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Safety of paracetamol in osteoarthritis

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Declaration

I declare that the findings presented in this thesis are from original research conducted by myself. I have acknowledged every guidance and assistance received while conducting this research. It is the first time to submit this work for consideration for a Doctor of Philosophy.

Unless specifically stated, all work conducted for the thesis was my own. I received guidance for this study from Professor Weiya Zhang, Professor Michael Doherty, Professor Abhishek Abhishek, and Dr Georgina Nakafero. Dr Siewli Goh and Burak Kundakci assisted with data validation for the meta-analysis.

Abstract

Background

Pain is one of the most troubling symptoms that warrant people with chronic conditions such as osteoarthritis (OA) to seek pharmacological treatment options. Paracetamol is currently the first-line drug recommended by most practice guidelines for managing pain in OA due to its perceived safety profile over other analgesics. Despite its modest effectiveness, the usage of paracetamol is widespread either as a prescription medication or over the counter drug for acute and chronic painful conditions. Nevertheless, the adverse effects have been overlooked in its long-term therapeutic usage. There is a growing controversy, highlighted in the National Institute for Health and Care Excellence OA (NICE) 2014 guidance on OA, that paracetamol is not as safe as thought previously, especially at the highest therapeutic dose of 4gm/day for the long term.

Additionally, based on a limited number of studies, the association of gastrointestinal, cardiovascular, and renal events and all-cause mortality with the use of paracetamol is still unclear. Gaining knowledge of these adverse effects would help address this gap in the evidence and provide insights for clinical decision-making. Eventually, it might inform modification of the current recommendations and guidelines for chronic painful conditions such as OA and help clinicians discuss these side effects with patients when considering treatment with paracetamol.

Aim

To examine the long-term safety of paracetamol in people with OA and the general population.

Objectives

Objective 1: To systematically review the research evidence, including randomised controlled trials (RCTs) in people with OA and observational studies (irrespective of any specific underlying condition) on adverse effects of paracetamol.

Objective 2: To undertake a propensity-score matched cohort study to confirm the associations identified from the systematic review and examine the incidence of perforation ulcer bleeding (PUB), uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure in those exposed to paracetamol in the

general population compared to unexposed people using electronic medical records of patients registered in UK general practices. Also, to examine the dose-response relationship between paracetamol and related adverse events using real-world data in the general population.

Methods

1) A systematic literature search and meta-analysis of published RCTs and observational studies

For systematic review and meta-analysis (SR/MA), the databases: MEDLINE, PUBMED, EMBASE, AMED, CINAHL, Web of Science, and Google Scholar were systematically searched for published literature in any language to the end of November 2018 for (1) RCTs of paracetamol in symptomatic and radiographic OA, and (2) observational studies for the treatment of any underlying conditions, to assess the risk of gastrointestinal, liver, renal and cardiovascular adverse events. The SR/MA included studies investigating oral paracetamol in people aged ≥18 years and reporting adverse effects. RCTs and cohort studies were estimated using the risk ratio (RR) or hazard ratio (HR), while case-control studies used the odds ratio (OR) and 95% confidence interval (CI). The results were pooled based on the random-effects model, as appropriate. The risk of bias was assessed using the modified Cochrane risk of bias tool for RCTs and the modified Newcastle Ottawa scale for observational studies, respectively.

2) A propensity-score matched cohort study using the Clinical Practice Datalink (CPRD)

Study participants were 65 years old and over registered with up-to-date practices for at least 12 months from January 1998 to July 2018. Participants who received at least two paracetamol prescriptions from their general practitioner (GP) within six months were defined as exposed to paracetamol. The first prescription date of these two prescriptions was the index date. Paracetamol non-exposure was defined as participants who did not receive two paracetamol prescriptions within six months over the study period. They were matched with the exposure by age, gender, and propensity score and assigned the same index date as their matched exposure.

Logistic regression was used to calculate the propensity score. Follow-up started 12 months after the index date (i.e., the landmark date) to minimise immortal-time bias and provide an exposure window between the index date and landmark date to accumulate several prescriptions and doses for dose-response analysis. Participants were followed until the first incidence of the outcome of interest, deregistration from the practice, death, or end of the study, whichever came first. Kaplan-Meier (Nelson-Aelon) curves were used to estimate the cumulative probabilities of the outcome. The HR and 95% confidence interval (CI) were calculated using the Cox-proportional hazards model. Multiple imputations (MI) were conducted to account for missing data, followed by the inverse probability treatment weighted method (IPTW) to balance the covariates.

Results

1) SR/MA of published RCTs in people with OA and observational studies without any underlying condition

There were 3,722 citations (1,997 RCTs and 1,725 observational studies) for titles and abstracts screening. After reviewing the full text, 24 RCTs, 16 cohort studies, and 26 case-control studies met the inclusion criteria.

GI risk

In 24 RCTs (7,299 participants), paracetamol was associated with increased incidence of any treatment-related adverse events (RR 1.37; 95%CI 1.06, 1.77), diarrhoea (RR 2.12; 95%CI 1.36, 3.32) and liver function complications (RR 3.99; 95%CI 2.05, 7.77) compared to placebo. In 12 age and gender-matched case-control studies (7,894 participants), the pooled OR associated with paracetamol for upper GI bleeding was 1.34 (95%CI 1.10, 1.63). A cohort study including 382,404 participants reported a dose-response relationship between paracetamol doses and perforation ulcer bleeding (PUB). The RR was 1.11 (95%CI 1.04, 1.21) with low dose paracetamol (measured as medication possession rate) and 1.49 (95%CI 1.34, 1.66) with very high dose.

CV risk

In two cohort studies (137,955 participants), there was an indication of the association between paracetamol exposure and CV risk, as the pooled RR showed a dose-response relationship with RR of 1.11 (95% CI 1.00, 1.22) when paracetamol was used for 1-4 days/month to 1.52 (0.92, 2.51) with exposure >22 days/month, but not from two RCTs (1,011 participants) (RR 1.05; 95%CI 0.07 to 15.38) and three case-control studies (42,180 participants) (OR 0.93; 95%CI 0.80 to 1.09).

Renal risk

The data for renal adverse effects was insufficient in RCTs. However, one cohort study with 19,163 participants reported a dose-response relationship between paracetamol exposed and end-stage kidney disease compared to unexposed. Three case-control studies also suggested an increased risk for end-stage kidney disease with the high therapeutic dose of paracetamol compared to unexposed. Two cohort studies suggested a dose-response relationship between paracetamol exposure and chronic renal failure.

2) A propensity-score matched cohort study using the Clinical Practice Datalink (CPRD)

GI risk

From 1998 to 2018, 180,483 paracetamol users were identified from the database. They were successfully matched with 402,487 non-users by age, sex, and practice. There were 158,048 successfully PS-matched, i.e., 79,024 paracetamol users and 79,024 non-users. Paracetamol was associated with an increased risk of PUB (HR 1.24; 95%CI 1.16, 1.34), uncomplicated ulcer (HR 1.20; 95%CI 1.10, 1.31), and lower GI bleeding (HR 1.36; 95%CI 1.29, 1.46). A dose-response was observed for PUB and uncomplicated ulcers with significant P for the trend.

CV risk

Paracetamol exposure was associated with an increased risk of heart failure (HR 1.09; 95%CI 1.06, 1.13) and hypertension (HR 1.07; 95%CI 1.04, 1.11), not for myocardial infarction (HR 0.99; 95%CI 0.94, 1.04).

No dose-response was observed for any CV outcome in the present cohort study.

Renal risk

Paracetamol exposure was associated with an increased risk of chronic renal failure (HR 1.19; 95%CI 1.13, 1.24) compared to unexposed in the present cohort study. A dose-response trend was also apparent, with a significant P for the trend for chronic renal failure.

Conclusion

Paracetamol is associated with diarrhoea and abnormal liver function from RCTs evidence. It is also associated with an increased risk of gastrointestinal, cardiovascular, and renal adverse events from published observational studies. The population-based propensity score-matched cohort study of Chapter 3 in this thesis has confirmed most of these adverse effects, where the likelihood of confounding by indication has been minimised. Thus, adverse events identified through this research should be carefully weighed against the potential benefits of paracetamol. Notably, in conjunction with published paracetamol efficacy data for individual patients, while deciding to prescribe paracetamol, especially for older people or people with osteoarthritis and other chronic painful conditions.

Further study on other outcomes, such as all-cause mortality, has yet to be confirmed.

List of Presentations at conferences

Annual European Congress of Rheumatology (June 2019) Madrid: A systematic review and meta-analysis assessing gastrointestinal, liver, renal, and cardiovascular adverse events of paracetamol (oral presentation in the opening plenary session).

Dedication

This thesis is dedicated to my most influential people, my beloved grandfather, late Dr Karam Singh Judge and Auntie, late Smt. Indira Devi.

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List of Abbreviations

Abbreviation	Full-Form
AA	Arachidonic acid
AAPC	Average annual percentage change
ACE	Angiotensin-converting enzyme
ACL	Anterior Cruciate Ligament
ACR	American College of Rheumatology
ADD	Average daily dose
AF	Atrial fibrillation
AF	Attributable fraction
AHRQ	Agency for healthcare research and quality
AIDS	Acquired immune deficiency syndrome
AMED	Allied and complementary medicine database
ARA	Angiotensin receptor antagonist
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
BH	Bradford Hill
BIFAP	Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria
BK	Burak Kundakci
BMD	Bone mineral density
BMI	Body mass index
BMJ	British Medical Journal
BNF	British National Formulary
BP	Blood Pressure
CC	Calcium channel blockers
CCI	Charlson Comorbidity Index
CI	Confidence interval
CINAHL	Cumulative Index of Nursing and Allied literature
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COX	Cyclooxygenase
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CPRD	Clinical Practice Research Datalink
CSF	Cerebrospinal fluid

Abbreviation	Full-Form
CV	Cardiovascular
d	standardised mean difference
DDD	Daily defined dose
DF	Degree of freedom
DMARD	Disease-modifying antirheumatic drugs
DOB	Date of birth
DU	Duodenal ulcer
EBSCO	Elton B. Stephens CO (company)
ECG	Electrocardiogram
EGB	Echantillon Généraliste de Bénéficiaires
eGFR	Estimated glomerular filtration rate
EMBASE	Excerpta Medica database
EOS	End of supply
ES	Effect size
ESCEO	European Society for Clinical and Economic Aspects of Osteoporosis
ESCISIT	(European League Against Rheumatism) Standing Committee for Internal Clinical Studies Including Therapeutic Trials
ESR	Erythrocyte Sedimentation rate
ESRD	End-stage renal disease
EULAR	European Alliance of Associations for Rheumatology
FASEB	Federation of American Societies for Experimental Biology
FDA	Food and Drug Administration
GFR	Glomerular Filtration rate
GI	Gastrointestinal
GIFA	Gruppo Italiano di Farmacovigilanza nell'Anziano
GP	General practitioner
GPRD	General Practice Research Datalink
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GSH	Glutathione
GU	Genitourinary
HDL	High Density lipoprotein
HES	Hospital Episode Statistics
HR	Hazard ratio
IACS	Intra-articular cortico-steroids
ICD	Implantable cardioverter defibrillator
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICRS	Integrated Care Records Service
ID	Identification
IL	Interleukin
IMD	Index of multiple deprivation

Abbreviation	Full-Form
IMS	International Marketing Statistics
IPTW	Inverse probability treatment weighted
IQR	Interquartile Range
ISAC	Independent Scientific Advisory Committee
ITT	Intention to treat
JAMA	The Journal of the American Medical Association
JK	Jaspreet Kaur
KL	Kellgren and Lawrence
LGIB	Lower gastrointestinal bleeding
MA	Meta-analysis
MDD	Maximum daily dose
ME	Measure of effect
MEDLINE	Medical Literature Analysis and Retrieval System Online
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Multiple imputations Chained Equations
MI	Multiple imputations
MMP	Matrix metalloproteinases
MPR	Medical Possession rate
MRI	Magnetic resonance imaging
MSJP	Multiple sites joint pain
MSK	Musculoskeletal
MTX	Methotrexate
N	Number of participants
NAPQI	N-acetyl-p-benzoquinone imine
NC	Number of participants in the control group
NEC	Necrotizing enterocolitis
NGOA	Nodal generalised osteoarthritis
NHANES	National Health and Nutrition Examination Survey
NHANESIII	National Health and Nutrition Examination Survey-III
NHS	National Health Services
NI	Number of participants in the intervention group
NICE	National Institute for Health and Care Excellence
NOS	Newcastle Ottawa scale
NSAIDs	Non-steroidal anti-inflammatory drugs
NNH	Number needed to harm

Abbreviation	Full-Form
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ONS	Office of National Statistics
OR	Odds ratio
OTC	Over the counter
OVID	Objective View and Interaction Design
OXMIS	Oxford Medical Information System
PACES	Patient Preference for Placebo Paracetamol or Celecoxib Efficacy Studies
PAF	Population attributable fraction
PCM	paracetamol
PERFORM	Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic stroke or transient ischaemic attack study
PGE	Prostaglandin E-alpha
PGF1	Prostaglandin F-alpha
PGHS	Prostaglandin G/H Synthase
PH	proportional hazards
PICO	Patient Intervention Comparator Outcome
POX	Peroxidase
PP	Per protocol
PPI	Proton pump inhibitors
PRAC	Pharmacovigilance Risk Assessment Committee
PRB	rectal bleeding
PRISMA	Preferred reporting items for SR/MA
PROMOTE	Pain reduction with oral methotrexate in knee osteoarthritis, a pragmatic phase III trial of treatment effectiveness
PROSPERO	International Prospective Register of Systematic Reviews
PS	Propensity score
PTOA	Post-traumatic osteoarthritis
PU	Peptic ulcer
PUB	Perforation ulceration bleeding
QOF	Quality and outcomes framework
RA	Rheumatoid arthritis
RAMQ	Régie de l'assurance maladie du Québec
RBT	Risk of bias
RCTS	Randomised controlled trial
RF	Rheumatoid factor
ROB	Risk of bias
ROC	Receiver Operating Characteristic Curve

Abbreviation	Full-Form
RR	Relative risk
SD	Standard deviation
SE	Standard Error
SG	Siewli-Goh
SMR	Standardised mortality rate
SR	Systematic review
STATA	a complete, integrated statistical software package
TC	Total number of participants in the control group
TENS	Transcutaneous electrical nerve stimulation
THIN	The Health Improvement Network
TI	total of number participants in the intervention group
TIA	Transient ischemic attack
TJR	Total joint replacement
TNF	Tumour necrosis factor
UGIB	Upper gastrointestinal bleed
UK	United Kingdom
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organisation
Wk	week
WMD	Weighted mean difference
WZ	Weiya Zhang
YC	Number of participants in the control group
YI	Number of participants in the intervention group with an outcome

Overview of thesis

Osteoarthritis (OA) is the most typical form of painful arthritis, mainly affecting people over 55, and accounts for a high proportion of people taking long-term oral analgesics. Most guidelines recommend oral paracetamol as the first-choice analgesic over oral non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, primarily because of its perceived safety. However, there is growing concern about whether the long-term use of paracetamol is safe, especially in older people.

This thesis aimed to undertake a systematic review (SR) of OA randomised controlled trials (RCTs) and observational studies that report paracetamol side effects in the general population. Subsequently, because the SR identified caveats in the published literature, a cohort study was performed in an extensive UK primary care database (paracetamol users versus paracetamol non-users) not limited to people with OA. The study population was defined using all the older people to catch paracetamol prescriptions in the Clinical Practice Research Datalink (CPRD) database and to understand its association with gastrointestinal (GI), cardiovascular and renal events. A range of confounders, including age, gender, Charlson co-morbidity index, body mass index (BMI), smoking and alcohol consumption and other analgesics, were adjusted using the Cox-proportional hazard model.

Chapter 1: Introduction

1.1. Osteoarthritis

OA is a highly prevalent joint condition that affects the synovial joints. It can result in pain, physical impairment and may have a significant socio-economic impact, especially in older people. It is a complex disorder evident from its different terminology, including osteoarthrosis, degenerative joint disease, and arthrosis deformans. OA changes have been discovered in the fossil bones of a wide range of species, from pre-hominids to Homo-sapiens (Jurmain et al., 1995; Rogers et al., 1981). The first evidence of OA changes in humans was discovered in the Egyptian skeletal remains in the early 20th century (Ruffer et al., 1911).

Although OA has affected the synovial joints of humankind throughout evolution, its aetiology is still unclear (Dequeker et al., 2008). The initial speculations were that it is limited only to cartilage. However, it is now recognised as a multifactorial condition affecting the whole joint (Martel-Pelletier et al., 2016). In the absence of any recommended disease-modifying treatment options for OA. People with OA may require a long-term intake of analgesics for symptomatic relief. Its high prevalence, pain, disability and healthcare-related costs have created a tremendous public health burden and psychological impact (Roemer et al., 2014). Due to the ageing of the population, it becomes imperative to research more treatment options that are safe and effective in the older population.

Therefore, the focus of this introduction is not only on OA as a condition but also on related analgesic usage and its complications.

1.2. Definition and nature of osteoarthritis

The definition of OA is fundamental for epidemiological and clinical studies, describing its distribution in a population and examining risk factors for its occurrence and progression (Corti et al., 2003; Zhang et al., 2010b). The definition of OA has been evolving with ongoing research and increased knowledge.

The term ‘osteoarthritis’ is a combination of the Greek words ‘osteo’ (bone) and ‘arthros’ (joint), and the ending ‘-itis' signifies inflammation (Attur et al., 2002). However, OA is not primarily an inflammatory process compared to rheumatoid arthritis, and the term ‘osteoarthrosis’ has been used to highlight this (Attur et al., 2002).

Clinically, there may be pain, stiffness or loss of mobility, and recurrent occurrences for knees, hips, hands, feet and spine (Huffman et al., 2021). Pathologically, there is focal loss of hyaline articular cartilage in the diarthrodial joints, together with new bone formation in the subchondral region and at the margins of affected joints (Chen et al., 2017).

Epidemiological studies widely use a radiographic definition of OA, characterised as focal loss of joint space width, increased density of juxta-articular bone, marginal osteophytes, and subchondral cysts and sclerosis (Buchanan et al., 2002; Jacobson, 1996).

However, there is a frequent lack of correlation between radiographic and clinical features of OA. For example, OA may or may not proceed to become an illness. Some people with OA might experience pain, but others may remain asymptomatic, and for a few others, painful OA may either improve or become pain-free. A small proportion of people might experience progression of OA symptoms resulting in worsening disability and culminating in surgical intervention. This indicates that OA is a polymorphic condition with a varied clinical presentation that challenges its definition.

Various international guidelines have tried to standardise the definition of OA. For example: according to the American College of Rheumatology (ACR), OA is "*a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of cartilage, in addition to the related changes in the underlying bone and at the joint margin*" (Altman et al., 1986).

The Osteoarthritis Research Society International (OARSI) definition of OA acknowledges the anatomic, molecular, and physiologic aspects of OA (Kraus et al., 2015). The stated lay version of the OARSI definition is that OA is a disorder that can affect any moveable joint of the body, such as the knees, hips, and shoulders. It can show itself as a breakdown of tissues and abnormal changes to joint cell structure initiated by injury (Kraus et al., 2015). Furthermore, osteoarthritis first shows itself as a change to the biological processes within a joint, followed by abnormal changes to the joint itself (such as the breakdown of cartilage, bone shaping, bony lumps, joint inflammation, and loss of joint function). It can result in pain, stiffness and loss of movement (Blackburn et al., 2016).

The most notable feature of the OARSI standardised definition was differentiating between OA as an illness and a disease. According to their terminology, the disease OA relates to pathophysiological changes that are anatomic, molecular, and physiological. Whereas, when all these changes occur within an individual and result in pain, stiffness, disability, and other symptoms related to OA, it is termed an illness as described in Figure 1.1.

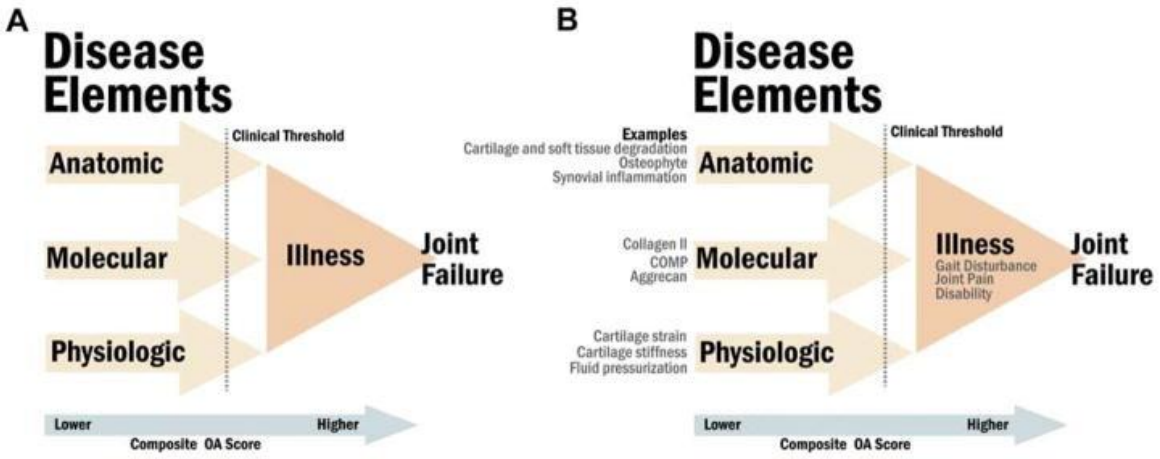


Figure 1.1. Osteoarthritis Taxonomy (A) shows the anatomic, molecular, and physiological aspects of the disease progressing towards illness (B) shows examples indicating anatomic, molecular, and physiologic changes suggesting disease elements and their progression towards illness. Reference: (Kraus et al., 2015). It is reproduced with permission from Elsevier.

Previously, OA was considered to be an inevitable process of growing old and was described as a "*degenerative disease*" and "*wear and tear"* of the related tissues (De-Rezende et al., 2013). However, this perspective has been challenged by the proposed hypothesis that OA is an active process of adaptive regeneration and metabolic changes in response to joint insult, often resulting in successful repair of the synovial joint (Doherty et al., 1983; Hutton, 1987). Therefore, OA is not just "*wear and tear"* but more "*wear, tear and repair*" and a potentially regenerative, rather than purely degenerative, condition (Doherty et al., 2016).

This new concept has re-established interest in achieving in-depth knowledge regarding its signs and symptoms, causation, and clinical presentation to prevent disability. Most importantly, future research must focus on potential safe treatment options that can be effective in the long term and improve the quality of life of people with OA.
Generally, OA remains asymptomatic while compensating for joint insults and resultant increased mechanical loading (Brandt et al., 2003).

However, sometimes there may be discordance between the increased demands placed on a joint and the compensatory potential within the joint (Brandt et al., 2003). Although the joint may alter its regenerating capacity, it may not compensate for the joint insults, as shown in Figure 1.2. With time, either overwhelming insults or an inherently flawed reparative response might reach a particular threshold, resulting in "*joint failure*" (Doherty et al., 2016). Furthermore, it manifests the clinical symptoms and functional impairment that lead to the presentation of a "*patient with OA*" (Brandt et al., 2003).

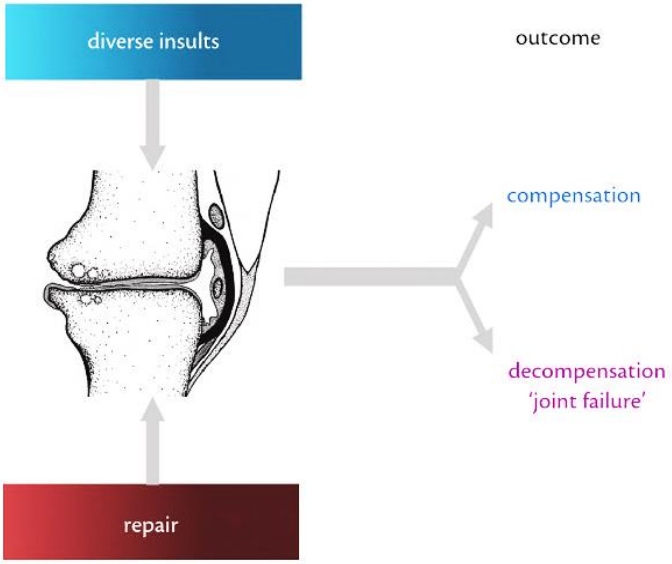


Figure 1.2. The joint failure process in OA, involving various joint insults, responses from all the joint tissues, and variability in outcome. Reproduced with permission from Doherty et al. (2016).

Such joint failure is analogous to other organ failures in the body, such as heart failure and renal failure, where various initiating insults may eventually lead to a single homogenous end-stage phenotype. OA as an illness might cause problems for individuals due to pain. Pain is the primary worrying element that persuades people to seek medical opinion and may result in the long-term intake of analgesics, which may have complications.

1.3. Clinical and radiological classification of OA

Classification criteria are essential for clinical trials and observational studies to define the target population with the condition of interest. They might also help to identify the disease in its early stage and may assist in an early intervention to restore joint homeostasis or delay irreversible joint damage. As the complexity of OA increases in its advanced stage, many secondary and confounding elements make it challenging to treat (Mahmoudian et al., 2021). The ACR criteria are formally validated and widely used for diagnosing symptomatic or clinical OA (Altman et al., 1990). Table 1.1 illustrates that OA cases can be identified if there is a positive history of OA or the presence of OA symptoms. Furthermore, radiographic abnormalities and negative laboratory tests used to diagnose Rheumatoid arthritis (RA), such as erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF), have not been identified for OA.

Table 1.1. American College of Rheumatology (ACR) classification criteria according to clinical and laboratory (+/-) assessments.

Knee	Hip
Knee pain, plus at least five of below nine: Age >50 years old Stiffness <30 minutes Crepitus Bony tenderness Bony enlargement No palpable warmth ESR<40mm/hour RF<1:40 Synovial fluid signs of OA	Hip pain, plus Hip internal rotation <15 plus ESR ≤45 mm/ hour (or hip flexion ≤115) OR Hip internal rotation ≥15 plus pain on hip internal rotation plus morning stiffness ≤60 minutes plus >age 50 years old

OA - osteoarthritis, RF - rheumatoid factor, ESR - erythrocyte sedimentation, Reference: (Altman et al., 1986; Altman, 1991). It is reproduced with permission from John Wiley and Sons.

However, the ACR classification criteria have their own limitations, for example, 1) their inadequacy to provide a standardised definition, 2) varied pain descriptions, and 3) failure to identify early or mild OA. Peat and colleagues analysed the primary health centre data and reported that only 41% of the population with symptomatic OA were able to fulfil the ACR classification criteria (Peat et al., 2006).

Radiological imaging has long been considered as the gold standard for identifying people with OA. The majority of the prevalence studies (58%) used radiological imaging criteria to evaluate the OA prevalence (Pereira et al., 2011; Roemer et al., 2014). It has been readily accepted and based on Kellgren and Lawrence (KL) radiographic grading system, and a cut-off combined score was established to indicate the presence of radiographic OA (Kellgren et al., 1957). For example, Grade 2, defined as definite osteophyte and possible narrowing, was considered the standard cut off for the presence of OA. However, sometimes grade 3 can be used because it involves the combination of both definite osteophyte and definite joint space narrowing, as observed in Figure 1.3.

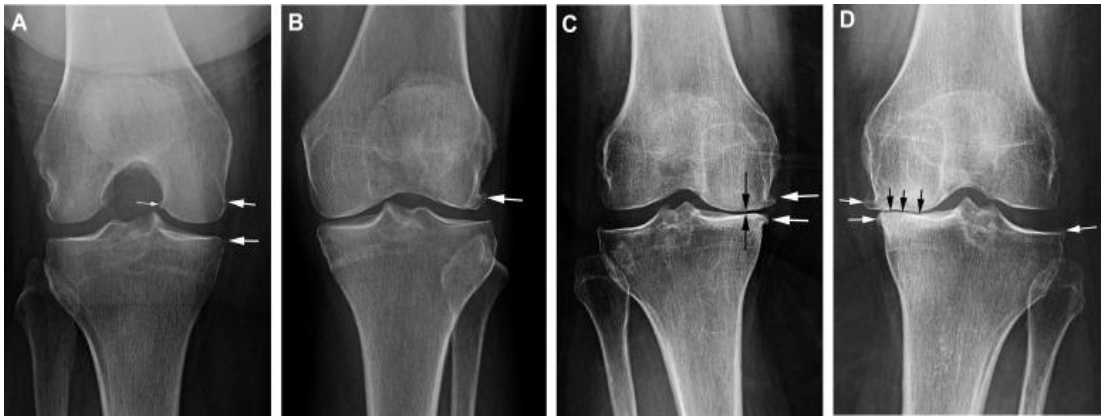


Figure 1.3. Kellgren Lawrence grading classification of osteoarthritis in anterior-posterior radiograph representing four grades. In image A, the large arrows represent grade 1 changes with minimal osteophytes at the margins of the medial tibiofemoral joint. Image B shows the grade 2 changes with definitive osteophytes, indicated by the arrows, but no joint space narrowing. Image C presents grade 3 changes with white arrows pointing to definite osteophytes and black arrows showing joint space narrowing. Finally, image D explains grade 4 changes with complete joint space loss, and "bone-on-bone" (black arrows) marginal osteophytes (white arrows). Reference: (Hayashi et al., 2016). They were reproduced with permission from Elsevier.

Ultrasound imaging has also become a popular tool for assessing joint disease in the musculoskeletal system. In OA, the main benefit of ultrasound over radiographs is that it allows the assessment of joint effusion and synovitis, including peri-articular lesions such as bursitis.

Magnetic resonance imaging (MRI) is another valuable non-invasive diagnostic tool to visualise changes in joints, including soft tissues (for example, synovial hypertrophy), cartilage thickness and oedema of the bone marrow. The SR/MA of 16 studies, including 1,220 people with OA, informed that overall MRI has high specificity. In comparison to radiographs, it permits more comprehensive imaging of the joint with OA changes. However, its sensitivity does not meet the clinical and radiological standards and is comparatively lower than other cost-effective tools (Menashe et al., 2012). Moreover, it is possible to rate the presence and absence of “radiographic OA” using X-rays, but no such scoring system is available for MRI (Hunter et al., 2015). Nonetheless, it is also important to mention that the absence of “radiographic OA” does not necessarily mean that they do not have early OA.

Overall, conventional radiographic imaging is the preferred method for diagnosing OA in clinical settings because of its affordability, accessibility, and availability, while ultrasound or MRI are frequently used in clinical trials or epidemiological observational studies (Oudenaarde et al., 2017).

1.4. Epidemiology of osteoarthritis

The incidence and prevalence rates of OA are complex to determine due to varying OA definitions and follow-up periods used in epidemiological studies (Pereira et al., 2011; Suri et al., 2012). Also, the clinical onset of OA is insidious, and it is quite challenging to establish a threshold to determine OA due to the poor correlation between symptoms and severity of structural changes (Neogi, 2012). Additionally, the radiographic insensitivity of OA might underestimate prevalence rates (O'Neill et al., 2018).

1.4.1. Incidence and prevalence of osteoarthritis

OA incidence varies from 14.6 per 1000 person-years (95%CI 14.0, 14.8) for physician-diagnosed OA in Canada to 6.8 (95%CI 6.7, 6.9) per 1000 person-years for any OA in the UK (Rahman et al., 2014; Swain et al., 2020b). The lifetime risk of symptomatic hand OA was 39.8% (95%CI 34.4, 45.3), less than the corresponding risk of symptomatic knee OA 44.7% (95%CI 40.0, 49.3), though greater than symptomatic hip OA 25.3% (95%CI 21.3, 29.3) (Murphy et al., 2008; Qin et al., 2017). By the age of 85, it was observed that approximately one in two women (47.2%; 95%CI 40.6, 53.9) and one in four men (24.6%; 95%CI 19.5, 30.5) might have hand OA (Qin et al., 2017). The lifetime risk estimated for symptomatic knee OA was 40% in men compared to 47% in women, and for hip OA was 19% for men versus 29% for women (Murphy et al., 2008).

According to the Framingham study, the cumulative incidence of hand OA was 34.6% in women and 33.7% in men (Haugen et al., 2011). The pooled global incidence estimates for knee OA from 88 studies, including 10,081,952 participants, was 203 per 10,000 years (95%CI 106, 331) in adults ≥20 years (Cui et al., 2020). The age-gender standardized incidence rate for symptomatic hip OA estimated in /100,000 person-years was 88 (95%CI 75,101) (Oliveria et al., 1995).

Furthermore, the SR/MA of 72 studies, including nine on the incidence and 63 on prevalence worldwide, suggested that the overall prevalence of OA was higher for hand OA (43.3%; 95%CI 42.7, 42.9) in comparison to knee OA (23.9%; 95%CI, 23.6, 24.2) and hip OA having lowest prevalence with 10.9% (95%CI 10.6, 11.2) (Pereira et al., 2011). There is a significant heterogeneity reported in prevalence rates of OA due to different study populations, varied age groups and gender distribution, eligibility criteria, type of radiographs and methods of OA diagnosis. For example, according to SR/MA of 23 studies by Dagenais et al. (2009), there were approximately 39 estimates of the overall prevalence of hip OA ranging from 0.9%-27%. Table 1.2 also shows a significant disparity in the prevalence rates according to OA pain, age, and gender in these OA-prevalence studies (studies based on the published analysis of national surveys).

Table 1.2. Different population-based studies vary in the prevalence of radiographic OA in the hand, knees, and hips according to the site of OA pain, age, and gender. Adapted from Lawrence et al. (2008) with John Wiley and Sons permission.

Author and Year	Study	Age (years)	Anatomical site of OA	Radiographic estimates for men	Radiographic estimates for women	Overall estimates (radiological)	Age-standardised Symptomatic estimates
Zhang et al. (2002)	Framingham OA study	≥26	Hands	25.9	28.2	27.2	6.8%
Felson et al. (1987)	Framingham OA study	≥26	Knees	14.1	13.7	13.8	4.9%
Felson et al. (1987)	Framingham OA study	≥45	Knees	18.6	19.3	19.2	
Jordan et al. (2007)	Johnston County OA project	≥45	Knees	24.3	30.1	27.8	16.7%
Dillon et al. (2006)	NHANESIII	≥60	Knees	31.2	42.1	37.4	
Helmick et al. (2003)	Johnston County OA project	≥45	Hips	25.7	26.9	27.0	9%

NHANES III - National Health and Nutrition Examination Survey, OA - osteoarthritis.

The prevalence of radiographic OA was higher than that of symptomatic OA for all joint sites. For example, the radiographic prevalence of hand OA was 48.7% (95%CI 48.0, 49.3), in comparison to symptomatic hand OA of 15.0% (95%CI 14.1, 15.9) (Pereira et al., 2011).

Age plays an essential role in the development and progression of OA (Lawrence et al., 1998; O'Neill et al., 2018). Neogi and colleagues found that 13.9% of adults aged ≥25 have clinical OA in at least one joint, and this proportion increases to 33.6% by the age of ≥65 years (Neogi et al., 2013). Figure 1.4 shows a graphical representation of the association of OA and age and indicates that the prevalence increases steadily after age 40-45 years. The prevalence may plateau and even fall after the age of 75-80 years, which is the so-called “healthy survivor effect” (Bagge et al., 1992). According to the Global Burden of Diseases (2010) report, knee OA was 2-4.5 times more common than hip OA (Cross et al., 2014). The OA prevalence was higher in women than in men for almost all joints, but especially for knee OA after the age of 50 years (Oliveria et al., 1995; Woolf et al., 2003).

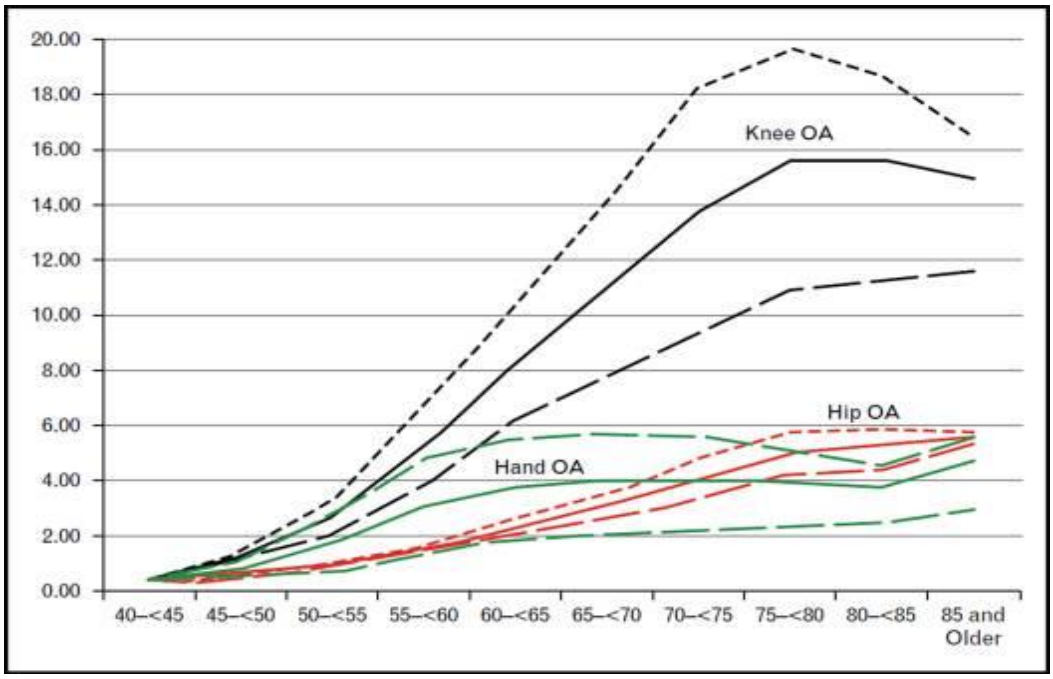


Figure 1.4. Age and sex-specific incidence rates of knee OA (black), hip OA (red), and hand OA (green). Solid lines - all population, short dash - women, long dash - men. Reference : (Prieto-Alhambra et al., 2014). Reproduced with permission from British Medical Journal Publishing Group Ltd. and European League against Rheumatism.

However, hip OA was exceptionally more common in men at younger ages before the 50s and in women in the later years of life (Dagenais et al., 2009). Nevertheless, OA is a common condition observed in many older people, either as radiographic changes or clinical symptoms.

1.4.2. Burden on society

The Global Burden of Disease (2010) reported that hip and knee OA were 11th in the rank out of 291 conditions causing global disability and positioned at 38th for disability-adjusted life years (DALYs) (Cross et al., 2014; Murray et al., 2012; Vos et al., 2012). The burden of OA on individuals is noteworthy in terms of ageing-population, restricted physical functions, or participation restrictions due to pain (Huffman et al., 2021; Hunter et al., 2014).

In the absence of any cure, the burden of OA would continue to increase due to an increase in the ageing population, longevity, and injuries, with an estimated 303 million people being affected worldwide in 2017 (James et al., 2018; O'Neill et al., 2018; Sun et al., 2007; Woolf et al., 2003). Of these, 30.8 million people were from the United States (USA), and 8.8 million were in the United Kingdom (UK) (Abramoff et al., 2020; Litwic et al., 2013). In 2000, 600 million people were ≥60 years old. There has been a three-fold increase estimated in the ageing population since the 1950s and is anticipated to reach 9 billion by 2050 (Bloom et al., 2011). Reportedly, 10% of the aged population ≥60 years worldwide might have significant OA-attributable clinical issues (Vos et al., 2012). The progressive increase in obesity is a serious concern because of its association with OA and other comorbid conditions such as early mortality, heart disease, and type II diabetes mellitus (Afolabi et al., 2020).

The personal impact of OA is also substantial and comparable to that of RA (an auto-immune disease with severe consequences) (Huffman et al., 2021). In contrast to the non-OA population, OA patients experience increased levels of pain, physical disability, or restricted movements with a substantial psychological impact and reduced quality of life, sometimes resulting in a surgical intervention (Huffman et al., 2021).

The burden of OA is not only on the society or personal level but also impacts healthcare resources and costs. Given the high prevalence of OA in the population, its economic burden is enormous. Direct expenses related to the treatment of OA, such as a hospital stay due to total joint replacement (TJR), is almost half of the direct expenditure, and 10% of the direct cost is related to analgesics (Hunter et al., 2014). The indirect cost comprises work absenteeism, early death, and early retirement. Some studies suggest that indirect costs related to OA could be eight times higher than the direct costs (Hunter et al., 2014). The annual cost of prescribing oral painkillers was £25 million in the UK, and the expenditure related to adverse effects of analgesics costs £44.8 - £98 million per year (Cheng et al., 2012). There is a pressing need for an effective and long-term safe treatment for OA. It would delay surgical therapies and reduce the cost of hospitalisation and the adverse effects of analgesics.

1.4.3. Co-morbidities

An epidemiological study from 60 primary care practices suggested that the risk of having co-morbidities, either musculoskeletal or non-musculoskeletal conditions, is twice as high in the OA population compared to the non-OA population (OR 2.35; 95%CI 2.16, 2.50) (Kadam et al., 2004).

Two out of five people with OA who sought GP advice had been affected by anxiety and depression (Axford et al., 2008). There was a 25%-35% increased prevalence of sleep disorder in symptomatic OA compared to the asymptomatic OA population (Allen et al., 2008). It is highly likely that people with OA might have at least one chronic condition, such as stroke, peptic ulcer, or depression and that one third might have two or more states, i.e., multi-morbidity (Huffman et al., 2021; Swain et al., 2020a).

People with OA who have other chronic conditions may require adaptation of their pharmacological interventions (Cooper et al., 2019). For example, firstly, people with OA and concomitant diseases have limited access to NSAIDs, complicating the treatment selection to treat OA symptoms (Huffman et al., 2021). Because NSAIDs are significantly associated with various complications such as gastrointestinal toxicity, acute myocardial infarction, and acute kidney injury (Cooper et al., 2019). In the OA population with prescribed opioids, an increased risk had been reported for the number of falls and fractures (Rolita et al., 2013). It might, in part, explain the increased rate of mortality among the symptomatic OA compared to the non-symptomatic OA population (Liu-Bryan et al., 2015). Secondly, these co-morbidities might add another level of complexity to the increasing levels of pain, inactivity, and disability because people with OA might struggle to perform routine activities (Huffman et al., 2021).

Additionally, various risk factors responsible for metabolic disorders and cardiovascular disease are shared risk factors for OA, explaining the strong association between OA and other comorbid conditions (Engstrom et al., 2009; Findlay, 2007; Rahman et al., 2013). (Rahman et al., 2013). Therefore, it was not surprising that the people with OA had a considerable risk for all-cause mortality compared to the non-OA population.

The reason could be reduced physical movements, concomitant diseases, and adverse effects of pharmacological treatment options along with pathology of OA itself, challenging the conventional perspective that OA is not a severe condition (Huffman et al., 2021; Nuesch et al., 2011). This impact of co-morbidities also raises serious concerns for the optimal management of OA symptoms.

1.5. Risk factors

OA results from a combination of genetic, constitutional, and environmental risk factors (Heidari, 2011; Hunter et al., 2014; Karlson et al., 2003; Katz, 2006; Srikanth et al., 2005). The risk factors for OA might differ from risk factors of chronic pain, and although OA could be considered one of the risk factors for joint pain, it might not wholly explain the presence or severity of the pain experienced.

1.5.1. Genetics

The interplay of multiple genes in the cartilage, collagen, and subchondral bone might explain the development of OA (Huffman et al., 2021). It was estimated that heritability of OA accounts for 60% of the risk for hand and hip OA and 40% of the risk for knee OA (Palazzo et al., 2016). The children and siblings of people with OA are at two to three times higher risk of developing OA than those without affected first-degree relatives (Kellgren, 1963). For example, someone whose mother has Heberden nodes is twice as likely, and the sister of someone with Heberden nodes is three times as likely to demonstrate the same OA changes (Conaghan et al., 2017). A single nucleotide polymorphism of GDF5 (a gene involved in skeletal development) has shown a significant association with knee OA in East Asian and White European cohorts (Conaghan et al., 2017; Valdes et al., 2010). A locus at chromosome 7q22 is associated with knee and hand OA, especially in European populations (Conaghan et al., 2017). Although there are approximately 30 known loci associated with increased risk of developing either knee or hip OA, this explains only 25% of the heritability of OA at those sites suggesting that the majority of genetic risk factors are yet to be identified (Zengini et al., 2018).

1.5.2. Constitutional susceptibility

Age, gender, obesity, and malalignment are well-known constitutional risk factors for OA.

1.5.2.1. Age

Age is one of the strongest predictors of OA. The prevalence of radiographic OA and, to a smaller extent, symptomatic OA increases rapidly for men at ≥50 years and women at ≥40 years (Conaghan et al., 2017). The mechanism to explain the association between age and risk of OA is still debatable and considered multifactorial involving oxidative damage, age-related changes in cartilage, weakened muscles, reduced skeletal muscle, and reduced body's ability to sense its movements (Figure 1.5) (Johnson et al., 2014; Litwic et al., 2013; Palazzo et al., 2014). Additionally, increasing age itself is not responsible for OA. Basic cellular mechanisms and other risk factors that maintain tissue equilibrium decline with growing age, perhaps making a joint more vulnerable and less competent to repair itself. Its inability to maintain its stability leads to weak or no response to stress or injury to the joint, thus impairing the joint tissues (Litwic et al., 2013; Loeser et al., 2016).

