($P \leq 0{\cdot}05$).

Consumption of milk alternatives and milk alternative products had no relationship with UIC in both years (2016–2017, r 0·093, $P = 0{\cdot}722$, r 0·454, $P = 0{\cdot}160$, 2019, r −0·575, $P = 0{\cdot}136$, r– 0·400, $P = 0{\cdot}600$). Many varieties of alternative milk were fortified with vitamins and minerals; however, fewer than 12 % (2/17) of varieties were fortified with iodine. Iodine-fortified alternative milks provided an average of 47·6 μg/200 ml portion of iodine (compared with 85 μg/200 ml cows' milk)[21].

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Iodine knowledge

Iodine knowledge was poor in both years (Table 8), with median knowledge scores of 3 (2016–2017) and 5 (2019) reported out of a total of 17. There was no difference in total iodine knowledge scores between dietary groups (2016–2017, $P = 0{\cdot}219$; 2019, $P = 0{\cdot}532$).

Most participants stated awareness of the importance of adequate dietary iodine intake. However, more than half of participants 'did not know' or were unable to correctly identify a health condition related to iodine deficiency. The most common symptom identified was goitre or enlargement of the thyroid gland, followed by cretinism. Other symptoms recognised included: tiredness, being sensitive to cold or weight gain.

A considerable selection of participants could not recognise the main food sources of iodine in the UK diet (dairy and whitefish). Many participants perceived foods such as leafy green vegetables and oily fish to be iodine rich. Overall, there was no significant difference in knowledge of iodine-rich foods between different dietary groups. However, vegetarians in 2016–2017 had significantly better knowledge of the role of cows' milk as a good source of iodine ($P = 0{\cdot}007$).

Other demographics such as age were assessed as predictors of iodine knowledge. Younger participants tended to have lower iodine knowledge scores in 2016–2017 ($r\,0{\cdot}409$, $P = 0{\cdot}004$). However, no relationship existed between age and iodine knowledge in 2019 ($r\,0{\cdot}409$, $P = 0{\cdot}529$).

Discussion

To the best of our knowledge, this is the first study to monitor iodine in different dietary groups at two time points. In support of our hypothesis and conclusions from previous research[31], we show that achievement of adequate iodine intake and status remains problematic for those following vegan and vegetarian diets. Our research also indicates that many university students may be vulnerable to iodine deficiency regardless of dietary practice. In 2014, the Scientific Advisory Committee on Nutrition reported on the current state of iodine nutrition in the UK, identifying vegans and vegetarians as a subgroup with increased risk of iodine deficiency[16]. Since publication, only one study has specifically addressed iodine in these diets in the UK[39].

Dietary intake

Our results confirm that those not consuming animal-derived foods continue to have lower dietary iodine intake. Although our study contains a relatively small unbalanced sample of vegans and vegetarians in both years of study and may be subject to a high prevalence of under-reporting, estimated average dietary intake for vegans and vegetarians was below the Lower Reference Nutrient Intake of 70 μg/d using FD data. This was consistent with current data comparing iodine between dietary groups in the UK[39,51,54–56], Europe[32,33,35–38,57–64] and the USA[65]. When iodine requirements are not met, thyroid hormone synthesis is disrupted[2]. Persistent mild–moderate deficiency may put strain on the thyroid gland, stimulating thyroid stimulating hormone independent growth and thyroid autonomy[66]. Individuals experiencing thyroid autonomy at a young age may continue to have altered thyroid function in later life, even if adequate iodine intake is resumed[66]. Vegans and vegetarian diets that do not provide adequate iodine are a concern given that meat-free diets are often frequented by women of childbearing age (18–34 years)[67]. Although there is limited recent evidence among UK vegans for the presence of low iodine compromised pregnancies[68], the rapidly expanding population comprising an increasing proportion of those less attentive to dietary requirements (REF) increases the number of individuals at greater risk of iodine deficiency in pregnancy and associated consequences for the developing fetus[68]. Adequate iodine intake is essential for those considering future pregnancy, as intra-thyroidal stores must be maximised before conception to facilitate fetal growth and neurological development[69–71]. Removing the possibility of pregnancy, those with increased risk should be shielded from the consequences of poor iodine nutrition. In both years of study, individuals following vegan diets had very low iodine intake (2016–2017, 47·6 μg/d, 17·3 μg/d). This is of significant concern as dietary intake <50 μg/d can potentiate the development of endemic goitre and hypothyroidism[5]. Although clinical manifestations are rare in Western nations experiencing mild-to-moderate iodine deficiency (UK), studies have observed meat-free diets be associated with the occurrence of iodine deficiency disorders[72–74]. In both years of study, all dietary groups had median iodine intake below the current RNI (140 μg/d), highlighting the difficulty in achieving adequate iodine intake on any diet[75].

Various challenges are associated with dietary assessment methods including accurate recall, memory retrieval and recording duration[76–78]. We selected two dietary methods to measure iodine intake, a 3-d FD and iodine-specific FFQ. FD typically underestimate usual dietary intake, whereas FFQ frequently overestimate[79,80]. In both years, the FFQ indicated that median dietary intake was above the RNI for vegetarians and omnivores, while FD estimates were below the RNI. The disparity in estimates may be due to different periods of recording (6 months *v.* 3 d). Additionally, the FFQ covered the top food sources of iodine in the UK (cows' milk, dairy, eggs, fish and seafood), possible non-animal sources applicable for vegans and foods that are rarely consumed such as seaweed. The FFQ did not include other possible sources of iodine, for example, fruits, vegetables, grains, etc. that did contribute to dietary intake for all groups. Shortening the FFQ to provide limited food choices may have resulted in overestimation of items that are not frequently consumed or perhaps iodine-rich food items were not covered in the time covered by FD[80]. Due to methodological challenges associated with FFQ, we are unable to establish if iodine intake over time (6 months) is indeed adequate in our cohort. We have focused on FD estimates for our analysis as these records reflect recent iodine intake and are likely to correspond more closely to UIC[6].

In Western diets, iodine is incorporated from adventitious sources such as iodine feed supplements and iodophors used in the dairy industry along with differing food practices between producers[81]. Hence, cows' milk and milk products are good sources of iodine. One portion of cows' milk (200 ml) may

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Table 8. Baseline record of iodine knowledge (%) by dietary group in years 2016–2017 and 2019*
(Medians and ranges)

	Vegans				Vegetarians				Omnivores				*P*	
	2016–2017 (*n* 12)		2019 (*n* 7)		2016–2017 (*n* 5)		2019 (*n* 10)		2016–2017 (*n* 32)		2019 (*n* 18)			
Responses	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	Median	Range	2016–2017	2019
Awareness of the importance of adequate dietary intake														
Yes	41·7		85·7		80·0		100·0		71·9		89·5		0·132	0·508
No	58·3		14·3		20·0		0·0		28·1		10·5			
Symptoms correctly identified														
Yes	41·7		42·9		60·0		60·0		46·9		42·1		0·788	0·635
No	58·3		57·1		40·0		40·0		53·1		57·9			
Knowledge of iodine deficiency symptoms														
Compromised growth	0·0		0·0		0·0		10·0		0·0		5·3		NA	–
Goitre/enlargement of the thyroid gland	16·7		42·9		20·0		40·0		25·0		26·3		0·832	–
Neurological impairment	8·3		0·0		20·0		0·0		12·5		5·3		0·797	–
Cretinism	16·7		0·0		60·0		10·0		21·9		5·3		0·141	–
Reduced thyroid function	25·0		0·0		0·0		10·0		3·1		0·0		0·048	–
Hypothyroidism	8·3		14·3		40		0·0		12·5		5·3		0·209	–
Other	0·0		28·6		0·0		10·0		0·0		0·0		NA	–
Do not know/no response	0·0		57·1		0·0		40·0		0·0		57·9		NA	–
Understanding of the importance of iodine in pregnancy and infancy														
Yes	25·0		28·6		40·0		60·0		43·8		36·8		0·523	0·357
No	75·0		71·4		60·0		40·0		56·3		63·2			
Perceptions of the main food sources of iodine in the UK diet														
Cows' milk	33·3		42·9		100·0		60·0		38·7		47·4		0·026	0·742
Organic cows' milk	25·0		28·6		40·0		40·0		75·0		47·4		0·772	0·684
Yogurt	33·3		28·6		60·0		10·0		75·0		26·3		0·280	0·546
Whitefish	25·0		57·1		80·0		40·0		50·0		63·2		0·099	0·489
Oily fish	50·0		28·6		40·0		20·0		40·6		52·6		0·663	0·190
Sea salt	33·3		71·4		60·0		50·0		56·3		47·4		0·590	0·540
Table salt	41·7		42·9		40·0		37·5		53·1		10·5		0·928	0·128
Leafy green vegetables	50·0		71·4		60·0		60·0		43·8		57·9		0·909	0·818
Wholemeal bread	33·3		28·6		20·0		10·0		68·8		10·5		0·855	0·457
Total iodine knowledge score														
Total score	1·5	17·0	6·0	8·0	7·0	7·0	6·5	7·0	3·0	10·0	5·0	14·0	0·219	0·532

NA, no measures of association were calculated as at least one variable was continuous.
* Significant between dietary groups for nominal data assessed by χ^2 and continuous by Kruskal–Wallis ($P \leq 0{\cdot}05$).
No analysis was conducted by χ^2 as the minimum expected count was under 5.
Normality was assessed by Shapiro–Wilk ($P = 0{\cdot}001$).

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provide an average iodine concentration up to around 85·4 μg, although this is subject to seasonal variation[81]. In the current study, cows' milk and dairy products were positively associated with UIC in 2016–2017, suggesting their importance as sources of dietary iodine. Contrary to recent findings[82,83], consumption of cows' milk exhibited no relationship with UIC in 2019. This finding may be explained by lower cows' milk intake in our cohort paralleling recent UK data which show that national dairy product consumption has reduced, particularly among younger people[18]. The majority of our study cohort comprised young adult females, a group in whom milk reduction is particularly noticeable[18,84].