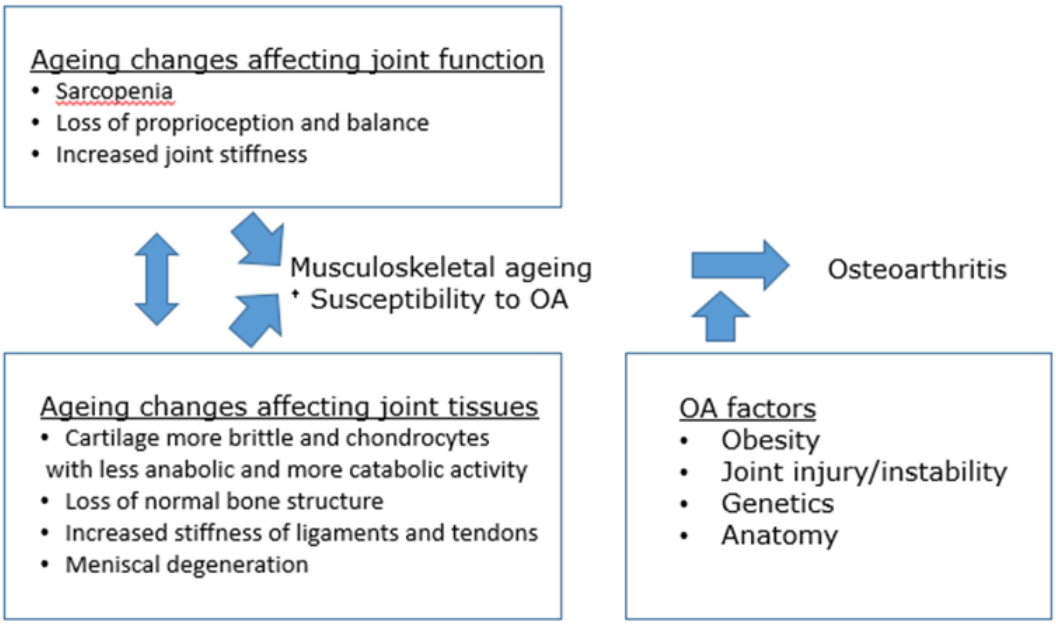


Figure 1.5. Relationship between musculoskeletal ageing and osteoarthritis. It describes the changes that affect joint structure with the susceptibility of osteoarthritis occurrence with growing age. However, there is also a contribution of other risk factors. Reference: (Anderson et al., 2010). Reproduced with permission from Elsevier.

Various epidemiological studies have demonstrated that the prevalence of OA increases with age, as shown in Figure 1.6 and Figure 1.7 (Anderson et al., 2010). Figure 1.6 also depicts an age-related difference between men and women.

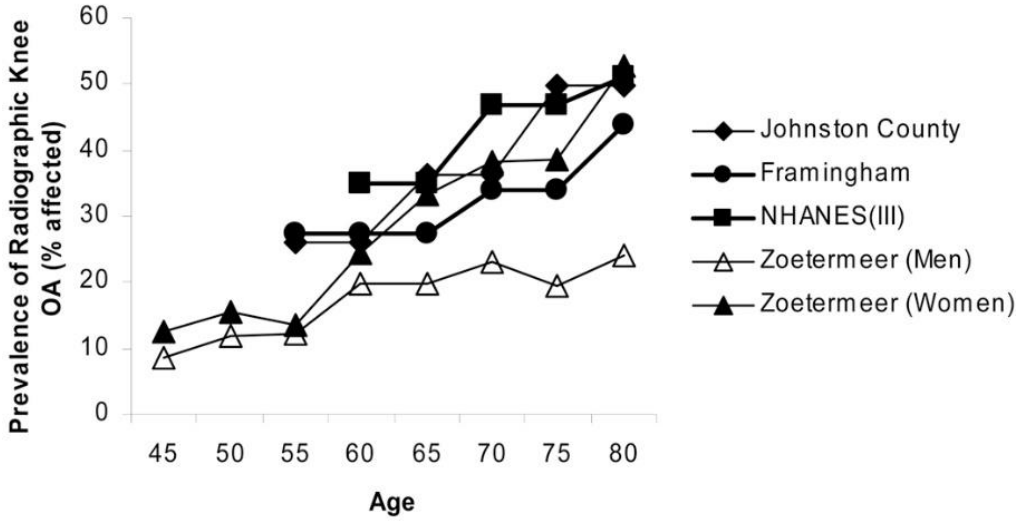


Figure 1.6. Relationship between increasing age in years and the increase in the prevalence of radiographic knee osteoarthritis within different studies. There is a steep rise in the rate after 55 years. Reference: (Anderson et al., 2010). Reproduced with permission from Elsevier.

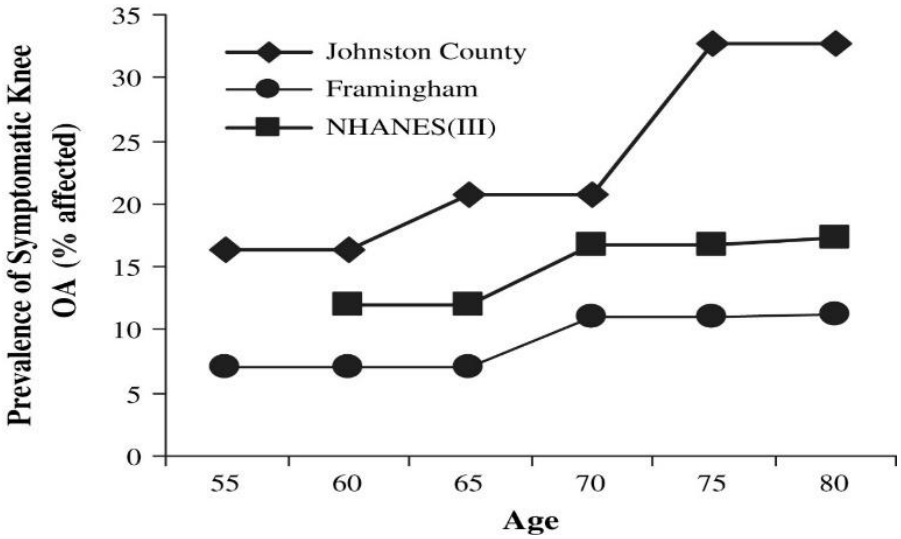


Figure 1.7. Relationship between age in years and the prevalence of symptomatic knee osteoarthritis. Reference: (Anderson et al., 2010). It is presented with permission from Elsevier.

1.5.2.2. Gender

A significant gender disparity has been observed that varies according to increasing age, site of joints, incidence, and prevalence rates (Oconnor, 2007; Srikanth et al., 2005). In a meta-analysis (MA) of 34 studies, men had a 37% lower risk for knee OA compared with women (RR 0.63; 95%CI 0.53, 0.75) and 19% lower risk for hand OA (RR 0.81; 95%CI 0.73, 0.90) (Srikanth et al., 2005). In contrast, hip OA was relatively more prevalent in men than women at younger ages (Conaghan et al., 2017). However, the sex-specific difference was statistically non-significant, with a RR of 1.18 (95%CI 0.91,1.52) (Srikanth et al., 2005). This sex-specific difference becomes statistically significant if the age is ≥55 years. This increase in the female preponderance of OA coincides with menopause, implying that sex hormone-mediated effects, particularly oestrogen deficiency, might have been involved (Litwic et al., 2013). This could be explained further as oestrogen deficiency could affect articular cartilage, subchondral bone, synovial lining, peri-articular muscles, ligaments and the articular capsule (Martin-Millan et al., 2013). For example, Herzberg and colleagues have indicated the protective role of oestrogens in their SR/MA for anterior cruciate ligament injuries, which might lead to OA in later stages (Herzberg et al., 2017). Similarly, a nationwide survey also reported that the incidence of spinal OA was decreased with the use of oral contraceptives containing mainly oestrogen (Park et al., 2017). Apart from these factors, according to the Million women study, every additional birth was associated with an increase in the incidence of knee OA with a 2% (95%CI 1, 4) increase in the RR of total hip replacement and 8% (95%CI 6, 10) for total knee replacement (Liu et al., 2009). The mechanism for incidence of OA and gravidity are still evolving however, it could relate to both hormonal and biomechanical factors. In addition, women have less cartilage thickness, especially at the knee, so less cartilage reserve to lose and lower muscle strength compared to men, which might increase OA risk and contribute to the gender disparity for OA (Eckstein et al., 2014).

1.5.2.3. Malalignment

There is a strong association between mechanically maligned knee joints and increased biomechanical insult and structural damage to the knee compartment under increased compressive stress (Sharma et al., 2001). It has been reported that progression of medial tibiofemoral OA is four-fold more significant in participants with Varus alignment (bow-leg) (Sharma et al., 2001). In this context, the load-bearing axis was calculated from a line drawn

from the centre of the head of the femur to the centre of the ankle joint passes medial to the centre of the knee (Cerejo et al., 2002; Sharma et al., 2010). This misalignment imposes higher stress on the medial tibiofemoral compartment. Additionally, lateral progression was five times greater in valgus alignment (knock-knee). This axis passes laterally from the centre of the knee and increases the force across the lateral tibiofemoral compartment (Cerejo et al., 2002; Sharma et al., 2010). A SR suggested mechanical knee misaligned as an independent risk factor for increased radiographic knee OA (Tanamas et al., 2009). According to a multicentre observational study, valgus malalignment can increase the risk of radiographic knee OA progression, including lateral cartilage damage (Felson et al., 2013).

1.5.3. Environmental

1.5.3.1. Obesity

Obesity is the most significant and established modifiable risk factor for developing OA, according to various SR/MA reports, as shown in Table 1.3. It was estimated that 50% of people in the USA and 42% in the UK might have been prevented from developing OA by modifying obesity (Doherty et al., 2016; Muthuri et al., 2011). According to MA for observational studies, people with obesity were almost three-fold more likely to have an increased incidence of knee OA, the overall pooled OR for BMI >30 compared to normal BMI was 2.63 (95%CI, 2.28, 3.05) (Blagojevic et al., 2010). In contrast to knee OA, there was an inconsistency reported by the Rotterdam Study and other studies regarding the association between obesity and incident or progressive hip OA (Grotle et al., 2008; Karlson et al., 2003; Reijman et al., 2007). An increase in BMI might increase the risk for OA either through systemic mechanisms, such as the release of immune regulatory cytokines favouring inflammation detrimental for vascular joint tissue health and locomotive mechanisms, primarily through increased loading of weight-bearing joints such as the knee (Blagojevic et al., 2010; Palazzo et al., 2014).

Table 1.3. BMI and risk of OA.

Authors	No. of studies	Risk factor	Outcome	Pooled OR (95%CI)
Zhou et al. (2014)	dose-response meta-analysis of 12 studies	BMI 25.0kg/m2	incidence of radiographic knee OA	1.59 (1.34, 1.81)
Jiang et al. (2012)	SR/MA of 21 studies	a 5-unit increase in BMI	incidence of radiographic and clinical knee OA	1.25 (1.17, 1.35)
Lee et al. (2012)	review article of four studies	BMI≥30kg/m2	incidence of radiographic and clinical knee OA	ranged from 2.81 (1.32, 5.96) to 8.1 (5.3, 12.4)
Blagojevic et al. (2010)	SR/MA of 85 studies	overweight compared to normal weight	the onset of knee OA, knee pain, knee disability, or physical limitations related to knee or radiographic knee OA	2.18 (1.86, 2.55)
Richmond et al. (2013)	SR/MA of 13 studies	overweight or obesity vs normal weight	presence or development of knee and hip OA	ranged from 1.6 to 15.4
Muthuri et al. (2011)	SR/MA of 47 studies (14 cohorts, 19 cross-sectional and 14 case-control studies)	overweight and obesity	potential risk reduction for knee OA	2.02 (1.84, 2.22) overweight 3.91 (3.32, 4.56) obese

OR - odds ratio, CI - confidence interval, OA - osteoarthritis, SR - systematic review, MA - meta-analysis, BMI - body mass index.

1.5.3.2. Trauma

An acute impact, overloading of the articular surface, or twisting movements could lead to damage and eventually to `post-traumatic' OA (PTOA) (Buckwalter, 2003). The risk of developing knee OA was twice with overt, direct injuries such as meniscal and cruciate ligament (Huffman et al., 2021). Approximately 12% of all symptomatic OA might be referred to as PTOA, and 70-90% of ankle injuries and 2-10% of the knee and hip injuries might subsequently develop into OA (Brown et al., 2006; Delco et al., 2017). The prevalence of all knee OA outcomes was 2-3 times higher in male ex-footballers (professional) compared to men in the general population, and a significant knee injury was the main attributable risk factor (Fernandes et al., 2017). According to two SRs, people with a self-reported knee injury had approximately four times higher risk of developing knee OA conferring a 15% greater lifetime risk of symptomatic knee OA (Blagojevic et al., 2010; Muthuri et al., 2011). Even surgical interventions or rehabilitation for such injuries may not reduce the risk of developing subsequent OA (Padua et al., 2018).

Apart from acute severe injury, repetitive local micro-trauma to the knee associated with occupation might also cause knee OA, which could be avoidable (Litwic et al., 2013; Suri et al., 2012). It is mainly relevant to occupations that involve certain activities, such as frequent squatting or kneeling. According to a SR, people in occupations requiring frequent kneeling and heavy lifting were 1.6 times more likely to have knee OA than people in low-risk professions such as office work (McWilliams et al., 2011).

1.5.4. Other factors

Other factors such as oestrogen deficiency, high bone mineral density (BMD), and poor nutrition have mixed evidence and require further investigation to determine their possible association with OA (Felson et al., 2004; Palazzo et al., 2016). The effect of modifiable factors in the diet, such as Vitamin D supplementation in humans, remains inconclusive (Garfinkel et al., 2017).

1.6. Pathology

The pathological changes in joints are still debatable, although modern technology has notably improved the visualisation of the diverse joint tissues.

1.6.1. Articular cartilage

Changes in articular cartilage take place throughout life. The hyaline cartilage, with up to 2-4 mm thickness, is a viscoelastic compressive connective tissue (Fox et al., 2009). The osmo-sensitive and mechano-sensitive chondrocytes are the single resident cells present in the cartilage that maintain its structure, matrix, and biochemical composition (Hall, 2013). Under normal circumstances, chondrocytes produce type II collagen and aggrecan proteoglycan for its growth and stimulate the repair process by providing the cartilage elasticity during extra-loading times (Goldring et al., 2010). Cartilage has no blood vessels, lymphatics, or nerve tissue, which is advantageous when tissue compression occurs. The chondrocytes receive oxygen and nutrition diffusion from the synovial fluid and blood vessels in the subchondral bone.

The loss of hyaline cartilage is a primary event in an OA model. During abnormal mechanical loading, the number of chondrocytes increases to form clones or nests of the cells, producing a “hypertrophic phenotype,” with increased production of components of the extracellular matrix. It expands further with pathological changes within the subchondral bone (Hall, 2013). The depletion of articular cartilage due to abnormal mechanical stress affects the focal part of the cartilage while adjacent areas continue to be intact (Hall, 2013). In an advanced stage of OA, the progression involves multiple adjacent regions of the joint surface (Pritzker et al., 2006). Histologically, there is enzymatic damage to the collagen matrix and a reduction in the concentration of collagen and aggrecan during an early stage, causing oedema through osmosis. When the simple matrix is open to shear forces within the joint, lesions develop in the superficial layers “*fibrillation,*” and small fragments of articular cartilage can be seen in the synovial fluid (Hall, 2013). These features eventually lead to fissuring and breakdown of the integrity and thickness of cartilage. In established progressive OA there may be chondrocyte necrosis, with reduction in cell number, particularly at sites of maximum load bearing, fissuring and loss of cartilage depth are occurring, as shown in Figure 1.8.

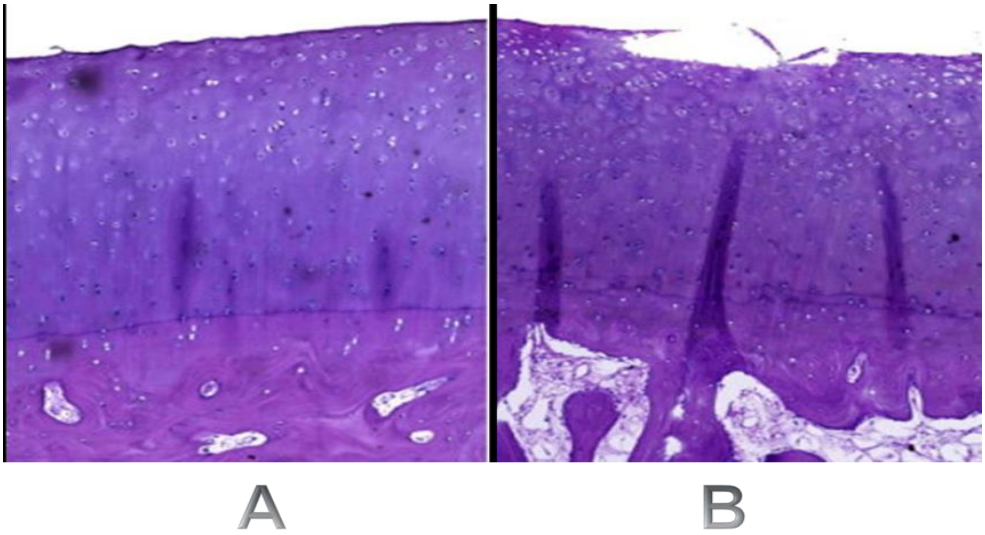


Figure 1.8. Cartilage change difference between a regular joint and an osteoarthritic joint. Image A represents the smooth cartilage surface in the normal joint, and image B shows the loss of cartilage in osteoarthritis. Reference: (Elmesiry et al., 2014). It is presented with permission from Taylor and Francis Academic Journal Permission team.

There is a progressive loss of matrix until it is exposed to mineralised bone or cartilage by eroding the non-mineralised cartilage (Hall, 2013). Hyaline cartilage is irreplaceable in adult joints. However, new fibrocartilage containing type I collagen could be a part of an attempted repair, but this is less efficient than hyaline cartilage in load transmission (Mainil-Varlet et al., 2003).

1.6.2. Subchondral bone

The lower part of the hyaline cartilage is calcified near the cartilage-bone interface and is defined as the tidemark (Donell, 2019). The subchondral bone is the region from this tidemark to the bone marrow, constituting the subchondral plate and trabecular bone (Donell, 2019). The subchondral bone acts as a bridge between calcified cartilage and underlying trabecular bone. The structural or compositional changes in OA can be identified in bone and cortical plate bony tissue, including increased bone production and thickness, sometimes with bone cysts (Donell, 2019).

Figure 1.9 shows the bony alterations that are also frequently observed on radiographic imaging consist of osteophytes, subchondral plate thickening, and sclerosis are the significant pathological changes of bone in OA and subchondral bone cysts (Abramson et al., 2009).



Figure 1.9. Bony alterations evident on a radiograph in an osteoarthritis joint reproduced from Altman and Gold (2007). They were presented with permission from Elsevier.

There is also a change in the tidemark related to vascular penetration of the calcified cartilage. The characteristic “osteophytes” are bony outgrowths that differentiate OA from other arthritides. Osteophytes develop as new fibrocartilage growths at the joint margin, which then undergo calcification and osteogenesis by replacing hyaline cartilage with bony tissue (Altman et al., 1986; Goldring et al., 2010). They are part of bone remodelling, which attempts to compensate and maintain joint stability due to abnormal mechanical joint loading (Goldring et al., 2010). According to other theories, they are abnormal repair of the fractures caused by increased stress in the subchondral bone at the joint margins (Abramson et al., 2009). At later stages of OA, this exuberant growth of bone may restrict joint movement and contribute to deformity and malalignment.

The subchondral changes could be secondary to cartilage degeneration (Madry et al., 2010). The consistently increased insults cause micro-fractures at the osteochondral junction and subchondral bone, leading to subchondral bone sclerosis (Donell, 2019). In contrast, an alternative hypothesis suggests that the sclerosis of the subchondral bone precedes cartilage changes and reduces the ability to cushion the cartilage during force transmission, thereby making it vulnerable to injury (Lajeunesse et al., 1999; Radin et al., 1986). Although the changes that take place at first remain debatable, it might be that the site of the first change in response to insult varies between individuals and joint sites.

The aetiology of subchondral cysts is also unclear. According to the synovial fluid intrusion hypothesis, the increased intra-articular pressure results in cavity formation through the intrusion of synovial fluid by fissured/ulcerated cartilage into the subchondral bone (Chen et al., 2015; Landells, 1953). However, the bone contusion concept theory states that subchondral cysts result from damaged bone oedema. The necrosis is secondary to a collision between two articulating surfaces (Chen et al., 2015; Rhaney et al., 1955). Subchondral bone is slightly vascular and innervated, which contributes to OA's pain sensation, whereas any change in cartilage would not trigger nociception directly.

1.6.3. Synovial inflammation

As its earlier synonym, “osteoarthrosis,” indicates, OA is a non-inflammatory joint condition. However, some MRI-imaging studies reported a high prevalence of synovitis in the early stages of OA and its association with the severity of pain. (Hill et al., 2007; Loeuille et al., 2005). Although these changes appear identical to RA to some extent, however, the role of synovial inflammation in OA is still debatable (D'Agostino et al., 2005). For example, the degree of inflammation in OA is comparatively less than in RA, and unlike RA, it is usually limited to discrete regions within the joint, close to the peripheral chondropathy. It never leads to marginal erosion of bone in the bare areas of the joint (where synovium is in direct contact with bone). According to one hypothesis, the inflammation in OA is a reaction to the joint insult or joint tissue injury, which may be even beneficial in terms of an attempted repair.

Others have assumed that OA is, to some degree, secondary to synovial inflammation, perceiving it more as a cause than an outcome of cartilage breakdown (Pelletier et al., 2001).

The standard synovial lining includes a thin layer of cells comprised of macrophages and fibroblasts. In OA, there is hyperplasia in the synovium with infiltration of macrophages, lymphocytes and fibrosis of both the synovium and capsule (Scanzello et al., 2012). The ongoing process of synovial reaction may result in the synthesis of a range of cytokines and chemokines. These inflammatory mediators (e.g. interleukin -1β(IL-1β), tumour necrosis factor (TNF) alpha) can be identified in synovial fluid and serum of OA patients, indicating a role of inflammation in OA pathogenesis (Scanzello et al., 2012). Further, there is a production of cytokines, such as matrix metalloproteinase (MMP) and proteases, which impact T-lymphocytes and may also cause the chondrocytes to break down (Scanzello et al., 2012). Based on these in vitro and pre-clinical findings, numerous RCTs have been conducted to evaluate the efficacy of conventional disease-modifying anti-rheumatic drugs (DMARDs) and biologics typically used for RA, in OA. This may be because they are typically used in inflammatory arthritis such as RA. These treatment modalities suppress the aggressive inflammatory functions of neutrophils, macrophages, monocytes, dendritic cells, and lymphocytes as well as decrease the secretion of inflammatory cytokines (NICE, 2018). However, in their MA of 11 studies, Persson et al. (2018a) reported six conventional DMARDs studies with 757 participants and five biologics studies with 448 individuals, indicating that neither conventional DMARDs nor biologics were effective at reducing pain associated with OA.

Thus, based on the above discussion regarding the findings of conventional DMARDs and biologics, it can be inferred that the pain associated with OA might not necessarily result from inflammation.

1.7. Clinical presentation

OA has varying clinical presentations according to the joint site, severity, and the total number of included joints. The onset of symptoms is insidious with the involvement of only one or a few joints. The most debilitating symptom of OA is pain. It is predominantly related to the use of joints (irrespective of any specific joint sites) and is relieved by rest. However, in later stages of the condition, pain continues even at rest or at night with the development of synovitis. Unlike inflammatory arthritis, early morning stiffness is mild and short-lived. The change in the severity of OA symptoms, either getting worse or improving, characteristically occurs slowly.

Nodal generalised OA (NGOA) is a recognised clinical subset with female predominance, marked heritability (60%), and usual onset in middle age (Chan et al., 2012). It was previously called "menopausal arthritis." Generally, NGOA first involves predominantly distal finger interphalangeal joints, intermittently painful as postero-lateral bony swellings (Heberden and Bouchard nodes) slowly develop. Once nodes are fully established after many years, symptoms often decline or cease, with a good prognosis. Subsequently, affected people are at higher risk of developing OA at joint sites such as the knee, hip, and first metatarsophalangeal joints (Chan et al., 2012).

In general, pain, stiffness, and functional impairment are the predominant OA symptoms. On examination, there might be crepitus, bony swelling of the joint, and eventual deformity, as explained in Table 1.4., adapted from Abhishek et al. (2013).

Table 1.4. Significant symptoms of OA and their description were presented with permission from Abhishek et al. (2013).

Symptoms	description
Pain	Typically affecting one to two joints simultaneously, slow progression over some time. Variable intensity throughout the day and the week may be intermittent and relapsing, increased by joint use and relieved by rest; night pain may occur in severe OA.
Stiffness	short-lived (<30min) early morning and inactivity-related stiffness
Swelling	few people might present symptoms such as swelling and deformity
Age	>40 years
Systemic symptoms	absent

1.7.1. Nature of pain

Chronic pain is the main symptom of OA that leads to a medical consultation (Croft, 2005). It is a complex symptom influenced by nociception in and around the damaged OA joint, including individual factors such as illness, misconceptions about OA, mood, non-restorative sleep, obesity, daily activity, and occupation. Pain has variable severity that might or might not occur continuously, and it is conditional on joint usage, minor trauma, or low-pressure weather. Pain fluctuates through the day and tends to be least in the morning, then worsens towards the end (Allen et al., 2009; Hutchings et al., 2007). It is mainly described as a dull ache that is worst during movement and usage of the joint but relieved by rest (Chan et al., 2012). Chronic pain can be highly debilitating and result in a long-term intake of analgesics and affect the physical health and quality of life of an individual. The origin of the pain is still evolving. It is observed to be transmitted from pain receptors fibres or mechanoreceptors present in various parts of the joint, such as synovium, capsule, and subchondral bone. It also involves peri-articular tissues such as ligaments, tendons, and bursae due to secondary strain injury from the altered biomechanics (especially in large joints such as knees and hips) (Abhishek et al., 2013). It may be accompanied by other symptoms such as restricted movements, reduced strength, fear of moving the painful site, poor sleep quality, and fatigue (Rejeski et al., 1998; Williams et al., 2004). Even though the origin of the pain is still debatable, progressive pain may follow three stages, as explained in Table 1.5. It is not valid for all people with OA.

Table 1.5. Various stages of OA-pain were reproduced with permission from Abhishek et al. (2013) and Hawker et al. (2011).

Stages of pain in OA	
Stage 1 (Early onset)	Predicable sharp pain is usually brought on by a mechanical insult that eventually limits high-impact activities. They may only be a minimal effect on function.
Stage 2 (Mild-moderate)	Pain becomes a more regular feature and begins to affect daily activities. There may be unpredictable episodes of stiffness.
Stage 3 (Advanced)	Constant aching/dull pain is punctuated by short periods of often-unpredictable intense, exhausting pain resulting in severe functional limitations.

OA - osteoarthritis.

1.7.2. Stiffness

The other symptom of OA is stiffness, which is different from that of RA, being modest and only short-lived. It is a subjective feeling of inability to move the joint freely. Usually, stiffness is present in the early morning first movement of the joint but can also be present following rest. Early morning stiffness is attributed to mild inflammation with fluid accumulation in the immobile joint that stretches the capsule. It typically lasts for just a few minutes (<30minutes) before it wears off with continuous movement. OA pain is experienced mainly while the joint is being used (Abhishek et al., 2013).

1.7.3. Functional disability

Physical function impairment depends on the joint affected and the degree of structural change. For instance, complicated gripping can be observed in the first carpometacarpal joint OA, and for hip/knee OA a person might have difficulty getting up from a chair and walking (Abhishek et al., 2013). The disability and participation restriction that results from physical impairment is person-specific and depends on their occupation, social, and routine daily activities.

1.7.4. Signs of osteoarthritis

Table 1.6 describes that coarse crepitus, tenderness along the line of the joint, swelling of bone or joint deformity, and movement restriction are the main signs of OA. The friction between roughened articulating cartilage and bone produces a crunching sensation which is termed coarse crepitus (Abhishek et al., 2013). It is present more during active than passive movement during a physical examination because this increases the proximity of the two sides of the joint (Abhishek et al., 2013). Secondly, tenderness is commonly present in and around a joint affected with OA. If the tenderness is present along the joint line, it is suggestive of intra-articular pain. However, if it is away from the joint, this indicates involvement of peri-articular tissues (e.g. secondary bursitis, enthesopathy of capsule or tendon) (Abhishek et al., 2013).

Table 1.6. The observed signs in people with osteoarthritis adapted from Abhishek et al. (2013), Reproduced with permission.

Signs	Description
Appearance	swelling (usually bony +/-fluid/soft tissue)
	resting position (attitude)
	deformity
	muscle wasting
Feel	absence of increased warmth
	swelling: bony or effusion
	effusion, if present, is usually small-modest
	joint-line tenderness
	peri-articular tenderness
Movement	coarse crepitus
	reduced range of movement
	weak local muscle

1.7.5. Holistic assessment for OA

According to NICE (2014), pain assessment is essential for managing OA. For an optimal evaluation, the complete holistic examination of the individual is crucial rather than just focusing on pain alone (NICE, 2014). Figure 1.10 describes the pain as a biopsychosocial sensation influenced by various factors such as the presence of other conditions, other musculoskeletal pain (MSK), non-restorative sleep, fatigue, traumatic experience, anxiety, or depression (Kloppenburg et al., 2019). The general management approach is similar for all OA-affected people. However, the anatomical site of the pain, the joints involved, and the characteristics of the individual would influence the development of the individualised management plan.

Several guiding bodies provide recommendations for managing OA, and the ones mentioned in this thesis are primarily based on guidelines by NICE, the European League against Rheumatism (EULAR), Osteoarthritis Research Society International (OARSI) and the American College of Rheumatology (ACR). NICE is the main governing and recommending body in the UK, and almost all the intervention protocols in the UK reflect NICE guidelines.

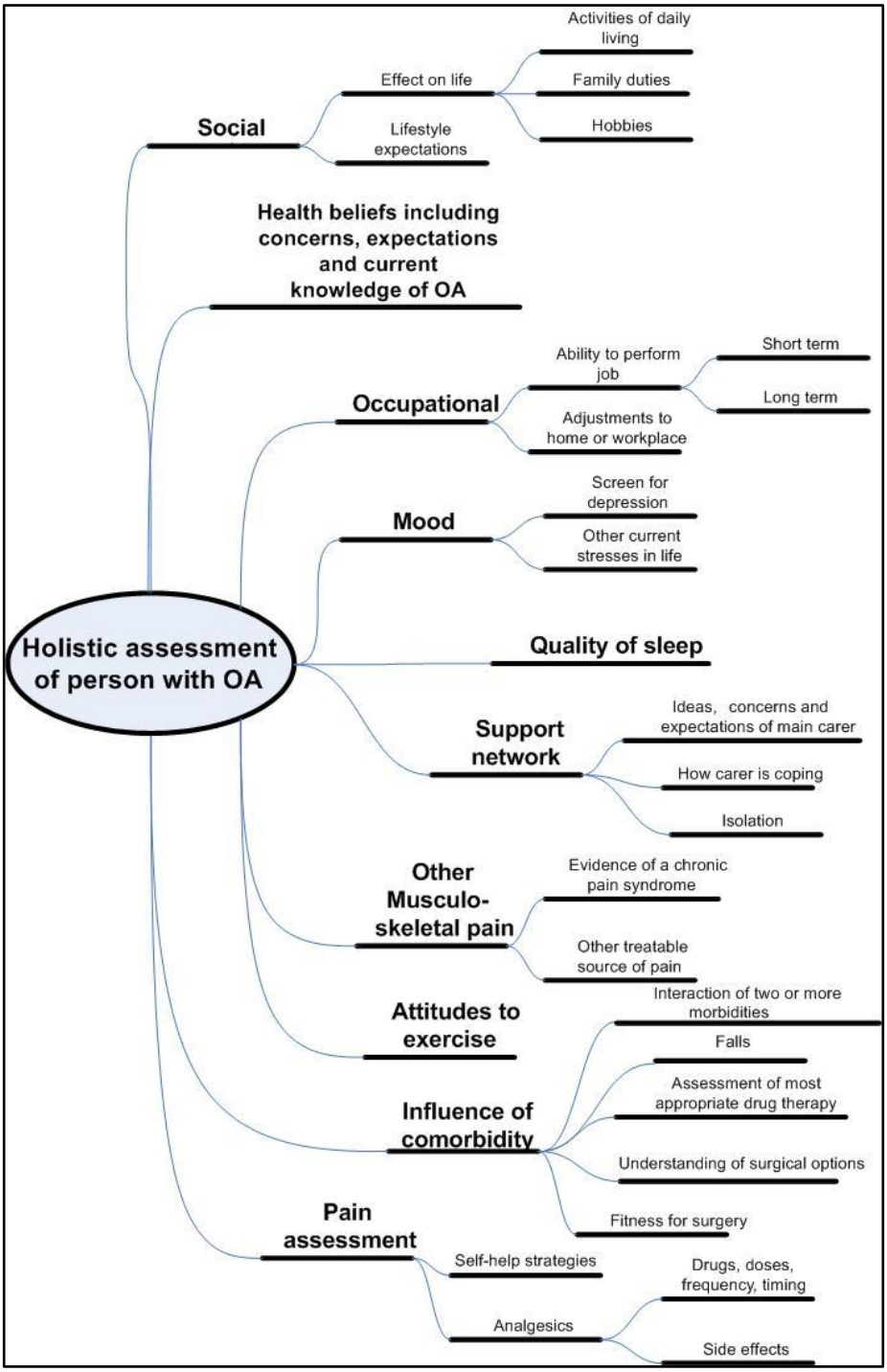


Figure 1.10. The holistic assessment of a person with OA. This Figure has been intended as an "aide memoir" to provide critical topics that might be important while assessing people with OA and vary according to every individual. According to the publisher, this image is presented without violating copyrights as the image is freely available to use (NICE, 2014).

1.8. Management of OA

To date, there has been no particular cure for OA. Generally, there is a requirement to provide information regarding OA. There is also shared decision making and individualised care offered by involving non-pharmacological and pharmacological therapies and eventually considering surgical treatment for worsening symptoms or resistance to other measures (Kloppenburg et al., 2019). The goal of management should be to achieve the best care possible to reduce pain, optimise function, improve participation, minimise adverse effects, and improve quality of life (Kloppenburg et al., 2019).

1.8.1. Treatment modalities for OA

1.8.1.1. Non-pharmacological treatment

Almost all clinical guidelines for OA recommend non-pharmacological interventions as core first-line treatment at all the stages of OA, regardless of the joint involved (Brand et al., 2013; NICE, 2014). The core non-pharmacological approaches are also advised by most current guidelines, especially for knee and hip OA, including education, exercise, and weight-reducing regimes if overweight or obese (Geenen et al., 2018; Hochberg et al., 2012; Kloppenburg et al., 2019; McAlindon et al., 2014; NICE, 2014; Zhang et al., 2008). Other treatments such as Tai Chi, balneotherapy, acupuncture, and transcutaneous electric nerve stimulation (TENS) are some of the more highly debated non-pharmacological options recommended by just a few guidelines. However, EULAR policies also include psychological and sleep interventions as options for the overall management of OA pain (Geenen et al., 2018).

Education is a crucial part of any management and underpins the success of any treatment, including for people with knee and hip OA, and can be delivered in numerous ways (Brand et al., 2013; Mazzuca et al., 1997). The ACR recommendations highlighted the importance of self-management programs for people with OA (Hochberg et al., 2012). The main aim of education programs is to create awareness regarding the nature of OA, its causes, associations, possible outcomes, and individualised treatment options. Once fully informed, they can play an essential role in shared decision-making for optimal OA treatment. However, the reported effect size of education programs for pain relief had been relatively modest (ES 0.06; 95%CI 0.02, 0.10) (Chodosh et al., 2005; Fernandes et al., 2013; Zhang et al., 2010a).

In many countries, Rheumatology societies provide brochures, leaflets, or booklets containing information regarding OA, which may be given during consultations, and websites such as Versus Arthritis UK and the Arthritis Foundation websites in the USA that can be useful for patients.

Secondly, it is a common misconception in people with OA that regular physical activity might cause further damage to their joints (Doherty et al., 2016). The musculoskeletal system has been designed for movement and being sedentary can be detrimental to all musculoskeletal tissues. Furthermore, exercise was considered an effective treatment modality for knee and hip OA to improve pain and physical impairment (Jamtvedt et al., 2008; Zhang et al., 2010a). There are two main types of exercise. Firstly, local muscle strengthening exercises, which can reduce pain, improve function and proprioception. It also helps to restore the reduced balance and decreases the susceptibility of falls in people with painful knee or hip OA. Secondly, aerobic exercises, which can ease the pain through different mechanisms, such as increasing descending pain inhibition. It also improves the sleep quality and well-being in people with OA associated with co-morbidities. Both are recommended as core treatments. EULAR guidelines have published convincing evidence for the effectiveness of exercise in reducing pain (ES 0.40; 95%CI 0.30, 0.50) and improvement in function (ES 0.37; 95%CI 0.25, 0.49) for knee OA and, to a lesser extent for hip OA (ES 0.38; 95%CI 0.08, 0.68) and hand OA (Fernandes et al., 2013; Kloppenburg et al., 2019). Even though exercise is an evidence-based treatment that is highly recommended by guidelines, many international surveys have reported that it is not being used effectively to treat OA (Li et al., 2011; Paskins et al., 2014). Additionally, poor adherence often reflects inadequate education and motivation as another potential barrier to exercise for achieving its benefit. Other factors such as age, sex, education levels of patients, and degree of disability may also challenge the effectiveness of exercise for OA (Brand et al., 2013).

A SR of effective weight loss in participants with OA has reported significant improvement in symptoms, with the pooled effect size for improvement in pain and function as 0.20 (95%CI 0.00, 0.39) and 0.23 (95%CI 0.04, 0.42), respectively, following an average of 6.1kg (95%CI 4.7, 7.6) weight loss (Christensen et al., 2007). Additionally, mechanical loading and malalignment exacerbate pain in weight-bearing joints (Yusuf et al., 2011).

The use of orthotics, for example, shoe inserts or knee braces, could help minimize excessive loading, reduce pain, and potentially reduce the structural progression of OA (Lafeber et al., 2006). These were relatively inexpensive though RCTs evidence favouring the benefit of knee bracing or laterally wedged insoles in people with knee OA was not convincing (Brouwer et al., 2005; Roddy et al., 2006). Observational studies reported symptomatic improvement from laterally wedged insoles for medial compartment knee OA (Anandacoomarasamy et al., 2010). Such devices and appropriate footwear (thick compressible soles and no raised heel) were advocated for pain relief. Similarly, a walking stick might help unload a painful knee or hip joint. In the absence of RCTs, these assumptions are purely based on expert opinions and patient experience (Anandacoomarasamy et al., 2010). The nine SRs published between 2006-2009 have supported the effectiveness of acupuncture in the treatment of OA, especially for improving OA pain (Zhang et al., 2010a).

Lastly, the application of local heat might be beneficial for chronic pain, and conversely, the application of local cold heat could help acute pain exacerbation. However, there is little research evidence to support this treatment option because it is impossible to blind patients to heat and cold treatment (as with walking sticks and many other physical interventions). Still, it is an inexpensive and safe adjunct to pain management, especially for hand and knee OA.

1.8.1.2. Pharmacological treatment

Pharmacological treatment options are the mainstay for alleviating pain. Many pharmacological options are available for OA, and individuals often rely on them for many years. Pharmacological interventions for OA pain can be the sole treatment option, or an adjunct therapy with core non-pharmacological interventions are suggested to alleviate pain.

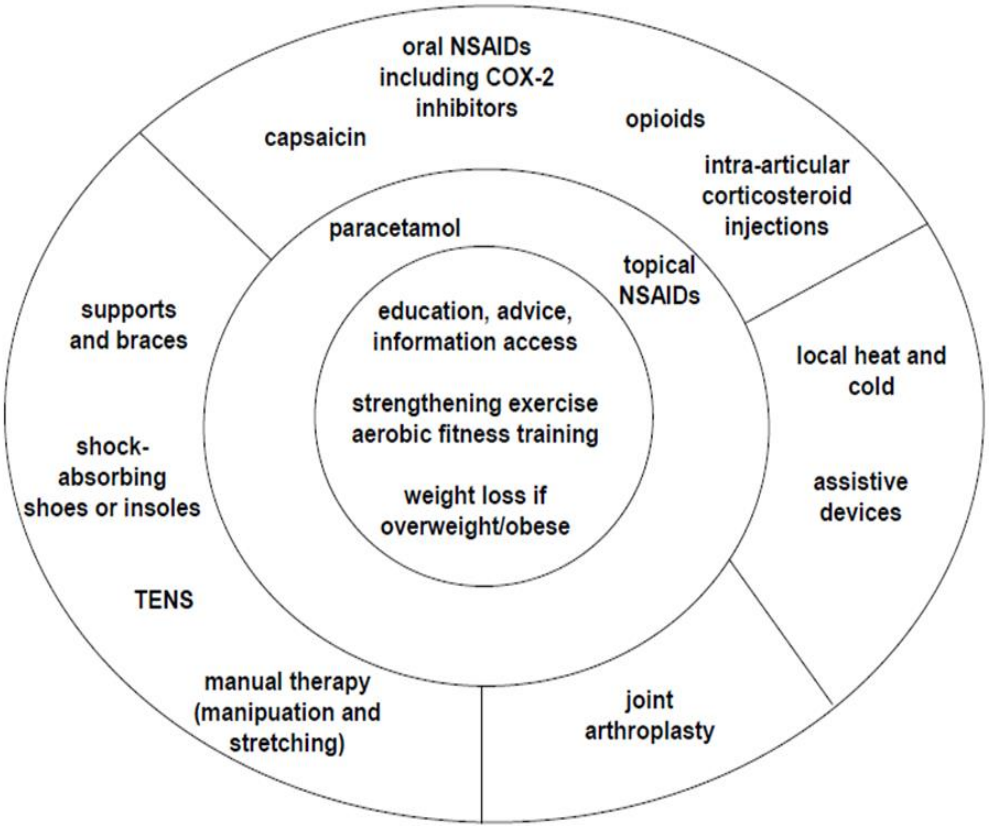


Figure 1.11. NICE emphasizes the core options approach for recommended treatments. First-line treatment options are placed in the centre, then first-line analgesics are in the second ring, followed by other interventions in the outer ring Conaghan et al. (2008). Presented with permission from British Medical Journal publishing group limited.

The main aim of analgesics is to reduce pain and support the maintenance of physical function. However, their ability to cause adverse effects can limit their usage. Therefore, a general principle for managing OA is to use local topical analgesics first, where possible. If required, move on to oral-systemic painkillers and only progress to more potent pain relief as needed. Guidelines suggest that choosing a drug depends on the balance of effectiveness and safety, in addition to cost and availability, as described in Figure 1.11 (NICE, 2014) According to NICE (2014), topical NSAIDs were considered the first-line treatment for hand and knee OA (Jordan et al., 2007; Kloppenburg et al., 2019; NICE, 2014; Zhang et al., 2005;

Zhang et al., 2008). Topical Capsaicin is another highly advised topical agent made from chilli peppers that bind specifically to the subtype one vanilloid receptor (TRPV1) on peripheral nociceptive C fibres (Frias et al., 2016). At first, it may cause a burning discomfort. The continuous application might relieve the pain by depletion of the neurotransmitter substance-P. The meta-analysis of 28 RCTs (7,372 participants) comparing capsaicin to placebo in people with OA suggested that it is well tolerated and may be recommended for peripheral joint OA to alleviate pain (Persson et al., 2018b). In contrast, the ACR recommendation for topical capsaicin is limited to hand OA and is not recommended for knee OA (Hochberg et al., 2012).

The next step in managing OA is oral systematic analgesics, including paracetamol, NSAIDs, coxibs, and opioids. Paracetamol is widely available and is the first systemic analgesia on the WHO-pain ladder, which is also the standard reference for analgesics in NICE guidelines (Hochberg et al., 2012; NICE, 2014; Zhang et al., 2005; Zhang et al., 2008). The justification for its recommendation is based on its widely accepted safety profile, even with long-term usage. However, this belief has been questioned in a systematic review of cohort studies (Roberts et al., 2016). They reported that long-term consumption of paracetamol is not safe and can cause cardiovascular, gastrointestinal (GI), and renal adverse events and increased risk of mortality, as primarily observed with NSAIDs. Based on these findings, the OA guidelines might need revision in the future in terms of long term usage of paracetamol (Battaggia et al., 2016). For example, the updated EULAR guidelines now acknowledged the safety concerns related to paracetamol and recommended it as the preferred oral analgesic merely for limited periods (Kloppenburg et al., 2019). Paracetamol-related complications are also the focus of this PhD project. A detailed discussion regarding the long-term usage of paracetamol is described in section 1.9 of this thesis.

The other widely recommended systemic oral analgesics are NSAIDs and specific cyclo-oxygenase-2 (COX-2) inhibitors (coxibs) which are reserved as a second-line option if there is an insufficient response to either local treatment or oral paracetamol (Hochberg et al., 2012; McAlindon et al., 2014; NICE, 2014; Zhang et al., 2005; Zhang et al., 2008). NSAIDs are the second most commonly used oral analgesics after paracetamol for OA treatment (Day et al., 2013; Pelletier et al., 2016).

Regulatory authorities highly recommend these analgesics from both sides of the Atlantic to treat people with OA, RA, ankylosing spondylitis, acute gout, and juvenile idiopathic arthritis (Simon et al., 2016). The selection of NSAIDs is limited, and there is a strong recommendation to be prescribed in combination with proton-pump inhibitors (Kloppenburg et al., 2019). Numerous studies have demonstrated the effectiveness of oral NSAIDs in managing symptomatic OA. The SR/MA of published randomised controlled-placebo trials suggested that NSAIDs, including coxibs, were significantly better than placebo in reducing pain and improving functional impairment in knee OA (ES 0.32; 95%CI 0.24, 0.39 and ES 0.29; 95%CI 0.18, 0.40, respectively) (Bjordal et al., 2007). The SR of placebo-controlled trials suggested that NSAIDs are effective, especially for hip OA, with the effect size for pain relief 0.69 (95%CI 0.12, 1.26) (Zhang et al., 2005). The head to head comparison of NSAIDs and paracetamol further reported an aggregated effect size of RR 0.20 (95%CI 0.10, 0.30), indicating a relative effectiveness of NSAIDs to control OA-pain (RR 1.24; 95%CI 0.10, 1.41) and being highly popular with patients (RR 2.46; 95%CI 1.50, 4.12) (Zhang et al., 2004). However, even these studies did not advocate the long term recommendation of oral NSAIDs for OA (Bjordal et al., 2007). The reason explained is the association of long-term usage of oral NSAIDs with adverse effects on the GI tract, kidney, cardiovascular (CV) system, skin, and respiratory tract. The harmful effects associated with NSAIDs relate primarily to the inhibition of COX-1 (Bannwarth, 2006). GI complications are considered the most significant adverse effects ranging from mild dyspepsia (a common reason to discontinue NSAIDs) to severe life-threatening perforation, peptic ulceration, and bleeding (PUB). The evidence from RCTs and epidemiological studies both support the strong association between the use of conventional NSAIDs and PUB (Ofman et al., 2002). Laine had reported an annual incidence of PUB of approximately 2.5-4.5% in people receiving traditional NSAIDs (Laine, 2003). The reported increased risk of PUB from nine cohort studies was RR 2.7 (95%CI 2.10, 3.50) (Ofman et al., 2002).

NSAID usage is also strongly associated with increased risk for cardiovascular events. The reported differential cardiovascular risk in a SR suggested diclofenac as having the highest risk with RR 1.40 (95%CI 1.16, 1.70) followed by rofecoxib (RR 1.33; 95% 1.00, 1.79) and the least modest risk reported for ibuprofen with RR 1.07 (95%CI 0.97, 1.18) (McGettigan et al., 2006). In contrast, lower doses have not been associated with increased risk (McGettigan et al., 2006). The SR/MA for athero-thrombotic complications of COX-2 inhibitors and NSAIDs demonstrated a serious CV event in 0.9% of people taking NSAIDs with RR 1.16 (95%CI 0.97, 1.38); however, it was not statistically significant (Zhang et al., 2008).

Abnormal intraglomerular changes may explain nephrotoxicity associated with NSAIDs. The use of angiotensin-converting enzyme (ACE) inhibitors may increase this detrimental effect through inhibition of the counteracting influence of ACE-II on the vasodilation of the afferent arteriole, thus reducing glomerular pressure (Bouvy et al., 2003). Specifically, it is common in patients who already have reduced renal perfusion, for example, in shock or with reduced intravascular volume. NSAIDs tend to induce renal sodium retention, resulting in peripheral oedema in patients with a history of heart failure (Perazella, 2002). Therefore, oral NSAIDs have well-known gastrointestinal, cardiac, and renal adverse effects that limit their usage.

For more resistant moderate to severe OA pain, opioid analgesics have been proposed as an efficient option by EULAR guidelines and the American Pain Society. The SR/MA of 18 placebo-controlled RCTs of opioids had shown moderate to large effect size to reduce pain intensity with ES 0.78 (95%CI 0.59, 0.98) and moderate ES for physical function improvement (0.31, 95%CI 0.24, 0.39) (Avouac et al., 2007; Zhang et al., 2010a). However, long term use of opioids has been reported to associate with weight loss, sarcopenia, cognitive impairment, cancer, and shortened survival (Guerriero, 2017). Furthermore, the tolerability of opioids is poor, as observed in two SRs that reported high drop-out rates due to side effects with an odds ratio (OR) of 3.96 (95%CI 3.43, 4.56) and pooled RR of 1.49 (95%CI 1.35, 1.63), respectively (Da-Costa et al., 2014; Gehling et al., 2011).

Additionally, opioids might predispose OA-people to an elevated risk of falls, fractures, cardiovascular, gastrointestinal, and kidney adverse effects (Chou et al., 2015; Pelletier et al., 2016).

Intra-articular corticosteroid injections are used most commonly for OA, especially when an effusion is present, particularly during a "*flare of symptoms*" either in knee OA or hip OA that cannot be managed with other medications (Hochberg et al., 2012; McAlindon et al., 2014; NICE, 2014). Several RCTs have confirmed the short-term efficacy of intra-articular corticosteroids compared to placebo (Lane, 1997). In contrast, a recent SR/MA of multiple intra-articular corticosteroids (IACS) has reported no better than placebo for long term usage, and their safety has yet to be confirmed (Ayub et al., 2021).

Thus, the safety of oral NSAIDs in GI and CV concerns is widely established, and accordingly, management advice has been modified over the last ten years. However, opioid use for OA pain remains a significant concern. The perceived safety of paracetamol is still controversial. Therefore, it is essential to monitor its long-term adverse events closely.

1.8.1.2.1. Trends in prescriptions for OA

It has been predicted that the burden of OA will increase because of the ageing of the population and the increased prevalence of obesity. Usually, a stepwise management plan is advised for managing OA, starting with topical NSAIDs and paracetamol. If the initial therapy is not sufficient to relieve OA pain, it is followed by the next step, i.e., intake of oral NSAIDs and opioids are used further if required.

An observational study that analysed The Health Improvement data (THIN) in the UK found that initial prescriptions for OA (occurring within 30 days after the date of diagnosis of incident OA) for topical NSAIDs, paracetamol, and oral opioids had a higher incidence compared to oral NSAIDs during 2000-2016 (Zeng et al., 2021). Furthermore, a sharp increase in topical NSAID prescriptions, 12.8% from 4.7%, was observed in 2016, especially after the 2008 NICE guidelines recommendation of topical NSAIDs as the first-line treatment of OA in the UK (Zeng et al., 2021).

The prescription of paracetamol is quite diverse, 0% in Germany to 6% in Spain and 10.7% in the UK (Kingsbury et al., 2014; Zeng et al., 2021). The rate of paracetamol prescription increased from 8.0% to 14.4% in 2011, followed by a slight decrease of 10.7% in 2016 in the UK (Zeng et al., 2021). In Belgium, a positive trend was observed in the overall prescriptions of paracetamol for people with knee OA with an average annual percentage change (AAPC) of 6.7 (95%CI 5.6 to 7.7) during 1996-2015 (Spitaels et al., 2020). This variation in prescribed medication for OA between countries could be due to recommendations by several guidelines and differences in health system funding (Kingsbury et al., 2014). For example, the prescription rate of paracetamol may be low in countries where medical consultation and prescription costs exceed its counter price. However, the medical outcome resulting from non-prescribed medications is always a significant concern. It may lead to discrepancies in calculating the actual use of drugs when paracetamol is used as non-prescription medication, as over-the-counter usage may go unrecorded or unreported. It becomes highly important to evaluate the risk-benefit ratio of paracetamol, especially when it is widely used over the counter and considered the first-line treatment option in all chronic pain conditions such as OA.

The usage of prescribed NSAIDs was highest in Germany (82%) and lowest in France (47%) (Kingsbury et al., 2014). Furthermore, in 2002, the USA National Ambulatory Medical care survey demonstrated a decline in oral NSAID use during 1989-1998, especially in the older population (Ausiello et al., 2002). Yu and Colleagues analysed the UK based CPRD-dataset and notified a similar trend for oral NSAIDs, i.e. a significant decline after 2004 (Yu et al., 2017). This decrease in the NSAIDs prescription might suggest the awareness of risks associated with oral NSAIDs intake for OA. In comparison, NSAIDs were a highly prescribed medication for prevalent cases of knee OA. The prevalence of NSAID prescriptions in people with knee OA was higher than paracetamol use in Belgium (29.4% versus 19.2% in 2015 and 28.4% versus 5.3% in 1996) (Spitaels et al., 2020).

The US-based cross-sectional study with multimodal treatment patterns for OA showed that paracetamol and opioids (current and ever) prescription were exponentially higher in the severe pain group compared to oral NSAIDs (Nalamachu et al., 2020). A substantial increase in opioid medication was observed from 31% to 40% between 2003 and 2009 in the USA (Wright et al., 2014). In the UK, the prescription for oral opioids also rose from 3.8% in 2000 to 9.0% in 2013, showing no further changes in the trend (Zeng et al., 2021). For weak opioids, the AAPC was 4.0 (95%CI 0.9, 7.3), and for glucosamine, the AAPC was 8.6 (95%CI 2.4, 15.1). A significant increase from 1996 to 2003 was observed for opioids, with an AAPC of 9.0 (95%CI 2.5, 16) for the people with knee OA in Belgium (Spitaels et al., 2020). However, this trend decreased from 2003 to 2015 with an AAPC of 2.0 (95%CI 3.7, 0.3). This may reflect the impact of guidelines on managing OA pain to consider opioids only if other analgesics produced no effect on OA pain (Bedson et al., 2016). However, as OA continues to be a disease burden, the public health impact of greater opioid use requires conscientious monitoring.

The concomitant prescription of gastro protective therapy and oral NSAIDs remained suboptimal, even if the patients had a prior history of peptic ulcers. A tremendous geographical variability was observed for opioids in the UK: Scotland had high rates of oral opioids prescriptions, Northern Ireland had high transdermal opioids, and the trend of using oral opioid medication was highest in the deprived parts of the country (Zeng et al., 2021). Women, the elderly population, people with obesity, current alcohol drinkers, current smokers, and those with a prior history of GI or cardiovascular events were the highest users of oral opioids in the UK (Zeng et al., 2021).

1.8.1.3. Surgical

Invasive surgical procedures are generally performed for people with significant clinical disabilities. Evidence of structural OA and conservative interventions have failed to improve their symptoms sufficiently. The primary surgical interventions for OA, predominantly knee or hip, are joint debridement with lavage, osteotomy, and partial or total joint replacement.

It has been reported in a Cochrane review of RCTs and quasi-RCTs that joint lavage, with or without debridement, has modest benefit in reducing the pain of knee OA at three months. The reduction in pain was 0.3cm, and the improvement in function was 0.2cm on a 10cm visual analogue scale (VAS) in comparison to sham lavage (Reichenbach et al., 2010). NICE does not recommend such treatment for OA. Apart from lavage, the main aim of other surgical options, such as osteotomy, is to prevent the progression of OA (Katz et al., 2010).

Lastly, total joint replacement (TJR) is a thoroughly recommended surgical procedure in all guidelines as an appropriate treatment option for people with severe OA resistant to more conservative management. The evidence from observational studies favoured significant improvements in pain, function, and quality of life following total joint replacement (Jones et al., 2000). No, RCTs comparing TJR to sham replacement have been undertaken.

Guidelines further recommend trapeziectomy, arthrodesis or arthroplasty for hand-OA, total or uni-compartmental knee replacement and osteotomy for knee-OA, and osteotomy, surgical procedures to preserve the joint or total hip replacement for hip OA (Jordan et al., 2003; Karlson et al., 2003; Katz, 2006; Katz et al., 2010; Kloppenburg et al., 2019; Zhang et al., 2003).

1.9. Introduction to paracetamol

Paracetamol is a non-prescription, inexpensive, and widely available drug. Generally, it is considered very safe, which largely explains its widespread usage worldwide. It is present in many formulations, including short-acting or immediate release, long-acting or modified release. In 2011, the Food and Drug Administration (FDA) revised the dosage of paracetamol, and in 2017 the European Medicines Agency Pharmacovigilance Risk Assessment Committee (PRAC) ceased the marketing of the modified release of paracetamol due to safety concerns (Burgess, 2011; Koletic et al., 2019).

1.9.1. History of paracetamol

The first use of paracetamol in humans was credited to Mering in 1893 (Bertolini et al., 2006; Prescott, 2000). The discovery of paracetamol was purely by chance when a similar molecule named `acetanilide' was prescribed as an antipyretic and analgesic to a febrile patient with an infestation (Prescott, 2000). However, unlike acetanilide and phenacetin, paracetamol was recognized as non-carcinogenic at its recommended doses. Initially, paracetamol was launched with aspirin and caffeine as `Trigesic' in the United States during the 1950s (Silverman et al., 1992). Subsequently, the occurrence of agranulocytosis in three patients led to its removal from the market even though those side effects were not attributable to paracetamol itself (Silverman et al., 1992). In 1953, it was marketed again as Panadol and highly promoted by the Sterling-Winthrop Company. Comparatively, it was considered safer than aspirin, especially in children and in people with peptic ulcers (Duong et al., 2016). TYLENOL Elixir and Panadol became popular in the UK for children and adults, respectively. Finally, in 1963, paracetamol was included in the British Pharmacopoeia and was made available as non-prescription over-the-counter medication (Duong et al., 2016). Since then, it has gained wide acceptance and popularity due to its apparent low incidence of adverse events and minimum interaction with other pharmaceutical agents. In the 1980s, the use of high-dose aspirin was significantly associated with an increased risk of Reye syndrome in children (Prescott, 2000). This became a turning point in paediatric analgesics options. It allowed paracetamol to become a standard reference medication for all age groups, either as an antipyretic or an analgesic, and it gained immense popularity (Graham et al., 2013).

Subsequently, a commercial demise was seen for phenacetin due to its risk of haematological toxicity and analgesic nephropathy (Bertolini et al., 2006). Paracetamol is an active metabolite of phenacetin, and its chemical structure is shown in Figure 1.12.

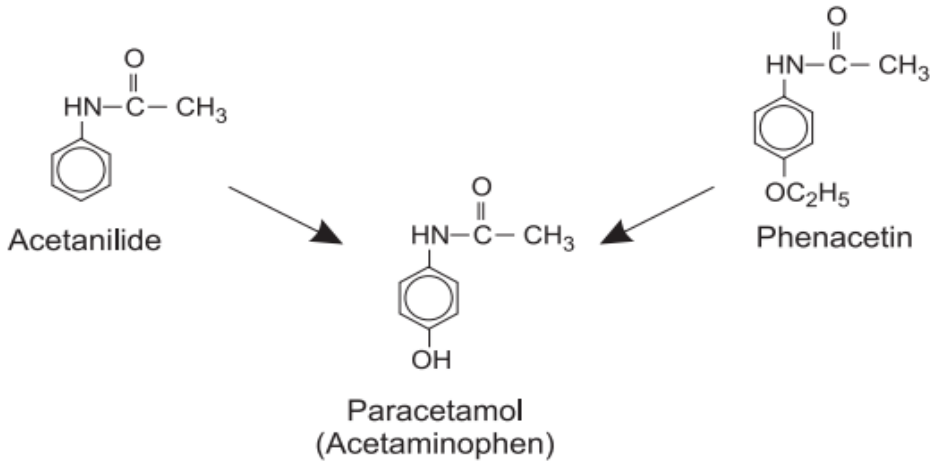


Figure 1.12. Chemical structure of analgesic aniline derivatives. Reference: (Jóźwiak-Bebenista et al., 2014). It is presented with permission from the Polish Pharmaceutical Society.

During the 1960s and 1970s, concerns were raised regarding the safety profile of non-prescription drugs. In the 1970s-1980s, phenacetin was combined with various mixtures such as `Saridon'. Later it was withdrawn from the market in America as its long-term use was linked to kidney damage and carcinogenicity (Bannwarth et al., 2016; Jóźwiak-Bebenista et al., 2014). In 1966, it was recognized that an overdose of paracetamol could cause fatal liver damage. Apart from that, paracetamol consistently maintained its safety record and replaced phenacetin as the first option analgesic and antipyretic. Even until now, paracetamol has been considered a first-line analgesic in the WHO additive pain ladder, shown in Figure 1.13, and to reduce fever in many patients, including children, pregnant women, and the elderly population, for minor headaches and non-inflammatory joint-pain conditions such as OA (Prescott, 2000).

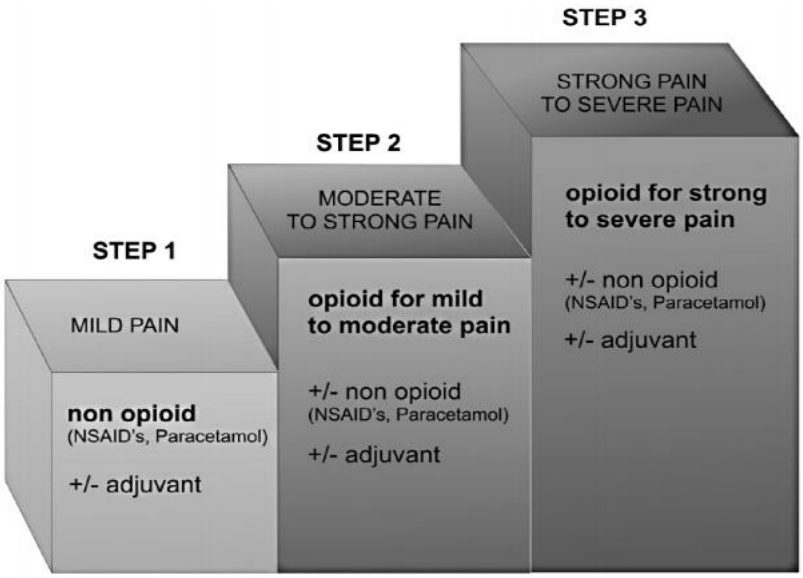


Figure 1.13. Paracetamol is on the WHO analgesic pain ladder criteria of using analgesics that consider the individual intensity of the pain source. Reference: (Jóźwiak-Bebenista et al., 2014). It is presented with permission from the Polish Pharmaceutical Society.

1.9.2. Mechanism of action of Paracetamol

Paracetamol was discovered 100 years ago and has been in use now for more than half a century. Advocated as a first-line treatment therapy for OA pain, its mechanism of action is still open to question. Most importantly: 1) whether it has central or peripheral actions or both; 2) targets opioidergic, serotoninergic, or COX systems; and 3) the associated side-effects need further confirmation (Mallet et al., 2017). For the last three decades, it has been thought that paracetamol acts centrally and is a weak inhibitor of prostaglandin production by cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) (Hinz et al., 2012; Jóźwiak-Bebenista et al., 2014). Based on Vivo results, Graham et al. (2005) explained that paracetamol's effects are similar to selective COX-2 inhibitors. Paracetamol may suppress the concentration of prostaglandins in experiments.

This concept was based on the assumption by Flower and colleagues that paracetamol has ten times more capacity to inhibit prostaglandin production in brain tissue than in spleen tissue (Flower et al., 1972; Graham et al., 2005).

After extensive research by Graham and Colleagues, the hypothesis of paracetamol acting centrally through inhibition of cyclooxygenase (COX) isoform derived from a similar gene as COX-1 and COX-2 was rejected (Graham et al., 2005; Hinz et al., 2012). There was no measurable inhibition of prostaglandins in the broken cell experiments; however, a significant suppression was observed in intact cells. Therefore the mechanism of action of paracetamol, defined as the suppression of COX-isoform, is still debatable (Hinz et al., 2012). In addition, paracetamol had no inhibitory effect on peripheral COX enzymes holding its widely accepted superior safety profile over oral NSAIDs.

Alternatively, the published studies highlighted the inhibitory tissue-dependent impact of paracetamol on central and peripheral COX enzymes, explained in sections 1.9.2.1 and section 1.9.2.1.1 (Hinz et al., 2012). This debate has raised questions regarding the formerly underestimated COX-related side effects of paracetamol (Hinz et al., 2012).

1.9.2.1. Mode of cyclooxygenase inhibition

Although paracetamol and NSAIDs both have analgesic and antipyretic properties. Paracetamol lacks apparent anti-inflammatory effects. Unlike NSAIDs, it is not classified within the NSAIDs group (Jóźwiak-Bebenista et al., 2014). All the conventional NSAIDs inhibit the transformation of arachidonic acid (AA) to prostaglandin H2 (PGH2). This stage is influenced by prostaglandin-H synthase (PGHS), more appropriately called COX, which comprises iso-enzymes COX-1 (PGHS-1) and COX-2 (PGHS-2) (Jóźwiak-Bebenista et al., 2014). However, PGHS is a bi-functional enzyme that includes two different enzymatic activities - COX and peroxidase (POX). AA is converted into PGH2 in two steps: firstly, COX-site produces the unstable intermediate hydro-peroxide, prostaglandin G2 (PGG2) which is further transformed to PGH2 via POX (Figure 1.14.) (Sharma et al., 2013).

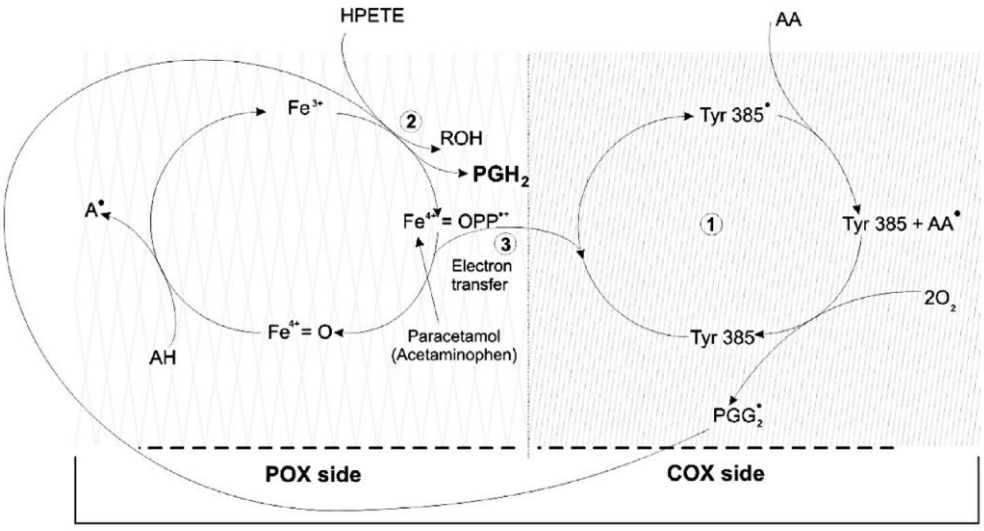


Figure 1.14. Mechanism of action of paracetamol. As shown in the image, paracetamol reduces an iron cation in the protoporphyrin ix radical (fe4+=opp*+) in the peroxidase (POX) part, contributing to a lower amount of tyr385* radical formation reference: (Jóźwiak-Bebenista et al., 2014) presented with permission from the Polish Pharmaceutical Society.

Prostaglandin H2 (PGH2) acts as a substrate for the cell and tissue-selective prostanoid synthases and isomerases. It is further catalysed into different prostaglandins of the D (PGD2), E (PGE2), and F (PGF2) series, the endogenous regulators and prostacyclin (not a prostaglandin) (Jóźwiak-Bebenista et al., 2014). They all have different biological and anti-inflammatory activities. The traditional NSAIDs and coxibs inhibit COX by competing with arachidonic acid to enter the COX (Jóźwiak-Bebenista et al., 2014). This selective mode of action to inhibit COX may result in adverse effects of traditional NSAIDs such as gastric ulceration and imbalance in homeostasis. In contrast, the enzymatic activity of COX, which relied on it for being in an oxidized form, and paracetamol acts as a reducing agent while interfering indirectly and reducing co-substrate at the POX site (Sharma et al., 2013).

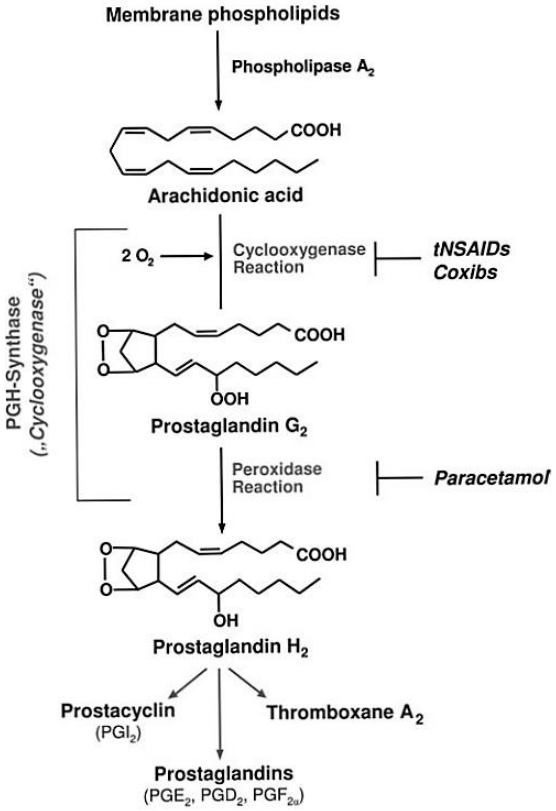


Figure 1.15. The biochemical functions of the cyclo-oxygenase enzyme and pharmacological targets within its two activity sites. Unlike NSAIDs, paracetamol may function as a reducing agent within the peroxidase site by quenching a radical responsible for propagating the cyclooxygenase reaction. Reference: (Hinz et al., 2012). Permission was granted by British Medical Journal Publishing Group limited and European League against Rheumatism.

1.9.2.1.1. COX-2 inhibition by paracetamol

To date, two studies have suggested a selective COX-2 inhibitory action of paracetamol illustrated under different clinical conditions (Hinz et al., 2012). In their experiment on the whole blood of 5 healthy subjects who had consumed one gram of paracetamol, Hinz and colleagues reported that paracetamol could suppress COX-2 monocyte up to 80% (Hinz et al., 2008). This inhibition rate was quite similar to NSAIDs and coxibs, but it could not reach the level of COX-1 obstruction (i.e., >95%) to inhibit the function of platelets. The paracetamol-induced COX-2 inhibition was short-lived. Therefore, frequent administration is required to provide continuous 80% COX-2 inhibition (Hinz et al., 2012). Secondly, in an acute inflammatory and tissue injury model, it was found that one gram of paracetamol is a selective inhibitor of COX-2 dependent prostaglandin E2 (PGE2) formation in the case of low concentrations of arachidonic acid, as explained in Figure 1.15 (Lee et al., 2007).

1.9.2.2. Analgesic properties of paracetamol

The predominant explanation for the analgesic activity of paracetamol lies in the central nervous system (CNS), which is highly debatable (Flower et al., 1972; Smith, 2009). The most widely accepted theory is its positive effects on descending serotonergic inhibitory pathways. Although it also interacts with eicosanoid systems, opioidergic systems, and nitric oxide pathways. It is also hypothesized that signals from endocannabinoid pathways may activate the effect of paracetamol on serotonergic inhibition pathways (Smith, 2009). According to experimental studies using animals, it is suggested that paracetamol might affect neuropathic pain through cannabinoid receptors (Curros-Criado et al., 2009; Dani et al., 2007).

Therefore, overall it can be concluded that there are multiple mechanisms to account for the analgesic activity of paracetamol (Smith, 2009).

1.9.2.3. Antipyretic properties of paracetamol

It is believed that paracetamol exerts its antipyretic effect through COX-2 inhibition in the hypothalamus (Flower et al., 1972). Paracetamol attains similar cerebrospinal fluid (CSF) levels to the serum by crossing the blood-brain barrier (Anderson et al., 1998). The maximum duration for decreasing temperature and providing pain relief is 1-2 hours. The levels of central nervous system (CNS) prostaglandin E2 (PGE2) increase during pyrexia, and paracetamol administration causes a fall in these levels (Feldberg et al., 1972). Primarily, paracetamol prevents COX production of PGE2, which lowers the thermoregulatory point (Aronoff et al., 2001).

1.9.2.4. Anti-Inflammation properties of paracetamol

Initially, paracetamol was classified as an NSAID (Ghanem et al., 2016). However, it was later demonstrated that paracetamol was an ineffective anti-inflammatory drug (Ghanem et al., 2016). This dictum could result from older studies claiming no effect of paracetamol in suppressing significant inflammation in RA (Boardman et al., 1967; Ring et al., 1974). The high extracellular concentrations of arachidonic acid and peroxide in rheumatoid tissues reduce the ability of paracetamol to show an effect on prostaglandin synthesis (Graham et al., 2005; Ouellet et al., 2001). Also, paracetamol does have some weak anti-inflammatory properties through its peripheral COX-inhibition (Hinz et al., 2012).

Certainly, paracetamol can decrease tissue swelling associated with oral surgical treatment in humans, similar to ibuprofen (Bjørnsson et al., 2003).

Several animal studies have indicated that paracetamol can inhibit oedema formation in the rat carrageenan footpad model (Honore et al., 1995; Smith et al., 1998).

1.9.3. Pharmacokinetics properties of paracetamol

1.9.3.1. Absorption of paracetamol in the body

The routes of administration for paracetamol are oral, intravenous, or per rectum. Oral administration is followed by rapid absorption from the GI tract. The systemic bioavailability of paracetamol is dose-dependent and varies between 70-90% (Forrest et al., 1982; Prescott, 1980). However, the serum concentration of paracetamol does not directly correlate with its antipyretic or analgesic effects (Bannwarth et al., 2003). Several factors can influence the oral absorption rate of paracetamol. For example, being healthy, having an empty stomach, and taking metoclopramide can increase absorption, whereas post-prandial intake and taking pethidine, propantheline, or diamorphine can delay absorption (Forrest et al., 1982; Prescott, 1980).

1.9.3.2. Distribution of paracetamol in the body

The rate of distribution of paracetamol in the body is rapid. The distribution volume bound to red blood cells varies between 10-20% (Forrest et al., 1982). Based on the assumption that the antipyretic and analgesic effect is located centrally, its efficacy can be estimated from the concentration of CSF and plasma. Peak CSF concentrations of paracetamol occur in 4 hours after a single intravenous dose of paracetamol (Bannwarth et al., 1992). However, the elimination rate of paracetamol is shorter in plasma compared to CSF, being 2.4 hours and 3.2 hours, respectively (Bannwarth et al., 1992). According to one open-label study in children, the highest paracetamol CSF concentration was detected 57-minutes after oral administration (Kumpulainen et al., 2007). This rapid and significant transfer into the central nervous system (CNS) can enable immediate central analgesic and antipyretic action of paracetamol, especially when administered intravenously (Kumpulainen et al., 2007). However, it was unclear whether the adverse effects of paracetamol are due to its pharmacokinetics or pharmacodynamics properties (Kumpulainen et al., 2007).

1.9.3.3. Metabolism and Elimination of paracetamol

A major part of paracetamol is metabolised, and only a small amount (2-5%) is excreted in the urine without any transformation. It is metabolised mainly in the liver, intestine, and kidney (Prescott, 1980). Sulphate and glucuronide are its primary metabolites, and a small proportion of these are converted and oxidized into a highly reactive alkylating metabolite through mixed hepatic function (Prescott, 1980). Usually, reduced glutathione keeps it in an inactive form, and it is excreted as cysteine or mercapturic acid (Prescott, 1980). It is well recognized that higher than recommended doses of paracetamol can cause acute hepatic impairment and results in reduced glutathione covalent binding of raised metabolites with vital cell nutrients (Prescott, 1980).

Similarly, it can cause renal necrosis dependent on the activity of microsome enzymes and the availability of glutathione (Prescott, 1980). The plasma half-life of paracetamol in healthy and young people is approximately 2 hours (ranging from 1.5-2.5) (Prescott, 1980). Despite claims that the metabolism of paracetamol in older people is impaired due to prolonged half-life or sulphate conjugation, the plasma half-life in the elderly is also approximately 2 hours (Prescott, 1980). However, the plasma half-life of paracetamol is declined in people with chronic liver disease. In the context of paracetamol poisoning, the prolonged half-life of its plasma concentration is considered an index of severe liver damage (Prescott, 1980).

In healthy people, the mean renal elimination of paracetamol is 13ml/minute. The clearance of paracetamol through the kidney relates to urine flow and not its ph. However, in renal impairment, although the plasma half-life of paracetamol is not prolonged, the conjugates are retained and accumulate.

1.9.4. Clinical efficacy of paracetamol in OA

According to best practice guidelines shown in Table 1.7, Paracetamol is recommended as a reference standard for managing knee and hip OA pain with a therapeutic dose of 3-4g. Despite being the first treatment standard for OA, paracetamol has an increasing concern regarding its analgesic efficacy. The 2006 Cochrane review performed more than a decade ago reported a modest reduction in pain for OA (ES 0.13; 95%CI 0.04, 0.22) in comparison to a previous MA in 2004 (ES 0.21; 95%CI 0.02, 0.41) (Towheed et al., 2006; Zhang et al., 2004).

Table 1.7. Treatment recommendations in different guidelines for OA.

	joint-specific OA-pain	Details of treatment recommendation
NICE	hand, knee	paracetamol and topical NSAIDs are the first lines of pharmacological treatment options (NICE, 2014)
ACR	hand	topical NSAIDs are highly recommended(Hochberg et al., 2012)
	knee	paracetamol and topical NSAIDs ahead of oral NSAIDS(Hochberg et al., 2012)
	hip	paracetamol is highly recommended as the first line of treatment option (Hochberg et al., 2012)
EULAR	hand	prescribed for a limited duration of time, taking into account its adverse effects (Kloppenburg et al., 2019)
	knee	paracetamol is the preferred first step in terms of oral pharmacological options and for a long time (Jordan et al., 2003)
OARSI	knee	preferred in OA-patients without comorbidities (McAlindon et al., 2014)
WHO	any kind of pain	the first step in the WHO pain ladder (Jadad et al., 1995)

OA - osteoarthritis, NICE - National Institute of Health and Care Excellence, EULAR - European League against Rheumatism, OARSI - Osteoarthritis Research Society International, WHO - World Health organisation.

Additionally, according to two OARSI-OA recommendations, the ES of paracetamol was only 0.18 (95%CI 0.11, 0.25) and 0.14 (95%CI 0.05, 0.23) for pain associated with OA (McAlindon et al., 2014; Zhang et al., 2010a). In addition, based on better quality evidence by excluding the studies with methodological limitations in the sensitivity analysis, the ES became non-significant for pain associated with knee OA (0.10; 95%CI -0.03, 0.23) (Zhang et al., 2010a). It also demonstrated there was no significant effect of paracetamol on stiffness with ES 0.16 (95%CI -0.05, 0.37) or physical function ES 0.09 (95%CI -0.03, 0.22).

Machado and colleagues also reported a minimal short-term effect of paracetamol in people with OA. High-quality evidence derived from 9 clinical trials showed that paracetamol had significant but not clinically meaningful effects for a short duration in people with hip or knee OA with a weighted mean difference (WMD) of -3.7, (95%CI -5.5, -1.9) for pain and -2.9 (95%CI -4.9, -0.9) for disability (Machado et al., 2015). For the duration of <2 weeks, the effect of paracetamol on pain was much lower with a WMD of -3.3 (95%CI -5.8, -0.8), and there was no immediate impact on function (WMD -1.7; 95%CI -6.0, 2.6). Similarly, the 2017 network MA of analgesic medication for knee and hip OA management concluded that there was no role for single-agent paracetamol in treating pain in OA irrespective of dose (Da-Costa et al., 2017). These findings were also consistent with an observational study that reported insufficient pain relief after >2 weeks of physician-prescribed medication for people with moderate to severe pain for knee OA (Conaghan et al., 2015).

All these findings on the effectiveness of paracetamol in people with OA were based on short term clinical trials. A recent MA that examined the long-term efficacy of analgesics for OA identified that there was only one RCT of >12 months which compared paracetamol 2600mg/day to naproxen 750mg/day in people with OA (Gregori et al., 2018). This RCT concluded similar efficacy between paracetamol and naproxen among patients who completed the two years of the study (Williams et al., 1993). However, the withdrawal rate was substantially higher in the paracetamol group (22%) than in the naproxen group (16%), indicating that paracetamol might not have been as effective for OA pain causing more participants to withdraw from the study. Additionally, findings of a cohort study for multiple site joint pain (MSJP), which combined people with OA, back pain, and soft tissue disorders, showed that 62% of participants used paracetamol, out of which 26% stopped taking paracetamol, and 98% of them documented the reason that it was inadequate to relieve MSJP (Raja et al., 2016). A network analysis that investigated the effectiveness of pharmacological modalities for knee OA similarly reported that paracetamol was the least effective intervention among all the available interventions, including NSAIDs, opioids, and intra-articular injections (Bannuru et al., 2015).

Thus, there is substantial evidence of the inadequacy of analgesic benefits from paracetamol for people with OA compared to contemporary analgesics such as conventional NSAIDs (Bannuru et al., 2015; McAlindon et al., 2014).

From the above discussion, it can also be observed that inadequate pain relief is prevalent even though there is a range of available analgesics and is mainly associated with a significant functional loss with altered quality of life in people with OA.

1.9.4.1. Therapeutic dose

According to NICE guidelines, the maximum recommended dose is up to 4g/day of paracetamol for hip and knee OA (Zhang et al., 2010a). Due to its short half-life (approximately 2 hours), repetitive 1g-doses of paracetamol are required (Hinz et al., 2012).

However, there are several unclear issues regarding the efficacy and safety of paracetamol in the long term at its standard therapeutic dose. For instance, it has been reported in an observational study that the higher doses (>3g/day) of paracetamol can result in PUB in comparison to the lower amount of paracetamol with an HR of 1.20 (95%CI 1.03, 1.40) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a) (Rahme et al., 2008; Zhang et al., 2010a).

1.9.5. Adverse effects of paracetamol

So far, it has been assumed that paracetamol effectively relieves pain even though it has a negligible effect size with a relatively better safety record than NSAIDs. It is highly recommended that treatment selection should be based on the overall balance of several elements, including the level of effectiveness, safety, tolerability, acceptability, availability, and cost-effectiveness, and paracetamol was thought to be acceptable in all of these respects (Zhang et al., 2004). Recent OARSI OA recommendations have tempered the perceived safety of paracetamol because concerns have been arising regarding its safety in the literature, which is described as follows (McAlindon et al., 2014).

1.9.5.1. Hepatic

A higher than the recommended dose of paracetamol can cause acute liver failure. In the 1980s, the first fatal cases of paracetamol poisoning were reported in the United States, UK, and Europe (Ostapowicz et al., 2002). A similar study reported liver failure to be 2-3 times more commonly due to paracetamol exposure at its usual therapeutic dose than NSAID exposure (Gulmez et al., 2013).

Liver toxicity can result from either intentional or unintentional overdosing of paracetamol. Intentional single administration overdose is the most usual form of a suicide attempt from drugs, perhaps reflecting its broad accessibility. Unintentional, exceeded doses of paracetamol are also quite common. The main reason behind this could be that being an over-the-counter drug is perceived as safe, and sometimes people do not read the label or follow the instructions on "*how to administer the drug."* Therefore either the therapeutic dose may be miscalculated, or there may be excessive intake for >3 days (Ghanem et al., 2016). Concomitant intake of other non-prescription formulations, including paracetamol, can also result in overdose. However, it is essential to note that in some circumstances, paracetamol-exposed liver failure can also occur when paracetamol is taken at its regular therapeutic dose. Several well-reported attributable risk factors decrease the threshold level for paracetamol toxicity, such as alcohol abuse and the use of other medications. They all influence the activity of the cytochrome CYP450 enzyme nutrition and reduce the storage of thiols that have a protective effect on the liver (Ghanem et al., 2016).

The standard recommended dose of paracetamol is metabolised through conjugation and formation of paracetamol-glucuronide (40-67%) and paracetamol-sulphate (20-46%) (Dear et al., 2020; Ghanem et al., 2016). The oxidase enzymes, predominantly CYP2E1, help oxidise 5-10% of paracetamol, forming a highly reactive N-acetyl-p-benzoquinoneimine (NAPQI) (Ghanem et al., 2016). The NAPQI is neutralised after reduced glutathione (GSH) conjugated and eliminated as cysteine and mercapturic non-toxic conjugates in either urine or bile, as described in Figure 1.16 (Dear et al., 2020; Ghanem et al., 2016).

In case of excessive consumption of paracetamol, the conjugation process is saturated. In this case, paracetamol is then metabolised through oxidation to NAPQI. It results in glutathione depletion, leading to hepatocellular death (Dear et al., 2020; Ghanem et al., 2016).

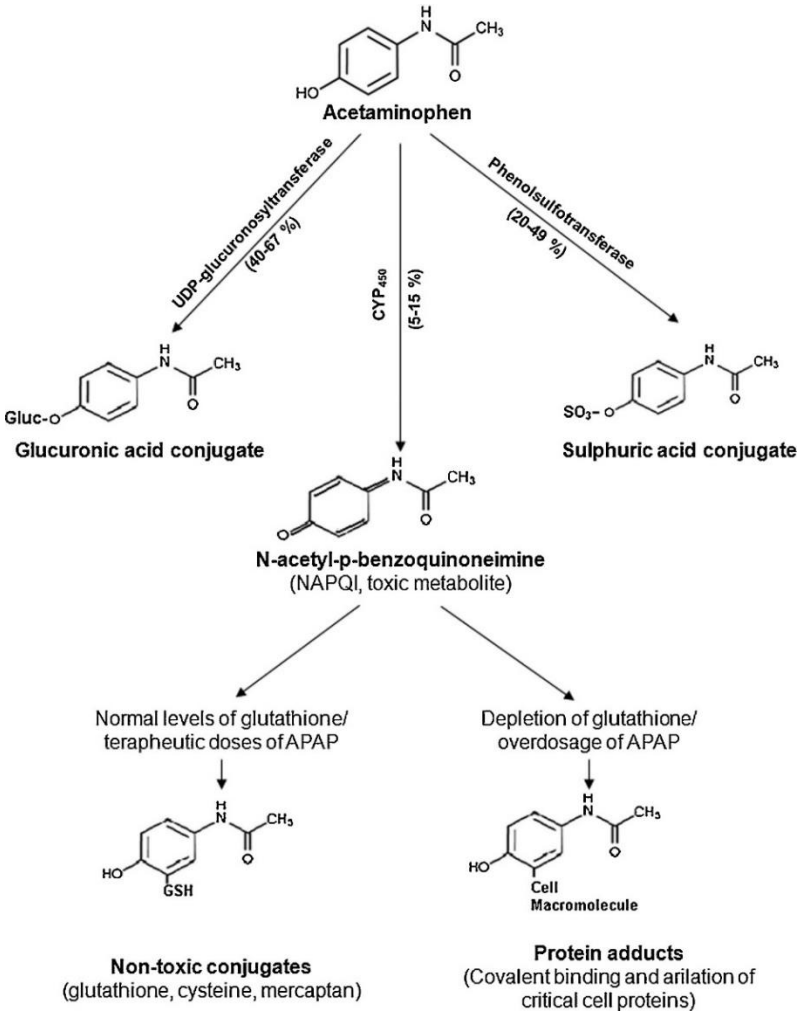


Figure 1.16. Different metabolic pathways of paracetamol in the liver at therapeutic or overdose amounts of paracetamol. Reference: (Ghanem et al., 2016). It is reproduced with permission from Elsevier limited.

There are mixed views about liver impairment. One SR and two RCTs have concluded that paracetamol is safe and can be used as a first-line analgesic even in alcoholic patients regardless of liver status at its maximum recommended daily doses (Courtney et al., 2002; Hayward et al., 2016; Kuffner et al., 1999; Kuffner et al., 2001).

In contrast, several other case reports stated that chronic intake of paracetamol at recommended doses could cause liver injury or idiosyncratic allergic reactions (Vitols, 2003). Equivalent results had been reported in a recent SR and MA for RCTs placebo trials that claimed to be high-quality evidence. This demonstrated that people taking paracetamol were more than three times more likely to have abnormal liver function tests with RR 3.8 (95%CI 1.9, 7.4) (Machado et al., 2015).

However, the clinical significance of this effect is still inevitable, and it appears prudent to monitor liver function in patients with alcoholism or liver disease who receive paracetamol (Graham et al., 2005).

1.9.5.2. Gastro-intestinal

Paracetamol is generally considered a safer drug when compared with NSAIDs in terms of GI side effects. However, the evidence from RCTs and observational studies contrast with each other regarding the safety profile of paracetamol. According to the MA of RCTs by Zhang et al (2004), paracetamol and placebo share a similar safety profile in people with OA. The MA also reported that paracetamol is less prone to cause GI upset than NSAIDs. The results from case-control studies and double-blinded RCTs that assessed healthy subjects endoscopically for GI effects of paracetamol reported that paracetamol causes no more clinically significant mucosal injury than placebo (Bannwarth, 2004; Graham et al., 2005; Lanza et al., 1998).

Additionally, few observational studies have questioned its safety and reported that it carries similar risks to NSAIDs (Courtney et al., 2002). The evidence also suggests that daily doses >2 grams can increase the risk of serious upper GI complications, including GI bleeding or perforation (De-Vries et al., 2010; Rahme et al., 2002; Rodriguez et al., 2001). The corresponding adjusted RR was 3.6 (95%CI 2.60, 5.10) for paracetamol and RR 4.1 (95%CI 3.60, 4.80) for conventional NSAIDs, respectively (Rodriguez et al., 2001).

1.9.5.3. Cardiovascular

There is enough evidence to support that long term use of NSAIDs can cause an increase in blood pressure with possible subsequent cardiovascular complications. However, unlike inflamed tissue, vascular endothelial cells have reduced peroxide levels that result in undisturbed COX-2 inhibition caused by paracetamol (Boutaud et al., 2002). It further corresponds with three prospective cohort studies, which reported that continuous intake of paracetamol is significantly associated with an increased risk of hypertension compared to non-users (Curhan et al., 2002; Dedier et al., 2002; Forman et al., 2007). The RR of incident hypertension was most marked in healthy middle-aged women, and results for paracetamol were similar to conventional NSAIDs ≥22 days every month (RR 2.00; 95%CI 1.52, 2.62 and RR 1.86; 95%CI 1.51, 2.28, respectively) (Curhan et al., 2002).

In contrast, the results from short-term RCTs for an association between paracetamol and blood pressure were inconsistent (Egan, 2002; Graham et al., 2005).

1.9.5.4. Renal side-effects

According to Graham et al. (2005), paracetamol at its standard therapeutic dose (≤4 grams daily) causes no renal side effects. However, there is some evidence available to support that long term paracetamol intake (≤3 g/day) can cause a slight reduction in renal function in women with an OR 2.04 (95%CI 1.28, 3.24) (Zhang et al., 2010a).