In the UK, there has been a sizable increase in the availability and popularity of non-dairy alternative milks (e.g. soya, oat and almond, etc.). Research by Mintel identified that adult household consumption of alternative milks increased from 14 % in 2017 to 23 % in 2019[18]. Displacement of iodine-containing cows' milk may increase the risk of deficiency. Label-based analysis conducted in 2015 revealed that alternative milks available in the UK had an average iodine content that is 1–5 % of that of cows' milk, unless fortified[21]. We found that milk alternative and milk alternative product consumption had no relationship with UIC in 2016–2017 or 2019. Our findings did not match those observed in UK woman of childbearing age who were consumers of soya milk and a recent analysis of the National Diet and Nutrition Survey (2014–2017) which indicated that iodine nutrition was significantly lower in those who regularly consumed milk alternatives[11,83]. This study also showed intake of alternative milks to be significantly greater in vegans than vegetarians and omnivores. In our study, milk alternative consumption was not limited to vegan participants and was consumed by all dietary groups. Iodine-fortified milks were not greatly consumed, in either cohort, perhaps due to cost or low availability in the UK or lack of iodine awareness at the time of study. In 2016–2017, the iodine contribution of alternative milks appeared to be significant in the diets of vegans and vegetarians despite having a low iodine content. The iodine intake of vegans and vegetarians in our study was so low that the proportion contributed by foods that are not considered good sources of iodine (alternative milks, alternative meats, fruit, vegetables, breads, grains, pulses and drinks) appeared significant even though the absolute quantity was small. Given that it is likely that vegan and vegetarian influence on the food sector will continue to grow, individuals relying on alternative milk products to meet iodine requirements must be advised to select fortified varieties or to consume iodine from other food sources or supplements.

Milk is often consumed daily, whereas fish and seafood are not consumed as frequently and may not always be included in dietary records. Apparent elevated consumption of fish among vegetarians in 2016–2017 was due to the inclusion of a number of pescatarians in this group. In both years, average consumption of fish (for consumers) was greater than average fish consumption among adults in the UK between 30–60 g/week[85]. However, we did not see the expected positive relationship between UIC and fish and seafood consumption, presumably due to the low number of consumers across all groups. Fish intake in the UK is low, and thus may not serve as a good source of iodine for the general population. Barriers to fish intake include: cost, availability, cooking knowledge and palatability[86].

The UK currently does not have a universal iodised salt programme[28]. Only one omnivore in 2016–2017 recorded consuming iodised salt in 3 d of records, contributing largely to iodine intake (61 %). Despite using iodised salt, the intake of this individual was below recommended intake of 150 μg/d (119·3 μg/d). Vegan and vegetarian dietary choices are often linked with engagement in healthier behaviours and have been found to have lower salt intake compared with other groups[87]. Iodised salt is not routinely available from supermarkets for public purchasing, and varieties that are offered tend to be expensive compared with regular table salt[28]. Participants were not specifically asked to record salt added to meals and consequently, as suggested by previous work[88], estimates of salt intake are likely to be low.

None of our participants indicated suffering from celiac disease; however, we cannot rule out the presence of undiagnosed disease. Iodine absorption in those with celiac disease is impaired compared with a healthy population and so those with disease coupled with restriction of iodine-rich foods may further exacerbate deficiency[89]. Specific diagnoses of celiac disease were beyond the scope of this study, but the likelihood of a significant impact of undiagnosed disease on our findings is low.

Supplements

In regions where no universal iodised salt coverage exists, iodine supplementation is particularly useful for prevention of deficiency[11,90]. Supplement use was widely adopted in vegan groups in our study, yet most consumed supplements were non-iodine containing. The most frequently used supplement for all groups was B_{12} (27 %), followed by non-iodine-containing multivitamin formulations (17 %). Since restrictive diets increase the risk of nutritional deficiencies (B_{12}, vitamin D, Zn, fatty acids, etc.)[54,91], individuals may consume micronutrient complexes over concerns for dietary adequacy. One participant, an omnivorous male in 2019, had dietary intake above the criteria for iodine excess (>300 μg/d) according to FD data[6], likely owing to consumption of a diet rich in cows' milk, dairy products, eggs and fish alongside daily use of iodine-containing micronutrient supplements. Improved awareness of iodine-containing supplements to populations not consuming iodine-rich foods is required.

Seaweed is a very rich and sustainable source of iodine. The iodine content of seaweed species can vary between 60 μg 100/g to 624 500 μg 100/g (dry weight)[92]. Currently, seaweed is not recommended to improve iodine due to potential adverse effects relating to over-consumption[7], with regular intake of seaweeds providing >45 μg/g of iodine shown to compromise thyroid function[93]. Despite this, research has shown low-level seaweed supplementation to improve status of iodine-insufficient individuals in the UK and Europe[37,51,55,56,59]. Seaweed has been suggested as a possible source of iodine for vegans[92] but has been shown to frequently contribute to excessive iodine intake[31]. In the present study, seaweed supplements did provide an additional 1541 μg/d to

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dietary intake of two omnivores. Values at this level would exceed the upper tolerable limits of iodine and could lead to the development of alternative thyroid disorders[94]. Seaweed products are becoming more widely accepted in the UK[95]. To prevent excess associated with seaweed consumption products should be routinely monitored and their iodine content disclosed. Additionally, the risks involved with supplementing seaweeds should be communicated.

Iodine status

Despite low sample sizes, the present study aligns with existing studies signifying that UK adults, particularly those following vegan and vegetarian diets, are at risk of iodine deficiency[39,51,54–56]. The iodine status of omnivores was significantly greater than vegans in both years and vegetarians in 2019. The UIC values for all dietary groups in our study were lower than those of the UK population. Nationally representative data collected in accordance with years of our study (2016–2017 to 2018–2019) recorded median UIC of 98 μg/l for women of childbearing age (19–49 years) and 106 μg/l for adults (19–64 years)[22]. However, omnivorous participants presented values signifying mild deficiency and both vegans and vegetarians had values within the criteria for moderate deficiency in 2016–2017, and severe in 2019. Worryingly, this result is indicative of a time-related decline in iodine status. Aligning with national trends, whereby, UIC averages fell between years 2014 and 2019 in both adults (3 %), and women of childbearing age (9 %)[22].

UIC is the internationally recognised criteria for measuring population iodine status[6]. Spot samples are criticised for their inability to precisely detect mild-to-moderate iodine deficiency (median UIC > 50 μg/l) due to diurnal variation in UIC[96,97], which are lowest between 08.00–11.00 hours and slowly increase after 12.00 hours, before peaking 4–5 h after feeding. Our study was strengthened by concurrent collection of spot samples. By noon most participants would have consumed a meal; hence, UIC values would be above baseline. UIC has been found to be significantly lower in non-breakfast consuming individuals[97]. Given that numerous studies have concluded that breakfast skipping is widespread among young adults at universities[98], this may have contributed to lower UIC in our study.

Iodine knowledge

Sufficient iodine knowledge has been shown to be positively correlated with iodine nutrition with iodine intake and status[14,15]. Our study was populated by university students and staff; therefore, most participants were of a high education level. We found no difference in total iodine scores between the dietary groups, suggesting that dietary practice was not a predictor of iodine knowledge in this cohort. Limited research exists investigating the difference in dietary knowledge between vegans, vegetarians and omnivores. Iodine knowledge scores were lower than that recorded for UK females (2·1 (SD 0·8) out of a possible 8)[14] and were lower in younger participants in 2016–2017. This may reflect the stage of education, such that first year undergraduate students may be less aware of the role of iodine in the diet, but this was not addressed in our study. Iodine awareness in general was low, with most participants being unable to identify a health condition related to iodine deficiency. Our findings also indicated that misconceptions exist in our population regarding which foods are iodine rich. Many selected leafy green vegetables and oily fish as good sources of iodine. Awareness of foods contribution to iodine varied by dietary group. A larger proportion of vegetarians in our study were able to correctly identify cows' milk as a useful iodine source, which did not translate to greater dietary intake. Understanding the role of cows' milk in iodine provision varies across studies. In the UK, 16 % of respondents showed good understanding and Australia 9 %, while this rose to 47 % in a Norwegian cohort[13,14,99]. Other foods rich in iodine (such as whitefish and yogurt) had variable responses between dietary groups. Iodine knowledge may not translate to behaviour change in more restrictive dietary groups, for example, it is unlikely that strict vegans will decide to consume animal products based on iodine content. Our results suggest that public health strategies are needed to improve public awareness of iodine and good sources of iodine for those not consuming cows' milk, dairy, whitefish or eggs need to be communicated, in addition to choosing foods that are fortified with iodine.

Energy intake

We found no significant association between energy and iodine intake; however, in both years of study, average daily energy intake was below the current UK recommendations for weight maintenance (female: 2000 kcal; male: 2500 kcal) despite most participants recording BMI within the healthy range[47]. In 2016–2017, vegetarians had BMI values that were significantly lower than omnivores. However, in our current study average energy intake (kcal) did not differ between dietary groups (2016–2017, $P = 0{\cdot}438$; 2019, $P = 0{\cdot}802$). Lowered energy intake may be attributed to high prevalence of under-reporting in our study. The incidence of under-reporting ranges between 18 and 54 % in dietary studies[100]. In our study, the rate of under-reporting was much greater (73 %). This finding could be attributed to common determinants of misreporting. Our sample was largely female, and women tend to report energy intake to be significantly lower than daily recommendations[100]. We did not record PAL as part of our study; therefore, EI:EE cut-offs are likely to be inaccurate. Misreporting of iodine-containing foods may have impacted our collected results. Healthy foods (fruit and vegetables) are often over-reported and females classed as under-reporters have been shown to consume significantly lower levels of foods rich in iodine, including cows' milk, dairy products, eggs and fats[101].

Study limitations

There are few validated FFQ specifically assessing iodine intake in Western or UK populations, of which none is tailored for vegans[102–104]. Despite our FFQ being based on that used in the EPIC study, which has been extensively validated[44], the FFQ used in our study was not validated following modifications and so inaccuracies may occur due to difficulties distinguishing between categories. The Nutritics software, used to analyse FD,

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uses food tables to estimate average intake and cannot account for variability in iodine content within food[81]. The iodine content of foods is not adjusted per season to constitute changes in content throughout the year[81]. Cows' milk iodine concentration is highest in winter and since our data were collected in different seasons, winter 2016–2017 and summer 2019, the data may be subject to seasonal variation[81]. Additionally, many manufacturers of vegan products cannot accurately provide measures of iodine[55].

Median UIC is the principle method for assessing population iodine status, as up to 90 % of absorbed iodine is excreted in the urine. Several factors may influence UIC measured by spot samples, including daily variation in the iodine content of recently consumed foods and circadian rhythms[97]. Moreover, UIC varies by recent fluid intake as UIC is expressed per volume of urine[105]. We were unable to account for fluid intake as creatinine was not measured and many participants did not record fluid intake within FD.

Finally, inclusion of pescatarians and individuals who had recently transitioned onto a vegan diet as part of the 'vegetarians' dietary group may not be reflective of the restrictions included in these groups. To retain sample size, even vegans and vegetarians with low dietary adherence (i.e. occasional consumption of cows' milk/dairy) were included into analysis. Lastly, most participants were students and so our cohort is therefore likely to be highly motivated and well-educated.

Conclusion

Vegans and vegetarians are a subgroup at increased risk of iodine deficiency. Regardless of dietary choice, the exclusion or substitution of iodine-rich animal products appears to act as a barrier to achieving iodine recommendations. Individuals following restricted diets should be encouraged to select iodine-containing supplements or fortified foods. At policy level, mandatory fortification of products mimicking cows' milk may be beneficial given the popularity of these foods and potential for them to be a useful vehicle to improve iodine intake. Formal education focusing on providing accurate and reliable information to vulnerable groups (vegans, vegetarians and young women) should be considered at national level. Further monitoring and assessment of the consequences of lowered iodine intake in individuals implementing strict dietary choices is required.

Supplementary material

For supplementary material accompanying this paper visit https://doi.org/10.1017/S0007114522000113

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APPENDIX D

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Systematic review and meta-analysis of iodine nutrition in modern vegan and vegetarian diets

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Abstract

Vegan and vegetarian diets are widely supported and adopted, but individuals following such diets remain at greater risk of iodine deficiency. This systematic review and meta-analysis was conducted to assess the iodine intake and status in adults following a vegan or vegetarian diet in the modern day. A systematic review and quality assessment were conducted from October 2020 to December 2022 according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidance. Studies were identified in Ovid MEDLINE, Web of Science, PubMed, and Scopus. Eleven articles were eligible for review containing 4421 adults (aged ≥ 18 years). Vegan groups had the lowest median urinary iodine concentration (mUIC) (12·2/l). None of the dietary groups had mUIC within the optimal range for iodine status (100–200 µg/l) (WHO). Vegan diets had the poorest iodine intake (17·3 µg/d) and were strongly associated with lower iodine intake ($P = < 0{\cdot}001$) compared with omnivorous diets. Lower intake in vegan diets was influenced by sex ($P = 0{\cdot}007$), the presence of voluntary or absence of Universal Salt Iodisation (USI) programmes ($P = 0{\cdot}01$ & $P = < 0{\cdot}001$), and living in a country with adequate iodine nutrition ($P = < 0{\cdot}001$). Vegetarians and particularly vegans living in countries with no current USI programme continue to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake. Further research into the usefulness of mandatory fortification of vegan appropriate foods is required.

Key words: **Iodine: Iodine intake: Micronutrients: Vegan: Vegetarian**

Environmentally sustainable diets, that are rich in plant foods, are advocated as a solution to feeding the growing human population and reducing the impact of our food systems on the planet[1]. Today, vegetarian and vegan diets are widely supported and adopted throughout the population, particularly among young people and women[2–4]. Vegans do not consume any animal products, whereas vegetarians exclude only meat and fish[5]. The inclusion of fish in a vegetarian diet is often called a pescatarian diet[5]. There are also growing numbers of people in Western countries reducing their animal product consumption who define as flexitarian[5,6].

The rising interest in plant-based eating has increased demand for a diversity of commercially available alternative products (e.g. plant-based milk) suitable for vegetarians, vegans or those wishing to reduce their intake of animal products[7]. Fast-food chains have similarly designed animal-free products targeting consumers[7,8], and restaurants have expanded menu options to suit all dietary requirements[7,8]. Individuals now have a more diverse pool of foods suitable for their dietary preferences than before, permitting huge variations in food and nutrient intake. However, although the breadth of choice is beneficial for diet diversity, there continue to be difficulties in achieving adequate quantities of some micronutrients, most notably iodine[9].

Iodine is essential for the synthesis of the thyroid hormones (triiodothyronine (T3) and thyroxine (T4)) and is dependent on adequate supply via the diet[10]. The WHO recommends a daily intake of 150 µg/d for adults (18+ years) and 250 µg/d for pregnant and lactating women to maintain thyroid hormones synthesis and prevent the development of associated 'iodine deficiency disorders' (IDD)[10,11]. However, iodine recommendations are often country-specific, in the UK a Reference Nutrient Intake (RNI) of 140 µg/d is advised for adults (19–50 years)[12]. The UK currently has no RNI set for pregnant/lactating women[12]. The thyroid hormones have a vital role in the regulation of metabolism, growth and fetal neurological development[13–15]. IDD include hypothyroidism, goitre, the formation of thyroid nodules and cretinism (as a consequence of gestational exposure)[10,14,16]. Iodine excess (consumption of > 1000 µg/d iodine) can also have health repercussions, including hypo- and hyperthyroidism[17,18].

Abbreviations: UIC, urinary iodine concentration.

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Iodine deficiency remains a public health issue worldwide[19], although the number of countries with adequate iodine intake has nearly doubled over the past 20 years[20]. Improvements in global iodine intake and status have largely been due to the effective implementation of universal salt iodisation (USI)[19,20]. However, not all countries currently facilitate USI programmes, and other factors (e.g. low household coverage, low usage, low or no accessibility, and inadequate quality) may limit its effectiveness[19]. Currently in industrialised countries, the predominant dietary iodine sources are iodised salt, cows′ milk, dairy products, fish and seafood, eggs and fortified foods (e.g. bread)[21]. Plant foods are generally low in iodine, unless bio-fortified, with seaweed being an exception[22,23]. The iodine content of seaweed is highly variable and can be linked to iodine excess in certain populations[24–27].

Individuals who restrict iodine-rich foods from their diet or are solely dependent on iodine provision from plant foods are at risk of iodine deficiency[28]. The increased risk of iodine deficiency in vegans and vegetarians was highlighted by the Scientific Advisory Committee on Nutrition (SACN) in 2014[29]. Since its publication, several studies have assessed iodine nutrition to be poorer in these groups[4,30–34]. Innovation in the vegan and vegetarian food sector has resulted in a rapid proliferation of products. Many items, such as meat alternatives, are not often fortified with iodine[35,36]. Alternative dairy products such as alternative 'milks' and 'yogurts' are now regularly fortified with vitamin B_{12}, D and Ca[36–40], but rarely with iodine[36,37,39]. Additionally, iodine supplements are still not universally consumed by individuals following vegan and vegetarian diets[34].

We previously reviewed the literature on iodine intake and the status of vegans and vegetarians living in industrialised countries in 2020[28]. Our study concluded that those individuals' not consuming seaweed or iodine-containing supplements were at risk of poor iodine nutrition. However, half of the studies included in our review were published before meat-free diets entered the mainstream in many countries (2010) and, therefore, may not represent the diversity of 'modern-day' vegan and vegetarian diets observed in today's society[28]. In the past, traditional vegan diets were reliant on the consumption of wholegrains, pulses, fruit and vegetables[9]. Whereas, modern-day vegan dietary patterns conflict with traditional vegan dietary patterns due to the improved availability of foods that are often designed for convenience and are ultra-processed (e.g. snacks foods, alternative milks and meats, etc.)[9]. Greater food availability and choice have permitted a larger number of dietary patterns to be followed within the standard definitions of vegan and vegetarian[9].

Following the publication of our review, many new studies have examined iodine in the diet of vegans and vegetarians. Iodine deficiency is still a major public health issue and given that sustainable diets are being promoted in many countries worldwide, a re-evaluation of the literature is needed to monitor iodine nutrition and deficiency in those who select to follow a vegan or vegetarian diet in the modern day.

This review aims to assess the iodine intake and status in adults following a vegan or vegetarian diet in the modern day. The objectives included (1) determination of the iodine intake and food consumption in vegan and vegetarian adults; (2) assessment of the iodine status and prevalence of iodine deficiency using urinary iodine concentration (UIC); (3) comparison of the iodine intake, status, and prevalence of deficiency between modern-day vegans, vegetarians, and omnivores; and (4) completion of a meta-analysis to provide a more precise estimate of the effect size results of individual studies. We hypothesise that vegans and vegetarians will continue to be a subgroup at risk of iodine deficiency; however, given the increase in the availability of iodine fortified foods suitable for individuals following these diets, iodine deficiency may be less severe.

Methods

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analyses of Observational Studies (MOOSE) checklist were used to complete this systematic review[41,42]. A systematic search of the literature was performed from 5 October 2020 to 16 December 2022. Electronic databases (Ovid MEDLINE, Web of Science, PubMed and Scopus) were explored. Searches were completed with appropriate text terms with truncation and medical subject headings. Our search strategy is the same as that described in our previous systematic review[28] (online Supplementary Table 1). All database searches were refined by 'humans, adults (aged > 18 years), English language, full-papers, and publications between January 2020–December 2022'. Search lists were exported into EndNote™ before the removal of duplicates. Additional studies were identified via reference lists of relevant published materials and citation searching. A review protocol has not been published prior to our literature search.

Population and outcomes

The population–intervention–comparison–outcome (PICOS) formulation was used to assess study eligibility (Table 1)[43].

Data extraction

Extraction forms identified study information including author name, journal, publication date, study location, participant characteristics, dietary groups addressed and grouping method, relevant outcome measures (length of diet, iodine intake, status and supplement use), and any key findings or study considerations (limitations, etc.). Where possible, gendered data were considered separately. Data extraction was completed by the first author.

Classification of outcomes

The nomenclature defining dietary preferences can vary; therefore, dietary groups were compared according to the following classifications (Table 2). We also recorded the method of dietary grouping used and the length of dietary adherence for each study. For articles where individuals are following vegan/vegetarian/etc. diets as part of an intervention, post-intervention data were used.

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Table 1. Population–intervention–comparison–outcome (PICOS) criteria for study inclusion and exclusion[43]

Criteria category	Inclusion	Exclusion
Population	Adults (aged ≥ 18 years)	Individuals (aged < 18 years), unless results display separate data; adults residing in developing countries; populations with a high prevalence of thyroid disorders
Intervention/exposure	Participants with any type of dietary preference or restriction. Voluntary or otherwise	Use of a dietary grouping without defining diet characteristics
Comparators	Differing dietary preference or restriction	None
Outcome measure	Iodine intake or status measured by urinary iodine concentration (UIC) or analysis of dietary records	No analysis of iodine intake or status; use of thyroid measures alone for iodine intake and status
Study design	Any study design with relevant outcomes	None

Table 2. Definition of common vegetarian and vegan diet types

Type	Definition
Omnivore*	Includes meat, poultry, fish, eggs and dairy products
Flexitarian†	Occasionally excludes meat and poultry but remains consumption of fish, eggs and dairy products
Pescatarian†	Excludes meat and poultry but remains consumption of fish, eggs and dairy products
Lacto-ovo vegetarian†	Excludes meat, poultry and fish but remains consumption of dairy products and eggs
Lacto vegetarian†	Excludes meat, poultry, fish and eggs but remains consumption of dairy products
Ovo vegetarian†	Excludes meat, poultry, fish and dairy products but remains consumption of eggs
Vegan†	Excludes all animal products (meat, poultry, fish, eggs and dairy products)
Strict raw‡	Excludes all animal products (meat, poultry, fish, eggs and dairy products) and heated food items.