1.9.5.5. Hypersensitivity reactions

Unlike with NSAIDs, frequent use of paracetamol does not associate with an increased risk of asthma either in children or adults (Dharmage et al., 2011). However, an observational study by Kim et al. (2014) showed that paracetamol at therapeutic doses might exacerbate existing asthma, rhinitis, and urticaria (Kim et al., 2014). Similarly, an observational study reported a dose-response between paracetamol and asthma, with everyday paracetamol users having OR for asthma of 2.38 (95%CI 1.22, 4.64). The presumed causal link between asthma and paracetamol is COX-inhibition, as with NSAIDs (Courtney et al., 2002; Graham et al., 2005).

1.10. Justification of the study

The healthcare burden of OA is increasing. OA is a debilitating chronic condition associated with physical impairment and morbidity, especially in people ≥45 years, that often require long-term use of analgesics to alleviate pain and improve physical activity (Hochberg, 2012). Best practice guidelines advocate paracetamol as a first-line pharmacological treatment option for OA, even though it has a small effect size for pain relief. It is also the first treatment choice for the highly selected population, such as pregnant women or those who are contraindicated for more potent analgesics. This is mainly because of its low potential for drug-drug interactions and perceived safety.

However, the evidence regarding the association between paracetamol use, GI, CV, renal side effects, and all-cause mortality is debatable in RCTs and observational studies, as described in section 1.9.5 of this thesis.

Despite the widespread use of paracetamol for acute and chronic conditions, its harmful effects with long-term therapeutic use have been questioned due to its risk-benefit issues indicating a knowledge gap concerning how detrimental paracetamol could be when taken for a long time. According to some experimental studies, it has now been hypothesized that paracetamol can cause similar COX-dependent side effects analogous to NSAIDs. In a similar controversial yet influential hypothesis, this thesis attempts to identify the side effects of paracetamol through both the published literature and an observational study.

The main aim and objectives of this thesis are:

Aim: To examine the long-term safety of paracetamol in people with OA and the general population.

Objectives:

Objective 1: To systematically review the research evidence, including randomised controlled trials (RCTs) in people with OA and observational studies (irrespective of any specific underlying condition) on adverse effects of paracetamol.

Objective 2: To undertake a propensity-score matched cohort study to confirm the associations identified from the systematic review and examine the incidence of perforation ulcer bleeding (PUB), uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure in those exposed to paracetamol in the general population compared to unexposed people using electronic medical records of patients registered in UK general practices. Also, to examine the dose-response relationship between paracetamol and related adverse events using real-world data in the general population.

Chapter 2: Systematic review and Meta-analysis

2.0. The Concept

In 1976 Gene Glass highlighted the importance of statistical analysis regarding the great quantity of literature available rather than narrative discussion and coined the term “Meta-analysis” insight of “meta-mathematics”, “meta-psychology”, and “meta-evaluation” (Glass, 1976). This definition highlights the concept of combining all identical studies resulting in a large sample size despite having few dissimilarities (Glass, 1976).

Furthermore, there are six fundamental steps to perform a high-quality MA, which are explained as follows:

The first four steps are similar to that of SR in the MA.

Define the question: It is one of the essential components of the MA. The research question could be associated with any major public health issue to a controversial medical situation, which may further need adequate treatment as a potential solution to the current healthcare requirement of the community. For example, the research question for this thesis was based on the debate highlighted in NICE guidelines (2014) regarding paracetamol and whether to keep it as a reference standard for chronic pain conditions such as OA because concerns have been raised in the literature regarding its perceived safety and modest efficacy.
This step is highly important as it forms the foundation for the remaining steps.

Reviewing the literature: It can be achieved by going through various scientific resources such as electronic database search, controlled clinical reports, other biomedical databases, non-English literature, or grey literature such as thesis, reports from the pharmaceutical industry or the reference lists of relevant studies. It assures the researchers that all the relevant literature was considered. For the current SR/MA, 6 relevant databases were searched, including a reference list of the included studies explained in section 2.1.1.

Identification and Selection of the relevant studies: This step is based on the explicit inclusion and exclusion criteria described in section 2.1.2 for this SR/MA, reflecting the elements of the research question to identify the relevant studies. It is essential to ensure that one must identify all the relevant literature and include them for further examination at this stage.

Assess the quality of the included studies: The critical appraisal of every included research is vital to understand the strengths and weaknesses of that study. The reason is that the poor-quality studies might raise concerns regarding the validity of their findings, details given in section 2.1.3.3.

Create a summary effect measure: The quantitative method of summarising the literature findings differentiates MAs from SRs. The research question is answered in a SR by collecting, reviewing, and summarising all the empirical evidence that fits the previously set eligibility criteria. In contrast, MA is an objective, scientific, mathematical, and statistical two-step approach. Firstly, to calculate the effect size for each study to explain the observed treatment effect as described in detail in section 2.1.4.2. Then, to compile and analyse these different results such as ORs, RRs or means, differences in means, or HRs from more than two clinical trials or observational studies into summary effect measures which indicate the direction and magnitude of the relationship between treatment and an outcome, by calculating the weighted average of these statistics across the studies using an appropriate specific statistical technique, either fixed effect model or random effect model meta-analysis (details in section 2.1.4) (Garcia-Alamino et al., 2020). The approach to statistically aggregated results from numerous studies is quite reliable and comparatively more robust than individual study results (Higgins et al., 2011).

Presentation: Transparency is of great importance throughout the process of SR, promoted by following the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) recommendations (Moher et al., 2010). Therefore, there is a requirement to present the literature search findings using a visual flow chart of the number of studies included and excluded at every stage, as shown in Figures 2.2.1 and 2.3.1 in this thesis. Forest plots were used to present the meta-analysis results of this thesis, as given in the results section.

Subgroup analysis and sensitivity analysis:

The subgroup analysis includes stratifying the analysis based on different subgroups. For example, considering trials on males and females separately or the follow-up duration. It is conducted to evaluate the difference between each subgroup.

Further, sensitivity analyses were also performed to analyse if the results of this SR/MA change by modifications in the data. For example, the implication of including only high-quality studies or with large sample size.

This further concludes that if the estimates change based on excluding the poor-quality or small studies, the primary endpoint results need to be interpreted cautiously.

2.0.1. Importance of meta-analysis in the field of evidence-based medicine

In evidence-based medicine, MA is of paramount importance. It is regarded as a "*state of the art*" way of assuring that knowledge of the efficacy and safety of available treatments is based on the best available evidence. For example, the potential side effects can sometimes occur at a low incidence or rarely happen, making their effect challenging to measure from a single study. Therefore, a series of studies are often required to provide sufficient information to investigate the risk of these potential side-effects (Borenstein et al., 2011).

The other advantage could be that the MA uses explicit methods that limit bias and draw reliable and accurate conclusions that are easily communicated to healthcare providers. This may further reduce the delay in implementing research findings or generate new hypotheses regarding the subgroups for future research.

2.1. Methods for the Systematic review and conventional meta-analysis of the safety of paracetamol

The protocol for this SR/MA was registered in the PROSPERO database with registration number-CRD42017079645. This SR/MA followed the Cochrane Handbook for Systematic Reviews of Interventions guidelines (Higgins et al., 2011). The findings were reported according to PRISMA guidelines in the results section of this chapter (Moher et al., 2009). Unless specified, the analyses for SR/MA were conducted using Stata software (Stata Statistical Software: Release 15 and 16. College Station, TX: StataCorp LP).

2.1.1. Systematic literature search terms and strategies

RCTs and observational studies were identified through a systematic literature search. Both study designs had different eligibility criteria to address adverse effects associated with paracetamol exposure stated in Section 2.1.2. Therefore, the eligible RCTs and observational study reports were identified using two different comprehensive search strategies in the Medline database (Peryer et al., 2021). These search strategies were then modified according to other databases described in Table 2.1.1, such as Embase, PubMed, and Web of Science. For RCTs, the three main components, study design, disease, and intervention, were combined, as mentioned in Appendix 1.1 and recommended by Bramer et al. (2018). (1) terms for study design were 'randomised controlled trials', 'randomized controlled trials', 'random allocation', 'random*' and 'randomly'; (2) terms for OA were 'osteoarthritis', 'osteoarthrosis', 'knee osteoarthritis', 'hip osteoarthritis', and 'hand osteoarthritis'; and (3) terms for paracetamol were 'paracetamol', 'acetaminophen', 'analgesic', 'Tylenol' 'panadol', 'paracetamol', 'acamol' and 'acephen'. The search was limited to human studies, and there was no limit on language.

Similarly, there were three elements in observational studies intervention, study design, and outcomes, as demonstrated in Appendix 1.2. In contrast to RCTs, there was no specific underlying disease for the participants in the observational studies. The keywords for the observational data search were: 'paracetamol' and 'acetaminophen'; 'cohort studies', 'cohort$', 'case-control studies' 'case$ and control$' and 'observational studies'; and 'gastrointestinal bleeding' or 'duodenal ulcer' or 'peptic ulcer', 'heart failure' or 'cardiovascular disease' or 'cardiovascular failure' or 'myocardial infarction' 'acute renal failure' and 'kidney failure or renal failure.

Additionally, Medical subject heading (MeSH) terms were used to maximise the search fields scope and reduce the risk of missing relevant studies (Bramer et al., 2018). The search strategies for this SR also included a few search terms from a previous SR/MA and were expanded by adding more search terms identified through the internet (Leopoldino et al., 2019; Roberts et al., 2016). These search strategies were then combined using Boolean operators '*or*,' '*and*' and '*not*' to retrieve eligible reports.

2.1.1.1. List of databases searched

A comprehensive literature search was conducted using the following databases outlined in Table 2.1.1 from their date of inception until 31/08/2018. The updated investigation was performed on 20/07/2020. Several optimal databases were combined to avoid availability bias instead of searching only university subscribed journals (Bramer et al., 2017).

Table 2.1.1. List of databases and their years of coverage.

Name of databases	Description	Period
Medline	OVID	1946-2018
PubMed	OVID	1996-2018
EMBASE- Excerpta Medica database	OVID	1974-2018
Web of Science	Core collection	1900-2018
CINAHL- Cumulative Index of Nursing and Allied Literature (CINAHL)	EBSCO-host	All years
Allied and complementary- Medicine database (AMED)		1985-2018
Google Scholar		2018

OVID - objective view interactive design, EBSCO - Elton B. Stephens Company.

PubMed was also included in the search process because it is a free version of Medline and consists of the most revised studies that are still not updated in Medline (Higgins et al., 2011). The bibliographies of the included publications and previous systematic reviews were also screened for any additional eligible study to augment the search and avoid citation bias (Higgins et al., 2011; Higgins et al., 2019). A Google search alert was set up for any relevant RCTs or observational studies published.

Lastly, supervisors (Professor Weiya Zhang and Professor Michael Doherty) were also approached in time if they knew any newly published study.

2.1.1.2. Managing database-literature search output

Following the searches, the identified citations were collated and downloaded in Endnote 8.2 (Clarivate Analytic PA USA) by the first reviewer Jaspreet Kaur (JK). Duplicate sources were identified and removed using the Endnote software tool, which manages bibliographies. While retrieving eligible articles, a few segmented publications were characterised by similar research aims, methods, and results except for text similarity (Supak, 2013). Even the software failed to detect these duplicate publications, i.e., Salami publications. Such studies were counted as a single study to avoid double counting, and the references of these studies were combined to acknowledge them (Supak, 2013; Wager, 2015).

Furthermore, the articles were excluded at title screening only if related to parenteral paracetamol usage. When an article passed the title screening, the abstracts were screened to assess the eligibility of the study. At this stage, they were rejected based on the failed inclusion criteria, review articles, editorial letters, clinical practice guidelines, case reports, or case series. Then full texts were retrieved for those articles that had the potential to meet the eligibility criteria. At this stage, the studies were excluded if they lacked safety data to determine whether paracetamol use was associated with adverse clinical outcomes. The results achieved through this methodology were presented according to the PRISMA guidelines (Moher et al., 2015).

2.1.2. Inclusion and exclusion criteria

All RCTs related to the usage of paracetamol in participants with OA were eligible for inclusion. In contrast, it was not limited only to the OA condition for the observational studies, as described in Table 2.2. The abstracts were not included because they did not provide sufficient information.

The treatment duration was a minimum of one week. Further details of inclusion to assess the eligibility of any study and their exclusion criteria for both study designs are given in Tables 2.1.2 and 2.1.3. The eligibility criteria were based on four domains (PICO), Participants, Interventions/exposure, Comparator, and Outcomes (Bramer et al., 2018).

Table 2.1.2. Inclusion and exclusion criteria for RCTs assessing side effects of paracetamol in OA.

Domain	Inclusion	Exclusion
Participants	participants aged 18 years or older with OA (symptomatic and radiographic) at any joint	participants with other conditions such as RA, non-OA joint pain, post-operative pain, and injury,
Intervention	paracetamol – oral paracetamol at a standard therapeutic dose of 1g every 4-6 hours to a maximum of 4g/day	studies examined overdose of paracetamol concomitant use of paracetamol with other drugs. Studies reported only on the efficacy of paracetamol or follow up period was less than one-week studies comparing paracetamol with other treatments such as non-pharmacological interventions because there were insufficient safety data
Comparator	placebos, active comparators such as NSAIDs and Coxibs	
Outcome	gastrointestinal, cardiovascular, renal adverse effects and all-cause mortality	
Study design	single or double parallel, cross-over and N of one trial	non-randomised or quasi-randomised controlled trials, review articles, case reports, editorials, published studies that only have abstracts

NSAIDs - nonsteroidal anti-inflammatory drugs, OA - osteoarthritis.

Table 2.1.3. Inclusion and exclusion criteria for observational studies assessing side effects of paracetamol in OA.

Domain	Inclusion	Exclusion
Participants	participants ages 18 years or older for any underlying conditions	studies focusing on short-term pain from cancer, tooth extraction, headache, surgery, injury, or overdose
Exposure	studies analysing paracetamol at its regular therapeutic dose report any adverse outcomes in humans	studies examining overdose of paracetamol or intravenous administration of paracetamol
Comparator	paracetamol non-users	
Outcome	gastrointestinal, cardiovascular, renal adverse effects and all-cause mortality	
Study design	cohort, case-control, nested case-control studies	

OA - osteoarthritis.

2.1.2.1. Study design

This SR/MA included reports from RCTs, either single or double-blinded, placebo-controlled trials, and parallel-group or crossover trials in people with OA. Although the MA in medicine predominantly uses data from the RCTs. However, sometimes RCTs might not be considered the optimal design for detecting side effects because of the given reasons:

1) They were underpowered to detect detrimental effects that were relatively rare or had a low incidence.
2) The follow-up duration was not long enough in the clinical trials.
3) RCTs were highly selective based on strict inclusion and exclusion criteria. For example, they might have excluded participants with co-morbidities.

Therefore, the non-randomised or observational studies such as cohort, nested case-control, or case-control studies with longer follow-up duration were also relevant and included to achieve the best evidence regarding the safety of paracetamol, irrespective of the underlying condition for which it was prescribed or being taken. The rationale to include observation studies regardless of the underlying condition was based on the assumption that the susceptibility of paracetamol causing adverse effects was similar across different disease groups. Therefore, it was worth analysing the safety profile of paracetamol without restricting it to one specific disease group.

2.1.2.2. Participants

RCTS

- Adults (≥18 years) with symptomatic or radiographically diagnosed OA irrespective of affected joint-site and not limited to the magnitude or period of symptoms explained in Table 2.1.2 were eligible for RCTs. The rationale for restricting the paracetamol use to people with OA in RCTs was due to the following reasons:
    - Firstly, the main objective was to identify the adverse effects of paracetamol in the longer term, and OA is one of the chronic pain conditions where paracetamol is prescribed for longer durations.
    - Secondly, due to logistical restrictions such as achieving a feasible number of papers for evaluation during the limited PhD period, the search was focused on RCTs related to people with OA since the other chronic pain conditions were abundantly reported in the literature.
- Studies that included people accessing healthcare at any level, for example, primary or secondary, or tertiary care, were included.
- If the RCTs reports were based on either a combination of RA and OA and it was not possible to extract the information related to OA patients, then those studies were excluded.

Observational studies

- All the participants aged 18 years or older with any underlying condition were included in observational studies. The justification for this inclusion criteria is that paracetamol is a highly prescribed analgesic for treating mild to moderate acute pain, chronic non-malignant pain, and fever. The mechanism of impairment and its susceptibility to adverse effects, such as GI and cardiovascular events, were assumed to be similar across participants with different conditions, which could be addressed together. Additionally, there were limited data on the harmful effects of paracetamol in the RCTs for the OA population. Therefore, it was worth analysing all available data for the whole adult population who take paracetamol for the long term, even if the studies were aimed at different disease conditions.

Lastly, the studies on short-term pain such as tooth extraction, headache, injury, and paracetamol overdose were excluded.

2.1.2.3. Intervention or exposure

RCTs

The intervention of interest in RCTs and observational studies was the consumption of oral paracetamol at its standard therapeutic dose (up to 4gm in 24 hours) in any formulation (Tablets, capsules, effervescent) for at least seven days.

If a study had more than two arms (e.g. two arms with different doses of paracetamol versus placebo), similar interventions were grouped as a single intervention (Higgins et al., 2011). Studies with two arms either comparing two different doses of paracetamol or comparing the same doses with varying formulations in both treatment arms were excluded (Bacon et al., 2002; Benson et al., 2009).

The data in the RCT studies comparing benefits or side effects of paracetamol with concomitant use of NSAIDs (for example, Ibuprofen) were also excluded, as shown in Table 2.1.2.

Observational Studies

There were different definitions of paracetamol exposure in the observational studies. For example, one of the studies defined it as "*i) first prescription patients who receive their paracetamol prescription at least 12 months after the start of CPRD data collection, who had not previously prescribed aspirin or other NSAIDs, ii) long gap, patients with at least six months between a preceding prescription for paracetamol, ibuprofen, aspirin or other NSAID and the current prescription for paracetamol, ibuprofen, or concomitant ibuprofen and paracetamol iii) repeat use with a low MPR, for patients who had been prescribed ibuprofen and/or paracetamol in the preceding six months. The MPR was defined "as the ratio of the duration of the previous prescription, to the time between that prescription and the current prescription (equal to <0.40), repeat use with a medium MPR, as above but with ratio equal to 0.40-0.59, repeat use with a high MPR, as above but with ratio equal to 0.60-0.79, vi) repeat use with a very high MPR, as above but with ratio equal to >0.8 and (vii) repeat use with no information on the number of days prescribed, and consequently no information on compliance (De-Vries et al., 2010)*."

The observational studies focusing on an overdose of paracetamol or intravenous paracetamol were excluded, as stated in Table 2.1.3.

2.1.2.4. Comparators

RCTs

In RCTs, the comparators were placebo or active treatments such as NSAIDs and Coxibs. The studies with multiple arms, for example (three interventions) paracetamol, placebo, and active comparator, were also included and compared individually with each comparator ((1) paracetamol versus placebo (2) paracetamol versus active group)) mentioned in Table 2.1.2. (Higgins et al., 2011).

Observational Studies

The comparators for observational data were non-users of paracetamol described in Table 2.1.3.

2.1.2.5. Outcomes of interest

RCTs

A hybrid approach was applied to capture the prespecified adverse effects of paracetamol or those that were not listed previously. For example, the outcomes of interest were decided a priori to the review, such as 1) GI adverse effects – GI bleeding, GI ulcer, any form of GI upset, dyspepsia, abdominal pain, "nausea and vomiting," and heartburn, or diarrhoea; (2) cardiovascular outcomes - myocardial infarction, incident hypertension, stroke, and ischaemia; (3) acute or chronic kidney diseases; and (4) mortality.

Although the main aim was to synthesize the data on the pre-specified outcomes described above, however, the "abnormal liver function" and "withdrawals due to adverse events" (i.e., the total number of participants who stopped the treatment due to an adverse event), and the "total number of participants who experienced any side effect" at least once during the trial were also found in the included studies. Therefore, they were also included as secondary outcomes.

Observational studies

For observational studies, the primary outcomes assessed were all-cause mortality, cardiovascular adverse events (incident myocardial infarction, hypertension, heart failure, or stroke), GI adverse events (incidence of upper GI bleeding, peptic ulcer), PUB, renal adverse events (Chronic renal failure defined as increased concentration of serum creatinine or decreased estimated glomerular filtration rate, acute renal failure, end-stage kidney failure).

2.1.3. Data collection

2.1.3.1. Data extraction

Data were extracted independently from included studies by the first reviewer (JK) using predesigned customised data extraction forms developed using Microsoft word. The data extraction form was based on the following information:

- Study identification: title, first author, and year of publication.
- General information
- Country
- Source of funding: commercial, non-commercial, not mentioned.
- Language: English or others
- Setting: hospital, community, or unclear
- Disease: site of OA pain - knee, hip, hand, or others
- Diagnostic criteria: symptomatic, radiographic.
- Methods
- Study type - randomised
- Blinded
- Placebo-controlled or comparative study
- Study design: parallel, cross-over, or “n of 1,” if crossover their wash-out period duration was recorded.
- Participant demographic features
- The number of participants and number of withdrawals.
- The number of withdrawals due to adverse events.
- Mean age, gender, and mean BMI.
- Intervention details
- Formulation and dose of paracetamol
- Type of comparator: placebo, NSAID or Coxibs.
- Treatment period.
- Frequency of the treatment.
- Outcome characteristics: GI, cardiovascular, renal, or mortality.

An adverse event refers to incident symptoms or an event (such as GI bleeding) that may or may not have been caused by the treatment.

Therefore, data were extracted from the reports if trials reported on the safety of paracetamol using the terms "*adverse drug reactions," "adverse*," or "*side effects*," or they explicitly mentioned that adverse effects might be related to paracetamol. Some trials also reported adverse events using laboratory investigations that were also examined if they were associated with the consumption of paracetamol. Adverse events were also categorised according to the severity of the reported events, such as "serious events."

The terms used to notify an adverse event were quite diverse. Therefore, the terms with similar meanings were grouped, such as diarrhoea or loose stools and GI-upset or flatulence. The hierarchy of extracting data for the primary endpoint results was intention to treat (ITT) analysis, modified ITT, and per-protocol analysis. To avoid double-counting, the data were only extracted if numerical values were provided for the number of participants reporting the side effects, not just the overall number of events reported. It is because some participants may suffer more than one event. In crossover trials, data were extracted according to the first phase and used for analysis. Details of using this data extraction form are provided in Appendix 2.1: Data extraction form for RCTs.

2.1.3.2. Data validation of review

The first reviewer (JK) conducted the title and abstract screening, full-text screening, data extraction, and the risk of bias. The second and third reviewers (BK, SG) already trained in conducting SR/MA repeated these steps independently on a sample of randomly selected citations. SG screened titles and abstracts of randomly selected 100 sources. BK further screened full text and conducted a risk of bias assessment for 10% of the randomly selected sample. The data extraction form was redrafted with a shorter version for data validation. BK extracted data for all the published reports in the English language using the shorter version of the validation form for 10% RCTs and 20% of the total observational studies (n=3 RCTs, n=9 for observational studies).

All differences in extraction between the two authors were resolved by reviewing the publication or by discussion between the reviewers, taking account of Cochrane guidelines for review (Higgins et al., 2019). If the reviewers could not reach a consensus, a senior researcher was approached for judgement (WZ or SG).

2.1.3.3. Study quality assessment

This SR/MA included two different study designs with varying eligibility criteria; therefore, different risk of bias tools were used to appraise the included studies (Peryer et al., 2021). The internal validity of all the included RCTs was assessed using a modified version of the risk of bias tool (RBT) recommended by the Cochrane collaboration (Higgins et al., 2019). The modified Newcastle Ottawa Scale (NOS) was used for observational studies (Peterson et al., 2011; Wells et al., 2004).

2.1.3.3.1. Modified Cochrane risk of bias tool

The seven characteristics assessed using the modified Cochrane RBT are as follows:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias (Higgins et al., 2011).

Compared to the previous narrative Cochrane RBT, the modified version has set domains scored as high, low, or unclear risk of bias (Hartling et al., 2009; Higgins et al., 2011). This objective manner of the tool helps avoid the inter-rater disagreement usually associated with subjective fields of the Cochrane RBT (Hartling et al., 2009). If the reported information was inadequate to make conclusions for bias, this was classed as “unclear” with verbatim notes from the reports. The judgement for each domain of the set question for RBT was strictly based on the Cochrane Handbook Chapter 8.5 (Higgins et al., 2011). The first three domains of modified RBT assessed the selection, performance, and detection bias and were scored as high, low, or unclear, based on included studies and explained in the Modified Risk of bias assessment for RCTs Guide in Appendix 2.2 (Higgins et al., 2011). The fourth domain measures attrition bias, and the judgement to determine the risk of bias depends upon a cut-off for acceptable drop-out rates, i.e. 5% (Schulz et al., 2002).

According to Schulz and Grimes (2002), a loss to follow-up for up to 5% was quite unlikely to introduce bias, whereas a loss of 20% was more likely to introduce bias. In case of disagreement, it was resolved either through discussion or by a senior member of the team (WZ). The risk of bias was presented for every domain in the included studies.

2.1.3.3.2. Modified Newcastle Ottawa Scale (NOS)

The modified Newcastle Ottawa scale is based on three domains: recruitment of the study groups, analysis-based comparability, and determination of either exposure to paracetamol (case-control studies) or outcome reporting (cohort studies). An example of modified NOS is presented in Figure 2.1.1 (and in Appendix 2.3) for a cohort study and case-control study in Appendix 2.4. The calculated score for modified NOS varies according to each domain. A star system was used to assess each item, and a maximum of one star was given for each component except comparability, where possibly two stars can be assigned.

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

No.	Criterion	Decision rule	Score (*=1, no*=0)	Location in text
SELECTION				
1	Representativeness of the exposed cohort	a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population* b) Not satisfying requirements in part (a), or not stated.		
2	Selection of the non-exposed cohort	a) Selected from the same source population* b) Selected from a different source population c) No description		
3	Ascertainment of exposure	a) Structured injury data (e.g. record completed by medical staff)* b) Structured interview* c) Written self-report d) No description		
4	Demonstration that outcome of interest was not present at the start of the study	a) Yes* b) No or not explicitly stated		
COMPARABILITY				
1	Comparability of cohorts on the basis of the design or analysis	a) Study controls for previous injury* b) Study controls for age* *Note:* Exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Alone statements of no differences between groups or that differences were not statistically significant are not sufficient.		
OUTCOME				
1	Assessment of outcome	a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g. imaging, structured injury data, etc.)* b) record linkage (e.g. identified through ICD codes on database records)* c) Self-report with no reference to original structured injury data or imaging d) No description		
2	Was follow-up long enough for outcomes to occur?	a) Yes (≥3 months)* b) No (<3 months)		
3	Adequacy of follow up of cohorts	a) Complete follow up – all participants accounted for* b) Subjects lost to follow up unlikely to introduce bias (<15% lost to follow up, or description provided of those lost*) c) Follow up rate <85% and no description of those lost provided d) No statement		
		SCORE:		

Figure 2.1.1. The modified Newcastle-Ottawa quality assessment scale for cohort studies.

The domains in the modified NOS for case-control studies are similar to those for cohort studies for selection and comparability, shown in Appendix 2.4. The only difference is in the last domain, "*exposure*," where the study is assigned a star if there was a structured record completed by medical staff. There was a possibility of providing an extra star if the interviewer was blinded to both cases/controls to ascertain exposure. If a similar method was used to define cases and controls, then the study was allocated another star. Lastly, a star was assigned if the dropout rates were similar in both cases and controls.

The number of stars provided was converted into Agency for Healthcare Research and Quality (AHRQ) standards as good, fair, or poor (Shamsrizi et al., 2020) as follows:

(1) Good quality: 3 or 4 stars in the selection domain, 1 or 2 in the comparability domain, and 2 or 3 for the outcome or exposure domain.
(2) Fair quality: 2 stars in the selection domain, 1-2 for comparability, and 2-3 in the outcome or exposure domain.
(3) Poor quality: 0 or 1 star in the selection domain, 0 stars in the comparability domain, and 0 or 1 for the outcome or exposure domain.

2.1.4. Data synthesis and analysis

For the safety of paracetamol, data from RCTs and observational studies were extracted separately, using the data extraction form mentioned in section 2.1.3.1 and managed using Microsoft access in Office 365 (Microsoft Corporation, Redmond, Washington, USA). Initially, a narrative synthesis was conducted. The extracted data were transferred from the access dataset to Microsoft Excel by generating queries. The dataset was cleaned, sorted, and formatted for analysis. The STATA 16-SE was used to conduct the statistical analysis.
The queries were further linked to the table of outcomes with study-level information. For example, it was used for sensitivity analysis, type of trial such as parallel or crossover linked with the outcome of interest.

2.1.4.1. Study stratification

Studies were stratified according to study design for pooled analysis, and effect size estimates were calculated separately for each stratum. Unless otherwise stated, cohort and case-control studies were stratified according to the definition of paracetamol exposure and comparable outcomes.

2.1.4.2. Data analysis

The quantitative synthesis was performed when there was a possibility to pool the studies for the primary or secondary outcomes. The fixed and random effects are the two most popular statistical models for meta-analysis. The pooled estimate is weighted by within-study variance in the fixed-effect model. The fixed-effect model could have been performed if the mathematical assumption that each study included in the meta-analysis share a common true effect size was justified (Deeks et al., 2021; Kanters, 2022). Another explanation for this might be that all the factors that may influence the effect size of the study might be similar across all the study populations. Hence, the effect size is likely to be the same across all the study populations. It implies that the observed effect size varies from one study to the other because it could be only due to random sampling error (Deeks et al., 2021; Kanters, 2022).

By contrast, the random-effect model was chosen, as it is the preferred method of taking account of significant variation between studies and within studies. For example, the studies were drawn from populations that were different from each other, e.g. studies done in the UK and Korea, the therapeutic dose of paracetamol in RCTs, duration of exposure in observational studies, and outcome definitions in the primary studies (Borenstein et al., 2011). These factors might influence the intervention effects. It further implies that the observed estimates differed across the studies for two reasons: firstly, due to a random sampling error and secondly, the true variation in the effect size across the included studies (Borenstein et al., 2011). Lastly, the random effect model was also a more appropriate choice for this meta-analysis of the safety of paracetamol because:

- It is a more conservative method than the fixed-effect model used in the prior meta-analysis
- It is based on the assumption that all the included studies do not estimate a similar intervention effect; however, they produce an estimate which follows a normal distribution across included studies (Deeks et al., 2021; Kanters, 2022).
- It is assumed to be more fit for the sampling distribution
- It did not restrict the standard effect size
- It allowed the generalisation of the conclusion to a broader population.

Most of the data had dichotomous outcomes, for example, gastrointestinal events yes or no. Accordingly, risk ratio (RR) (especially for RCTs) and hazard ratio (HR) or odds ratio (OR) (for observational data) were calculated to assess the degree of association between paracetamol exposure and its complications with 95%CI calculated to ascertain the level of certainty. 2x2 Tables were used to display dichotomous data, as shown in Table 2.1.4.

Table 2.1.4. Calculation of risk ratio.

	Event (yes)	Event (No)	Total number of participants
Intervention group	YI	NI	TI
Control group	YC	NC	TC

YI - participants in the intervention group with an outcome, NI - participants in the intervention group without an outcome, TI - total number of participants in the intervention group, YC - number of participants in the control group with an outcome, participants in the control group without an outcome, TC - total number of participants in the control group.

Meta-analysis is a two-stage process. In the first stage, using Table 2.1.4 and the following formula, a summary statistic (RR) was achieved for each study for the particular outcome because the data were primarily dichotomous.

Risk of developing event in the experimental group YI/TI

Risk of developing event in control group YC/TC

In the second stage, a combined effect was determined as a weighted average of the intervention effects estimated in each study using the formula:

Weighted average=sum of (estimate x weight)/sum of weights

When the intervention effect estimates were combined using all the included studies, inevitably, it incorporates the assumption of the random effect model that all those included studies were not estimating the same treatment effect. However, they evaluated a treatment effect that followed a distribution across the included studies.

The results from the MA were presented using the forest plot to show the summary statistics. The forest plot represents the effect size from all the included studies and MA. The pooled effect size is shown at the bottom of the forest plot as a diamond, with the weighted mean of all the effects from the included studies (Borenstein et al., 2011). Similar to confidence intervals, its width reflects its precision, and if the diamond meets the vertical line, it indicates that the overall results were not statistically significant.

A risk ratio of one indicates that the risk is the same in the paracetamol and comparison groups. However, if the RR is greater than one, this signifies a higher risk in that group. We

opted for RR as it is highly preferred to OR, especially by the clinician, as it is easy to interpret (Carlisle, 2007). The forest plots presented in this thesis estimated the effect size, which further reflects the strength of the association between exposure and outcomes (two variables) such as paracetamol and risk of GI complications or any other consequences. A risk ratio less than 1 means the risk is lower in one group than the other. The effect size was represented as blocks from the single studies. The horizontal line passing through these blocks in the middle indicates the CI. The P-value in each study represents the null hypothesis test corresponding to the 95%CI. The confidence interval displayed the probability of the effect size, which may fall between its two values, upper and lower, and it should not include the null value.

However, according to Hackshaw et al. (2011), the interpretation and reporting of borderline significant results could be challenging, especially in the case of rare events. Although, the borderline results may not be used as robust evidence regarding increased risk. In case if there was a clinically meaningful effect ascertained where the P-value was just above 0.05 or the upper or lower confidence interval limit was close to the null value, then it might be invalid to acknowledge it as “no-effect.” This is because it might reduce its likelihood of having an increased risk in case of “rare events.” In this case, if there was modest evidence for increased risk for the primary endpoints, they were reported as an indication or suggestion. For consistency of the estimates, the dose-response relationship was also examined if possible. If there were no events observed in either group, that study or variable was excluded from the MA (Leopoldino et al., 2019).

The included observational studies which had either reported summary statistics with 95%CI or sufficient details to estimate summary statistics were included in the meta-analysis. The RR, HR, or OR log was taken to analyse the data further. When there was significant heterogeneity, and it was not feasible to pool the data due to differences in outcome or reported a dosage of paracetamol, the individual summary statistics were presented for all results according to each study. In this case, the forest plots were shown only to determine the summary statistics visually.

Additionally, the comparisons were included in the separate meta-analysis as appropriate for studies with more than one active treatment group.

2.1.4.3. Data entry, missing information, and its calculations

Missing information was checked in the dataset and reviewed in the original study report to determine whether it was available. The corresponding author of the publication was contacted via email to request the relevant missing data required for this SR/MA. The reported information further analysed the data according to the intention to treat analysis (ITT).
If zero outcomes were reported, the standard contingency table adjustment was conducted according to Cochrane Handbook for Systematic reviews to ensure all study statistics had been defined appropriately (Higgins et al., 2011). One patient was added to each treatment and control group. This method had been used in previous SRs (Ofman et al., 2002).

2.1.5. Assessment of heterogeneity

A good MA helps to understand the differences in the results of the included studies in the meta-analysis. In epidemiology, the main aim of MA is to estimate the overall association and identify the source of bias and between-study variation. There might be several types of heterogeneity: for example, population heterogeneity which might be due to the location of the study conducted, age, gender, or type of condition. The other could be methodological heterogeneity, resulting from differences between the study designs or their analysis in the included studies in the MA. However, it was complicated to differentiate whether heterogeneity was due to population or methodological variation. The heterogeneity was determined using either chi-square or I2 statistics, where it was possible to pool the data. This statistical test provided an estimated measure of inconsistency amongst the study results due to heterogeneity in percentages (Higgins et al., 2003).

$I2 = 100\% \times (Q - df)/Q,$

Q: Chi-square statistic

df: degree of freedom of Q statistic (Ahn et al., 2018).

The predetermined value of I2 calculated as shown above lies between 0%-100%, where 0%-30% indicates no observed heterogeneity, and larger values show increasing heterogeneity, with 30%-60% referred to as moderate, 50%-90% substantial, and 75%-100% considerable heterogeneity that requires a careful explanation of results (Ahn et al., 2018; Higgins et al., 2011). The studies were sub-grouped according to clinical or methodological diversity if significant heterogeneity (I2 statistics >50%) was present.

2.1.6. Subgroup analysis

Subgroup analysis was performed if there was moderate heterogeneity present for the duration of the treatment. Subgroup analysis was also performed to check the trend for the duration of therapy in RCTs and observational studies.

2.1.7. Sensitivity analysis

Sensitivity analyses were undertaken to determine if the quality of trials could affect the primary endpoint results. The trials included in sensitivity analysis were only parallel trials, allocation concealment, duration of treatment, and sample size for RCTs. There were not enough studies to perform sensitivity analysis for observational studies.

2.1.8. Assessment of publication bias

The publication bias was examined in RCTs and observational studies. For each study design, a separate funnel plot of log risk ratio (RCTs only for the secondary outcome of any adverse events) and log odds ratio (case-control for GI outcome) were evaluated graphically for asymmetry resulting from non-publication of small or negative studies. Visual analysis of symmetry was used when there were sufficient studies in the meta-analysis (minimum of ten studies) for an outcome of interest. The Harbord test, a formal statistical test, was also used to examine publication bias. The P-value calculated using the Harbord test further indicated publication bias if it was less than 0.05, based on the assumption that the number of studies is equal to or more than 10 (Higgins et al., 2011). In contrast to the classical Eggers test, Harbord and colleagues proposed this test for dichotomous data (Egger et al., 1997; Harbord et al., 2006; Sterne et al., 2011). The funnel plot and Harbord test were conducted using the statistical package Stata 16.0.

2.2. Results for Systematic review and meta-analysis for the safety of paracetamol

2.2.1. Characteristics of studies (RCTs)

The systematic literature search produced 1,997 records (Medline: 839, Embase:137, AMED: 18, CINAHL: 48, PubMed: 510, and Goggle Scholar: 417). All the identified references of the studies were exported to the Endnote X8 software tool, where the duplicates were removed using this tool and left with 1,536 articles. The title screening was conducted for 1,536 articles, out of which 967 papers were further scrutinised. The full text was retrieved for 128 articles for further assessment and data extraction. The reasons for the exclusion at this stage were: an inability to extract outcomes data, concomitant treatment, or overdose of paracetamol, and not osteoarthritis or paracetamol related. Further, four articles were retrieved from the bibliography of the finally included articles, and two of them met inclusion criteria. The two studies were excluded due to the absence of a comparison group (Bacon et al., 2002; Benson et al., 2009) The update search in July 2020 found only one additional article that met the eligibility criteria and was included. Finally, there were 24 potential trials associated with oral intake of paracetamol in OA treatment, which met our inclusion criteria. Figure 2.1.1 represents a detailed screening process flow using a PRISMA flow diagram (Moher et al., 2010).

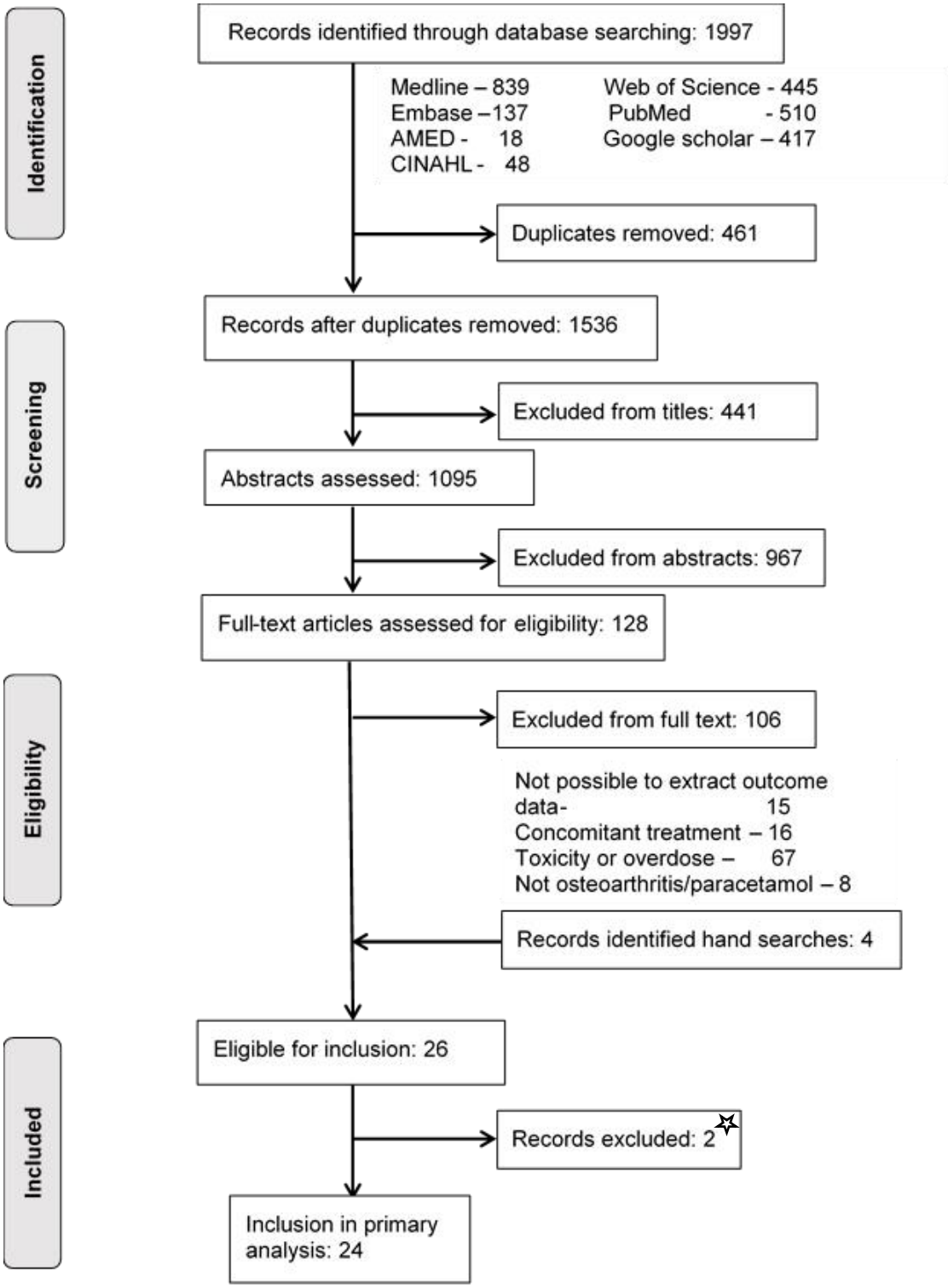


Figure 2.2.1. Flow Diagram showing the literature search results for appropriate randomised controlled trials of paracetamol in osteoarthritis. The ✧ denotes two studies that were excluded due to the absence of a comparison group (Bacon, Hole, North, & Burnett, 2002; Benson et al., 2009)

2.2.2. Description of included studies

The details of the 24 RCTs that met all inclusion criteria are summarised in Table 2.2.2. The 24 RCTs included 7,299 participants, with the majority being women (61%). The median age was 62.3 years, and the median BMI was 30.5 (range 27.7 to 33.2) kg/m2. Almost half of the studies included participants with knee OA, 33.3% comprised individuals with knee and hip OA, and 16.4% were undertaken in participants with OA of multiple joints. The diagnostic criteria for OA in the included studies were primarily based on the combination of clinical assessment and ACR classification criteria, followed by KL radiographic score, only ACR criteria, and other measures (Table 2.2.1). There were two studies that were solely based on clinical assessment by March et al. (1994); Yelland et al. (2007), and two studies used the EULAR OA classification system and Lequesne classification criteria by Lequesne et al. (1997); Miceli-Richard et al. (2004)

The publication year ranged from 1983 to 2018, and most (79%) of the studies were published after the Consolidated Standards of Reporting Trials (CONSORT) guidelines of 1996 (Begg et al., 1996). Of the included studies, 95% were published in English, 50% were conducted in the USA, 37% in Europe, 8% in Australia, and one study from Korea (Lee et al., 1998). In the absence of any native Korean speaker, the study from Korea was translated using Google Translate. One study by Pincus et al. (2004) comprised two separate RCTs.

There were 70% parallel-group trials and 20% cross-over trials conducted in multiple centres in included studies. Only 8% were N-of-1 trials undertaken in single centres. 21% were placebo-controlled trials (Altman et al., 2007; Amadio et al., 1983; Golden et al., 2004; Beaumont et al., 2007; Richard et al., 2004; Pincus et al., 2004; Prior et al., 2014; Reed et al., 2018; Zoppi et al., 1995), 21% three arms controlled trials (Golden et al., 2004; Pincus et al., 2004; Pincus et al., 2001) and 58% active-controlled trials (Boureau et al., 2004; Bradley et al., 1991; Geba et al., 2002; Golden et al., 2004; Gualda et al., 2007; Lee et al., 1998; Lequesne et al., 1997; March et al., 1994; Pincus et al., 2004; Schnitzer et al., 2009; Temple et al., 2006; Verkleij et al., 2015; Williams et al., 1993; Yelland et al., 2007). The number of participants, intervention dosage, and follow-up period are presented in Appendix 3 in Table 3.1.

The duration of treatment varied between 6-24 weeks in most of the studies. However, the shortest period was one week (Zoppi et al., 1995), and the longest was 104 weeks (Williams et al., 1993). The total oral dose of paracetamol and its regimen varied across the included trials from 1950 mg to 4000 mg per day. The details regarding the duration of follow-ups and dose of paracetamol are illustrated in Table 3.1 in Appendix 3 on P363.

Almost all the clinical trials underwent a washout period (i.e., stop using analgesics) before clinical trial, depending on the usage of painkillers. The washout periods recorded in different clinical trials were at least 12 weeks for oral corticosteroids, six weeks for intra-articular steroids, and from 3 days to 2 weeks for oral NSAIDs. However, in prior glucosamine intake, the washout period was six months, and two of the studies defined their washout period as "five half-lives."