* Diet definition includes descriptions of omnivore (basic) and omnivore (regular) from Kowalska *et al.* 2020[57]. Omnivore (basic) includes all food groups including meat, poultry, fish, dairy products and eggs; omnivore (regular) describes data collected from 24-h dietary recalls from ten Polish adults that were used to make standard 'menus' for omnivorous participants.
† Diet definitions from Phillips 2005[5].
‡ Diet definition from Abraham *et al.* 2022[53].

The WHO criteria were used to assess iodine status using UIC[11,44]. Therefore, a median UIC > 100 μg/l was considered 'sufficient' and a median UIC < 100 μg/l was considered 'deficient', with severity of IDD based on UIC being: 50–99 μg/l mild, 20–49 μg/l moderate and > 20 μg/l severe[11,44]. Recommended adequate iodine intake varies across countries, so the WHO RDA for adults and adolescents of 150 μg/d was used to assess iodine intake between studies[11,44].

Quality assessment

The quality of observational cohort, cross-sectional and case–control (matched pairs) studies was assessed using the Newcastle–Ottawa scale (good, fair or poor)[45]. The quality of modelling studies was not assessed (*n* 1). Quality assessment was completed by the first author and was reviewed by the study team (online Supplementary Table 2).

Statistical analysis. We performed meta-analysis and subgroup analysis to compare iodine intake and status in vegan and vegetarian diets compared with omnivores using the software RevMan (version 5) designed by Cochrane[46]. We assumed that the studies are heterogenous; therefore, we selected a random effects mode. For studies reporting data as medians (IQR), we estimated the sample mean and standard deviation using calculations as described by Wan *et al*[47].We separated comparisons of vegan and vegetarian diets into different forest plots to avoid arbitrary omission of relevant groups and double counting of participants. If the test for overall effect were $P = < 0{\cdot}05$, the following covariables for subgroup analysis for both meta-analyses were used: sex (female *v.* mixed sex), USI status and iodine status by country. Countries were categorised into iodine-deficient or -sufficient according to the Iodine Global Network (IGN) Scorecard[20].

Results

The initial literature search yielded 1208 articles. Following screening and exclusion, twenty-eight reports were assessed for eligibility. The PRISMA 2020 flow diagram outlines the study selection process for this review (Fig. 1)[48]. A total of eleven articles were identified as eligible for review inclusion (Table 3).

Urinary iodine status

Iodine status by UIC was investigated in five studies with a total of 700 participants (vegan; 271, vegetarian; 135, pescatarian; 35, omnivore; 189, flexitarian; 70)[34,49–52] (Fig. 2). Three studies assessed UIC using single-spot urine samples[34,50,52]; the remaining two studies used 24-h urinary samples[49,51]. We were unable to separate UIC estimates by sex, as all included studies provided either mixed-sex estimates or estimates in females alone.

Vegan participants had the lowest median UIC in all five studies (12·2–44·0 μg/l)[34,49–52], with the lowest value recorded by Eveleigh *et al.* in UK vegans (12·2 μg/l)[34]. In all studies, vegans had significantly lower median UIC compared with omnivores

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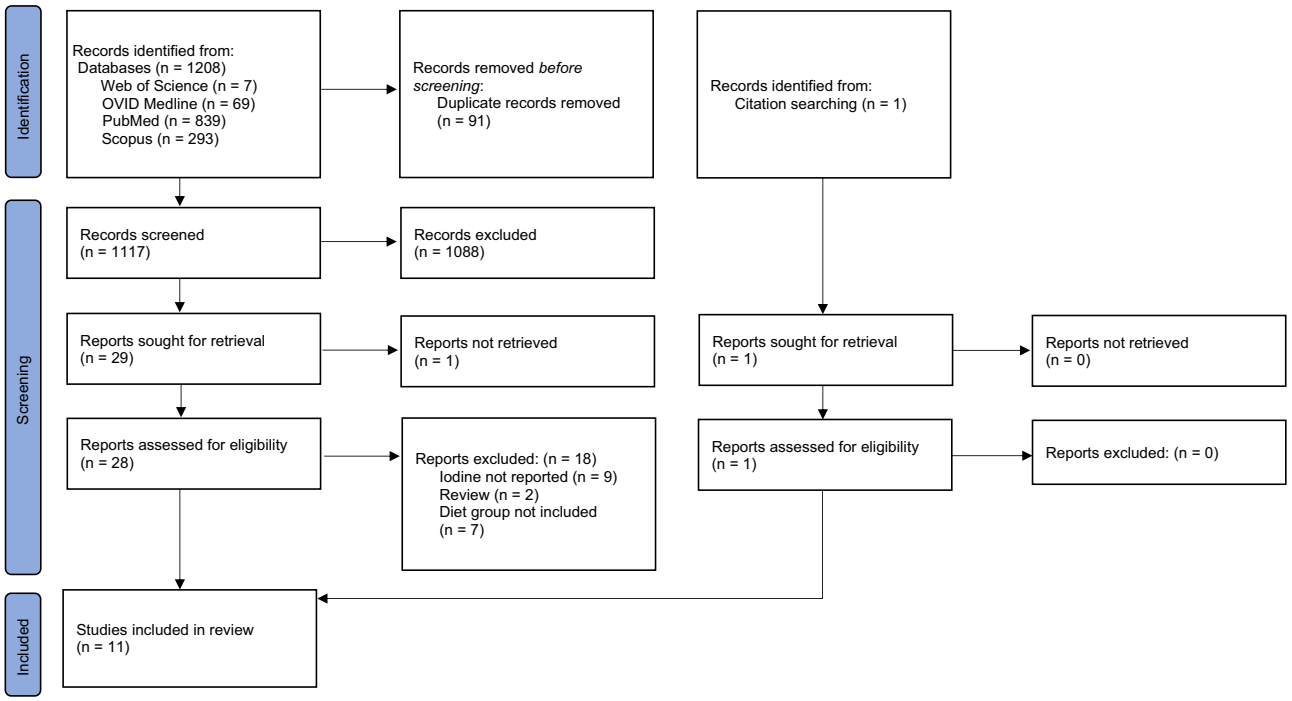


Fig. 1. PRISMA 2020 flow diagram of the study selection process[48]. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

($P < 0{\cdot}05$)[34,49–52]. Vegetarians in the included studies tended to have median UIC values greater than vegans but lower than omnivores, flexitarians and pescatarians[49,50]. Only one study reported the median UIC of vegetarians to be significantly lower than omnivores ($P < 0{\cdot}05$)[34]. Pescatarians in Norway experienced the greatest median UIC of 96·0 μg/l[50]. The median UIC of flexitarians was reported in one study (52·0 μg/l) and was slightly lower than the omnivores in the same study (53·0 μg/l)[49]. The included studies showed considerable variation in UIC recorded within dietary groups, for example, the upper range for median UIC for vegans in Dawcynski *et al.* study was 509 μg/l[49].

None of the dietary groups included in this review had median UIC values within the optimal range for iodine status (100–200 μg/l) according to WHO criteria and would be classified as iodine-deficient (mild–severe; 50–99 μg/l–> 20 μg/l)[34,49–52]. Severe iodine deficiency (> 20 μg/l) was observed in one study of vegans living in the UK[34]. Moderate deficiency (20–49 μg/l) was observed in all vegan diets and 75 % (3/4) of vegetarian diets[34,49–52]. Omnivores, flexitarians and pescatarians had median UIC values within the range of mild iodine deficiency (50–99 μg/l)[34,49–52]. None of the dietary groups in our current review had median UIC values relating to excessive iodine intake (> 300 μg/l)[34,49–52].

None of the studies investigating iodine status used creatinine correction[34,49–52].

Dietary iodine intake

Dietary iodine intakes were recorded in nine studies and included 678 participants (strict raw; 16, vegan; 280, vegetarian; 117, pescatarian; 35, omnivore; 230; Table 4; Fig. 3)[33,34,50,52–57].

All studies evaluated iodine intake between vegans and one or more dietary groups[33,34,50,52–57]. Most studies reported mixed-sex estimates of dietary iodine. Only two studies separated dietary iodine intake by sex[53,55], and three studies only recruited females to study[33,52,54]. Sixty-seven per cent of studies (6/9) were conducted in countries considered 'adequate' according to national data from the Global Scorecard of Iodine Nutrition (2021)[20,33,34,52,55–57].

Food diaries > 3 d (44 %, 4/9) and FFQ (44 %, 4/9) were the most commonly used dietary method to measure iodine intake[33,34,53,54,56]. Other dietary methods included 24-h food recalls (33 %, 3/9)[50,52,55]. Three studies addressed iodine intake using two dietary methods to assess both short-term and longer-term dietary intake[34,50,52].

Vegan participants living in the UK in 2019 had the lowest average iodine intake of 17·3 μg/d (17·2–21·4 μg/d; mixed-sex estimates)[34]. The greatest iodine intake was recorded in vegetarians in Oslo, Norway, at 843·0 μg/d (705·0–1590·0 μg/d; mixed-sex estimates)[50]. Omnivores had the greatest dietary iodine intake in 70 % (7/10) of included cohorts[33,34,52,53,55,57], whereas vegans had the lowest iodine intake in 73 % of cohorts (8/11)[33,34,52,55,57]. There was substantial variation in iodine intake within dietary groups with the greatest variation being observed by Groufh-Jacobsen *et al* in FFQ estimates of pescatarians (705·0–1590·0 μg/d)[50].

Seven studies recorded a significant difference in iodine intake between one or more dietary group ($P = < 0{\cdot}05$)[33,34,50,52,53,55,56]. Four studies found the iodine intake of vegans to be significantly lower than omnivores ($P = < 0{\cdot}001$)[33,34,52,55]. Vegans and vegetarians had significantly lower habitual iodine intake compared with pescatarians in one study[50]. Raw food eaters were recorded to have significantly

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Table 3. Studies investigating iodine among vegans, vegetarians and omnivores published after January 2020

Study, year	Study design	Location	Dietary groups	Sample		Method of dietary classification	Grouping adherence length	
				N	Female, male			
Abraham *et al.* 2022[53]	Cross-sectional	Berlin, Germany	Strict raw	16	5, 11	Classified according to RBVD study criteria. (not self-selected)	Diet for at least four months or at least one year	Raw food diet
			Vegan	32	18, 14			
			Omnivore	27	14, 13			
Blaurock *et al.* 2021[54]	Cross-sectional	Munich, Germany	Vegetarian	31	31, 0	Self-assessed	NA	
			Omnivore	30	30, 0			
Dawczynski *et al.* 2022[49]	Cross-sectional	Jena, Halle, and Leipzig, Germany	Vegan	58	41, 17	Self-assessed. Food intake data were also checked by researchers for discrepancies in diet selection	3·0	3·0*
			Vegetarian (lacto-ovo)	65	47, 18		6·0	10.*
			Flexitarian	70	56, 14		8·0	17·8*
			Omnivore	65	40, 25		32·0	20·0*
Eveleigh *et al.* 2022[34]	Cross-sectional	Nottingham, UK	Vegan (2016–17)	12	12, 0	Self-assessed. Food intake data were also checked by researchers for discrepancies in diet selection	> 6 months	
			Vegan (2019)	7	4,3			
			Vegetarian (including pescatarians) (2016–17)	5	5, 0			
			Vegetarian (including pescatarians) (2019)	10	9, 1			
			Omnivore (2016–17)	43	36, 7			
			Omnivore (2019)	19	14, 5			
Fallon and Dillon, 2020[33]	Cross-sectional	Lancashire, UK	Vegan	20	20, 0	The diaries were cross-checked to ensure they had correctly identified themselves	NA	
			Vegetarian	16	16, 0			
			Omnivore	26	26, 0			
García-Morant *et al.* 2020[55]	Cross-sectional	Spain	Vegan	102	67, 35	NA	NA	
			Omnivore	3323	1732, 1587			
Groufh-Jacobsen *et al.* 2020[50]	Cross-sectional	Oslo, Norway	Vegan	115	74, 41	Classified by researchers according to questions addressing animal product consumption	≥ 6 months	
			Vegetarian	55	43, 12			
			Pescatarian	35	31, 4			
Jakše *et al.* 2021[56]	Cross-sectional	Slovenia	Vegan	51	34, 17	Self-assessed. Food intake data were also checked by researchers for discrepancies in diet	Participants should have had the same (current) dietary pattern for ≥ 1 year	
			Omnivore (non-vegan)	29	16, 13			
Kowalska *et al.* 2020[57]	Data modelling	Poland	Vegan	Participants were only used for creation of the Omnivore (regular) diet. The other diets were generated by quantitative analysis of a total of 70 menus (10 for each diet type) prepared by dieticians		NA	NA	
			Vegetarian (lacto-ovo)					
			Pescatarian					
			Omnivore (fish free)					
			Omnivore (milk free)					
			Omnivore (basic)					
			Omnivore (regular)	30	12, 18			
Menzel *et al.* 2021[51]	Matched pairs (age and sex)	Germany	Vegan	36	18,18	Self-assessed	4·8	3·1–8·7*
			Omnivore	36	18,18			
Whitbread *et al.* 2021[52]	Cross-sectional	South Australia	Vegan	31	31, 0	Self-assessed	NA	
			Omnivore	26	26, 0			

NA, not assessed.
* Median and IQR.

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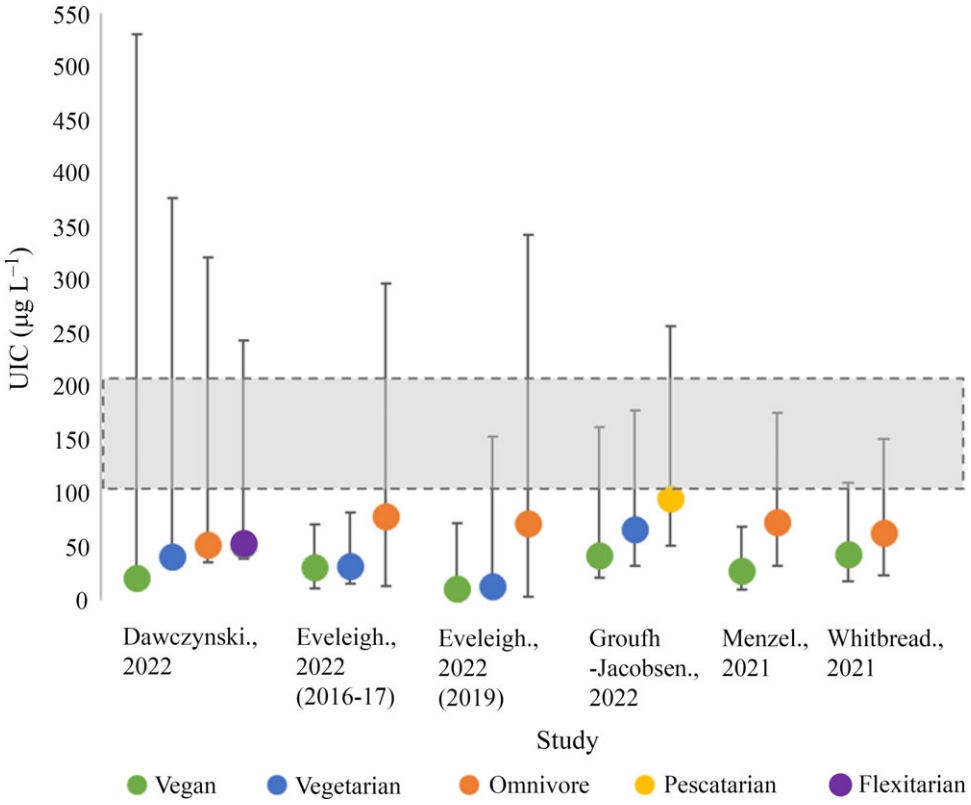


Fig. 2. Iodine status measurements of included studies by median urinary iodine concentration (UIC). Shaded grey areas illustrate the WHO criteria for optimal iodine status (100–200 µg/l)[11].

lower iodine intake than vegans and omnivores[53]. The study conducted by Kowalska *et al.* (2020) did not statistically evaluate the difference in iodine intake between groups. There were differences in significance between groups according to methods of assessing iodine intake. In the study by Groufh-Jacobsen *et al.* (2020), a significant difference in iodine intake between vegans, vegetarians and pescatarians was only observed in FFQ estimates and not 24-h recalls. However, Eveleigh *et al.* did not observe a significant difference in iodine intake by FFQ in their 2019 cohort but did see differences when measured using food diaries[34].

The WHO recommended iodine intake of 150 µg/d was used for the assessment of adequate dietary intake[11]. None of the included studies recorded estimates above the adequate range for all dietary groups. Iodine inadequacy was reported in all dietary groups in 75 % (9/12) of the cohorts assessed[33,34,50,52–57]. Only two studies reported at least one dietary group to have adequate average iodine intake[34,50].

Five studies addressed the types of foods consumed by different dietary groups[34,52–54,56], of which three estimated the possible contribution of specific food groups to total iodine intake[34,50,52]. Overall, the vegan and vegetarian groups consumed greater quantities of plant-based food groups (fruit, vegetables, legumes, tubers, cereals and grains)[34,52–54,56]. Two studies recorded alternative milk intake to be significantly greater in vegan and vegetarian groups[34,52]. Within these two studies, dairy products and eggs were the greatest source of iodine for individuals not restricting these foods. Kowalska *et al.* (2020) created model diets for each dietary group and used foods that were typically consumed according to dieticians' advice and current research[57]. Foods present in the models of vegan diets included cereal, fruit, vegetables, nuts, mushrooms, legumes, oils and alternative milk.

Mandatory or voluntary USI was present in seven of the included studies, and investigations conducted in the UK had no USI programme[33,34]. Only two studies addressed the relative consumption of iodised salt to total iodine intake[34,52]. Iodised salt was only consumed by vegan (*n* 4; 4/31)[52] and omnivorous participants (*n* 5; 1/34 & 4/26)[34,52]. Whitbread *et al.* (2021) was the only study to monitor the intake of bread fortified with iodine, an average quantity of 28 g/d and 36 g/d for vegans and omnivores consumed[52]. Consumption of iodised bread was similar between dietary groups and was acknowledged as a good source of iodine. The consumption of iodine-containing supplements to total iodine intake was recorded in five studies[34,50,54–56]. Two of the studies that reported supplement use did not provide data on the actual contribution of iodine-containing supplements to total intake[53,54]. One study prevented supplement intake during the study[52]. Four studies addressed the consumption of seaweed and microalgae in different dietary groups[34,50,52,54]; however, in two of these studies, the relative contribution of seaweed to iodine was not discussed[52,53]. Vegans (*n* 29) were most likely to consume seaweed as part of their diet. Seaweed intake was also reported in strict raw food eaters (*n* 1), vegetarians (*n* 8), pescatarians (*n* 4) and omnivores (*n* 2)[34,50,52,53].