Lastly, 71% of studies were commercially funded, 25% were non-commercially funded, and both commercial and non-commercial sources sponsored 4% of the included trials. The agreement between JK, BK, and SG was excellent for screening (97%), data extraction (94%), and risk of bias assessment (93%). The validation agreement depended on the items mentioned in the data extraction form in section 2.1.3.2.

Table 2.2.1. Summary of study characteristics.

Summary of included studies	No. of trials (%)
Site of pain	
Knee	12 (50.00)
Knee and Hip	08 (33.33)
Multiple	04 (16.40)
Diagnosis	
Symptomatic	02 (08.33)
Symptomatic and/or radiological	05 (20.83)
Symptomatic and/or KL	05 (20.83)
Symptomatic and/or ACR	06 (25.00)
Symptomatic and/or KL + ACR	04 (16.66)
Others	02 (08.33)
Publication year	
1980-1990	01 (04.00)
1990-2000	06 (25.00)
2000-2010	13 (54.00)
2010-till now	04 (16.00)
Study location	
USA	12 (50.00)
Europe	09 (37.50)
Australia	02 (08.33)
Korea	01 (04.17)
Language	
English	23 (95.83)
Others	01 (04.17)
Study design	
Parallel	17 (70.83)
Cross-over	05 (20.83)
N of one	02 (08.33)
Comparison group	
Paracetamol vs placebo	05 (21.00)
Paracetamol vs placebo vs active groups (more than two arms)	05 (21.00)
Paracetamol vs active agents (NSAIDS or Coxibs)	14 (58.00)
Source of funding	
Commercial	17 (71.00)
Non-commercial	06 (25.00)
Both	01 (04.00)

USA - United States, KL - Kellgren and Lawrence classification of osteoarthritis, ACR - American College of Rheumatology diagnostic criteria, NSAIDs - non-steroidal anti-inflammatory drugs.

Table 2.2.2. Summary of included studies.

Trial Name	Country	Funding Source	Design	Setting	Comparator	Joints affected
Amadio et al. (1983)	USA	non-commercial	crossover	community	placebo	knee
Bradley et al. (1991)	USA	non-commercial	parallel	community	ibuprofen	knee
Williams et al. (1993)	USA	non-commercial	parallel	community	naproxen	knee
March et al. (1994)	Australia	commercial/non-commercial	n of one trial	community	diclofenac	back, foot, hand, hip, knee
Zoppi et al. (1995)	Italy	non-commercial	parallel	community	placebo	hip, knee
Lequesne et al. (1997)	France	commercial	crossover	community	floctafenine	Femoro-tibial, hip, knee
Lee et al. (1998)	Korea	commercial	parallel	community	naproxen	knee
Pincus et al. (2001)	USA	commercial	crossover	hospital	diclofenac + misoprostol	hip, knee
Geba et al. (2002)	USA	commercial	parallel	community	celecoxib	knee
Miceli-Richard et al. (2004)	France	non-commercial	parallel	community	placebo	knee
Boureau et al. (2004)	France	commercial	parallel	community	ibuprofen	hip, knee
Golden et al. (2004)	Switzerland	commercial	parallel	community	naproxen, placebo	knee
Pincus et al. (2004) PACES-I	USA	commercial	crossover	community	placebo, celecoxib	hip, knee
Pincus et al. (2004) PACES-II	USA	commercial	crossover	community	placebo, celecoxib	hip, knee

Trial Name	Country	Funding Source	Design	Setting	Comparator	Joints affected
Altman et al. (2007)	USA	commercial	parallel	community	placebo,	hip, knee
Temple et al. (2006)	USA	commercial	parallel	community	naproxen	hip, knee
Herrero-Beaumont et al. (2007)	Spain	commercial	parallel	community	placebo	knee
Gualda et al. (2007)	Spain	commercial	parallel	community	Aceclofenac	knee
Yelland et al. (2007)	Australia	commercial	n of one trial	community	celecoxib	back, foot, hand, hip, knee, neck, shoulder
Schnitzer et al. (2009)	USA	commercial	parallel	community	rofecoxib	knee
Prior et al. (2014)	USA	commercial	parallel	community	placebo	hip, knee
Verkleij et al. (2015)	Netherlands	non-commercial	parallel	community	diclofenac	knee
Reed et al. (2018)	USA	commercial	parallel	community	placebo	hip, knee

US - United States, UK - United Kingdom, PACES - Patient Preference for Placebo Paracetamol or Celecoxib Efficacy Studies.

2.2.3. Risk of bias assessment

The risk of bias using the Cochrane modified risk of bias tool for included studies is presented in Figure 2.2.2. The major drawback was allocation concealment, as most studies (n=20) did not report how it was managed.

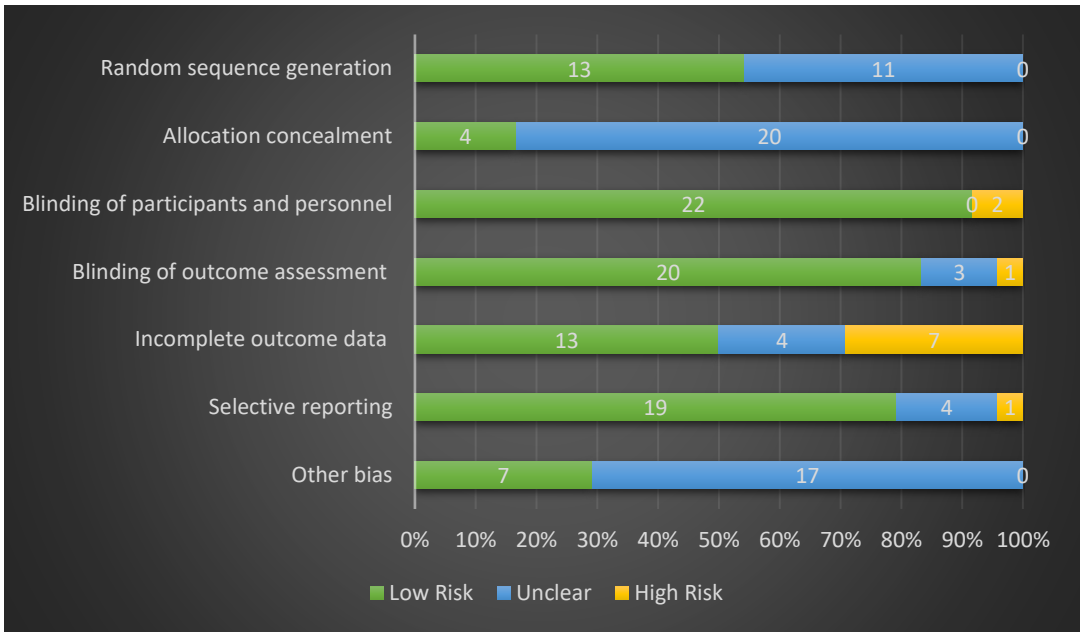


Figure 2.2.2. Risk of bias assessment for randomised controlled trials for paracetamol.

2.2.3.1. Randomisation and allocation

The method of the random sequence was reported adequately in 54% of studies, with most of them using computer-generated randomisation techniques, and this technique was unclear in 46% of the studies, as given in Figure 2.2.2. Notably, allocation concealment was reported infrequently, which led to its poor discriminative value and inadequate to assess selection bias in those studies. Only four studies adequately reported allocation concealment (Gualda et al., 2007; Herrero-Beaumont et al., 2007; Prior et al., 2014; Verkleij et al., 2015).

2.2.3.2. Blinding

Figure 2.2.2 illustrates a high percentage of studies adequately reported blinding for participants and personnel (92%) and outcome assessors (83%). Two studies had an increased risk of bias for blinding participants and personnel (Verkleij et al., 2015; Yelland et al., 2007), and one had a high risk for blinding the outcome assessor (Lee et al., 1998).

2.2.3.3. Incomplete outcome data

Nearly half the studies reported a minimal risk of bias as they had follow-up rates of 90% (Golden et al., 2004; Gualda et al., 2007; Miceli-Richard et al., 2004; Zoppi et al., 1995). However, seven studies had an elevated risk of attrition bias due to high dropout rates ⩾20%. The dropout rate was unclear in four studies.

2.2.3.4. Selective reporting

Only one study had a high risk of selective reporting of results. It did not report liver transaminase, bilirubin, and urinalysis, which were mentioned in the methodology of the study (Williams et al., 1993). Overall, 79% of studies adequately reported their work and followed their predetermined methods. For 17% of studies, there was inadequate information to determine the other bias domains, as shown in Figure 2.2.2.

2.2.3.5. Other potential bias

Figure 2.2.2 depicts that most of the included trials (71%) were funded by pharmaceutical companies that produced paracetamol. Therefore, they were at unclear risk of bias. Only 29% of studies appeared to be non-industry funded studies.

2.2.4. Adverse effects of paracetamol vs placebo

2.2.4.1. Association with Gastrointestinal (GI) adverse events

The meta-analysis of 4 studies, including 2,275 participants, observed an increased risk of "GI events (any)" with RR 1.13 (95%CI 0.89, 1.43), but not statistically significant. Based on two studies (n=786), paracetamol had a non-significant increased risk of abdominal pain, with RR 1.42 (95%CI 0.67, 3.02). In Figure 2.2.3, three studies (n=1496) reported an increased risk associated with paracetamol intake for dyspepsia and gastrointestinal upset (RR 1.93; 95%CI 0.97, 3.82 and RR 1.68; 95%CI 0.37, 7.57, respectively), but the estimates were not statistically significant compared to the placebo. Figure 2.2.3 presents five studies comprising 2,746 participants who had a non-significant increased risk associated with paracetamol use for "nausea and vomiting" with a RR of 1.47 (95%CI 0.94, 2.32) in comparison to the placebo group. However, six studies with 3,229 participants detected an increased risk for diarrhoea, which was twice as high in the paracetamol group compared to the placebo group with RR 2.12 (95%CI 1.36, 3.32). The results were homogenous among the six trials (I2 = 0%, P = 0.761). The number of trials included for each of these individual outcomes was less than 10. Therefore, publication bias and its statistical "Harbord test" were not determined.

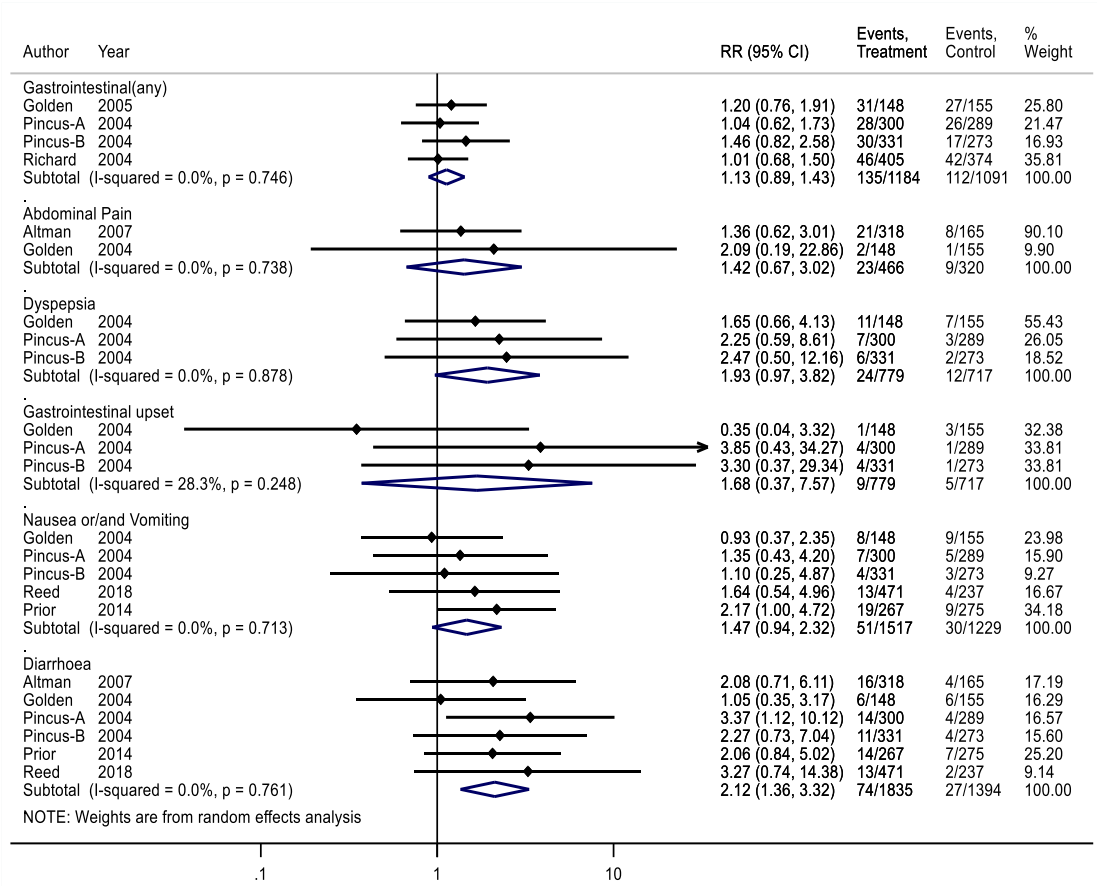


Figure 2.2.3. Paracetamol versus placebo in randomised controlled trials for knee and hip osteoarthritis. Outcome: Gastrointestinal adverse events at study endpoint follow-up. RR - Risk ratio, CI - confidence interval.

2.2.4.2. Association with adverse liver effects

The MA of 3 placebo-controlled trials (n=1,237 participants) showed that there was a significantly increased risk of liver adverse events (RR 3.99; 95%CI 2.05, 7.77) in the paracetamol group in comparison to placebo as given in Table 2.2.3 (forest plot: Appendix 3.2.). The endpoint assessment for Altman et al. (2007) and Reed et al. (2018) was 12 weeks, and the study by Prior et al. (2014) had a treatment duration of only two weeks. Table 2.2.3, however, shows a statistically significant risk of elevated aspartate transaminase (AST) levels (>3 times the upper normal limit) with RR 7.42 (95%CI 2.22, 24.77) was also associated with paracetamol use compared to placebo. The results for both outcomes were homogenous (I2 = 0%, P = 0.48). The number of studies assessing liver side effects was less than 10; therefore, publication bias was not performed.

Table 2.2.3. Results for liver side effects for paracetamol versus placebo trials.

Adverse events	Number of trials	Number of participants	Risk ratio (95%CI)	I2 (%)	P - value
Liver	3	1,237	**3.99 (2.05, 7.77)**	0	0.48
AST-level >3	3	1,535	**7.42 (2.22, 24.77)**	0	0.66

AST - aspartate aminotransferase test, I2 - heterogeneity significant results are in bold.

2.2.4.3. Association with cardiovascular adverse effects

Figure 2.2.4 illustrates that the meta-analysis of two RCTs with a relatively small number of participants (n = 1,011) had a small increased risk of cardiovascular side effects with paracetamol (RR 1.05; 95%CI 0.07, 15.38). These results were associated with considerable heterogeneity (I2 = 68.6%, P = 0.07) and were not statistically significant with a wide confidence interval. Due to a limited number of studies, it was not possible to determine the predictors of heterogeneity.

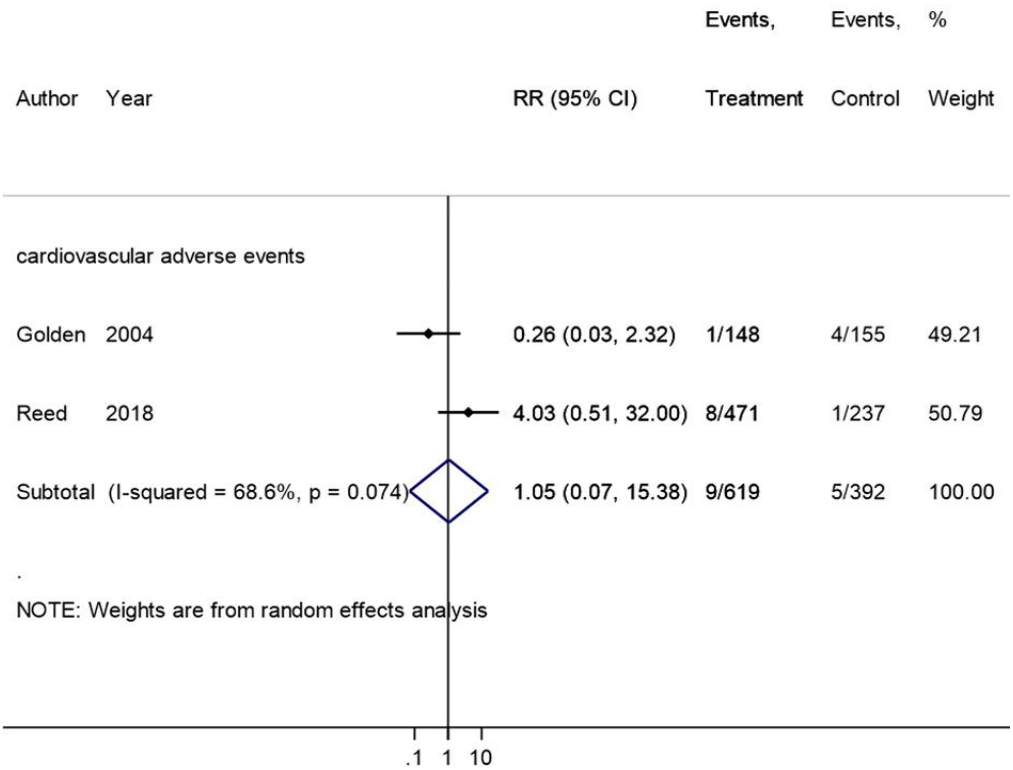


Figure 2.2.4. Paracetamol versus placebo in randomised controlled trials for knee and hip osteoarthritis. Outcome: cardiac adverse events at longest follow-up. RR - Risk ratio, CI - confidence interval.

2.2.4.4. Secondary outcomes for paracetamol versus placebo

A meta-analysis of 10 studies with 4,330 participants detected a small increased risk for "adverse event (any)" with paracetamol versus placebo, with a RR of 1.04 (95%CI 0.97, 1.11) that failed to reach statistical significance. Based on seven studies (n = 3,197), paracetamol was associated with a significant increase in "any treatment-related adverse events" with a RR of 1.37 (95%CI 1.06, 1.77). A non-significant increased risk of "severe adverse effects" was also observed among 3,917 participants taking paracetamol at its therapeutic dose, with a RR of 1.48 (95%CI 0.81, 2.73) compared to placebo described in Figure 2.2.5. It is noteworthy that the "number of withdrawals" was similar in both groups in 4 studies with 1,945 participants (RR 0.87; 95%CI 0.75, 1.00). Figure 2.2.6 exhibits an increased risk associated with "withdrawals related to adverse events" in those taking paracetamol compared to placebo (RR 1.21; 95%CI 0.94, 1.56) but was not statistically significant. The publication bias was not conducted, as the trials were less than 10 in number. Although not significant, no substantial heterogeneity was noted for all these risk measures ($I2 = 0\%$, $P > 0.1$).

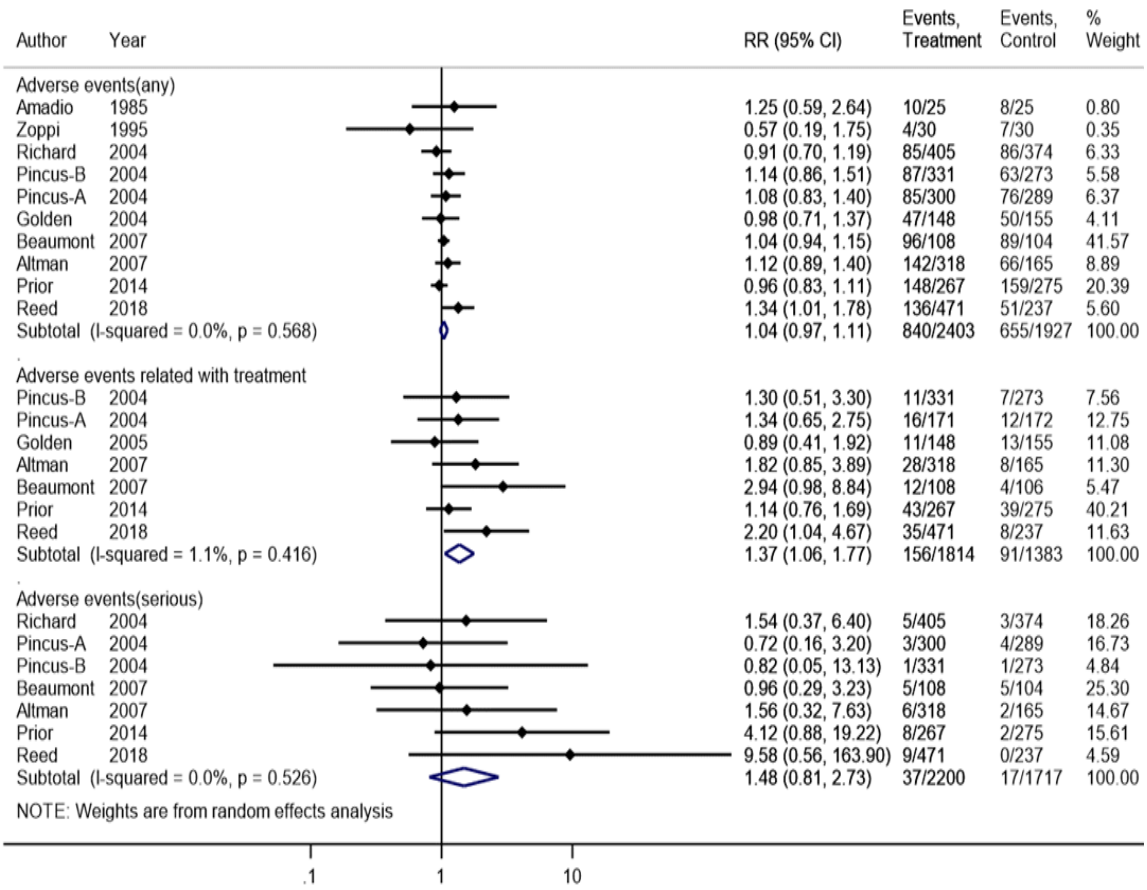


Figure 2.2.5. Paracetamol versus placebo in randomised controlled trials for hand, knee, and hip osteoarthritis. Outcome: (any) adverse events related to treatment, adverse events (serious) at endpoint follow-up. RR - risk ratio, CI - confidence interval.

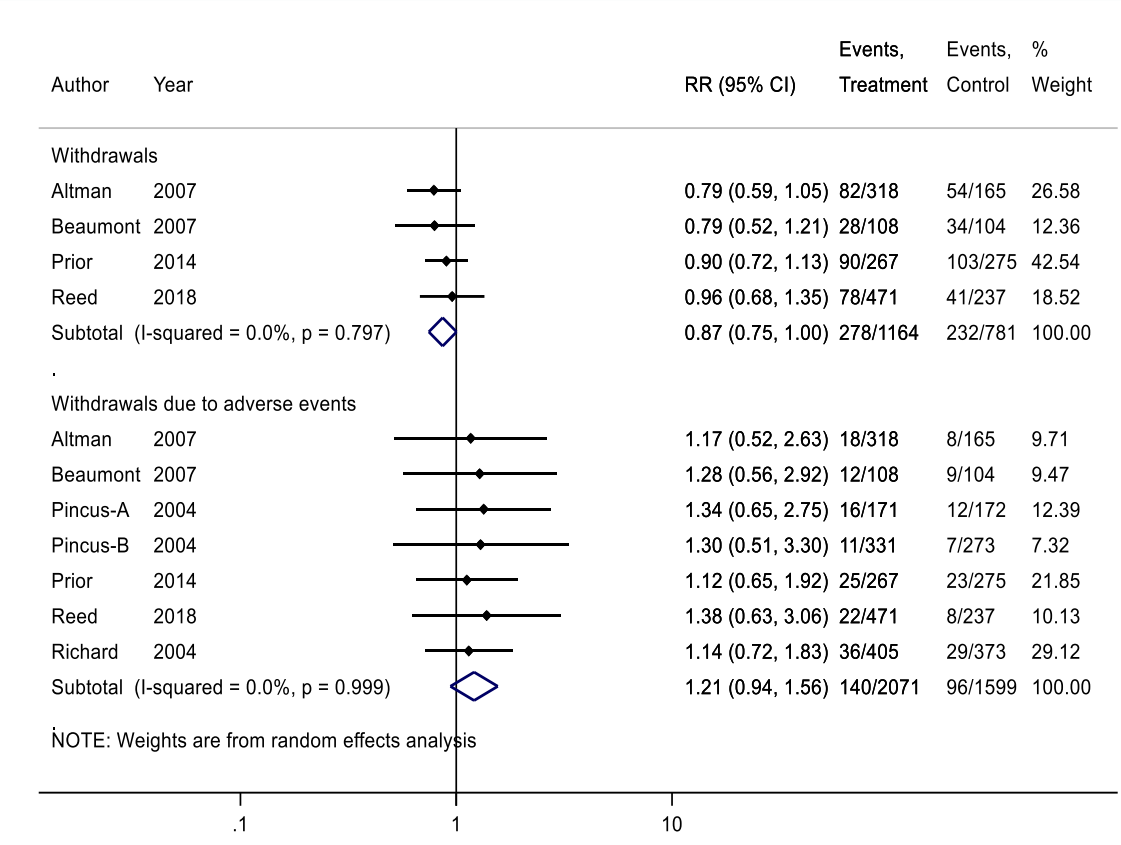


Figure 2.2.6. Paracetamol versus placebo in randomised controlled trials for knee and hip OA. Outcome: withdrawals at the endpoint observations. RR - risk ratio, CI - confidence interval.

2.2.4.4.1. Publication bias and small study effects

Figure 2.2.7 shows a funnel plot for RCTs published during 1980-2018, which reported "adverse events (any)" for paracetamol consumption. The log RR is represented on the horizontal x-axis using a logarithm scale, and this is compared with the standard error of log RR on the y-axis. The studies with dots at the top have slight variance or large sample sizes. The effect estimates from the smaller studies at the bottom scatter more widely than larger studies that appear at the top with a narrow spread. The vertical line in the middle shows the average RR from 10 studies. Visually, no publication bias was evident in RCTs for "any adverse event" other than the sample size (Higgins et al., 2019). The result of Harbord's test indicated non-significance with $P > 0.05$. The number of studies reporting GI and cardiovascular outcomes was <10; therefore, it was not feasible to generate the funnel plots.

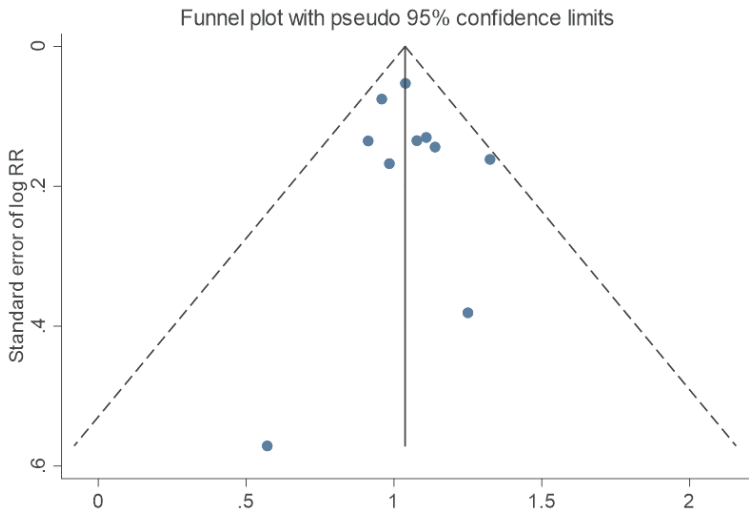


Figure 2.2.7. Funnel plot with 95% confidence interval for paracetamol versus placebo. Log risk ratio and standard error for a risk ratio for paracetamol versus placebo. The outcome is for any adverse event reported in the included studies for endpoint observations. RR - Risk ratio.

2.2.4.4.2. Sensitivity analysis

The studies included for primary outcomes were too few to support sensitivity analysis except for diarrhoea. The sensitivity analysis by excluding the cross-over trials for diarrhoea in paracetamol versus placebo studies suggested that the risk was still higher in the paracetamol group compared to placebo with RR of 1.87 (95%CI 1.08, 3.22) as shown in Appendix 3 as Figure 3.4.

Further, the sensitivity analyses were conducted to examine if the increased risk for adverse effects is associated with paracetamol after excluding low-quality studies (Table 2.2.4) for “adverse event (any)” (secondary outcomes). There were three indicators: allocation concealment, sample size n>100, and type of RCTs trials (parallel, cross over, or n of 1) allocated as surrogates for overall trial quality.

Inclusion of only large studies with sample size n>100 had a small increased incidence with a RR of 1.04 (95%CI 0.97, 1.11), which was not significant, and analysis restricted only to parallel study design also had a similar non-significant RR of 1.04 (95%CI 0.96, 1.14), and excluding studies with low quality did not change the association of “adverse events (any)” with paracetamol.

Table 2.2.4. Sensitivity analysis by study quality for paracetamol in osteoarthritis clinical trials, the outcome being adverse events (any) at or nearest to 12 weeks.

Study Quality	Trials	Number of Participants	Risk Ratio (95%CI)	I2 %(P-value)
All studies	10	4,330	1.04 (0.97,1.11)	0.00 (0.00)
Allocation concealment	2	754	1.01 (0.93,1.10)	5.70 (0.30)
Study design (parallel)	8	3,388	1.04 (0.96,1.14)	17.40 (0.30)
Number of participants >100 in treatment arm	8	4,220	1.04 (0.97,1.11)	0.00 (0.50)

CI - confidence interval, I2 – heterogeneity.

Figure 2.2.8 summarises the estimates for increased risk of having "any adverse effects" from paracetamol versus placebo up to 6 and up to 12 weeks of treatment. Although a modest increase in the risk was observed with the longest follow-up duration, still it was not significant, with RR varying from 0.94 (95%CI 0.78, 1.15) at 6 weeks to 1.06 (95%CI 0.98, 1.15) at or nearest to 12 weeks.

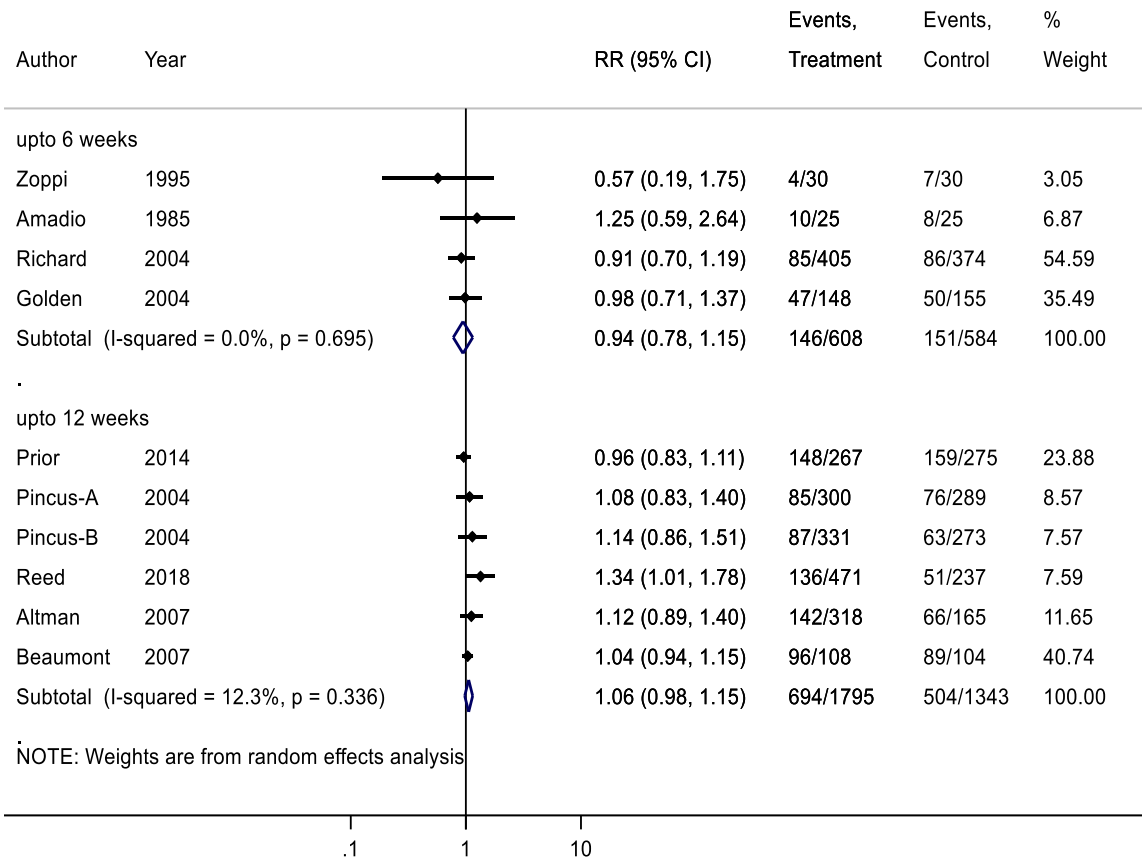


Figure 2.2.8. Subgroup analysis: Paracetamol versus placebo in osteoarthritis trials, the outcome being adverse events (any) by six or 12 weeks of treatment. RR - Risk ratio, CI - confidence interval.

2.2.5. Paracetamol versus NSAIDs

2.2.5.1 Association with gastrointestinal events

MA of GI events (any) was performed on trials comparing paracetamol versus NSAIDs. In 7 head-to-head comparison trials with 1,735 participants, the risk for “any GI event” among participants treated with paracetamol was 22% lower compared to NSAIDs (RR 0.78; 95%CI 0.64, 0.94), as shown in (Figure 2.2.9). The heterogeneity test was insignificant (P = 0.63), and the I2 statistics were 0%. The direction of increased risk favoured NSAIDs (from the visual aspect of the forest plot) except for abdominal pain and diarrhoea. The association between paracetamol exposure and abdominal pain compared to NSAIDs was observed in a few studies with 1,208 participants. Although there was an increased risk of abdominal pain associated with paracetamol use compared to NSAIDs, it was not statistically significant (RR 1.31; 95%CI 0.78, 2.19). In addition, the increased risk for dyspepsia was not statistically significant for 1,654 participants randomised to either paracetamol or NSAIDs, as shown in Figure 2.2.9.

The MA of 5 studies with 1,654 participants showed that the risk for constipation was 49% lower for paracetamol use in a head-to-head comparison with NSAIDs (RR 0.51; 95%CI 0.32, 0.81). The risk of “nausea and vomiting” in paracetamol users was not statistically different from NSAIDs users (RR 0.81; 95%CI 0.55, 1.19).

Figure 2.2.9 shows an increased risk of diarrhoea associated with paracetamol use when compared with NSAIDs. However, the confidence interval was borderline (RR 1.48; 95%CI 0.97, 2.25). The heterogeneity for almost all these outcomes remained very low at 0% and P > 0.001.

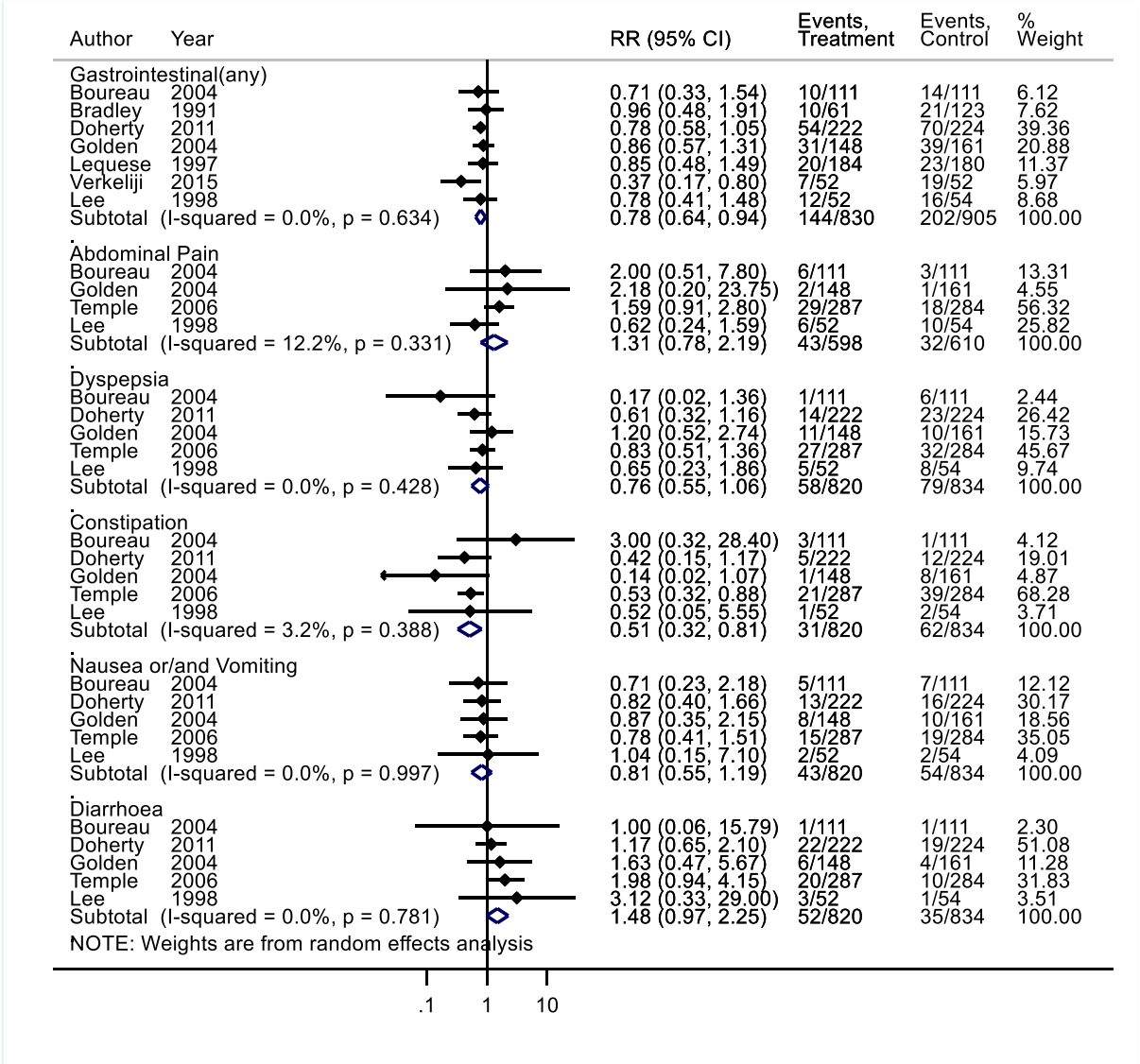


Figure 2.2.9. Paracetamol versus conventional non-steroidal anti-inflammatory drugs for gastrointestinal adverse events at the longest follow up. RR - risk ratio, CI - confidence interval.

2.2.5.2. Association with cardiovascular events

Figure 2.2.10 represents that the risk of cardiovascular events for paracetamol was 49% lower but not statistically significant compared to traditional NSAIDs in head-to-head comparisons from 4 studies with 1,206 participants (RR 0.51; 95%CI 0.16, 1.64). Although there was moderate heterogeneity due to the small number of studies, it was unlikely to predict the source of heterogeneity.

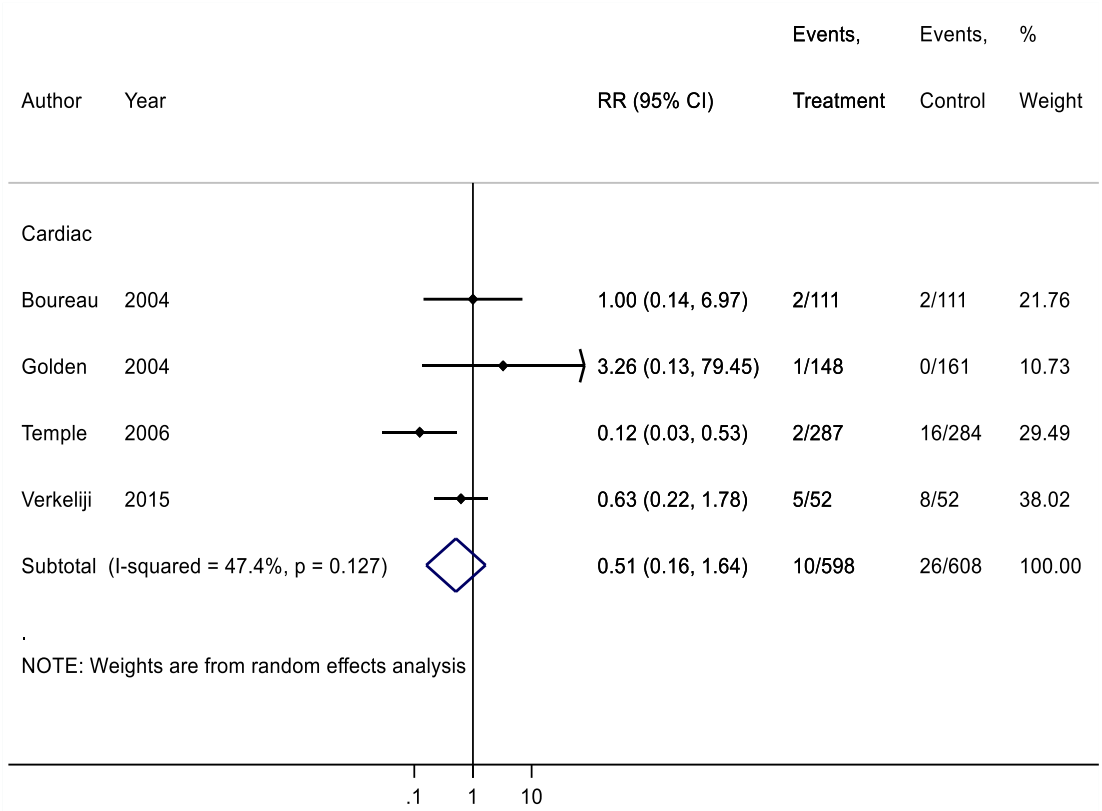


Figure 2.2.10. Paracetamol versus conventional non-steroidal anti-inflammatory drugs for cardiovascular adverse events for longest follow up. RR - risk ratio, CI - Confidence interval.

2.2.5.3. Secondary outcomes for paracetamol versus NSAIDs

Assessment of "adverse events (any)" in head-to-head comparisons for paracetamol (2,881 participants) was similar to traditional NSAIDs (RR 0.97; 95%CI 0.90, 1.04). The MA of 9 studies comprising 2,552 participants showed a significantly increased risk for "any withdrawals" of the participants taking paracetamol versus NSAIDs (RR 1.22; 95%CI 1.05, 1.43) shown in Table 2.2.5. Seven studies comprising 2,035 participants also estimated a small increased risk associated with "withdrawals related to adverse effects" in the participants taking paracetamol compared to NSAIDs, though it was not significant (RR 1.08; 95%CI 0.87, 1.34). There was no evidence of heterogeneity, as I2 remained 0% in all these outcomes with P > 0.001.

Table 2.2.5. Meta-analysis of osteoarthritis trials with active comparisons between paracetamol and non-steroidal anti-inflammatory drugs for the outcomes of any adverse events, withdrawals (any), withdrawals related to adverse effects.

Adverse events	Number of trials	Number of participants	Risk ratio (95%CI)	I2 (%)	p-value
Any adverse events	10	2,881	0.97 (0.90, 1.04)	0	0.50
Withdrawals					
any	9	2,552	1.22 (1.05, 1.43)	0	0.17
related with adverse effects	7	2,035	1.08 (0.87, 1.34)	0	0.86

I2 - heterogeneity, CI - confidence interval.

2.2.5.3.1. Publication bias

The funnel plot of paracetamol versus NSAIDs studies is presented in Figure 2.2.11 for "any adverse events" (number of studies >10). A precise symmetry was evident on visual inspection, and the presence of small-study effects was confirmed by the Harbord test for binary data (P < 0.05).

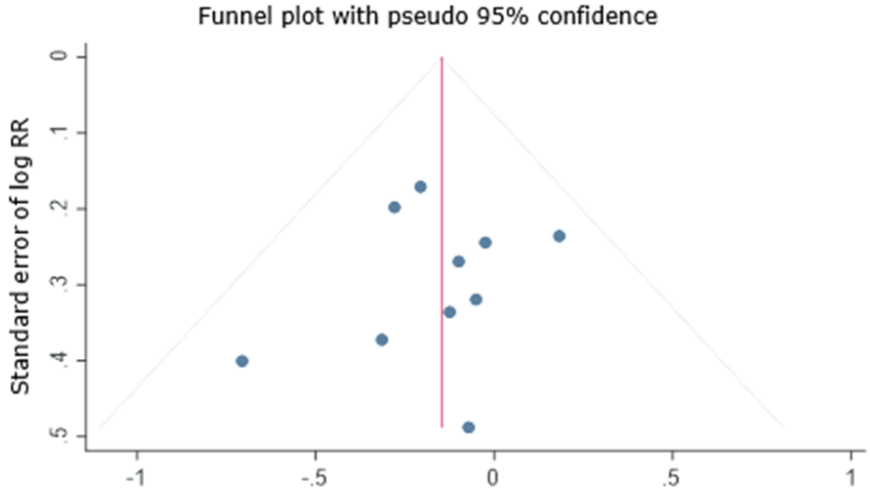


Figure 2.2.11. Funnel plot with pseudo 95% confidence limits for paracetamol versus conventional non-steroidal anti-inflammatory drugs in osteoarthritis. Outcome: adverse events (any) at endpoint observation.

2.2.5.3.2. Sensitivity analysis

Sensitivity analyses were conducted to examine if paracetamol exposure was associated with "adverse effects (any)" even after including only large studies and only parallel-controlled trials, as illustrated in Table 2.2.6.

The inclusion of only large studies with a sample size "n>100" produced a similar non-significant RR of 0.98 (95%CI 0.91, 1.06). Additionally, the inclusion of only parallel design RCTs had a non-significant RR of 0.98 (95%CI 0.91, 1.06) at endpoint observations given in Table 2.2.6.

Table 2.2.6. Sensitivity analysis for paracetamol versus conventional non-steroidal anti-inflammatory drugs for any adverse events.

Studies included	Trials	number of participants	RR (95%CI)	I2% (p-value)
All studies	10	2,881	0.97 (0.90,1.04)	0 (0.00)
Parallel study design	8	2,104	0.98 (0.91,1.06)	0 (0.45)
n>100 in treatment arm	6	2,325	0.98 (0.91,1.06)	0 (0.43)

RR - risk ratio, n - number of participants, CI - confidence interval, I2 – heterogeneity.

2.2.5.3.3. Subgroup analysis by the duration of treatment

Subgroup analysis was performed for "adverse events (any)" for paracetamol versus NSAIDs, with the RR being examined at each available duration of follow-up (Figure 2.2.12). Follow-up duration was categorised into three groups as 1-6 weeks, 7-12 weeks and >12 weeks. Paracetamol was not significantly associated with "adverse events (any)" during the first six weeks of intake compared with NSAIDs, and the direction of risk did not favour paracetamol. Although the risk increased with an increase in time at 12 weeks, but it still could not reach statistical significance. At 12 weeks, there were only two studies, one of which favoured paracetamol and the other NSAIDs. At durations longer than 12 weeks, there was no risk associated with paracetamol intake (RR 0.87; 95%CI 0.72, 1.05). Hence, there was no trend apparent at each time point. The heterogeneity remained low at 0% but not significant (P > 0.1).

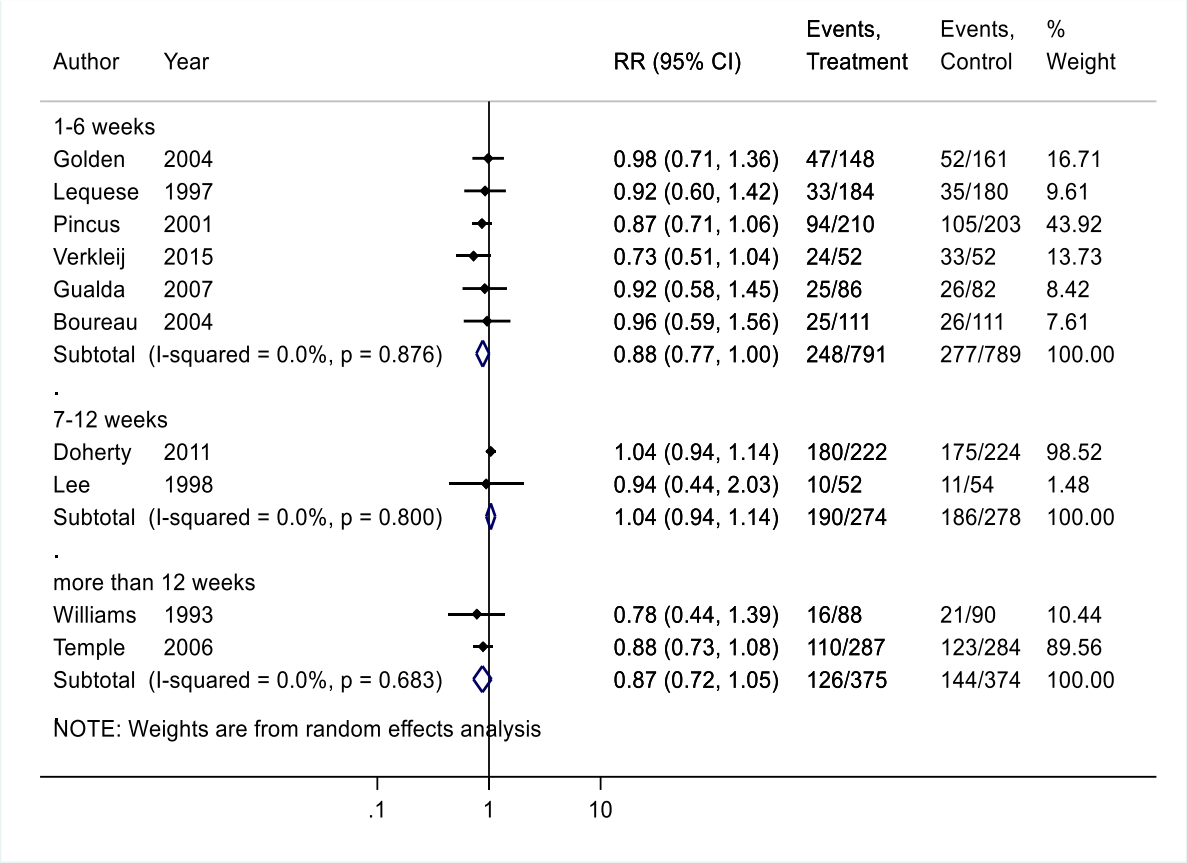


Figure 2.2.12. Subgroup analysis for the duration of treatment in randomised controlled trials for knee and hip osteoarthritis of paracetamol versus non-steroidal anti-inflammatory drugs using the random-effect model for any adverse events.

2.2.6. Paracetamol versus Coxibs

Paracetamol users had a similar risk for "GI events (any)," dyspepsia and "nausea or vomiting" to Coxibs users, as shown in Figure 2.2.13. There was no statistically significant difference between both groups with low heterogeneity (<40%). Although there was an increased risk associated with dyspepsia, abdominal pain, diarrhoea, and gastrointestinal upset with paracetamol users compared with Coxibs, it could not reach statistical significance (RR 1.10; 95%CI 0.62: 1.96, RR 1.66; 95%CI 0.81, 3.40, RR 1.43; 95%CI 0.84, 2.44, RR 1.25; 95%CI 0.85, 1.85 respectively). Additionally, none of the studies identified cardiovascular or renal adverse events when paracetamol was compared with Coxibs.

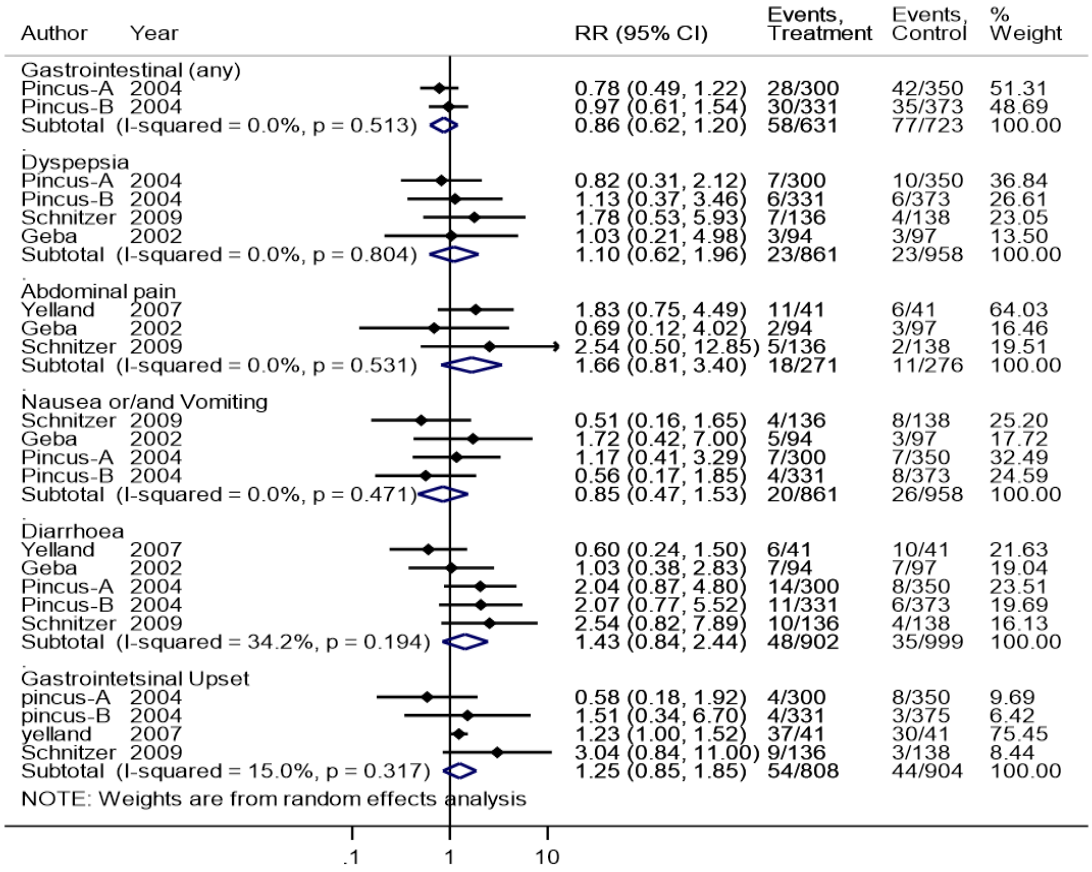


Figure 2.2.13. Paracetamol versus Coxibs for gastrointestinal events at the longest follow-up. RR - risk ratio, CI - confidence interval.

2.2.6.1. Secondary outcomes

The risk observed for “withdrawals” and “adverse events (serious)” was not significantly associated with paracetamol intake compared to Coxibs, with RR of 0.85 (95%CI 0.37, 1.93) and 0.89 (95%CI 0.22, 3.64), respectively. The MA of 4 studies with 1,819 participants suggested that the risk for “adverse events (any)” was similar in both groups (RR 1.00; 95%CI 0.88, 1.14), as shown in Figure 2.2.14, which was not significant and had a low level of heterogeneity.

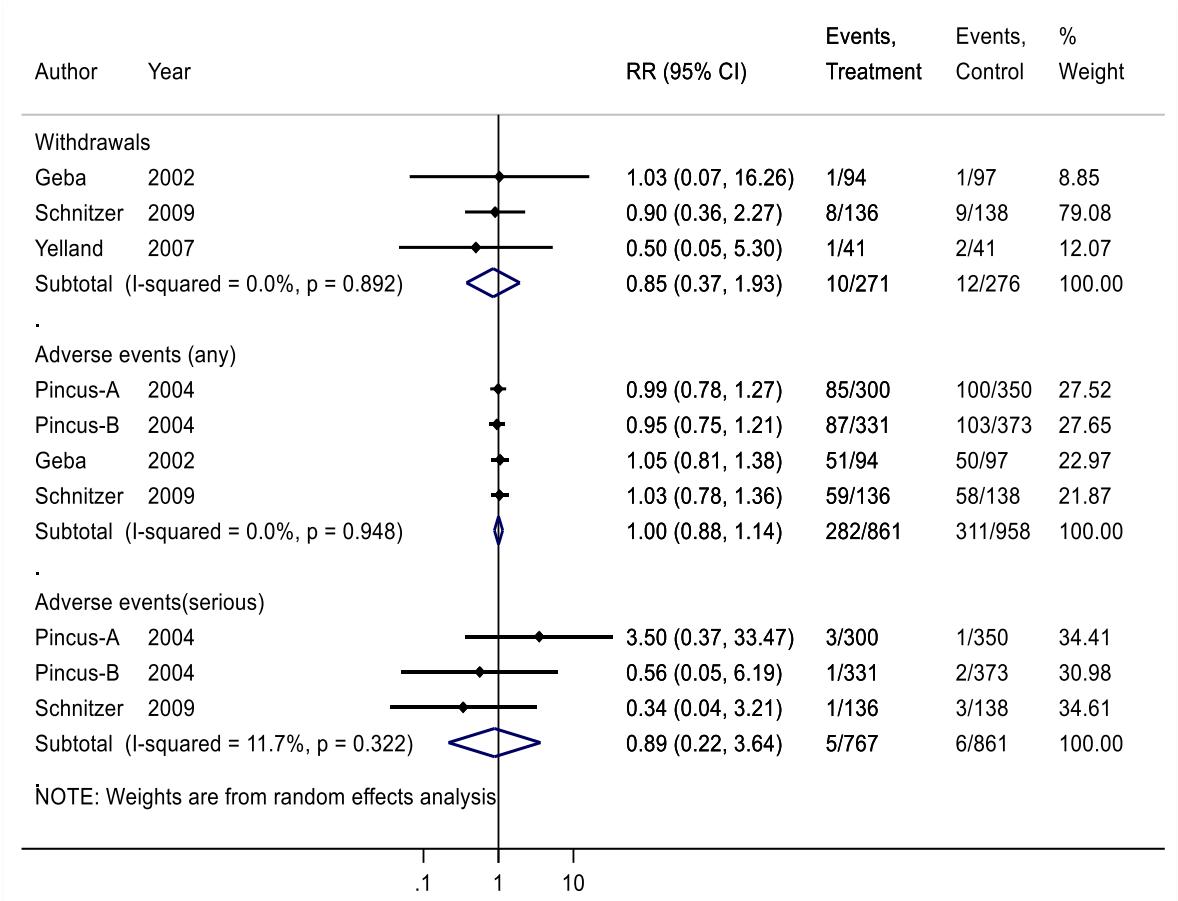


Figure 2.2.14. Paracetamol versus Coxibs for withdrawals and adverse events (any, serious) at longest follow up. RR - Risk ratio, CI - Confidence interval.

There were insufficient studies to detect “adverse events related to treatment.” Additionally, studies were inadequate to perform any sensitivity or subgroup analysis.

2.3. Characteristics of observational studies

The systematic literature search based on observational study design search strategies identified 1,725 citations (Medline: 395, Embase: 68, AMED: 2, CINAHL: 23, Web of Science: 342, PubMed: 795, Google Scholar: 100) illustrated in Figure 2.3.1. After the removal of duplicates, 1,310 citations remained for further screening. An additional 1,101 were scrutinised after abstract reading. The full text of 146 sources was read for potentially eligible articles. Out of 146, there were 16 cohort studies and 26 case-control that met our inclusion criteria. Two studies were excluded during data extraction. One study compared rates of hospitalisations for GI events, and the other investigated whether channelling bias existed in observational studies comparing paracetamol and ibuprofen (Rahme et al., 2008; Weinstein et al., 2017). The outcomes of these studies did not meet the inclusion criteria of this SR/MA.

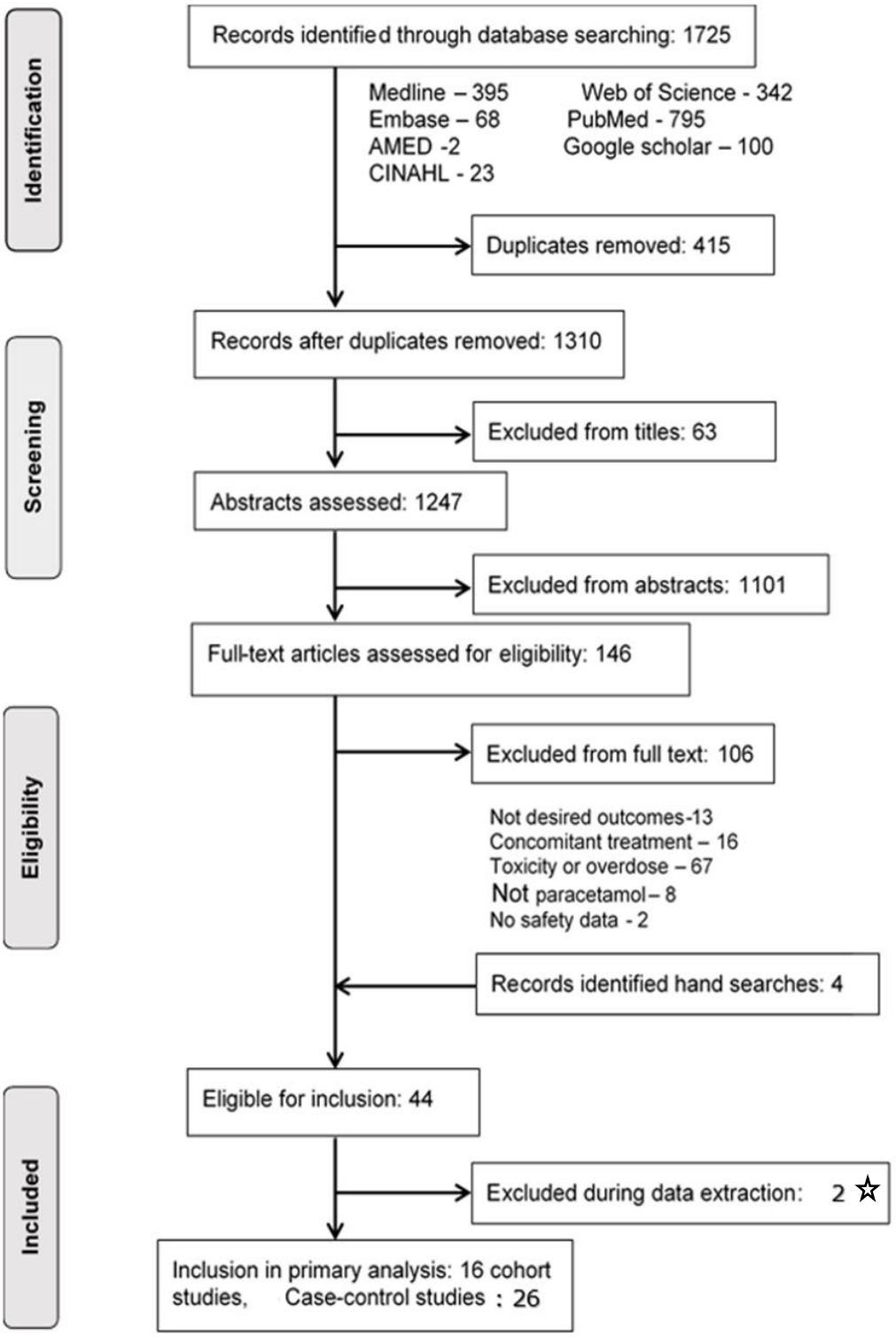


Figure 2.3.1. PRISMA flow chart for observational studies (cohort and case-control studies). The ☆ indicates that the two studies were excluded during data extraction. One study compared rates of hospitalisations for GI events, and the other investigated whether channelling bias existed in observational studies comparing paracetamol and Ibuprofen (Rahme, Barkun, Nedjar, Gaugris, & Watson, 2008; Weinstein et al., 2017).

2.3.0. Characteristics of included observational studies

There were 42 studies, comprising 16 cohorts and 26 case-control studies. Five case-control studies were nested in well-defined cohorts (De-Abajo et al., 2014; Garcia-Rodriguez et al., 2001; Garcia-Rodriguez et al., 2004; Gonzalez-Valcarcel et al., 2016; Roberto et al., 2015).

Among these 42 studies, 19 reports were from European countries (six from Spain, three from Italy, two each from France and Sweden, and one each from Germany, Belgium, Finland, and Denmark).14 out of 26 case-control studies used random digit methods to select their controls and 10/26 were unclear on how they decided their controls. All these studies reported the safety of paracetamol in the general population.

The specified exposure (duration of use) of paracetamol ranged from >7 days to more than 20 years (lifetime use), and the follow-up period ranged from 0.6-20 years. Studies evaluated current, daily, regular, recent, and past use of paracetamol. Additionally, the criteria for "current users," "regular users," and other exposure definitions of paracetamol were also quite diverse in the included studies. The maximum period between the study index date and stopping the use of paracetamol was also variable, ranging from 7 to 90 days.

In addition, the outcomes reported in each study were often not comparable. Therefore, MA was possible for a small number of outcomes: the incidence of hypertension, myocardial infarction, and upper GI bleeding. If a dose-response effect was reported in the study, then the individually adjusted summary statistics were reported within the appropriate adverse effect category. There has been a particularly good agreement between JK, BK, and SG for screening (96%), data extraction (98%), and risk of bias (94%).

Table 2.3.1. Summary of included cohort studies.

Author (year)	Source population	Population (n) and age range in years	Case validation	Confounders adjusted for	Exposure assessment	Exposure definition
Dedier et al. (2002)	registered nurses (only females), US	51,630 women aged 55 (IQR 49 to 61)	GP validation	Age, BMI, intake of sodium and alcohol, physical activity, family history of hypertension, history of diabetes, and smoking.	questionnaire	paracetamol consumption is based on the number of days each month, none, 1 to 4 days per month, five to 14 days per month, 15 to 21 days per month, and 22 days per month.
Rahme et al. (2002)	RAMQ-database, Canada	57,261 participants aged 65 or over	RAMQ procedures codes and ICD-9 (International Classification of Diseases, Ninth Revision) codes	age, sex, chronic disease score, number of concomitant drugs used at the index date, number of physician visits during the prior year, prior use of aspirin, non-aspirin NSAIDs, corticosteroids, anticoagulants, opiates, H/O hospitalisations, diagnosis of cancer, heart failure, musculoskeletal	first filled, newly started prescription for paracetamol	low dose <2600mg/day, high 2,601-3,250mg/day and >3,250 mg/day

				disease in the preceding year, H/O musculoskeletal disease, rheumatology visit, GI-events, duration of index prescription and season		
Curhan et al. (2002)	Nurses' Health Study II, USA	80,020 registered nurses aged 30-55	self-reported regarding physician-diagnosed hypertension	age, BMI, intake of ethanol and sodium, family history of hypertension, oral contraceptive pill use, category of use of the other individual analgesics	questionnaire	1-4 days/months, 5-14 days/month, 15-21 days/month, >22 days/month
Kurth et al. (2003)	Healthy physicians (males only), USA	22, 071 physicians (men) aged 40-70 years	blood chemistry diagnostics reports	age, BMI, history of hypertension, history of self-reported diabetes, physical activity, family history of MI, smoking status, HDL level baseline creatinine level, randomized beta carotene assignment, and total analgesic use.	questionnaire	never use (<12 tablets), 12 to 1499 tablets, 1500 to 2499 tablets, and 2500 tablets or more tablets

Lipworth et al. (2003)	Population-based study (North Jutland) prescription-based data, Denmark	49,890 participants aged >16 years	ICD codes	Nil	prescription based record	paracetamol prescription during lifetime.
Curhan et al. (2004)	Nurses' Health Study, USA	1,697 women aged 30-55	blood chemistry diagnostics reports	age, weight, history of hypertension, systolic and diastolic blood pressure, history of diabetes, current smoker, lifetime consumption of all analgesics.	questionnaire	total consumption of paracetamol 100-499 g lifetime paracetamol intake, 500-2999g lifetime paracetamol intake, >3000g lifetime paracetamol intake
Forman et al. (2005)	Nurses' Health Study, USA	NHS I cohort 121 700 female nurses aged 30-55 (older cohort) NHS II independent cohort 116 671 nurses aged 25-40 (younger cohort)	self-reported (NHS I cohort 91% and NHS II cohort 90%) validated with medical record review (100%)	NHS I - an age-adjusted and multivariable model including age (continuous), BMI (continuous), physical activity(quintiles), smoking (never, past, current), family history of hypertension, alcohol, caffeine, other nutrients, oral contraceptive use NHS II - adjusted for aspirin, paracetamol and NSAIDs in all the	questionnaire	current use of paracetamol (average daily dose) 0 mg /day, 1-100 mg/day, 101-500 mg/ day, >500mg/day.

				models, age, BMI, physical activity, smoking alcohol, caffeine, F/H hypertension, intake of folate and oral contraceptive use		
Kurth et al. (2005)	Healthy physicians (males only), USA	8,229 participants in the Physicians' Health Study Age 53-97 years with a mean age of 63.9 ±7.7 years	Self-reported along with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines	Model 1 - controlled for age (as an exponential term), body mass index (in quintiles), and other analgesic categories (except for the model including cumulative analgesic use). Model 2 controlled for all variables in model 1 plus indicators of chronic pain, including any report of arthritis, headache, or migraine, headache, and migraine frequency (≥6 vs <6 times). Model 3 controlled for all variables in model 2 plus potential risk	questionnaire	never use (<12 tablets), 12 to 1499 tablets, 1500 to 2499 tablets, and 2500 tablets or more tablets

				factors for hypertension, including alcohol consumption (≤1 drink/wk.; 2-6 drinks/Wk; ≥1 drink/d), exercise (<1/wk.; 1-4/Wk; ≥5/wk.), smoking (never, past, current), history of diabetes mellitus, history of high cholesterol or lipid-lowering treatment, parental history of premature myocardial infarction, and systolic and diastolic blood pressures		
Forman et al. (2007)	health professional's follow-up Study, USA	16,031 health professionals (men) with no history of hypertension, mean age 64.6 years, median age 63 years with	self-reported hypertension with 100% confirmation from medical record reviews	age (continuous), race, BMI, physical activity, smoking status, family history of hypertension, alcohol intake, intake of folates, potassium, calcium, magnesium,	questionnaires	use of paracetamol usual frequency 0 per week, 1 per week, 2-3 per week, 4-5 per week and 6-7 per week, number of Tablets per week 0 per week, 1-2 Tablets

		interquartile range (57-71)		sodium (quintiles), Secondary analysis excluding men who reported coronary heart disease at baseline and an additional analysis controlled for baseline systolic and diastolic blood pressure, paracetamol, NSAIDs and aspirin were simultaneously controlled for the use of other analgesics,		per week, 3-5 Tablets per week, 6-14 pill per week and ≥15 Tablets per week
Chan et al. (2006)	registered Nurses (only females), USA	70,971 women aged 30-55, no history of known cardiovascular disease or cancer	World Health Organization criteria such as ECG changes or elevated cardiac enzymes	Age, parental history of MI before age 60 years, history of diabetes, history of hypercholesterolemia, smoking history, BMI, regular moderate or vigorous exercise, postmenopausal hormone use, current multivitamin use, energy-adjusted quintiles of folate, omega-3- fatty acids, saturated fats, other	questionnaires	frequency of paracetamol uses none, 1-4 days/month, 5-14days/month, 15-21days/month, >22days/month according to days per week: none, one day/week, 2-3 days/week, 4-5days/week, >6days/week.

				analgesic use, history of hypertension.		
Evans et al. (2009)	population-based cohort, Swedish	801 participants aged 18-74years	blood chemistry data with additional evidence from medical records	1) gender, age, ACE, or ARB use, mean arterial pressure at baseline 2) gender, high level of proteinuria, high means arterial pressure at baseline, diabetic nephropathy	computer-aided face-to-face interviews	regular use (at least twice a week for two months before inclusion) and additionally depend on lifetime intake of paracetamol <99 g lifetime intake 100–499 g lifetime intake 500–2999 g lifetime intake >3000 g lifetime intake
De-Vries et al. (2010)	Clinical Practice Research Datalink, UK	382,404 paracetamol users with age ≥18	Used read terms and OXMIS + reviewed free text entries, death certificates	age, gender, BMI, Calendar Year, smoking history, ethanol use, number of visits to the general practitioner in the previous 12 months, hospital admission in the last year, socioeconomic status in the location of practice,	CPRD-prescriptions record	current, recent, past

Kuo et al. (2010)	National Health Insurance Database, Taiwan	19,163 newly diagnosed chronic kidney disease with a mean age of 59.6±15.9	Using ICD-9-CM	age, gender, the presence, or absence of such comorbid conditions as diabetes, hypertension, hyperlipidaemia, and atherosclerotic vascular disease (including coronary artery disease, cerebrovascular disease, transient ischemic attack, and peripheral vascular disease)	National health Insurance prescription claim data	average defined daily dose defined as no use, <0.568 and >0.569
Nderitu et al. (2014)	GPRD-linkage cohort, UK	4,145 patients with a mean age of 66 years and 55% females	GPRD-linkage data - Laboratory biochemistry data containing blood tests and diagnostic data	age, gender, deprivation quartiles, diabetes mellitus type 1 and 2, cardiovascular disease, hypertensive disease, ischaemic heart disease, heart failure, dysrhythmia, cerebrovascular disease and peripheral arterial	GPRD: linkage data – prescription data.	cumulative exposure using WHO anatomical therapeutic classification and defined daily dose categorised as non-users (0 daily defined dose (DDD)), (DDDs <85th centile), and high dose (DDDs >85th centile).

				disease, angiotensin inhibitors or renin inhibitors, chronic kidney disease, other analgesic use both aspirin, NSAIDs), baseline chronic kidney disease		
Fulton et al. (2015)	Clinical Practice Research Datalink, UK	224,496 hypertensive, age ≥65years	if there was the presence of at least a prior specified code	Age, sex, smoking, BMI, diabetes mellitus, ischaemic heart disease, peripheral heart disease, stroke, systolic blood pressure, diastolic blood pressure, NSAIDs use, aspirin use, statin use	CPRD-prescriptions record	depend on paracetamol prescription ≥3 and defined as a high, medium, and low
Duong et al. (2016)	Echantillon generaliste de beneficiaires (EGB)	342,494 participants >18 years	Using ICD-10 codes	high dose aspirin, other thrombotic agents, antidiabetic agents, cardiac therapies, antihypertensive agents, diuretics, peripheral vasodilators, vaso-protectors, ß-	EGB-Prescriptions dispensing records	the number of defined daily doses was 3g/day, the episode of usage was defined as consecutive dispensing, and the time between two prescriptions was less than 30 days.

			blockers, calcium channel inhibitors, agents acting on the renin-angiotensin system, serum lipid reducing agents	

RAMQ - Re´gie de l'Assurance Maladie du Quebec database, IQR - Interquartile range, EGB - Echantillon Généraliste de Bénéficiaires, UK - United Kingdom, USA - United States, GPRD - General Practice Research Database, CPRD - Clinical Practice Research Datalink, DDD - Daily defined dose, ICD-9-CM - International Classification of Diseases-9th revision Clinical Modification, WHO - World Health Organisation, ECG - Electrocardiograms, NHS - National Health Service, BMI - Body mass index, GP - General practitioner, NSAIDs - Non-steroidal anti-inflammatory drugs, ACEI - Angiotensin-converting enzyme inhibitor, ARB - Angiotensin receptor blocker, ECG - Electrocardiogram, GI - Gastrointestinal, MI - myocardial infarction, OXMIS - Oxford Medical Information System, F/H - family history, H/O - history of, wk - week.

Table 2.3.2. Summary for included case-control studies.

Author (year)	Duration of follow up	Country	Design/Study period/age if provided	Exposure definition	Variable controlled for
Coggon et al. (1982) + Langman et al. (1983)	5.4	UK	community matched case-control study median age 61 from Nov.1976 – Feb.1980	at some time in the past two days. at some time in the past week at some time in each of the last two weeks regularly for at least three months	age, sex, steroids, warfarin, and NSAIDs
McIntosh et al. (1985)	one year before the onset of initial ulcer symptoms, five years before the start of initial symptoms, lifetime until the beginning of ulcer symptoms	Australia	hospital-based case-control study	daily users defined as >/=7 tablets or capsules weekly for at least four consecutive weeks	age, gender, and social grade matched using the Sydney suburbs rating scale, adjusted for smoking, daily NSAIDs, and the effect of daily NSAIDs by type adjusted for smoking and daily analgesic drugs during the three-time periods
Levy et al. (1988)	7.2	USA	hospital-based case-control surveillance system with a median age of 36 from January 1977-March 1984	None	age, gender, date, smoking, use of any other analgesic, alcohol, caffeine, peptic ulcer, cirrhosis, steroids, anticoagulants, H2 blockers, education, geographical area, religion, myocardial infarction, stroke

				current use	
Faulkner et al. (1988)	2	UK	community-based case-control (Nottingham University and City hospitals) with a median age of 60 from April 1983-March 1985	regular use occasional use discontinued use within the prior 24 hours	age, gender, and NSAIDs
McIntosh et al. (1988)	3	Australia	out-participants referred for endoscopy with a median age of 58 from 1982 to 1985	use in the prior week regular use weekly: ≥4 consecutive weeks or daily for <4 consecutive weeks daily: ≥4 consecutive weeks	matched for each new case for gender, age within five years, smoking, indomethacin usage, aspirin use, and other drugs usage
Pommer et al. (1989)	2	Germany	multicentre, participants undergoing renal replacement therapy aged >20 years from 1984 to 1986	regular intake of analgesic with at least 15 doses in a month continuously for at least one year and the exposure of drug was recorded as in grams	age, gender-matched
Sandler et al. (1989)	2	USA	the multicentre study, hospitals of the USA where analgesics intake was on a higher note, 1980 -1982	never users, occasionally users, daily users, weekly users	age, gender, race, proximity to the study hospitals, income, and adjusted for effects of the other two analgesics

Steenland et al. (1990)	8	USA	identified participants from the Michigan Kidney registry that recorded new cases of ESRD aged 30-69, from 1976-1984.	regular use of paracetamol Note in this study, paracetamol was grouped with phenacetin because it is a metabolite of phenacetin	age, gender, lifestyle factors, non-occupational variables, missing data for lifestyles variables,
Laporte et al. (1991)	2.10	Spain	hospital-based case-control study aged >20 years from February 1987-December 1988	use in the previous week (7 days before index day)	age, gender, date, site of study, smoking, alcohol, caffeine, peptic ulcer disease, cirrhosis, coagulopathy, NSAIDs, usage of anti-ulcer medication
Holvoet et al. (1991)	2	Belgium	the multicentre, hospital-based study, May 1987-May1989	use in the previous week	age, gender, study site
Savage et al. (1993)			hospital-based case-control with a median age of 60 years	current use: paracetamol use in the previous week before hospital admission Regular use: paracetamol use for two or more days each week for </= 1 month	age, gender, smoking, alcohol, history of any bleeding disorders, NSAIDs and anticoagulants
Perneger et al. (1994)	0.6	USA	a community-based case-control study with an age range of 20-64 January 1991-July 1991	the average frequency of analgesic intake was based on lifetime ingestion of drug light: 0-104 Tablets per year or 0-2 Tablets per week, moderate: 105-365 Tablets per year or up to 1 pill per day, or heavy 366 or more Tablets per year or more than one pill per day cumulative	age, gender, ethnicity, use of other analgesics and drugs containing phenacetin

				intake low (0-999 Tablets), medium (1000-4999 Tablets), high (5000 or more Tablets)	
	4	UK	multicentre, hospital, and community-based case-control with a median age of 60 years	any use in previous three months	age, gender, study site, smoking, alcohol, peptic ulcer, dyspepsia, NSAIDs
Matikainen et al. (1996)	0.8	Finland	hospital-based case-control October 1992-May 1993	any use in the previous week	age, gender, date, and study site
Fored et al. (2001)	2	Sweden	Swedish population register aged 18-74 years May 1996- May 1998	lifetime exposures for paracetamol, regular use: at least twice a week for two months or longer	age, sex, education level, smoking status, use or non-use of other painkillers, Marital status, BMI, consumption of caffeine, alcohol, illicit drugs, history of hypertension, angina, claudication, kidney stones, gout
Garcia-Rodriguez et al. (2004)	4	Spain	population-based cohort with case-control study design Using GPRD-database with age 49-79 years from 1995-1999	current (0-30days), recent (31-180days), Past (>180days), further the effect of everyday dose and duration of paracetamol use was amongst current users <1,000mg, 1,001-2,000 mg, 2,001-4,000, paracetamol duration 1-30 days, 31-180 days, 181-365 days, >365 days	age, gender, calendar year, cohort, history of previous gastrointestinal symptoms, smoking cortico-steroid, gastro-protective drug, a non-aspirin non-steroidal anti-inflammatory drug, and use of aspirin
Nobili et al. (1992)	2	Italy	post marketing surveillance data from hospitals with	use during the week preceding hospital admission	age, gender, date, study site, smoking, peptic ulcer disease, cirrhosis, coagulopathy, NSAIDs

			median age 65 from 1987-1988		
Rodriguez et al. (2001) + Gonzalez-Perez et al. (2006)	5.6	Spain	population-based cohort with case-control study design Using GPRD-database with age 40-70 from 1993-1998	no-use: no record of paracetamol uses in the previous six months from the index date current: 0-30 days (prior index date) Recent: 31-90days (prior index date Past: 91-180 days (prior index date For current users of paracetamol: ≤1,000 mg use of paracetamol 1001-1999 mg 2000 mg (as commonly used dose stand-alone) 2001-3999 mg ≥4000 mg	age, gender, calendar year, smoking, history of upper gastrointestinal disorders, use of steroids, anticoagulants, non-aspirin NSAIDs, aspirin, paracetamol, H2 receptor blockers (cimetidine, famotidine, nizatidine and ranitidine), omeprazole and misoprostol,
Lanas et al. (2003)	2.3	Spain	hospital and community (mixed) based case-control aged 65 years from 1995-1998	any use of paracetamol in the previous seven days from hospital admission	age, gender, history of previous upper gastrointestinal complications, prior history of peptic ulcer, cardiovascular, cerebrovascular disease, anti-secretory drugs, nitro vasodilators, gender, and age

Gallerani et al. (2004)	2	Italy	GIFA (Italian Group for the Pharmaco-surveillance in the Elderly) database-cross-sectional study with different surveillance periods from 1988-1998 contributing to 24 months mean aged 70 years	any use of paracetamol in the previous seven days from hospital admission	age, year of observation, number of medications taken home (total), Charlson co-morbidity index, smoking and alcohol use, gastro-protective drugs, NSAIDs, anti-coagulant
Rosenberg et al. (2003)	3	USA	hospital-based case-control study aged 55 years Study period (1980-1983) (n=2035 cases, 2656 controls)	use of paracetamol at least once a week for at least three continuous months Based on episodes of paracetamol use of ≥3 months Ever use, Use for ≥ 3months (≥1 day/week: <1, 1-2, 3-4, ≥5), (≥4 days/week <1, 1-2, 3-4, ≥5), (daily <1, 1-2, 3-4, ≥5)	age, region, education, smoking, BMI, previous history of hypertension, prior history of angina pectoris MI risk factors, history of elevated cholesterol level, prior history of diabetes mellitus, family history of MI, alcohol.
De-Abajo et al. (2014)	6	Spain	a nested case-control study using Primary care database` aged 40-90 years from 2001-2007 (cohort: n=799, 371)	claimed prescriptions, current: EOS+30 days	age, gender, body mass index, rheumatoid arthritis, gout, calendar year, renal failure, depression, metamizole, paracetamol, high dose-aspirin, non-aspirin, antiplatelet drugs, number of visits, ischaemic heart disease, smoking, acute myocardial infarction, hypertension, peripheral artery disease, use of glucose-lowering medications, oral anticoagulants,

					alpha-blockers, calcium-channel blockers, ACE-inhibitors, ARA, diuretics, nitrates, corticosteroids, inhaled beta-agonist, antidepressant, sex hormones, dyslipidaemia, history of cerebrovascular, chronic obstructive pulmonary disease, history of heart failure, acid-suppressing drugs.
García-Poza et al. (2015)	6	Spain	BIFAP-a primary healthcare-based case-control study with 40-90 years old study period 2001-2007	prescription data in BIFAP	Age, gender, hospital visit, previous history of heart disease, diabetes, RA, gout, dyslipidaemia, hypertension, smoking. Alcohol, BMI, current use of aspirin, antiplatelet drugs, alpha-blockers, CC-blockers, ACE-inhibitors, angiotensin receptors, statins, glucose-lowering drugs, nitrates, diuretics, inhaled beta-antagonist, corticosteroid, acid-suppressing drugs.
Roberto et al. (2015)	10	Italy	a nested case-control study using IMS Health Longitudinal Patient Database with age <55 years from 2002-2010, (n=36,754: 2182 were matched up to 5 controls)	all paracetamol prescriptions are current (0-90 days), recent (91-180days), or past (181-365 days) users or non-users (more than 365 days).	age, gender, follow up duration, BMI, smoking, alcohol, family history of cardiovascular disease, other comorbidities such as cardiac arrhythmia, peripheral vascular disease, chronic heart failure, COPD, Anaemia, Diabetes mellitus, hypertension, lipid

					metabolism, renal disorders, thyroid disease, rheumatic disease, other in combination drugs, vasodilators, lipid-lowering, cardiac medication, systemic corticosteroids, anti-thrombotic, anti-hypertensive medication, NSAIDs and aspirin
Gonzalez-Valcarcel et al. (2016) – Study I	4	France	nested case-control studies using PERFORM trial aged 69.2	no use, occasional use, daily intakes dose <1500mg/day, 1500-2999mg/day, ≥ 3000mg/d. Duration: <31 days, 31-365days, ≥366 days	age, arterial hypertension, ischaemic stroke, event qualification diabetes mellitus, history of MI, TIA, another cardiovascular disease, peripheral artery disease, smoking, follow up duration
Gonzalez-Valcarcel et al. (2016) – Study II	4	France	nested case-control studies using PERFORM trial aged 69.2	no use, occasional use, daily intakes dose <1500mg/day, 1500-2999mg/day, ≥ 3000mg/d. Duration: <31 days, 31-365days, ≥366 days	age, arterial hypertension, ischaemic stroke, event qualification diabetes mellitus, history of MI, TIA, other cardiovascular diseases, peripheral artery disease, smoking, follow up duration
Kelkar et al. (2012)	9	USA	a case-control study using IMS life link health plans-data, aged 60.8; 1997-2009	at least one day in the last seven days before the index date, At-least 1 day on the last 30 days before the index date, seven days prior to index date (<=4gm), seven days pre-index(>4 gm), 30 days pre-index(<=4 gm), 30	adjusted for acute paracetamol use in 30 days pre-index, drugs in 365 days pre-index (antibiotics, NSAIDs, drugs, diuretics, ACE-inhibitors, corticosteroids, oral anti-coagulant, diagnoses in the 365 days pre-index

				days pre-index (>4 gm), 30 days pre-index (<=4 gm), 30 days pre-index (>4gm), cumulative dose in the pre-index year <=1 kg, cumulative dose in the pre-index year >1 kg, cumulative dose in the pre-index year >1 kg, recency of 0-30 days, recency of >30 days, total PCM use duration in pre-index- 1-30 days, total PCM use duration in pre-index (>30days), PCM use in the 30 days pre-index	
González-Pérez et al. (2014)	8	UK	nested case-control using THIN-database	current users seven days before the index date, recent use ending 8-30 days before the index, past users 31-365 days before the index date	adjusted for sex, age, year of the index date, number of primary care physicians' visits and specialist referrals, smoking, PPIs, histamine type 2 receptors antagonist, acetylsalicylic acid, NSAIDs

BIFAP- Base de Datos para la Investigacion Farmacoepidemiologica en Atencion Primaria), GIFA - Italian Group for the Pharmaco-surveillance in the Elderly, IMS - International marketing Statistics, PERFORM - Prevention of cerebrovascular and cardiovascular Events of ischaemic origin with teRutroban in patients with a history of ischaemic stroke or transient ischaemic attack study, MI - myocardial infarction, TIA - transient ischaemic attack, NSAIDs - Non-steroidal anti-inflammatory drugs, CPRD - Clinical Practice Research Datalink, THIN - The Health Improvement Network (THIN), PPI - Proton pump inhibitors, ESRD - End-stage renal disease, PCM - paracetamol, EOS - End of supply, ACE - Angiotensin-converting enzyme inhibitor, ARA - Aldosterone receptor antagonists, CC - Calcium Channel blockers.

2.3.1. Risk of gastrointestinal bleeding with paracetamol exposure versus non-exposure

2.3.1.1. Upper gastrointestinal bleeding (UGIB)

Table 2.3.1 and Table 2.3.2 illustrate that 14 studies reported either measures of RR or OR for UGIB (due to gastric/duodenal ulcer, perforation/haemorrhage due to peptic ulcer, or acute bleeding) with therapeutic doses of paracetamol exposure compared to unexposed. These comprised two cohort studies (De-Vries et al., 2010; Duong et al., 2016), and 12 case-control studies (Figure 2.3.2).

Table 2.3.3 demonstrates that Duong et al. (2016) used the EGB-database and reported a high incidence of UGIB (n=342,494) in people aged >60 years, with HR of 1.45 (95%CI 1.08, 1.95) compared with non-users. The incidence was also high and statistically significant if the number of daily defined doses (DDD) of paracetamol dispensed was <7DDD per treatment episode (HR 1.62, 95%CI 1.08, 2.43).

The cohort study by De-Vries et al. (2010) used the CPRD-database and identified 382,404 participants. It reported a statistically significant increased incidence with the overall exposure of paracetamol for UGI- ulcers and complications with HR 1.36 (95%CI 1.31, 1.41) compared to unexposed paracetamol, as shown in Table 2.3.3 (De-Vries et al., 2010).

Figure 2.3.2 indicates that there were 12 case-control studies that used a similar definition of paracetamol exposure (i.e., use in the previous week) and had comparable outcomes for UGIB. Therefore, the pooled estimates from the MA of these twelve case-control studies suggested that paracetamol use during the last week has a higher risk associated with UGIB with an OR of 1.34 (95%CI 1.10, 1.63) in comparison to non-users as given in Figure 2.3.2. The visual inspection of the forest plot in Figure 2.3.2 illustrates the between-study variation. These effect measures were associated with moderate heterogeneity (I2 = 33.2%, P = 0.13). Table 2.3.4 shows another study by Imhof et al. (1997) that reported a significant association between ulcer bleeding and paracetamol intake with an OR of 3.20 (95%CI 1.17, 8.73). However, it was excluded from the pooled analysis because of the unclear exposure definition.