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Table 4. Assessment of dietary iodine intake for vegans, vegetarians and omnivores in included studies

Study, year	Assessment of dietary iodine	Criteria for iodine intake	Dietary group		Dietary iodine intake (μg/d)		Contribution of iodised salt, seaweed, and iodine-containing supplements	Meeting criteria (Y/N)‡	National salt fortification status	National iodine intake from the Global Scorecard of Iodine Nutrition (2021)
			N	Female, male	Median/Mean	Q1 –Q3/SD				
Abraham *et al.* 2022[53]	3-d weighed food diaries	D-A-CH reference values: F:150 μg/d, M:180 μg/d	Strict raw 16	5, 11	F: 49·6 M: 78·9	37·4–64·6* 51·7–106·0*	Twelve participants (75 %) recorded intake of dietary supplements (B_{12} and vitamin D). The consumption of iodine-containing supplements and iodised salt was not stated. Only individuals in the strict raw diet group consumed seaweed, but the contribution to iodine was not discussed.	N	Voluntary	Insufficient
			Vegan 32	18, 14	F: 74·8 M: 88·0	48·9–124·6* 41·6–104·5*		N		
			Omnivore 27	14, 13	F: 100·5 M: 165·9	76·5–142·6* 106·2–181·5*		N		
Blaurock *et al.* 2021[54]	Self-administered, online 157-item FFQ as part of the eNutri2019-DE web application analysed by Bundeslebensmittelschlüssel, BLS database	Dietary reference values (DRV) Germany 200 μg/d (18–51 years)	Vegetarian 31	31, 0	F: 116·7	92–164*	Seventy-four percent of vegetarians and 63 % of omnivores reported consuming dietary supplements. The consumption of iodine-containing supplements, iodised salt and seaweed was not stated.	N	Voluntary	Insufficient
			Omnivore 30	30, 0	F: 108·6	75–144*		N		
Eveleigh *et al.* 2022[34]	Online iodine-specific 45-item FFQ and 3-d food diaries analysed by a dietary software program, Nutritics	Reference Nutrient Intake (RNI) for UK 140 μg/d		Vegan (2016–17) FFQ: 12 FD: 10	FFQ: 107·0 Food diaries: 47·6	88·0–131·5* 29·6–61·8*	Multivitamins containing iodine were consumed by 12 % of participants providing an average of 140 μg/d to dietary iodine. Multivitamin supplements provided significantly greater iodine to the diets of vegans compared with omnivores and vegetarians ($P = < 0·001$ and $P = 0·033$, respectively). Seaweed supplements kelp and/or kombu were consumed by two omnivores in 2019, providing an average iodine intake estimate of 1541 μg/d. Seaweed supplied a significantly greater iodine contribution to the diets of vegans compared with omnivores ($P = 0·040$). One omnivore in 2016–17 recorded consuming iodised	FFQ: N Food diaries: N	None	Adequate
				Vegetarian (2016–17) FFQ: 5 FD: 4	FFQ: 202·9 Food diaries: 68·8	176·5–291·7* 55·8–90·4*		FFQ: Y Food diaries: N		
				Omnivore (2016–17) FFQ: 34 FD: 27	FFQ: 299·6 Food diaries: 111·9	147·2–291·7* 85·4–145·6*		FFQ: Y Food diaries: N		
				Vegan (2019) FFQ: 7 FD: 4	FFQ: 124·9 Food diaries: 17·3	99·3–277·0* 17·2–21·4*		FFQ: N Food diaries: N		
				Vegetarian (2019) FFQ: 9 FD: 6	FFQ: 230·0 Food diaries: 71·4	122·0–363·4* 55·7–82·8*		FFQ: Y Food diaries: N		
				Omnivore (2019) FFQ: 19 FD: 11	FFQ: 221·9 Food diaries: 126·0	157·9–393·7* 108·5–233·8*		FFQ: Y Food diaries: N		

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Table 4. (*Continued*)

Study, year	Assessment of dietary iodine	Criteria for iodine intake	Dietary group *N*	Female, male	Dietary iodine intake (μg/d) Median/Mean	Q1 –Q3/SD	Contribution of iodised salt, seaweed, and iodine-containing supplements	Meeting criteria (Y/N)‡	National salt fortification status	National iodine intake from the Global Scorecard of Iodine Nutrition (2021)
							salt contributing 61 % of dietary iodine.			
Fallon and Dillon, 2020[33]	4-d food diaries analysed by a dietary software program, Nutritics	RNI for UK 140 μg/d and DRV 150 μg/d.	Vegan 20	(20, 0)	F: 24·4	12·7†	Seaweed, salt or supplements not measured.	N	None	Adequate
			Vegetarian 16	(16, 0)	F: 90·8	55·9†		N		
			Omnivore 26	(26, 0)	F: 112·6	62·1†		N		
García-Morant *et al.* 2020[55]	Online 24-h food recalls analysed by a dietary software program, DIAL and data from the Spanish Agency for Food Safety and Nutrition National Dietary Intake Survey	None provided	Vegan 102	(67, 35)	F: 79·0 M: 64·0	76·0† 42·0†	Dietary supplements were recorded and combined with dietary intake data. Seaweed and iodised salt not measured.	N	Voluntary	Adequate
			Omnivore 3321	(1589, 1732)	F: 100·0 M: 85·0	50·0† 47·0†		N		
Groufh-Jacobsen *et al.* 2020[50]	24-h food recalls and thirty-two-item FFQ updated from the Norwegian Food Composition Table 2019	Estimated Average Requirement (EAR) of 100 μg/d	Vegan 115	(74, 41)	24-h recall: 92·0 FFQ: 315·0	19·0, 171·0* 19·0, 361·0*	The median contribution of supplements to iodine intake of 24-h recalls were 150 μg/d for vegans (*n* 57), vegetarians (*n* 25) and pescatarians (*n* 18). For FFQ, estimates supplements also contributed a median average of 150 μg/d to dietary iodine intake of vegans (*n* 69), vegetarians (*n* 26) and pescatarians (*n* 10). Seaweed (microalgae) provided 865 μg/d (364, 1978) to vegans (*n* 23), 843 μg/d (705, 1590) to vegetarians (*n* 8) and 375 μg/d (110, 610) to pescatarians (*n* 4). Iodised salt not measured.	24-h recall: N FFQ: Y	Voluntary	Insufficient
			Vegetarian 55	(43, 12)	24-h recall: 70·0 FFQ: 843·0	17·0, 165·0* 705·0, 1590·0*		24-h recall: N FFQ: Y		
			Pescatarian 35	(31, 4)	24 h: 123·0 FFQ: 39·0	16·0, 176·0* 16·0, 324·0*		24-h recall: Y FFQ: Y		
Jakše *et al.* 2021[56]	52-item FFQ analysed by a dietary software program, Open Platform for Clinical Nutrition (OPEN)	D-A-CH reference values, F:150 μg/d, M:180 μg/d	Vegan 51 Omnivore (non-vegan) 29	34, 17 16, 13	112·0 96·0	60·0† 58·0†	Dietary supplements were recorded and combined with dietary intake data. Dietary supplements provided > 25 % of total iodine intake for vegans and omnivores (non-vegans) Seaweed and iodised salt not measured.	N N	Mandatory	Adequate

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Table 4. (*Continued*)

Study, year	Assessment of dietary iodine	Criteria for iodine intake	Dietary group *N*	Female, male	Dietary iodine intake (μg/d) Median/Mean	Q1 –Q3/SD	Contribution of iodised salt, seaweed, and iodine-containing supplements	Meeting criteria (Y/N)‡	National salt fortification status	National iodine intake from the Global Scorecard of Iodine Nutrition (2021)
Kowalska *et al.* 2020[57]	Modelled diets were created by trained dieticians	EAR for Poland 95 ug/d		Vegan	29·4	10·3†	Seaweed, salt, or supplements not measured.	N	Mandatory	Adequate
				Vegetarian (lacto-ovo)	37·6	9·2†		N		
				Pescatarian	39·2	11·1†		N		
				Omnivore (fish-free)	46·9	20·3[2]		N		
				Omnivore (milk-free)	62·8	46·4[2]		N		
				Omnivore (basic)	57·9	19·1†		N		
				Omnivore (regular)	87·2	45·0†		N		
Whitbread *et al.* 2021[52]	24-h diet food recalls by a smartphone app and food diaries analysed by a dietary software program, FoodWorks Dietary Analysis package	Recommended daily intake (RDI) 150 ug/d, EAR 100 ug/d and Nutrient Reference Values (NRV) for Australia and New Zealand (NHMRC)	Vegan 31	31, 0	78·0	62·0–91·0*	Participants who frequently consumed iodine-containing supplements were excluded. Six vegans reported ingesting seaweed (2·7 g/d), but iodine intake from seaweed was recorded as 0·0 ug/d. Iodised bread was the main iodised food source in vegans. Iodised salt was consumed by four vegan and four omnivore participants.	N	Mandatory	Adequate
			Omnivore 26	26, 0	125·0	86·0–175·0*		N		

* Median (Q1–Q3).
† Mean ± SD.
‡ According to WHO criteria of 150 ug/d.

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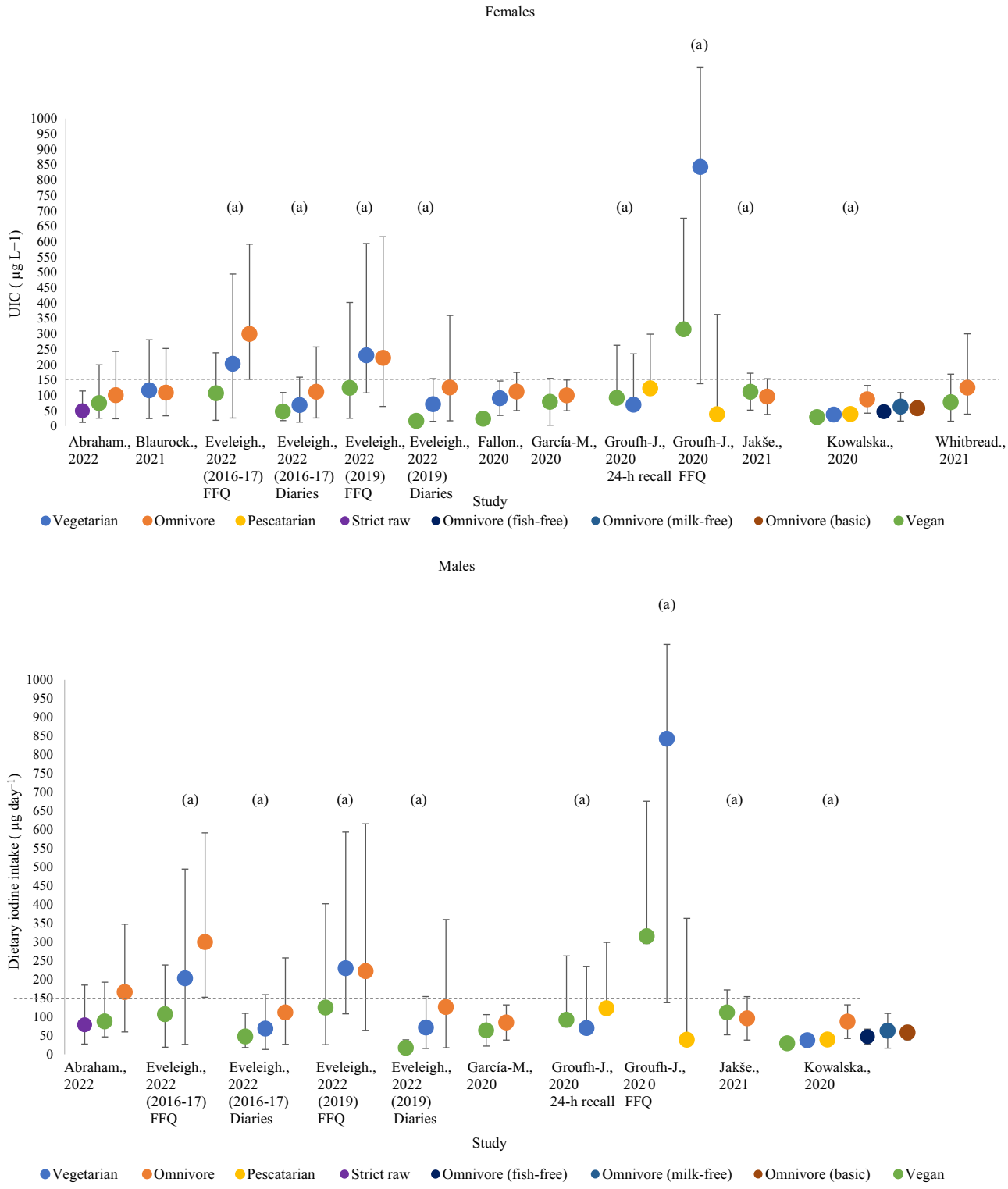


Fig. 3. Visual representation of estimated average iodine intake (µg/d) for females and males in included studies. The grey dashed line represents the adequate intake recommended by the WHO of 150 µg/d[11]. (a) mixed-sex values. Significance values are not presented within this figure. See Table 4.