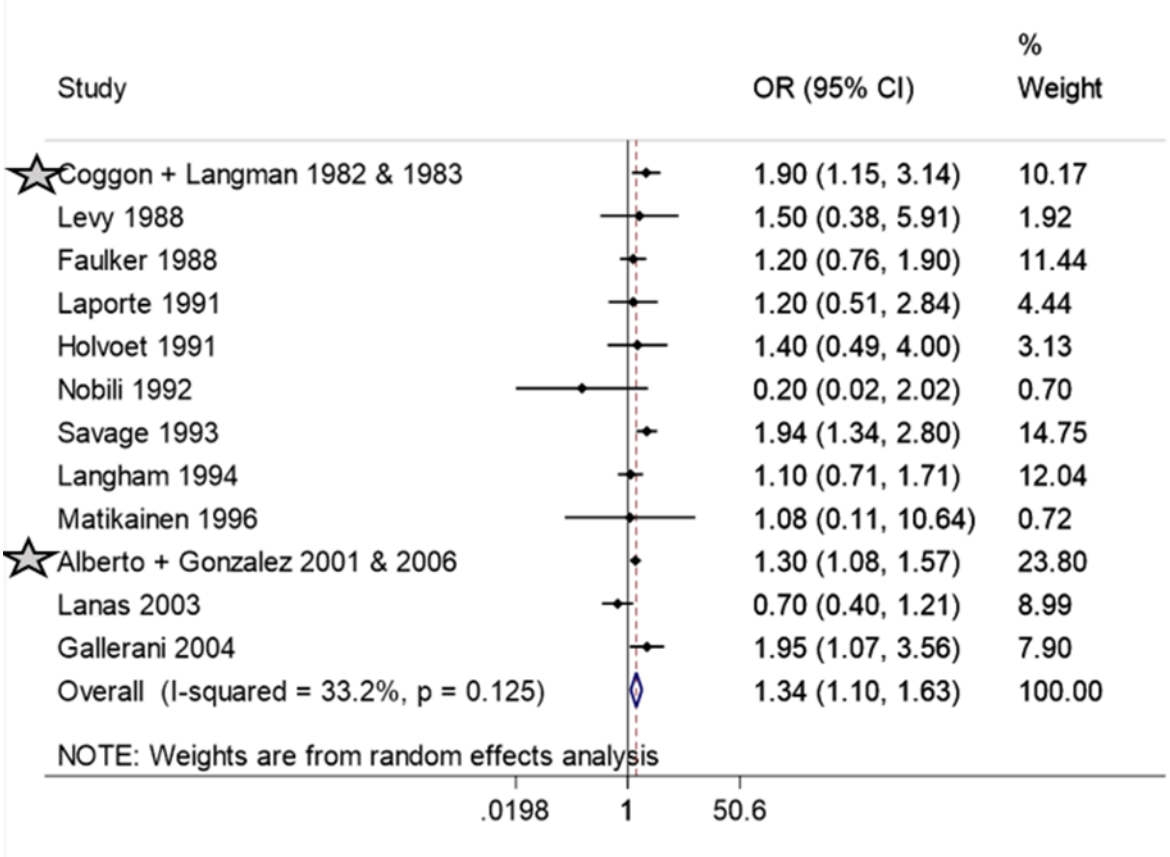


Figure 2.3.2. Meta-analysis of case-control studies for paracetamol use versus no use for upper gastrointestinal bleeding. The odds ratio of upper gastrointestinal bleeding with paracetamol use (in the previous week). A test for heterogeneity was provided as I-squared. The ★ denotes salami publications counted as two studies instead of four (Coggon et al., 1982; Langman et al., 1983) and (Garcia-Rodriguez et al., 2001; Gonzalez-Perez et al., 2006). OR - odds ratio, CI - 95% confidence interval.

2.3.1.2. Peptic ulcer

Figure 2.3.3 shows results from the three studies investigating the relationship between exposure to paracetamol and gastric or peptic ulcers. The daily exposure to paracetamol in the previous year was associated with a threefold increased risk in paracetamol cases compared to controls (OR 3.2; 95%CI, 0.0, 110.0). However, the wide CI signifies the imprecision of the estimate, and the results were not significant statistically (McIntosh et al., 1985). Although no dose-response was observed in two more studies, as described in Figure 2.3.3, paracetamol exposure was significantly associated with an increased risk for peptic ulcers. It was not possible to pool the results due to different paracetamol doses.

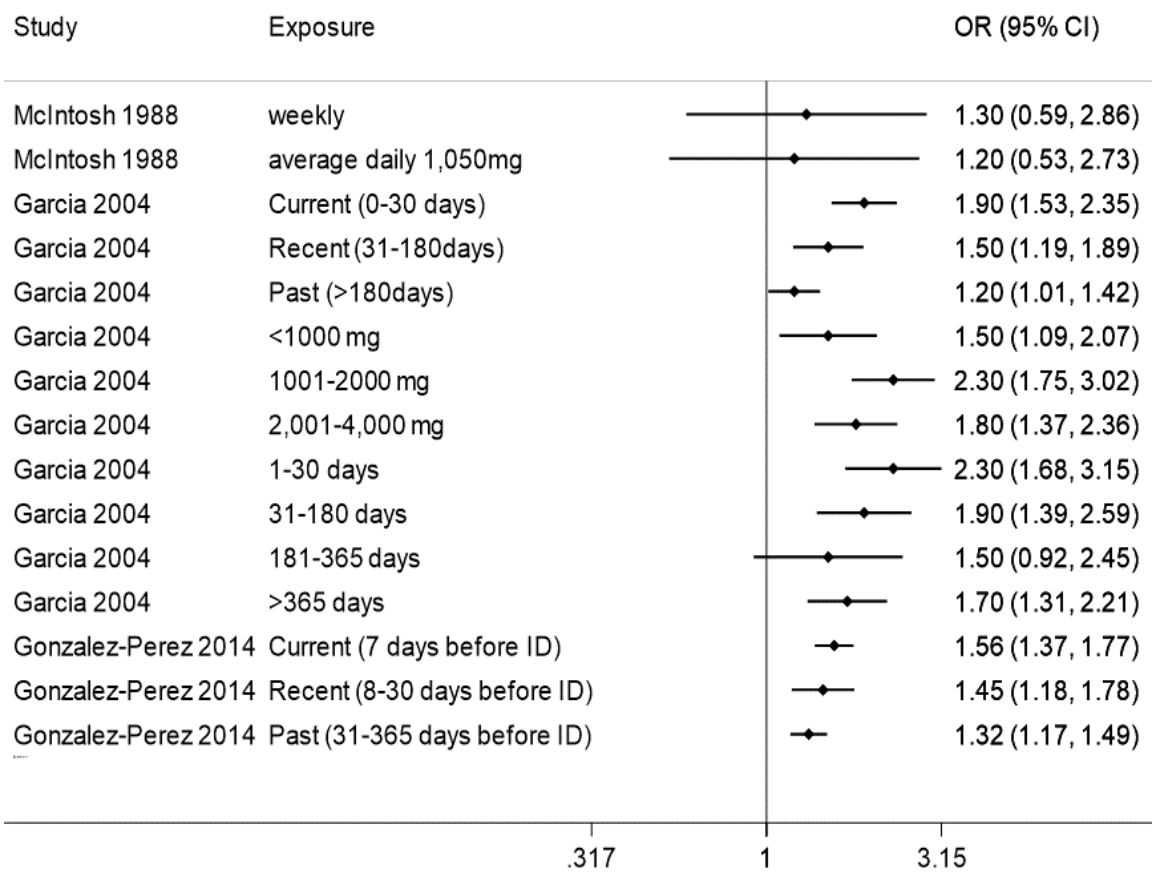


Figure 2.3.3. A Forest plot presented the summary statistics and 95% Confidence interval of case-control studies for Peptic ulcers with different paracetamol dosages. OR - odds ratio, CI - confidence interval, ID - index date.

Table 2.3.3. Cohort studies assessing gastrointestinal adverse effects.

Author (year)	Number	Duration of Follow up (years)	Outcome	Dose	Measure of effect	Results (95%CI)
Rahme et al. (2002)	21,207	3	GI-events	<2600mg/day	RR	**1.27 (1.13, 1.43)**
				2601-3250mg/day or >3250mg/day	RR	**1.34 (1.15, 1.54)**
De-Vries et al. (2010)	3,033	20	upper gastrointestinal (gastroduodenal ulcers and complications such as upper GI-haemorrhages)	overall	RR	**1.36 (1.31, 1.41)**
	235	20		first treatment	RR	**1.74 (1.53, 1.99)**
	336	20		long gap	RR	**1.30 (1.17, 1.46)**
	824	20		low MPR	RR	**1.11 (1.04, 1.21)**
	399	20		medium MPR	RR	**1.25 (1.12, 1.38)**
	208	20		high MPR	RR	**1.49 (1.29, 1.71)**
	367	20		very high MPR	RR	**1.49 (1.34, 1.66)**
Duong et al. (2016)	342,494	3	upper gastrointestinal bleeding without low dose aspirin		HR	**1.38 (1.10, 1.73)**
			<60years old		HR	1.13 (0.78, 1.63)
			>60years old		HR	**1.45 (1.08, 1.95)**
				< 7DDD	HR	**1.62 (1.08, 2.43)**
				8-14 DDD	HR	1.12 (0.72, 1.77)
				>14 DDD	HR	1.18 (0.83, 1.68)
				new episodes	HR	1.25 (0.90, 1.74)
				recent exposure	HR	1.28 (0.75, 2.18)
				past exposure	HR	1.47 (0.93, 2.33)

GI - gastrointestinal, RR - risk ratio, HR - hazard ratio, CI - confidence interval, MPR - medication possession rate, significant estimates are in bold.

Table 2.3.4. Case-control studies assessing gastrointestinal adverse effects.

Author (year)	**Cases N**	**Control N**	**Outcome**	**Dose**	**Measure of effect**	**Results(95%CI)**
Coggon et al. (1982)	277 matched pairs		upper gastrointestinal bleeding	at some time in the past two days	OR	**2.10 (1.10, 4.10)**
				at some time in the past week	OR	**1.90 (1.15, 3.14)**
				at some time in each of the last two weeks	OR	1.50 (0.70, 3.00)
				regularly for at least three months	OR	1.00 (0.40, 2.50)
McIntosh et al. (1985)	104	208	chronic gastric ulcer	daily use of paracetamol (one year before the onset of ulcer symptoms)	OR	3.20 (0.00, 110.00)
				five years before the onset of ulcer symptoms	OR	**3.00 (3.00, 20.40)**
				a lifetime before the onset of symptoms	OR	1.90 (0.30, 11.40)
Levy et al. (1988)	57	2417	major upper gastrointestinal bleeding due to upper gastrointestinal bleeding, gastric ulcer, gastritis			
				none	OR	1.00
				sometime previous week	OR	1.50 (0.38, 5.89)
				current use: occasional use	OR	1.20 (0.50, 3.20)
				discontinued	OR	1.20 (0.40, 3.60)
Faulkner et al. (1988)	230	230	bleeding ulcers (gastric and duodenal)	cases/hospital controls	unmatched OR	
				use in the previous 24 hours	Unmatched OR	1.50 (0.80, 2.80)

				use in the previous week	Unmatched OR	**1.10 (0.70, 1.80)**
				regular use	Unmatched OR	1.10 (0.60, 2.10)
				cases vs community controls		
				use in the previous 24 hours	Unmatched OR	0.90 (0.50, 1.70)
				use in the previous week	Unmatched OR	1.20 (0.76, 1.90)
				regular use	Unmatched OR	1.30 (0.60, 2.50)
Garcia-Rodriguez et al. (2004)	414	5,205	peptic ulcer	non-use (referent)	OR	Referent
	273	1,097		current (0-30 days)	OR	**1.90 (1.50, 2.30)**
	140	773		recent (31-180days)	OR	**1.50 (1.20, 1.90)**
	370	2,925		past (>180days)	OR	**1.20 (1.00, 1.40)**
				paracetamol dose (current users)		
	71	366		<1000 mg	OR	**1.50 (1.10, 2.10)**
	104	337		1001-2000 mg	OR	**2.30 (1.80, 3.10)**
	98	393		2,001-4,000 mg	RR	**1.80 (1.40, 2.40)**
				paracetamol duration (current users)		
	73	267		1-30 days	OR	**2.30 (1.70, 3.20)**
	66	276		31-180 days	OR	**1.90 (1.40, 2.60)**
	25	122		181-365 days	OR	1.50 (0.90, 2.40)
	109	432		>365 days	OR	**1.70 (1.30, 2.20)**
McIntosh et al. (1988)	196	87	peptic ulcer (new cases)	none	OR	Referent

	13	6		weekly	OR	1.30 (0.60, 2.90)
				daily (average 1,050mg)	OR	1.20 (0.50, 2.60)
Rodriguez et al. (2001) + Gonzalez-Perez et al. (2006)	1,494	9,532	upper gastrointestinal bleed/perforation	non-use(>180days)	OR	Referent
	376	1,069		current use in the previous week	OR	**1.30 (1.08, 1.57)**
	140	496		recent (31-90 days prior index date)	OR	1.10 (0.90, 1.40)
	95	403		past (91-180 days prior index date)	OR	1.10 (0.80, 1.40)
	142	610		current users <1,000 mg	OR	1.00 (0.80, 1.20)
	59	242		current users 1,001-1,999	OR	0.80 (0.60, 1.10)
	84	127		current users 2,000	OR	**1.90 (1.40, 2.60)**
	78	83		current users 2,001-3,999	OR	**3.40 (2.40, 4.80)**
	140	382		less than three months	OR	**1.40 (1.10, 1.70)**
	120	376		less than three months <2000 mg	OR	**1.20 (1.00, 1.60)**
	20	6		less than 3 months>2000mg	OR	**10.50 (3.80, 28.90)**
	236	687		three months and more	OR	**1.20 (1.00, 1.50)**
	165	603		three months and more <2000 mg	OR	1.00 (0.80, 1.20)
	71	84		three months and more >2000 mg	OR	3.20 (2.20, 4.60)
Laporte et al. (1991)	875	2682	all acute upper gastrointestinal bleeding were considered	use in the previous week (7 days before index day) +history of ulcer and GI bleeding	OR	1.50 (0.80, 2.50)

			gastric bleeding	use in the previous week (7 days before index day) +history of ulcer and GI bleeding	OR	1.00 (0.40, 2.50)
			duodenal bleeding	use in the previous week (7 days before index day) +history of ulcer and GI bleeding	OR	1.90 (0.90, 4.00)
Laporte et al. (1991)	480	2334	all acute upper gastrointestinal bleeding was considered (without previous history of GI-ulcer or bleeding)	use in the previous week (7 days before index day) without a history of ulcer and GI bleeding	OR	1.20 (0.50, 2.80)
			Gastric bleeding	use in the previous week (7 days before index day) without a history of ulcer and GI bleeding	OR	0.80 (0.20, 3.10)
			duodenal ulcer	use in the previous week (7 days before index day) without a history of ulcer and GI bleeding	OR	1.30 (0.40, 3.80)
Holvoet et al. (1991)	161		upper gastrointestinal bleeding such as peptic oesophagitis, gastric erosions, gastric and duodenal ulcers (single or multiple)	use in the previous week	OR	1.40 (0.50, 4.10)
Imhof et al. (1997)	209	209	Ulcer bleeding	Unclear exposure definition for paracetamol	OR	**3.20 (1.17, 8.73)**

Nobili et al. (1992)	441	1323	Acute upper gastrointestinal bleeding	Paracetamol use in previous week	OR	0.20 (0.02, 2.10)
Lanas et al. (2003)	1122	2231	Upper gastrointestinal bleeding	Any paracetamol used in the previous seven days from admission to the hospital	OR	0.70 (0.40, 1.20)
Savage et al. (1993)	494	972	Perforation and bleeding of peptic ulcer	Paracetamol use as current, regular use: ≤1,000mg/day	OR	1.20 (0.70, 2.10)
				>1,000mg/day	OR	**2.60 (1.90, 6.20)**
Langman et al. (1994)	1,144	1126 hospital controls, 989 community controls	Ulcer complications	Any paracetamol used in the previous week	OR	1.10 (0.71, 1.71)
Matikainen et al. (1996)	48		acute bleeding due to esophagitis, gastric or duodenal ulcer, or erosions	Any paracetamol used in the previous week	OR	1.08 (0.11, 10.68)
Gallerani et al. (2004)	940		Upper gastrointestinal bleeding	Any paracetamol used in the previous seven days from admission to the hospital	OR	**1.95 (1.07, 3.56)**
González-Pérez et al. (2014)	649	868	Peptic ulcer	Current users (7 days before the index date)	OR	**1.56 (1.38, 1.78)**
	190	281		Recent users (8-30 days before the index date)	OR	**1.45 (1.18, 1.78)**
	651	1,140		Past users (31-365 days before the index date)	OR	**1.32 (1.17, 1.49)**

OR - Odds ratio, RR - risk ratio, CI - confidence interval, and significant values are bold.

2.3.1.3. Dose-response (GI-events)

Figure 2.3.4 illustrates three cohort studies describing that paracetamol exposure was associated with an increased risk for GI events than unexposed paracetamol (De-Vries et al., 2010; Duong et al., 2016; Rahme et al., 2002). De-Vries et al. (2010) reported a significant dose-response relationship between paracetamol exposure and upper GI adverse effects such as gastro-duodenal ulcers and upper gastrointestinal haemorrhages than unexposed (De-Vries et al., 2010). The RR varied from 1.11 (95%CI 1.04, 1.21) for low medication possession rate (MPR) to 1.49 (95%CI 1.34, 1.66) for high MPR (Figure 2.3.4).

In Figure 2.3.4, the study by Rahme et al. (2002) reported an increase in the risk of GI events with an increase in paracetamol dosage using data from the RAMQ database (n= 57,261 participants) with a RR of 1.34 (95%CI 1.15, 1.54) in the high dose (3,250mg/day) and 1.27 (95%CI 1.13, 1.43) in low dose (2,600mg/day).

The study from France demonstrated no dose-dependent association between paracetamol use either for daily defined dose (DDD) exposure as shown in Figure 2.3.4 or types of episodes defined as new, recent, or past than non-users (Duong et al., 2016).

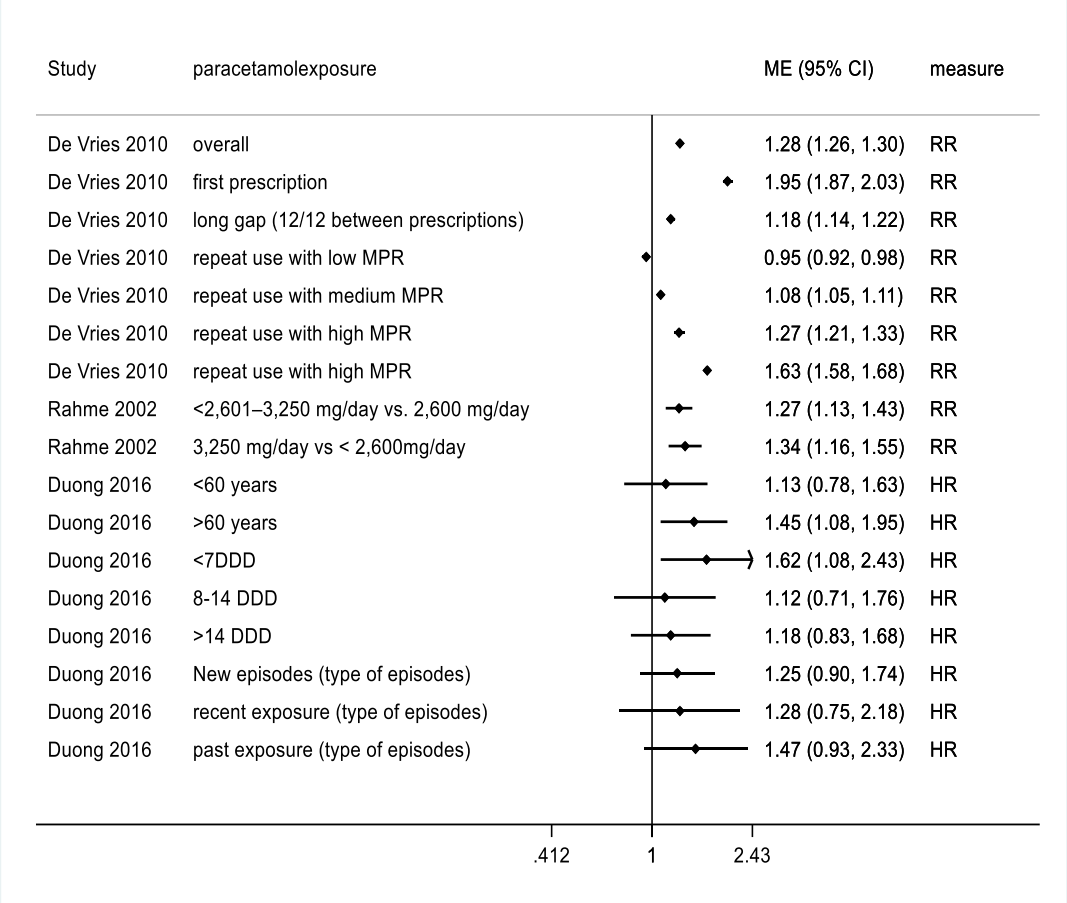


Figure 2.3.4. Risk of upper gastrointestinal events with paracetamol use: effects of dose. According to the respective studies, data are shown as adjusted risk or hazard ratios with a 95% Confidence interval (Data were not meta-analysed, and a forest plot was used for summary statistics for studies). ME - a measure of effect, RR - risk ratio, HR - hazard ratio, CI - confidence interval, MPR - medication possession rate, DDD – daily defined dose.

2.3.2. Cardiovascular events

2.3.2.1. Association between paracetamol exposure and incident hypertension

Two cohort studies (n=137,955) with similar frequency of paracetamol usage and comparable outcome of incident hypertension were pooled together (Curhan et al., 2002; Dedier et al., 2002). Figure 2.3.5 shows a significant dose-response relationship between paracetamol exposure and incident hypertension compared to unexposed with a considerable and unexplained heterogeneity (I2 = 91.5%, P = 0.001).

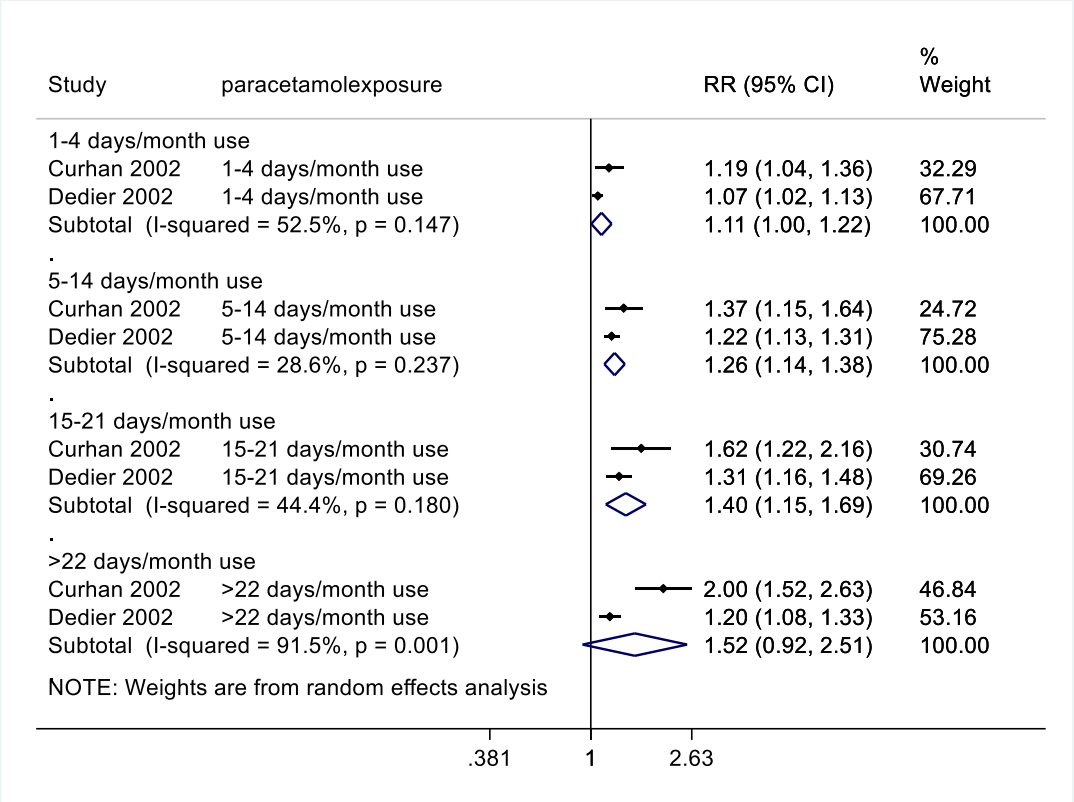


Figure 2.3.5. Risk of incident hypertension with therapeutic usage of paracetamol - effect of frequency of use. Pooled results from Curhan et al. (2002); Dedier et al. (2002). RR - risk ratio, CI - confidence interval.

Similarly, Figure 2.3.6 illustrates that Kurth et al. (2005) also reported an increase in the incidence of incident hypertension with an increase in the number of tablets consumed in the last month, with marginal significance. The HR varied from 0.95 (95%CI 0.67, 1.36) to 1.34 (95%CI 1.00, 1.80) with 8,229 participants aged 40-84 years, as shown in Figure 2.3.6 (Kurth et al., 2005).

The Nurses Health Study 1 comprised 121,700 women aged 30-55 years and reported a dose-response association within the older cohort for average daily exposure of paracetamol and risk of having incident hypertension compared with non-users of paracetamol as given in Figure 2.3.6. (Forman et al., 2005).

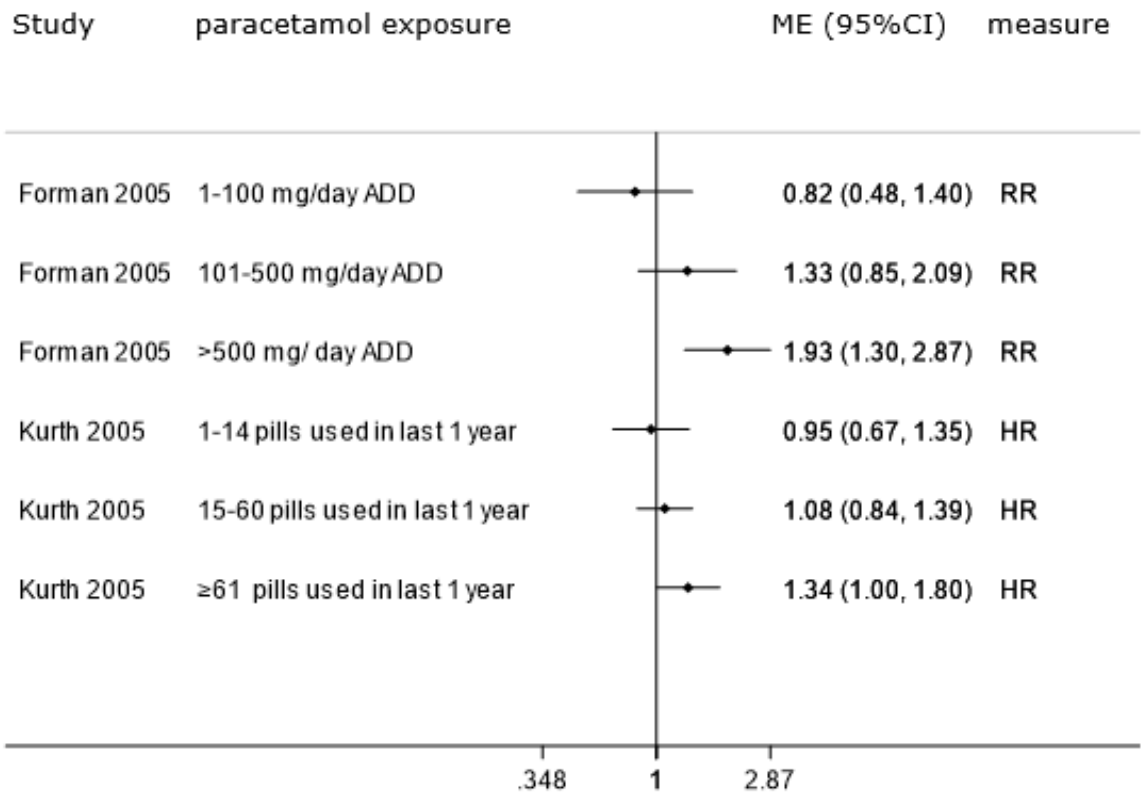


Figure 2.3.6. Forest plot for risk of having incident hypertension according to average daily dose (ADD) for one study (Forman et al., 2005) and number of Tablets used in the last 12 months or one year for another study (Kurth et al., 2005). ADD - average daily dose, ME - measure of effect, RR - risk ratio.

A study by Forman et al. (2005) used a younger cohort with 116,671 participants aged 25-42 years and identified a statistically significant risk of incident hypertension associated with paracetamol daily dose >500 mg per day with an HR of 1.99 (95%CI 1.39, 2.85) when compared with nonusers, summarised in Table 2.3.5.

Table 2.3.5 also shows that frequency of paracetamol use for 4-5 days/week or 6-7 days/week was also significantly associated with an increased risk of incident hypertension with RR of 1.59 (95%CI 1.13, 2.24) and 1.34 (95%CI 1.00, 1.79) in men (Forman et al., 2007).

2.3.2.2. Non-fatal myocardial infarction, non-fatal stroke, fatal coronary heart disease or fatal stroke or other cardiovascular events

Table 2.3.5 summarises four cohort studies (1,020,365 participants) that analysed either myocardial infarction, nonfatal/fatal coronary heart disease, fatal/non-fatal stroke, or acute coronary disease (Chan et al., 2006; De-Vries et al., 2010; Duong et al., 2016; Fulton et al., 2015). Figure 2.3.7 represents a significant dose-response relationship reported by Chan et al. (2006) between paracetamol exposure and myocardial infarction compared to the unexposed.

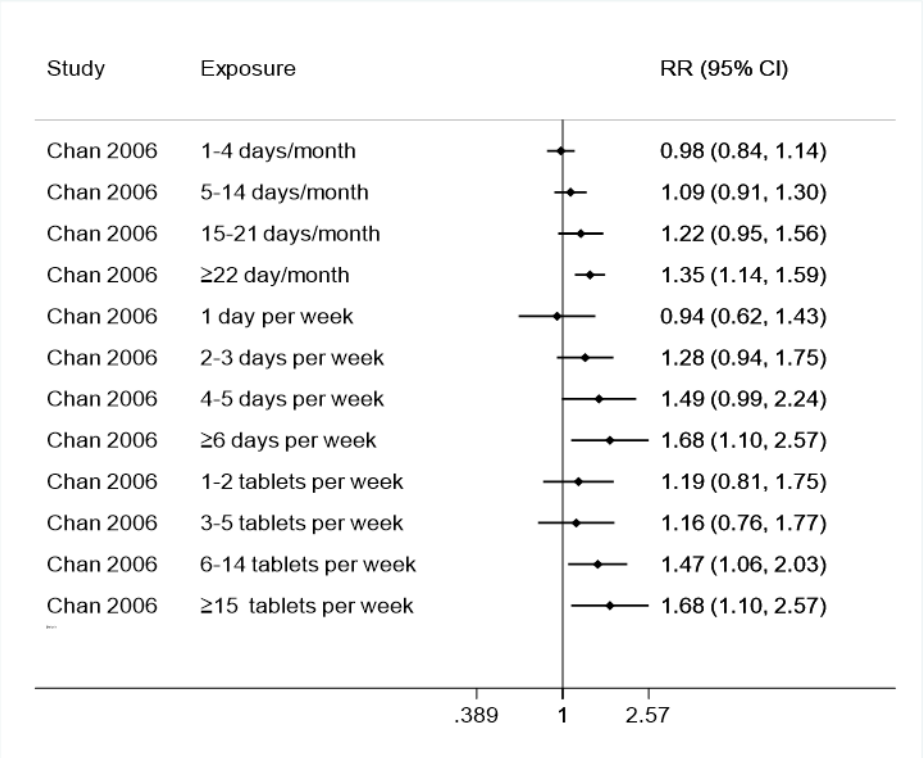


Figure 2.3.7. Forest plot summary statistics showing association of paracetamol use vs non-use with cardiovascular adverse events, either confirmed or not-confirmed non-fatal myocardial infarction, fatal coronary heart disease, fatal or non-fatal stroke. RR - risk ratio, CI - confidence interval.

The paracetamol exposure at a very high MPR in 382,404 participants, as shown in table 2.3.5, was associated with myocardial infarction and stroke with RR of 1.30 (95%CI 1.19, 1.41) compared to unexposed (De-Vries et al., 2010). Table 2.3.5 also indicates that the overall risk for developing heart failure was significantly higher in paracetamol exposure when compared with unexposed with RR of 1.19 (95%CI 1.16, 1.23) (De-Vries et al., 2010).
In contrast, there was no association found between a different frequency of paracetamol exposure (defined as a low, medium, and high) and increased incidence of myocardial infarction, stroke, and any cardiovascular event when compared with unexposed, as summarized in Table 2.3.5 (Fulton et al., 2015).

According to Duong et al. (2016), the incidence of acute coronary syndrome was higher in paracetamol exposed without using low dose aspirin when compared with non-users (342,494 participants) with adjusted HR 1.32 (95%CI 1.16, 1.49).

Furthermore, Figure 2.3.8 shows that the MA of three case-control studies, including 840,816 participants, showed that the current paracetamol use (defined as 90 days before the index date) was not associated with MI compared to the unexposed with an OR of 0.93 (95%CI 0.80, 1.09). These estimates were not statistically significant, as illustrated in Figure 2.3.8, with moderate and unexplained heterogeneity (I2 = 52.7%, P = 0.12).

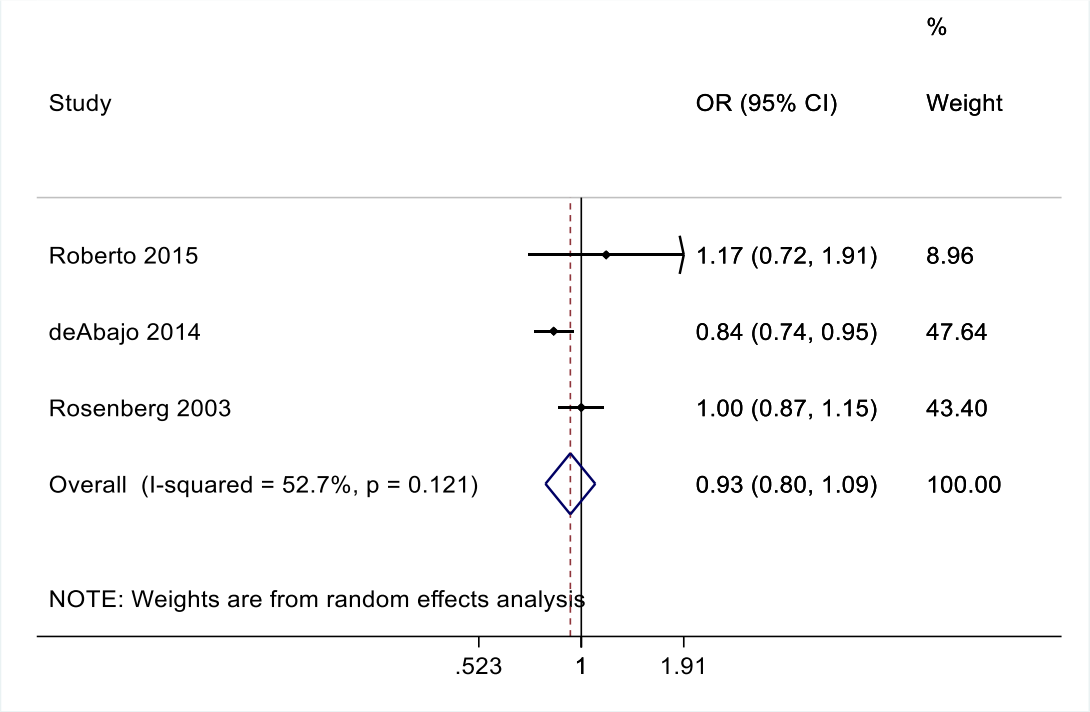


Figure 2.3.8. Forest plot for case-control studies analysing myocardial infarction using a random-effect model. OR - odds ratio, CI - confidence interval.

The paracetamol exposure with different paracetamol dosage regimens (< 2000mg, > 2000 mg) frequency of 31 days up to 365 days was not associated with non-fatal ischemic stroke when compared with non-users (García-Poza et al., 2015), as shown in Table 2.3.6. Gonzalez-Valcarcel et al. (2016) determined the association of different dosages and frequencies mentioned in Table 2.3.6 of paracetamol with major cardiovascular events such as death, MI, or stroke. The findings suggested that the “ever use of paracetamol” had an OR of 1.21 (95%CI 1.04, 1.42) for increased risk of major cardiovascular events such as MI, stroke, or death compared to non-users (Gonzalez-Valcarcel et al., 2016).

Table 2.3.5. Summary of cohort studies assessing cardiovascular events.

Author (year)	Number(n)	Person years	Duration of follow-up max. (years)	Outcome	Dose	Measure of effect	Results(95%CI)
Curhan et al. (2002)	369	45,014	2	incident hypertension	none (referent)	RR	1.0
	661	71,562			1-4 days/month	RR	**1.19 (1.04, 1.36)**
	229	17,706			5-14 days/month	RR	**1.37 (1.15, 1.64)**
	62	3,303			15-21 days/month	RR	**1.62 (1.22, 2.16)**
	72	2,847			≥22 days/month	RR	**2.00 (1.52, 2.62)**
Dedier et al. (2002)	4,037	156,739	2	incident hypertension	None(referent)	RR	1.00
	2,959	111,117			1-4 days/month	RR	**1.07 (1.02, 1.13)**
	1,033	32,144			5-14 days/month	RR	**1.22 (1.14, 1.32)**
	317	8,737			15-21 days/month	RR	**1.31 (1.16, 1.48)**
	457	12,994			22+ days/month	RR	**1.20 (1.08, 1.33)**
Kurth et al. (2005)	4,290		14	subsequent hypertension	<12 (referent)	HR	1.00
	2,517				12-1499 Tablets for 14 years	HR	0.86 (0.77, 0.95)
	264				1500-2499 Tablets for 14 years	HR	1.17 (0.93, 1.46)
	310				≥2500 Tablets for 14 years	HR	1.08 (0.87, 1.34)
	848				missing information	HR	1.02 (0.85, 1.23)
	7,176		14	subsequent hypertension	0	HR	1
	130				1-14 no. of Tablets used in last 12 months	HR	0.95 (0.67, 1.36)

	207				15-60 no. of Tablets used in the last 12 months	HR	1.08 (0.84, 1.40)
	129				≥61 used no. of Tablets in last 12 months	HR	**1.34 (1.00, 1.80)**
	587				missing information	HR	1.00 (0.78, 1.28)
Forman et al. (2005) NHS-I	107	3 365		incident hypertension	current use of paracetamol 0 mg per day (average daily dose)	RR	1.0
	20	551			1-100 mg per day	RR	0.82 (0.48, 1.39)
	34	636			101-500 mg per day	RR	1.33 (0.84, 2.08)
	50	716			>500 mg per day	RR	**1.93 (1.30, 2.88)**
Forman et al. (2005) NHS-II	118	6,066		incident hypertension	current use of paracetamol 0 mg per day (average daily dose)	RR	1.0
	47	2,531			1-100 mg per day	RR	1.11 (0.76, 1.60)
	76	3,495			101-500 mg per day	RR	1.09 (0.79, 1.50)
	58	1,313			>500 mg per day	RR	**1.99 (1.39, 2.85)**
Forman et al. (2007)	1,743	47,424	4	incident hypertension	0 per week	RR	1.00
	47	1,344			one day/week	RR	1.00 (0.74, 1.35)
	69	1,804			2-3 days/week	RR	1.00 (0.78, 1.29)
	36	618			4-5 days/week	RR	**1.59 (1.13, 2.24)**
	50	949			6-7 days/week	RR	**1.34 (1.00, 1.79)**
					0 pill per week	RR	1.0
					15 or more tablets per week	RR	1.04 (0.61,1.76)

Chan et al. (2006)	1,441	12	cardiovascular such as non-fatal myocardial infarction, non-fatal or fatal stroke, fatal coronary heart disease	none for 12 years	RR	1.0
	221			1-4 days/month for 12 years	RR	0.98 (0.84, 1.14)
	143			5-14 days/month for 12 years	RR	1.09 (0.91, 1.30)
	68			15-21 days/month for 12 years	RR	1.22 (0.95, 1.56)
	168			≥22day/month for 12 years	RR	**1.35 (1.14, 1.59)**
	326			none for 12 years	RR	1.0
	24			one day per week for 12 years	RR	0.94 (0.62, 1.44)
	48			2-3 days per week for 12 years	RR	1.28 (0.94, 1.75)
	26			4-5 days per week for 12 years	RR	1.49 (0.99, 2.24)
	50			≥Six days per week for 12 years	RR	**1.68 (1.10, 2.58)**
	326			none for 12 years	RR	1.0
	30			1-2 tablets per week for 12 years	RR	1.19 (0.81, 1.76)
	27			3-5 tablets per week for 12 years	RR	1.16 (0.76, 1.76)
	45			6-14 tablets per week for 12 years	RR	**1.47 (1.06, 2.03)**

	25		≥15 tablets per week for 12 years	RR	**1.68 (1.10, 2.58)**
De-Vries et al. (2010)	2,761	myocardial infarction	Overall	RR	**1.14 (1.10, 1.19)**
	177		first treatment	RR	**1.42 (1.22, 1.65)**
	254		long gap	RR	0.98 (0.86, 1.11)
	860		low MPR	RR	**1.11 (1.02, 1.19)**
	407		medium MPR	RR	**1.17 (1.05, 1.29)**
	157		high MPR	RR	1.04 (0.89, 1.23)
	313		very high MPR	RR	**1.17 (1.04, 1.32)**
	4,285	stroke	overall	RR	**1.14 (1.10, 1.18)**
	214		first treatment	RR	**1.17 (1.02, 1.35)**
	453		long gap	RR	**1.14 (1.03, 1.25)**
	1,248		low MPR	RR	1.03 (0.97, 1.10)
	655		medium MPR	RR	**1.17 (1.08, 1.27)**
	249		high MPR	RR	1.02 (0.89, 1.15)
	600		very high MPR	RR	**1.30 (1.19, 1.41)**
	5,673	heart failure	Overall	RR	**1.19 (1.16, 1.23)**
	355		first treatment	RR	**1.52 (1.36, 1.69)**
	579		long gap	RR	**1.23 (1.13, 1.34)**
	1,566		low medication possession rate (MPR)	RR	**1.06 (1.00, 1.12)**
	810		medium MPR	RR	**1.21 (1.12, 1.30)**
	398		high MPR	RR	**1.37 (1.24, 1.52)**
	733		very high MPR	RR	**1.38 (1.28, 1.50)**
Fulton et al. (2015)		myocardial infarction	any	HR	0.67 (0.40, 1.11)
			low frequency	HR	1.06 (0.78, 1.43)
			medium frequency	HR	0.70 (0.48, 1.02)
			high frequency	HR	1.11 (0.64, 1.93)

		any	HR	1.31 (0.92, 1.87)
	stroke			
		low frequency	HR	1.11 (0.84, 1.47)
		medium frequency	HR	0.73 (0.50, 1.06)
		high frequency	HR	0.87 (0.49, 1.55)
	any cardiovascular event	any	HR	1.16 (0.90, 1.50)
		low frequency	HR	1.10 (0.91, 1.23)
		medium frequency	HR	0.75 (0.59, 0.95)
		high frequency	HR	1.41 (0.98, 2.02)
Duong et al. (2016)	acute coronary syndrome	without low dose aspirin	HR	**1.32 (1.16, 1.49)**
		<60 years old	HR	1.05 (0.84, 1.32)
		>60 years old	HR	**1.38 (1.19, 1.61)**
		<7DDD	HR	**1.31 (1.06, 1.62)**
		8-14 DDD	HR	**1.36 (1.08,1.71)**
		>14 DDD	HR	1.19 (0.96, 1.47)
		new episodes	HR	1.18 (0.99, 1.42)
		past exposure	HR	**1.31 (1.04, 1.66)**
		recent episodes	HR	**1.60 (1.18, 2.19)**
	myocardial infarction	without low dose aspirin	HR	**1.56 (1.26, 1.93)**
	<60 years old		HR	1.08 (0.77, 1.51)
	>60 years old		HR	**1.91 (1.43, 2.54)**
		<7DDD	HR	**1.48 (1.04, 2.11)**
		8-14 DDD	HR	**1.81 (1.20, 2.71)**
		>14 DDD	HR	1.35 (0.93, 1.94)
		new episodes	HR	**1.46 (1.06, 2.00)**
		past exposure	HR	1.30 (0.88, 1.94)
		recent episodes	HR	**2.04 (1.14, 3.64)**

	stroke	without low dose aspirin	HR	**1.11 (0.94, 1.32)**
	<60 years old		HR	0.80 (0.54, 1.19)
	>60 years old		HR	1.13 (0.93, 1.37)
		<7DDD	HR	1.37 (0.97, 1.92)
		8-14 DDD	HR	**1.68 (1.20, 2.34)**
		>14 DDD	HR	0.67 (0.52, 0.87)
		new episodes	HR	0.93 (0.72, 1.19)
		past exposure	HR	1.20 (0.84, 1.70)
		recent episodes	HR	1.38 (0.90, 2.08)

OR - Odds ratio, RR - risk ratio, HR - hazard ratio, MPR - medication possession rate, DDD - daily defined dose, and significant results are in bold.

Table 2.3.6 Summary of results for case-control studies assessing cardiovascular adverse events.