Meta-analysis of iodine status and intake in vegans and vegetarians compared with omnivores. There was a strong trend for vegan or vegetarian diets to be associated with reduced iodine status as measured by UIC, but this did not quite reach significance (Fig. 4 and 5; $P = 0{\cdot}06$ & $P = 0{\cdot}18$), so no subgroup analysis was completed. There was, however, an overall significant negative effect of vegan diets on iodine intake ($P = < 0{\cdot}001$; Fig. 6), with no effect observed for vegetarian diets ($P = 0{\cdot}12$;

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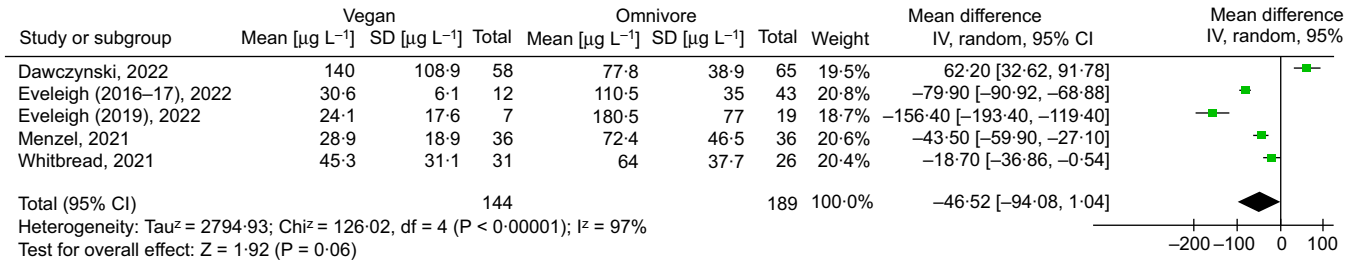


Fig. 4. Meta-analysis forest plot comparing the effect of a vegan *v.* omnivorous diet on iodine status. Data presented is female and mixed-sex estimates only.

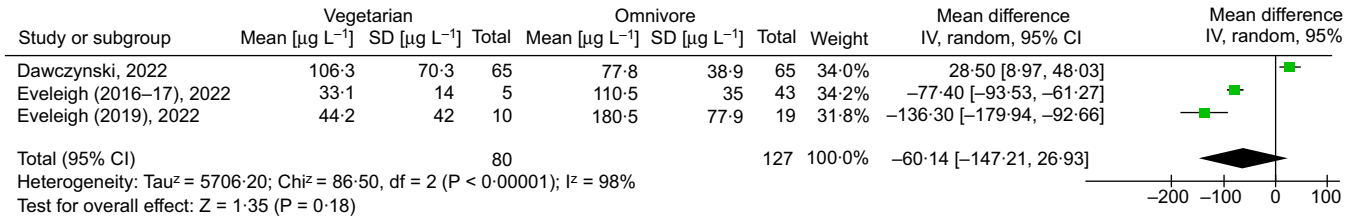


Fig. 5. Meta-analysis forest plot comparing the effect of a vegetarian *v.* omnivorous diet on iodine status. Data presented is female and mixed-sex estimates only.

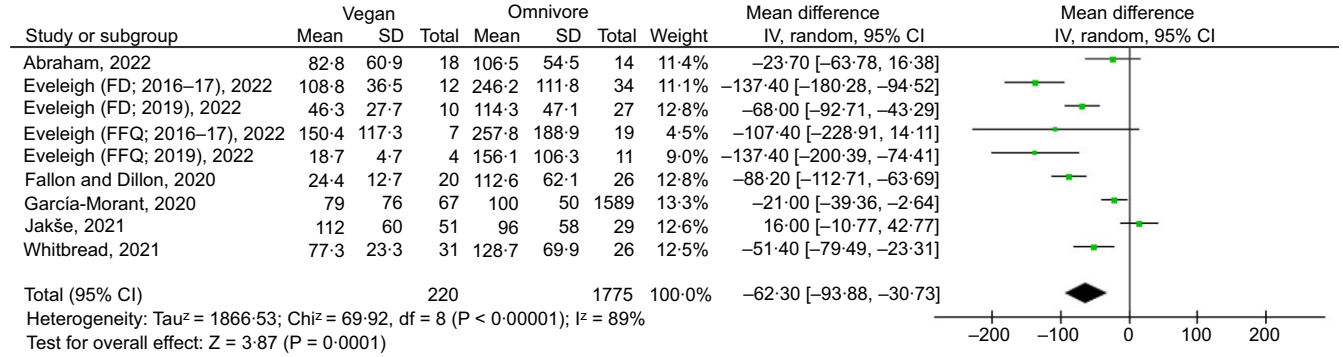


Fig. 6. Meta-analysis forest plot comparing the effect of vegan *v.* omnivorous diet on iodine intake. Data presented is female and mixed-sex estimates only.

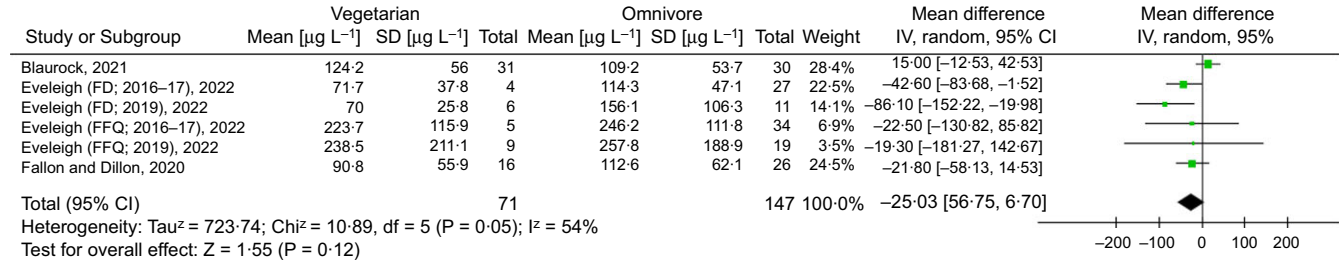


Fig. 7. Meta-analysis forest plot comparing the effect of vegetarian *v.* omnivorous diet on iodine intake. Data presented is female and mixed-sex estimates only.

Fig. 7). Subgroup analysis for iodine intake vegan *v* omnivore is shown in Supplementary Fig. 1. Significant effects were shown for female-only intake ($P = 0{\cdot}007$), mixed-sex intake ($P = 0{\cdot}01$), living in a country with voluntary ($P = 0{\cdot}01$) or no USI programme ($P = P < 0{\cdot}001$), and living in a country with national iodine intake considered as adequate ($P = <0{\cdot}001$). In countries with mandatory salt iodisation, there was no effect of vegan diet on iodine intake ($P = 0{\cdot}60$).

Discussion

This systematic review is an update of our previous work, investigating the evidence for iodine intake and status among adults following vegan and vegetarian diets, to reflect dietary consumption in the modern day. The publication of eleven studies eligible for inclusion in the past 2 years since our previous review demonstrates that there is an increased interest and awareness in this

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area. Our systematic review confirms that individuals following vegan and vegetarian diets, living in countries without mandatory salt iodisation, and not consuming seaweed or iodine-containing supplements, still have an increased risk of low iodine status, iodine deficiency, and inadequate iodine intake compared with less restrictive dietary groups[28]. Our review also highlights that iodine nutrition is poor in many subgroups of the global population and that difficulties achieving iodine recommendations are not unique to those following restrictive diets.

In our previous review[28], we found that the degree of vulnerability in all dietary groups appeared to be impacted by the standing of national iodine estimates, whereby the median UIC of omnivorous participants studied tended to reflect a country's national data. In our present review, we found that on average urine samples provided by omnivorous participants were lower in iodine than national estimates[34,49–52]. Only in studies conducted in Germany were omnivores within the same bracket of the WHO criteria as national data (89 µg/l; 50–99 µg/l mild)[11,20,49,51]. However, there is still a general trend in which vegans are likely to have median UIC corresponding to a lower bracket of the WHO criteria than omnivores recruited in the same study[34,49–52]. Although, the median UIC of all dietary groups studied in this review fell below the WHO criteria for optimal iodine status (100–200 µg/l)[11,34,49–52].

We found that 67 % (6/9) of studies investigating iodine intake were conducted in countries considered 'adequate' according to national data from the Global Scorecard of Iodine Nutrition (2021)[33,34,52,55–57]. But, none of the included studies recorded estimates above the adequate range for all dietary groups[33,34,50,52–57]. Equally, iodine inadequacy was reported in 75 % (9/12) of the cohorts assessed[33,34,50,52–57]. The global scorecard population monitoring uses the WHO recommendation of median UIC from school-aged children or women of childbearing age as a proxy for assessing adequate iodine intake on a national level[20]. The use of median UIC from school-aged children as an indicator of iodine intake has been criticised for masking particular subgroups with varying diets and/or iodine sources[19]. Women are a subgroup more vulnerable to the consequences of iodine deficiency and are twice as likely as men to adopt a vegan or vegetarian diet[58]. Three studies assessed iodine intake specifically in women of childbearing age[33,52,54]. Iodine intake was found to be below the WHO recommendation of 150 µg/d in all studies of women in our review regardless of dietary choice[33,52,54]. Moderate iodine deficiency pre-conception increases the risk of infant mortality by stillbirth and miscarriage[59,60]. Furthermore, iodine deficiency *in utero* may disrupt normal fetal neurodevelopment and cause irreversible neurological damage[59,60]. Our present review highlights that iodine intake must be assessed among different subsets of the population to identify groups at risk of deficiency.

Vegan participants living in the UK were recorded to have the lowest average iodine intake of 17·3 µg/d and 24·4 µg/[33,34]. Dietary intake estimates recorded by Eveleigh *et al* (2022) and Fallon *et al.* (2020) were much lower than past data collected on British vegans[32,61,62], suggesting that iodine intake has reduced over time. Vegans living in the UK may find it more challenging to meet their iodine requirements because along with restricting rich sources of iodine from animal sources, individuals selecting these diets also live in a country with no current USI programme. Salt iodisation is an effective and sustainable way of improving iodine intake[19]. Currently, 145 countries globally have enrolled in either mandatory (124/145) or voluntary (21/145) USI[19]. Apart from the UK, all other included studies were conducted in a country with USI[50,52–57]. Iodised salt can be purchased in the UK, but its availability is low and tends to be more expensive than non-iodised household varieties[63]. Eveleigh *et al* (2022) found that only one omnivorous participant recorded consuming iodised salt equating to 61 % of their total dietary iodine. However, it is very difficult to quantify the amount of salt added to meals and used or lost during cooking[19]. Additionally, the iodine content of fortified salt can vary considerably[19]. Whitbread *et al* (2021) was the only study, conducted in a location with USI, to estimate the relative contribution of iodised salt and foods containing iodised salt such as bread[52]. Hence, dietary iodine intake may be lower in many of the included studies because the involvement of iodised salt was not estimated.

Bread has been selected as a vehicle for iodine fortification in countries, including Australia, New Zealand (NZ) and Denmark[52]. In most countries, bread is a staple food product that can be consumed by nearly everyone in the population including those following vegan and/or vegetarian diets making it a practical method of iodine fortification. In the study by Whitbread *et al* (2021), iodised bread was the main iodised food source in the diets of Australian vegans and greater bread intake (g/d) correlated significantly with improved UIC[52]. The mandatory fortification of bread in Australia is estimated to be about 53–70 µg per 100 g[64]. The British Dietetics Association (BDA) denotes a portion of bread is equivalent to one slice or 34–36 g[65], if bread was fortified in the UK to the same level as in Australia, one portion would provide an average of 22 µg which could potentially boost iodine intake in all dietary groups.

Alternative milk has also been identified and promoted as a possible vehicle for iodine fortification for vegans and/or those who do not consume cows' milk[66]. A recent study investigating the iodine fortification status of plant-based dairy and fish alternatives in the UK found that only 28 % of milk alternatives and 6 % of yogurt alternatives were fortified with iodine[36]. Similarly, no cheese or fish alternatives were found to be currently fortified with iodine[36]. Other studies have identified that individuals who consume alternative milk exclusively tend to have significantly lower iodine intake than cows' milk consumers (94 *v.* 129 µg/d)[37]. Two studies in our review recorded alternative milk intake to be significantly greater in vegan and vegetarian groups[34,52], and the displacement of cows' milk may have contributed to lower iodine intake. In May 2021, the BDA's England Board and the Maternal & Fertility Nutrition Specialist Group completed a project to consider the case for the wider iodine fortification of alternative milk to improve iodine intake[67]. However, at present, no UK policy has been implemented for the mandatory iodine fortification of any foods; therefore, individuals following a vegan and/or vegetarian diet are responsible for planning their diet to include appropriate sources of iodine (e.g. iodine supplements, occasional seaweed consumption and/or iodine fortified alternative milk).

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Although mandatory USI measures are considered to be the optimal approach, most countries with voluntary fortification are iodine-sufficient[19]. We identified that individuals following a vegan diet living in countries with no mandatory USI programme were significantly more likely to have lower iodine intake. Our findings match the global experience; in that voluntary fortification may not benefit all subgroups of the population[68]. There is an urgent need to investigate the usefulness of mandatory iodine fortification to address the emergence of iodine deficiency in those selecting vegan or vegetarian diets.

The modelling study conducted by Kowalska *et al.* (2020) in Poland demonstrates the difficulty in achieving adequate iodine intake in a number of different diet types if iodine-fortified foods (including salt) or supplements are not available. In this study, modelled diet menus of vegan, vegetarian, pescatarian and variations of the omnivorous diet (fish free, milk free, basic and regular) were prepared by qualified dieticians with the use of methods avoiding nutritional deficiencies. Even though these diets had been appropriately planned by dieticians, all of the diets were characterised by insufficient iodine intake. In Poland, the main sources of dietary iodine are iodised salt and white fish including cod and pollock[57]. Therefore, it is unsurprising that iodine intake was observed to be lowest in individuals following diets that exclude fish (vegans, vegetarians and fish-free omnivores) when contribution of iodised salt was not added to intake estimates.

The greatest average iodine intake and status were recorded in Norwegian pescatarians (123·0 μg/d and UIC of 96·0 μg/l)[50]. Pescatarians do not consume meat but may eat fish, milk or eggs in varying quantities[5]. In a typical Norwegian diet, lean fish like cod, haddock and saithe are the richest sources of iodine along with cows' milk and dairy products[50]. However, the iodine content of fish can vary significantly between species and geographical locations[69]. The Norwegian Directorate of Health recommends one portion of fish two or three times a week; however, annual fish intake has dropped in Norway across all age groups apart from the elderly; this decline is particularly noticeable in young people (18–34 years of age)[70]. The authors suggest that greater iodine intake in pescatarians in this study was more due to consumption of iodine-containing supplements rather than that of fish[50], as this significantly improves iodine status[71,72]. A larger proportion of vegans and vegetarians consumed dietary supplements (inclusive of non-iodine-containing varieties) compared with omnivores, and in two studies, iodine-containing supplements provided between 140 and 150 μg/d to total iodine[34,50]. However, despite their consumption, the majority of participants had inadequate UIC and below-recommended iodine intake. The WHO recommends a daily iodine supplement dose of 150 μg/d for women of childbearing age (15–19 years) living in areas with insufficient access to iodised salt or vulnerable groups[11]. Considering the vulnerability of individuals in the included studies, the effect of iodine-containing supplements in vegan and vegetarian populations warrants further investigation.

We found previously that the greatest iodine intake was recorded for females following vegan diets, living in London (1448·0 ± 3879·0 μg/d), whose regular consumption of seaweed increased intakes to over six times the RNI[62]. In our present review, four studies addressed the consumption of seaweed and microalgae in different dietary groups[34,50,52,53]; however, not all studies considered their contribution to total iodine. Vegans were the most frequent consumers of seaweed which provided iodine intake close to the maximum tolerable level of 1000 μg/d. The iodine content of seaweed is high and varies considerably according to the species consumed[25,26], with kombu having the greatest iodine content (2523·5 mg/kg) and so is not recommended to improve iodine intake due to the significant risk of excess[25,26].

In our previous review, we discussed key issues with the methodology selected to record intake from vegan and vegetarian groups including accurately defining diets[28], the use of outdated food tables or databases, and variation in techniques used to measure iodine in the diet (e.g. 24-h food recalls *v.* FFQ). These issues are still relevant to the present review and may reduce the accuracy of dietary intake estimates. Further limitations of this study include the relatively small number of included studies, oversimplifying of dietary practice to enable comparison of studies and a lack of studies that were well populated or well represent the general public.

Conclusions

This review agrees with findings from our previous systematic assessment on this topic[28]. We found that vegans and vegetarians consuming seaweed or iodine-containing supplements continue to have increased risk of low iodine status, iodine deficiency and inadequate iodine intake compared with adults following less restrictive diets living in countries lacking mandatory iodisation of salt. Similarly to our previous review, there is a relationship between national iodine deficiency and the degree of vulnerability to vegans and vegetarians. However, we also conclude that iodine nutrition is inadequate in many subgroups, and that complications achieving iodine recommendations are universal. There is an urgent need to monitor iodine intake and status in at risk populations including young women and those following a vegan or vegetarian diet. In addition to research into safe routes of improving iodine intake in vegan and vegetarian populations living in regions where staple foods are not fortified or USI coverage is not present or is not mandatory. Further awareness of how to appropriately plan a vegan or vegetarian diet to achieve iodine recommendations is required.

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There are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S000711452300051X

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APPENDIX E

Professional Internship for PhD Students (PIPS)

In February 2022, I took part in the UK Research and Innovation (UKRI) Policy Internships scheme and completed a three-month placement at the UK Health Security Agency (UKHSA). At the UKHSA, I worked as a Senior Executive Officer as part of the Evaluation and Social Research Unit in the All Hazards Intelligence team.

My primary role was to statistically analyse national SARS-CoV-2 virus (COVID-19) data collected by two surveys the Test and Trace Contacts Insights Study and the and Test and Trace Cases Insights Study. These surveys were run by the Office of National Statistics (ONS) over 12 months of the global pandemic and collected data about the experiences of self-isolating in individuals who have tested positive COVID-19 (cases) and their contacts who have been contacted by the National Health Service (NHS) Test and Trace. My work was predominantly focused on identifying the social and behavioural factors influencing compliance to self-isolation guidance. To do this, I completed multinomial logistic regression in R to model nominal outcome variables using survey data (compliance to guidance- yes or no). The results from my analysis were featured in a written report that will be used by the UKHSA to develop governmental advice on self-isolating in the future and to improve compliance to guidance measures.

A secondary task was to collaborate with the ONS team and additional government stakeholders (e.g. the Department of Travel) to develop a new online national survey to identify the prevalence of ongoing symptoms (over 4 weeks after confirmed or suspected infection) following coronavirus (COVID-19) infection in the UK (Long COVID-19). During the design of our survey, the government guidance was constantly changing, for example on the 24$^{th\ of}$ February 2022 the legal requirement to self-isolate if you test positive for COVID-19 was removed. Therefore, I had to adapt my work throughout the change process and stay up-to date with national policies. The survey I designed was put into the field in the summer of 2022 and as of 2nd January 2023 has estimated that 2.0 million people living in private households in the UK are currently experiencing self-reported long COVID-19.

I learnt many skills during my time at the UKHSA. For example, before starting my placement I had not used R code for analysis. I undertook several Civil Service learning modules and online training to upskill in this area and now feel confident to complete complex regression analysis using large datasets using the software.

My role at the UKHSA also showed me how to identify and engage with government stakeholders in a range of different policy areas. Additionally, I applied my analysis and survey design skills to the role which have been developed while completing my PhD. Another benefit of completing the UKRI Policy Internships scheme is that I was able to network and socialise with other PhDs also undertaking placement at the UKHSA which helped me build bridges across departments.