Author (year)	Cases N	Control N	Outcome	Dose	Measure of effect	Results (95%CI)
Rosenberg et al. (2003)	1422	1890	acute myocardial infarction	never use	OR	1
	613	766		current use	OR	1.00 (0.87, 1.15)
	65	93		≥one day/week	OR	0.90 (0.60, 1.30)
	9	21		≥one day/week use for ≥three months for <1 year	OR	0.40 (0.20, 1.00)
	20	28		≥one day/week use for ≥three months for 1-2 years	OR	0.90 (0.50, 1.80)
	9	13		≥one day/week use for ≥three months for 3-4 years	OR	1.00 (0.40, 2.60)
	27	31		≥one day/week use for ≥three months for ≥five years	OR	1.10 (0.60, 2.00)
	37	57		≥four days/week	OR	0.80 (0.50, 1.20)
	8	16		≥four days/week use for ≥ three months for <1 year	OR	0.50 (0.20, 1.20)
	16	19		≥four days/week use for ≥ three months for 1-2 years	OR	1.10 (0.50, 2.40)
	6	5		≥four days/week use for ≥ three months for 3-4 years	OR	1.30 (0.40, 4.60)
	7	17		≥four days/week use for ≥ three months for ≥five years	OR	0.60 (0.20, 1.50)
	31	49		daily	OR	0.70 (0.40, 4.60)

	7	15		daily use for ≥three months for <1 year	OR	0.40 (0.10, 1.00)
	14	17		daily use for ≥three months for 1-2 years	OR	1.00 (0.40, 2.20)
	6	5		daily use for ≥three months for 3-4 years	OR	1.30 (0.40, 4.60)
	5	12		daily use for ≥three months for ≥five years	OR	0.50 (0.20, 1.60)
Roberto et al. (2015)	1957	9409	acute myocardial infarction, angina pectoris, ischemic stroke, transient ischemic attack, haemorrhagic stroke	non-use	OR	1
	22	84		current use	OR	1.17 (0.72, 1.92)
De-Abajo et al. (2014)	1532	7955	acute myocardial infarction	non-use	OR	1
	552	2798		current	OR	0.84 (0.74, 0.95)
	1060	5301		past	OR	0.89 (0.81, 0.98)
	689	3946		remote	OR	0.85 (0.77, 0.95)
				daily dose	OR	
	183	1018		up to 2000mg	OR	0.75 (0.62, 0.90)
	142	711		>2000mg	OR	0.87 (0.71, 1.07)

				treatment duration		
	198	1086		<31 days	OR	0.81 (0.68, 0.96)
	218	1107		31–365 days	OR	0.84 (0.71, 1.00)
	136	605		366 + days	OR	0.89 (0.72, 1.11)
				background CV risk		
	51	469		low	OR	1.11 (0.77, 1.59)
	165	1284		intermediate	OR	0.84 (0.68, 1.03)
	336	1045		high	OR	0.80 (0.67, 0.94)
García-Poza et al. (2015)	932	7078	non-fatal ischemic stroke	non-use	OR	1
	513	3448		current	OR	0.97 (0.85, 1.10)
	889	5651		past	OR	1.06 (0.95, 1.18)
	554	3823		remote	OR	1.05 (0.94, 1.19)
				dose		
	172	1202		< 2000 mg	OR	0.93 (0.78, 1.12)
	143	888		> 2000 mg	OR	0.99 (0.81, 1.21)
	198	1358		unknown	OR	0.99 (0.83, 1.18)
				treatment duration		
	186	1168		< 31 days	OR	1.06 (0.89, 1.27)
	208	1419		31–365 days	OR	0.94 (0.79, 1.12)
	119	861		366+ days	OR	0.89 (0.71, 1.10)
				background CV risk		
	62	579		low	OR	1.23 (0.87, 1.73)
	185	1613		intermediate	OR	0.93 (0.75, 1.15)
	266	1256		high	OR	0.94 (0.78, 1.14)
Gonzalez-Valcarcel et al. (2016)	1858	3803	a major cardiovascular event such as	none	OR	1 referent

		death, MI, or stroke			
295	503		paracetamol used	OR	**1.21 (1.04, 1.42)**
225	383		infrequent users	OR	**1.21 (1.00, 1.45)**
70	120		daily	OR	**1.20 (0.89, 1.63)**
			paracetamol dose		
1858	3803	a major cardiovascular event such as death, MI, or stroke	none	OR	1 referent
25	46		<1500mg/day	OR	1.13 (0.69, 1.87)
17	32		1500-2999mg/day	OR	1.00 (0.54, 1.87)
28	42		≥3000mg/day	OR	1.21 (0.82, 2.22)
			duration		
1858	3803	a major cardiovascular event such as death, MI, or stroke	none	OR	1 referent
39	69		<31 days	OR	1.17 (0.77, 1.77)
26	36		31-365 days	OR	1.42 (0.85, 2.37)
5	15		≥366 days	OR	0.61 (0.22, 1.73)

OR - odds ratio, RR - risk ratio, MI - myocardial infarction, CV - cardiovascular, and significant results are bold

2.3.3. Renal side effects

Five cohort studies and six case-control studies reported renal side effects with paracetamol users compared to non-users.

2.3.3.1. Acute renal failure

One cohort study with 382,404 participants reported that the overall paracetamol exposure, from low MPR to very high MPR, was significantly associated with renal failure, given in Table 2.3.7. Still, there was no dose-response with RR of 1.16 (95%CI 1.04, 1.29) for low MPR, RR of 1.27 (95%CI 1.10, 1.47) for medium MPR, RR of 1.44 (95%CI 1.18, 1.75) for high MPR and RR of 1.34 (95%CI 1.15, 1.57) for very high MPR (De-Vries et al., 2010) shown in Table 2.3.7.

2.3.3.2. Chronic renal failure

There was one cohort study by Evans et al. (2009) with 801 participants who reported no difference in the progression of chronic renal failure, defined as the change in estimated glomerular filtration rate (eGFR) in paracetamol exposed participants for different dose intake in 7 years described in Table 2.3.7 compared with unexposed. Similarly, participants exposed to paracetamol (twice a week) for two months showed no difference for time for renal replacement therapy compared with unexposed, as illustrated in Table 2.3.7. Two cohort studies demonstrated an altered estimated glomerular filtration rate (eGFR), as shown in Figure 2.3.9 (Curhan et al., 2004; Kurth et al., 2003). A dose-response was noted for decreased e-GFR of at least 30ml/min/1.73m2 for paracetamol exposure with different numbers of tablets taken in the last 14 years compared with non-users, but this was not statistically significant (Kurth et al., 2003). It appears from Figure 2.3.10 that the paracetamol exposure of 100-499g lifetime intake, 500-2999g lifetime intake, and >3000g lifetime intake were all significantly associated with a >30% decrease in estimated glomerular filtration rate. Still, no dose-response increase was observed in this study (Curhan et al., 2004).

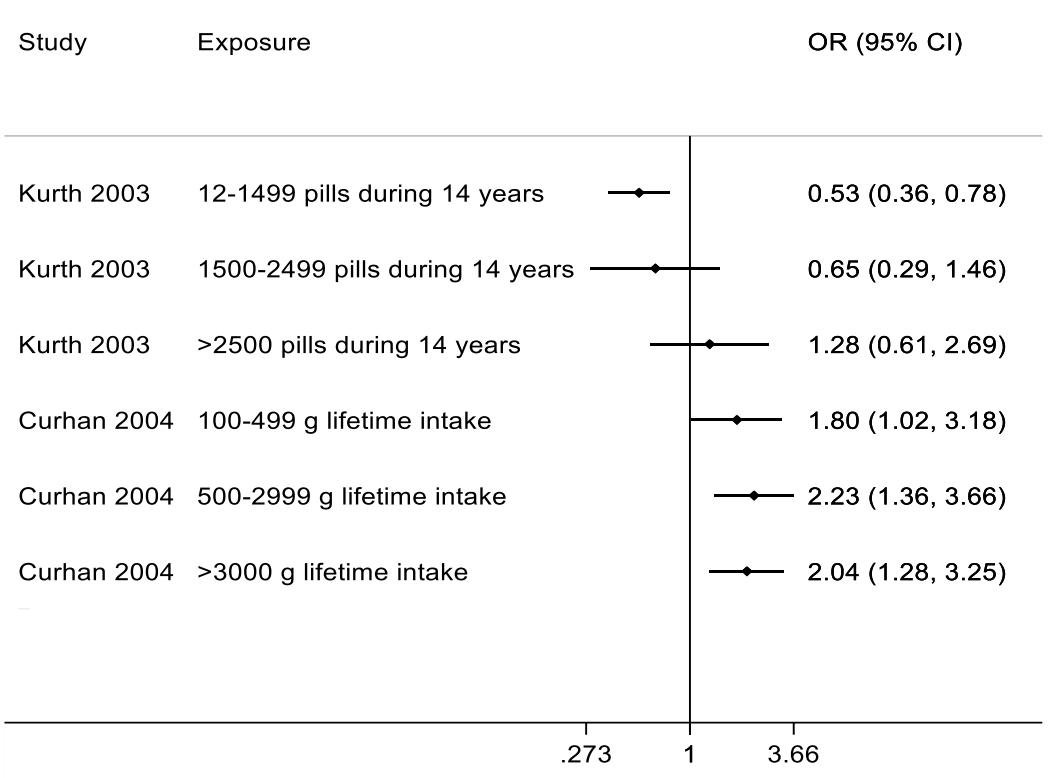


Figure 2.3.9. Forest plot showing summary statistics for dose-response (Kurth et al., 2003) for an increase in odds-ratio of >Glomerular 30mL/min/1.73m2 for estimated glomerular filtration rate and >30% decrease in estimated glomerular filtration rate (Curhan et al., 2004). ME - a measure of effect, OR - odds ratio, CI - confidence interval, note: OR were sub-optimally used in these two cohort studies by the original authors.

Table 2.3.8 shows that a case-control study with 928 newly diagnosed cases of chronic renal failure and 996 controls reported that regular use of paracetamol had a 2.5 times greater risk of chronic renal failure with an OR of 2.50 (95%CI 1.70, 3.60) (Fored et al., 2001). Additionally, paracetamol cumulative dose exposure >500g was three times significantly associated with chronic renal failure OR 3.30 (95%CI 2.00, 5.50).

2.3.3.3. End-stage renal failure

One cohort study with 19,163 participants and a study duration of 9 years reported a significant dose-response relationship between exposure to paracetamol with an average daily defined dose of < 0.568 or > 0.569 with end-stage kidney disease with a HR of 1.43 (95%CI 1.12, 1.82) and 5.21 (95%CI 4.31, 6.29), respectively, compared to non-users (Kuo et al., 2010) (Table 2.3.7).

Results from three case-control studies that reported end-stage kidney failure are shown in Table 2.3.8. It was impossible to pool the results due to different definitions of outcomes. Perneger et al. (1994) studied 716 cases matched with 361 controls and showed that there was a two folds higher risk of end-stage renal disease associated with the exposure to ≥366 tablets (users) in a year compared with 0-104 paracetamol tablets defined as non-users (OR 2.10; 95%CI 1.10, 3.70). Pommer and colleagues also indicated that the paracetamol exposure (1000-4999 kg lifetime intake) was associated with end-stage renal failure (RR 4.06; 95%CI 1.32, 12.43) and a dose-response with a wide confidence interval, as shown in Figure 2.3.10. (Pommer et al., 1989).

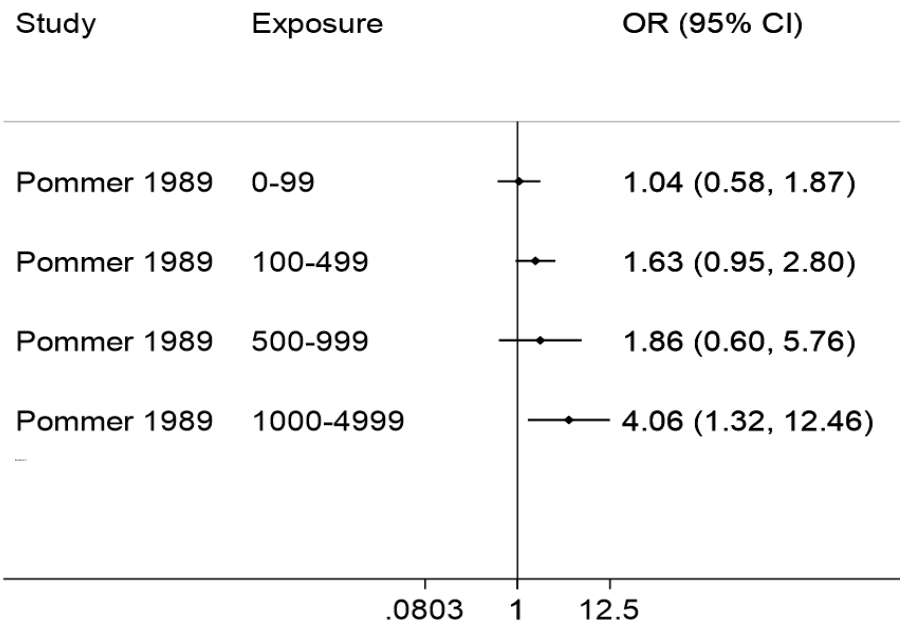


Figure 2.3.10. Outcome: End-stage renal failure in patients taking paracetamol versus patients taking no paracetamol. A dose-response was calculated by Pommer et al. (1989). OR - odds ratio, CI - confidence interval.

Regular exposure to paracetamol in a case-control study with 325 cases matched with 325 controls was associated with an over two-fold increased risk of developing new cases of end-stage kidney failure compared to those unexposed to paracetamol (OR 2.66; 95%CI 1.04, 6.82), given in Table 2.3.8 (Steenland et al., 1990).

2.3.3.4. Newly diagnosed kidney disease

According to the estimates summarized in Table 2.3.8, only one multicentre case-control study (n=554) had suggested an association between daily exposure to paracetamol and newly diagnosed kidney disease (defined as serum creatinine was ≥130 µmol per litre). This association was statistically significant, with an OR of 3.21 (95%CI 1.05, 9.80) (Sandler et al., 1989).

2.3.3.5. Any renal disorder

The association between paracetamol exposure and any renal disorder, including acute renal failure, chronic renal failure, renal failure, unspecified nephritis, nephrotic syndrome, or bilateral small kidney disease, using pharmacy claims data was reported by one case-control study (Kelkar et al., 2012) shown in Table 2.3.8. This study explained that paracetamol intake was significantly associated with an elevated risk of any renal disorder with a maximum daily dose of ≤4 gm 7 days before the index date with an OR of 1.68 (95%CI 1.38, 2.03) (n=4,724 cases, n=14,172 controls) (Table 2.3.8).

Table 2.3.7. Summary of cohort studies assessing renal adverse events.

Author (year)	Number(n)	Person years	Duration of follow-up max. (years)	Outcome	Dose	Measure of effect	Results(95%CI)
Kurth et al. (2003)*	4494		14	increase in creatinine levels	never use (referent)	OR	1.00
					12-1499 tablets during 14 years	OR	0.68 (0.48, 0.97)
					1500-2499 tablets during 14 years	OR	0.69 (0.31, 1.53)
					>2500tablets during 14 years	OR	1.11 (0.52, 2.36)
Curhan et al. (2004)*	56		11	decrease in estimated glomerular filtration rate of 30ml/min per 1.73m2	<100g lifetime analgesic intake(referent)	OR	1.00
	21				100-499g lifetime analgesic intake	OR	**1.80 (1.02, 3.17)**
	40				500-2999g lifetime analgesic intake	OR	**2.23 (1.36, 3.63)**
	45				>3000g lifetime analgesic intake	OR	**2.04 (1.28, 3.24)**
	66			30% or more significant decrease in estimated	<100g lifetime analgesic intake (referent)	OR	1.00

			glomerular filtration rate			
	19			100-499g lifetime analgesic intake	OR	1.40 (0.79, 2.49)
	34			500-2999g lifetime analgesic intake	OR	1.64 (1.00, 2.69)
	54			>3000g lifetime analgesic intake	OR	**2.19 (1.40, 3.35)**
Evans et al. (2009)	801 (overall)	7	differences in estimated progression rates, (change in eGFR in ml/min/1.73 m2 per year)	no use(referent)	Regression coefficient	1.00
				<99g intake during seven years	Regression coefficient	-0.17 (-0.90, 0.60)
				100-499g intake during seven years	Regression coefficient	0.60 (-0.30, 1.50)
				500-2999g intake during seven years	Regression coefficient	0.65 (-0.70, 2.00)
				>3000g intake during seven years	Regression coefficient	0.24 (-1.20, 1.70)
			time to renal replacement therapy	regular use (at least twice a week for two months before inclusion	HR	1.10 (0.90, 1.40)

Kuo et al. (2010)	19,163 (Overall)	9	end-stage renal disease	no use	HR	1.00
				the defined daily dose per person-year	HR	**2.92 (2.47, 3.45)**
				< 0.568	HR	**1.43 (1.12, 1.82)**
				> 0.569	HR	**5.21 (4.31, 6.29)**
De-Vries et al. (2010)	1,372	20	renal failure	overall	RR	**1.20 (1.14, 1.27)**
	66			first treatment	RR	**1.31 (1.03, 1.68)**
	142			long gap	RR	**1.21 (1.02, 1.43)**
	423			low medical possession rate (MPR)	RR	**1.16 (1.04, 1.29)**
	217			medium MPR	RR	**1.27 (1.10, 1.47)**
	109			high MPR	RR	**1.44 (1.18, 1.75)**
	182			very high MPR	RR	**1.34 (1.15, 1.57)**

OR - odds ratio, RR - risk ratio, HR - hazard ratio, MPR - medical possession rate, and significant results are in bold, Note: * OR was sub-optimally used in the cohort study by the original author.

Table 2.3.8. Summary of case-control studies assessing renal adverse effects.

Author (year)	Cases N	Control N	Outcome	Dose	Measure of effect	Results (95%CI)
Pommer et al. (1989)	262	319	end-stage renal failure (n=921 case group)	0 (grams/ lifetime intake)	OR	1.00 reference
	24	27		1-99	OR	1.04 (0.58, 1.87)
	31	24		100-499	OR	1.63 (0.95, 2.81)
	8	5		500-999	OR	1.86 (0.60, 5.75)
	14	5		1000-4999	OR	**4.06 (1.32, 12.43)**
Sandler et al. (1989)	418	439	newly diagnosed kidney disease (serum creatinine, ≥130 µmol per litre [1.5 mg per decilitre])	never or occasionally		
	72	49		weekly	OR	1.21 (0.77, 1.89)
	30	5		daily	OR	3.21 (1.05, 9.80)
Steenland et al. (1990)	325	325	new cases of end-stage kidney disease	regular users of paracetamol	OR	2.66 (1.04, 6.82) + trend of increasing risk with increasing duration of use
Perneger et al. (1994)	578	306	end-stage renal disease	0-104 number of tablets taken in a year	OR	1 referent
	60	31		105-365	OR	1.40 (0.80, 2.40)
	73	21		≥366	OR	**2.10 (1.10, 3.70)**
				lifetime intake of paracetamol tablets in grams		
	563	296		0-9999	OR	1 referent
				1000-4999	OR	**2.00 (1.30, 3.20)**
				≥5000	OR	**2.40 (1.20, 4.80)**
Fored et al. (2001)	230	376	chronic renal failure	never use	OR	1 referent
	345	413		ever use	OR	**1.30 (1.00, 1.60)**

	105	71		use/used regularly cumulative dose	OR	**2.50 (1.70, 3.60)**
	2142	1575		mean 1-99g	OR	1.20 (0.90, 1.50)
	525	275		median 100-499g	OR	1.30 (0.90, 1.80)
	6-34,969	9-35,416		range ≥500g	OR	**3.30 (2.00, 5.50)**
Kelkar et al. (2012)			renal disorders such as acute renal failure, chronic renal disease, renal failure unspecified, nephritis, nephrotic syndrome, small bilateral kidney,	acute paracetamol exposure		
	343	344		paracetamol exposure for at least one day in 7 days pre-index	OR	**1.93 (1.61, 2.30)**
	517	599		30 days prior index maximum daily dose (MDD): 7 days prior index date	OR	**1.71 (1.48, 1.97)**
	282	311		MDD ≤4gm	OR	**1.68 (1.38, 2.03)**
	61	33		MDD >4gm	OR	**4.60 (2.87, 7.39)**
				maximum daily dose: 30 days prior index date		
	404	483		MDD ≤4gm	OR	**1.64 (1.40, 1.92)**
	113	116		MDD >4gm	OR	**2.01 (1.49, 2.70)**
				average daily dose: 30 days prior index date		
	450	520		ADD ≤4gm	OR	**1.68 (1.44, 1.96)**
	113	116		ADD >4gm	OR	**1.89 (1.30, 2.74)**
				chronic paracetamol exposure cumulative dose in the pre-index year		
	1,351	2,327		≤1kg	OR	**1.13 (1.01, 1.26)**

15	20	>1kg	OR	0.97 (0.45, 2.12)
		the recency of paracetamol exposure		
517	599	0-30 days	OR	**1.84 (1.59, 2.13)**
849	1,748	>30 days	OR	**1.13 (1.01, 1.26)**
		total paracetamol use duration in the prior index date		
982	1,846	1-30 days	OR	**1.15 (1.03, 1.28)**
384	501	>30 days	OR	**1.00 (0.81, 1.23)**
517	599	paracetamol usage 30 days prior index date	OR	**1.73 (1.44, 2.07)**

OR - odds ratio, RR - risk ratio, HR - hazard ratio, significant results are in bold, MDD - maximum daily dose, ADD - average daily dose.

2.3.4. Mortality

Two cohort studies had found an increased risk of mortality for those exposed to paracetamol compared to those unexposed (De-Vries et al., 2010; Lipworth et al., 2003) (Table 2.3.9). One of these demonstrated a dose-response increase in the relative rate of all-cause mortality ranging from RR of 0.95 (95%CI 0.92, 0.97) for low MPR to RR of 1.63 (95%CI 1.58, 1.68) for very high MPR (Figure 2.3.11) (De-Vries et al., 2010).

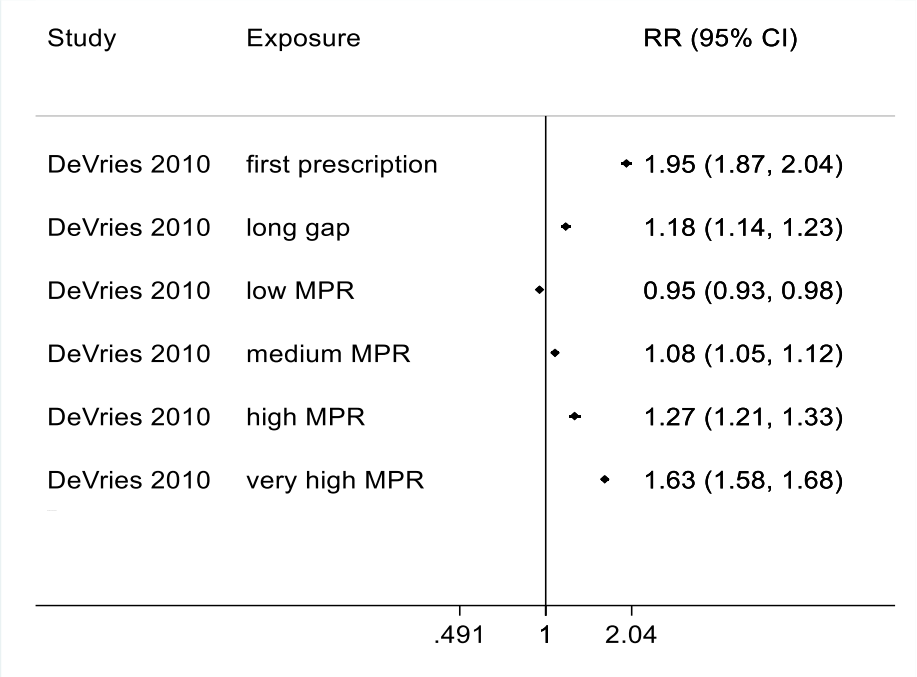


Figure 2.3.11. The forest plot shows an increased risk of all-cause mortality for paracetamol users versus non-users. The medical possession rate (MPR) was defined as the duration between previous and current prescriptions. Low medical possession rate defined as =<0.40, medium 0.40-0.59, high 0.06-0.79, very high => 0.8. RR - risk ratio, CI – confidence interval.

Lipworth et al. (2003) analysed 49,890 participants suggesting a significantly increased risk for standardised mortality rate (SMR) in paracetamol users when compared to non-users for all-cause mortality with an SMR of 1.90 (95%CI 1.88, 1.94) (Table 2.3.9).

Table 2.3.9. Summary of cohort studies assessing mortality.

Author (year)	Number(n)	Person years	Duration of follow-up max. (years)	Outcome (cause of death)	Dose	Measure of effect	Results(95%CI)
Lipworth et al. (2003)	15,342		7	all-cause mortality		SMR	**1.90 (1.88, 1.94)**
	3,263			ischemic heart disease		SMR	**1.60 (1.50, 1.60)**
	744			other heart diseases		SMR	**1.60 (1.50, 1.80)**
	570			artery disease		SMR	**1.80 (1.70, 2.00)**
	1,408			cerebrovascular disease		SMR	**1.60 (1.50, 1.70)**
	39			renal failure		SMR	**1.80 (1.30, 2.50)**
	31			other renal diseases		SMR	**2.00 (1.40, 2.80)**
	933	68,536		ischemic heart disease (according to number of prescriptions)	1 prescription in 7 years (referent)	SMR	**1.40 (1.30, 1.50)**
	914	46,357			2-4 prescriptions in 7 years	SMR	**1.60 (1.50, 1.70)**
	582	26,288			5-9 prescriptions in 7 years	SMR	**1.60 (1.50, 1.80)**
	834	34,525			10+ prescriptions in 7 years	SMR	**1.90 (1.70, 2.00)**
	182	68,536		other heart disease (according to number of prescriptions)	1 prescription in 7 years(referent)	SMR	**1.30 (1.10, 1.50)**
	207	46,357			2-4 prescriptions in 7 years	SMR	**1.70 (1.50, 2.00)**
	135	26,288			5-9 prescriptions in 7 years	SMR	**1.70 (1.40, 2.00)**
	220	34,525			10+ prescriptions in 7 years	SMR	**2.10 (1.80, 2.40)**
	155	68,536		artery disease (according to number of prescriptions)	1 prescription in 7 years(referent)	SMR	**1.60 (1.30, 1.80)**
	158	46,357			2-4 prescriptions in 7 years	SMR	**1.80 (1.50, 2.10)**

	117	26,288		5-9 prescriptions in 7 years	SMR	**2.10 (1.70, 2.50)**
	140	34,525		10+ prescriptions in 7 years	SMR	**2.00 (1.70, 2.40**
	394	68,536	cerebrovascular disease (according to number of prescriptions)	1 prescription in 7 years(referent)	SMR	**1.40 (1.30, 1.60)**
	394	46,357		2-4 prescriptions in 7 years	SMR	**1.60 (1.40, 1.70)**
	235	26,288		5-9 prescriptions in 7 years	SMR	**1.50 (1.30, 1.70)**
	385	34,525		10+ prescriptions in 7 years	SMR	**1.90 (1.70, 2.10)**
	9		renal failure (according to number of prescriptions)	1 prescription in 7 years (referent)	SMR	1.40 (0.60, 2.60)
	8			2-4 prescriptions in 7 years	SMR	1.40 (0.60, 2.80)
	9			5-9 prescriptions in 7 years	SMR	**2.40 (1.10, 4.60)**
	13			10+ prescriptions in 7 years	SMR	**2.40 (1.30, 4.10)**
	8		other renal disease (according to number of prescriptions)	1 prescription in 7 years (referent)	SMR	1.60 (0.70, 3.10)
	9			2-4 prescriptions in 7 years	SMR	2.00 (0.90, 3.90)
	4			5-9 prescriptions in 7 years	SMR	1.50 (0.40, 3.80)
	10			10+ prescriptions in 7 years	SMR	**2.90 (1.40, 5.30)**
De-Vries et al. (2010)	382,404			no use	RR	1.00
				first treatment	RR	**1.95 (1.87, 2.04)**
				long gap	RR	**1.18 (1.14, 1.23)**
				low medical possession rate (MPR)	RR	0.95 (0.92, 0.97)
				medium MPR	RR	**1.08 (1.05, 1.12)**
				high MPR	RR	**1.27 (1.21, 1.33)**
				very high MPR	RR	**1.63 (1.58, 1.68)**

SMR - standardised mortality rate, RR - risk ratio, and significant results are bold.

2.3.5. Risk of bias assessment

The quality of included studies was assessed using a modified Newcastle Ottawa scale. The cohort studies comparatively had higher quality than case-control studies, as described in Table 2.3.10.

Table 2.3.10. Quality assessment of cohort and case-control studies of paracetamol.

Author (year)	Design	Selection (max.4)	Comparability (max.2)	Exposure/Outcome (max.3)	Total (Max 9)
Rahme et al. (2002)	cohort	4	2	2	8
Curhan et al. (2002)	cohort	3	2	2	7
Dedier et al. (2002)	cohort	4	2	1	7
Lipworth et al. (2003)	cohort	4	2	2	8
Kurth et al. (2003)	cohort	4	2	2	8
Curhan et al. (2004)	cohort	4	2	2	8
Kurth et al. (2005)	cohort	4	2	2	8
Forman et al. (2005)	cohort	4	2	2	8
Chan et al. (2006)	cohort	3	2	2	7
Forman et al. (2007)	cohort	4	2	2	8
Evans et al. (2009)	cohort	4	2	2	8
Kuo et al. (2010)	cohort	4	2	2	8
De-Vries et al. (2010)	cohort	3	2	2	7
Fulton et al. (2015)	cohort	3	2	2	7
Duong et al. (2016)	cohort	4	2	2	8
Coggon et al. (1982)	case-control	3	1	1	5
McIntosh et al. (1985)	case-control	4	2	2	8
Levy et al. (1988)	case-control	4	2	3	8
Faulkner et al. (1988)	case-control	4	1	2	7
McIntosh et al. (1988)	case-control	4	1	2	7
Pommer et al. (1989)	case-control	4	1	3	8
Sandler et al. (1989)	case-control	4	1	2	7
Steenland et al. (1990)	case-control	4	1	2	7
Laporte et al. (1991)	case-control	4	2	2	8
Holvoet et al. (1991)	case-control	4	1	2	7
Nobili et al. (1992)	case-control	4	2	2	8
Savage et al. (1993)	case-control	4	2	2	8
Langman et al. (1994)	case-control	4	2	2	8
Perneger et al. (1994)	case-control	4	1	2	7
Matikainen et al. (1996)	case-control	2	1	2	5
Imhof et al. (1997)	case-control	4	2	1	7
Fored et al. (2001)	case-control	3	2	2	7
Garcia-Rodriguez et al. (2001)	nested case-control	4	2	2	8
Lanas et al. (2003)	case-control	4	2	2	8

Garcia-Rodriguez et al. (2004)	nested case-control	4	2	2	8
Gallerani et al. (2004)	case-control	4	2	2	8
Rosenberg et al. (2003)	case-control	3	2	2	7
De-Abajo et al. (2014)	nested case-control	3	2	1	6
García-Poza et al. (2015)	case-control	3	2	2	7
Roberto et al. (2015)	nested case-control	3	2	2	7
Gonzalez-Valcarcel et al. (2016)	nested case-control	3	2	2	7
Kelkar et al. (2012)	case-control	4	2	2	8
González-Pérez et al. (2014)	nested case-control	4	2	2	8

2.3.6. Publication bias and small study effects

It was not possible to determine publication bias for cohort studies because the number of studies was <10 for almost all the outcomes. The publication bias was performed for the 12 age-gender matched case-control studies investigating UGIB for paracetamol users compared to non-users. On visual inspection from Figure 2.3.12, a precise inverted funnel symmetry is evident. However, a minimal publication bias could be observed because it appeared from Figure 2.3.12 that the studies were skewed more towards the right, suggesting small studies with paracetamol related to UGIB were not reported. However, evidence-based on the formal Harbord statistical test suggested no publication bias since P > 0.001 was insignificant (Higgins et al., 2011).

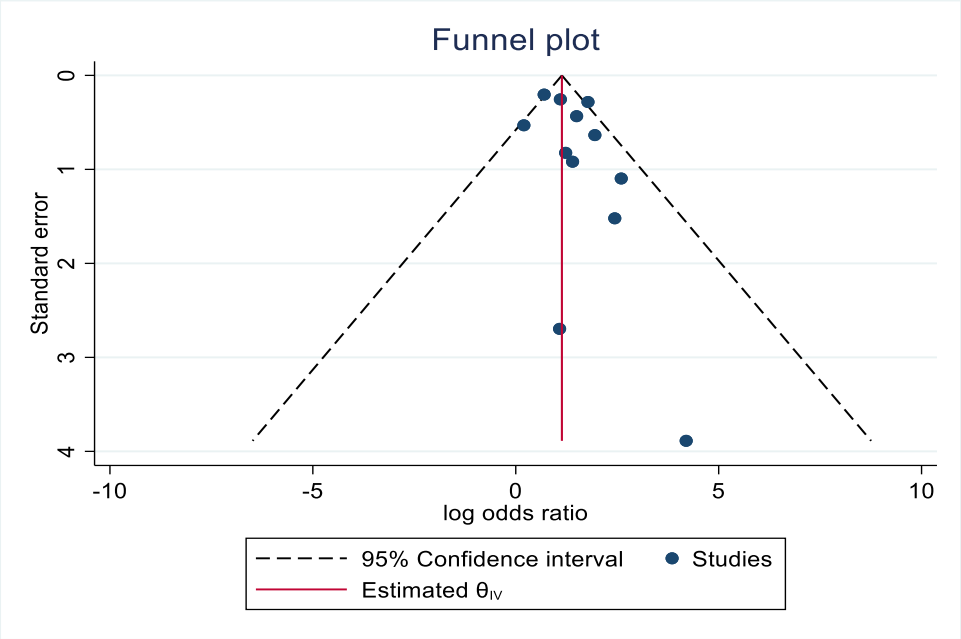


Figure 2.3.12. Funnel plot for case-control studies for paracetamol users versus non-users.

2.3.7. Subgroup analysis by the duration of treatment for upper gastrointestinal bleeding

From the examination of the trial description, it was found that Garcia-Rodriguez et al. (2001), Coggon et al. (1982), and Levy et al. (1988) differed substantially from the nine other studies in the duration of treatment. A separate subgroup analysis was performed according to the duration of the study to identify the reason for heterogeneity. Figure 2.3.13 shows a significant dose-dependent relationship between paracetamol users versus non-users by the duration of the study period ranging from 0.8 to 7.2 years. A statistically significant relationship could be ascertained between the studies with longer duration (>4 years OR 1.84; 95%CI 1.18, 2.85) than those up to smaller period up to 4 years with non-significant association with OR 1.31 (95%CI 0.95, 1.79). Thus, the studies with longer duration appeared to be more homogenous with I2 = 0.0% than those with short periods.

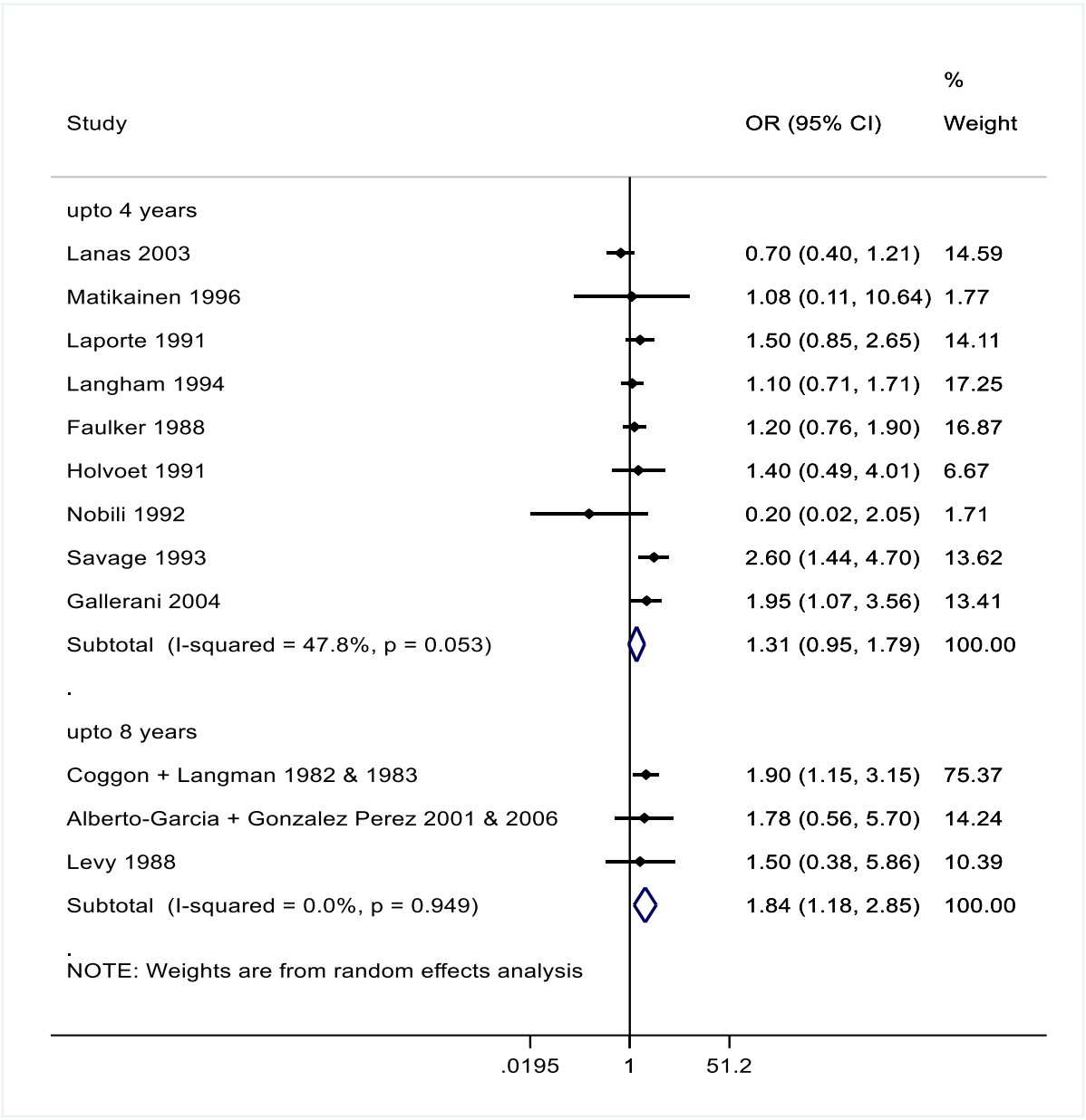


Figure 2.3.13. Subgroup analysis according to the duration of the study period for upper gastrointestinal bleeding. OR - odds ratio, CI - confidence interval.

2.4. Summary of findings

Table 2.4.1. Summary of included clinical trials and observational studies.

Outcomes	Number of studies (RCTs) paracetamol versus placebo (n)	Number of studies (RCTs) paracetamol versus NSAIDs (n)	Number of studies (RCTs) paracetamol versus coxibs (n)	Number of the cohort studies (n)	Number of the case-control studies (n)
Gastrointestinal					
Gastrointestinal (any)	4 (2,275)	7 (1,735)	2 (1,354)		
Abdominal pain	2 (786)	4 (1,208)	3 (547)		
Dyspepsia	3 (1,496)	5 (1,654)	4 (1,819)		
Gastrointestinal upset	3 (1,496)		4 (1,712)		
Nausea/Vomiting	5 (2,746)		4 (1,819)		
Diarrhoea	6 (3,229)	5 (1,654)	5 (1,901)		
Constipation		5 (1,654)			
UGIB				3 (782,165)	12 (7,894)
Peptic ulcer					4 (15,023)
Cardiovascular					
Cardiovascular	2 (1,011)	4 (1,206)			
Hypertension				5 (291,452)	
Non-fatal MI				4 (1,020,365)	3 (840,816)

Outcomes	Number of studies (RCTs) paracetamol versus placebo (n)	Number of studies (RCTs) paracetamol versus NSAIDs (n)	Number of studies (RCTs) paracetamol versus coxibs (n)	Number of the cohort studies (n)	Number of the case-control studies (n)
Renal					
Acute renal failure				1 (382,404)	
Chronic renal failure				1 (801)	1 (1,924)
End-stage renal failure				1 (19,163)	3 (2,648)
Glomerular filtration				2 (23,768)	
Newly diagnosed kidney disease					1 (554)
Any renal disorder					1 (18,896)
Liver					
Liver	3 (1,237)				
AST-level	3 (1,535)	1 (204)			
Mortality				2 (432,294)	

RCTs - randomised controlled trials, NSAIDs - non-steroidal anti-inflammatory drugs, n - number of participants, UGIB - upper gastrointestinal bleeding, MI - myocardial infarction, AST - aspartate test.

Table 2.4.2. Summary of Findings for Gastrointestinal events.

Outcome or subgroup	No. of studies	No. of participants	Statistical measures	Effect size and 95%CI
Study design: Randomised controlled trials				
Paracetamol versus Placebo				
Gastrointestinal (any)	4	2,275	RR	1.13 (0.89, 1.43)
Abdominal pain	2	786	RR	1.42 (0.67, 3.02)
Dyspepsia	3	1,496	RR	1.93 (0.97, 3.82)
Gastrointestinal upset	3	1,496	RR	1.68 (0.37, 7.57)
Nausea/Vomiting	5	2,746	RR	1.47 (0.94, 2.32)
Diarrhoea	6	3,229	RR	**2.12 (1.36, 3.32)**
Paracetamol versus traditional NSAIDs				
Abdominal pain	4	1,208	RR	1.31 (0.78, 2.19)
Diarrhoea	5	1,654	RR	1.48 (0.97, 2.25)
Paracetamol versus coxibs				
Dyspepsia	4	1,819	RR	1.10 (0.62, 1.96)
Abdominal pain	3	547	RR	1.66 (0.81, 3.40)
Gastrointestinal upset	4	1,712	RR	1.25 (0.85, 1.85)
Diarrhoea	5	1,901	RR	1.43 (0.84, 2.44)

Outcome or subgroup	No. of studies	No. of participants	Statistical measures	Effect size and 95%CI
UGIB				
Cohort	1	382,404	RR	**1.36 (1.31, 1.41)**
Cohort	1	342,494	HR	**1.45 (1.08, 1.95)**
Case-control	12	7,894	RR	**1.34 (1.10, 1.63)**

Outcome or subgroup	No. of studies	No. of participants	Statistical measures	Effect size and 95%CI
Peptic ulcer				
Case-control (weekly use of paracetamol)	1	312	OR	1.30 (0.59, 2.86)
Case-control (current use of paracetamol)	1	5,619	OR	**1.90 (1.53, 2.35)**
Case-control (2,000-4,000mg of paracetamol)	1	5,619	OR	**1.80 (1.37, 2.36)**
Case-control (7 days before index date)	1	1,517	OR	**1.56 (1.37, 1.77)**

Note: There was one study with 892 participants that suggested that the proportion of participants who experienced a decrease in haemoglobin of ≥2g/dl was similar in both groups 0.9% p = 0.011 in paracetamol versus 0.9%p = 001 in ibuprofen. There was an increase in the platelet count and a decrease in the mean cell volume suggesting blood loss.

RR - risk ratio, CI - confidence interval, UGIB - upper gastrointestinal bleeding, dl - decilitre, NSAIDs - nonsteroidal anti-inflammatory, OR - odds ratio, significant values are in bold.

Table 2.4.3. Cardiovascular adverse events.

Study design: Randomised controlled trials **Outcome or subgroup**	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Outcome: Cardiovascular (different comparison groups)				
Paracetamol versus Placebo	2	1,011	RR	1.05 (0.07, 15.38)
Paracetamol versus NSAIDs	4	1,206	RR	0.51 (0.16, 1.64)
Study design: Observational Studies **Study type: Cohort**				
Outcome: Incident hypertension				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
1-4 days/month paracetamol use	2	3,620	RR	**1.11 (1.00, 1.22)**
5-14 days/month paracetamol use	2	1,262	RR	**1.26 (1.14, 1.38)**
15-21 days/month paracetamol use	2	379	RR	**1.40 (1.15, 1.69)**
>22 days/month use	2	529	RR	1.52 (0.92, 2.51)
1-14 tablets in previous one-year paracetamol use	1	130	RR	0.95 (0.67, 1.35)
15-60 tablets in previous one-year paracetamol use	1	207	RR	1.08 (0.84, 1.39)
>61 tablets in previous one-year paracetamol use	1	129	RR	**1.34 (1.00, 1.80)**

Outcome: Incident Hypertension				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
1-100mg/day ADD	1	20	RR	0.82 (0.48, 1.40)
101-500mg/day ADD	1	34	RR	1.33 (0.85, 2.09)
>500mg/day ADD	1	50	RR	**1.93 (1.30, 2.87)**

Study type: Cohort **Outcome: Non-fatal myocardial infarction, non-fatal stroke, fatal coronary heart disease or fatal stroke**				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
1-4 days/month	1	221	RR	0.98 (0.84, 1.14)
5-14 days/month	1	143	RR	1.09 (0.91, 1.30)
15-21 days/month	1	68	RR	1.22 (0.95, 1.56)
>22days/month	1	168	RR	**1.35 (1.14, 1.59)**
1 day per week	1	24	RR	0.94 (0.62, 1.43)
2-3 days per week	1	48	RR	1.28 (0.94, 1.75)
4-5 days per week	1	26	RR	1.49 (0.99, 2.24)
>6 days per week	1	50	RR	**1.68 (1.10, 2.57)**
1-2 tablets per week	1	30	RR	1.19 (0.81, 1.75)
3-5 tablets per week	1	27	RR	1.16 (0.76, 1.77)
6-14 tablets per week	1	45	RR	**1.47 (1.06, 2.03)**
>15 tablets	1	25	RR	**1.68 (1.10, 2.57)**

Study type: Cohort				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Overall	1	2,761	RR	**1.14 (1.10, 1.19)**
First treatment	1	177	RR	**1.42 (1.22, 1.65)**
Long gap	1	254	RR	0.98 (0.86, 1.11)
Low MPR	1	860	RR	**1.11 (1.02, 1.19)**
Medium MPR	1	407	RR	**1.17 (1.05, 1.29)**
High MPR	1	157	RR	1.04 (0.89, 1.23)
Very high MPR	1	313	RR	**1.17 (1.04, 1.32)**
Study type: Case-control				
Outcome	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Myocardial infarction	3	8,660	OR	0.93 (0.80, 1.09)
MI or stroke	1	798	OR	**1.21 (1.04, 1.42)**

ADD - average daily dose, MPR - medication possession rate, RR - risk ratio, OR - odds ratio, CI - confidence interval, MI - myocardial infarction, significant values are in bold.

Table 2.4.4. Renal adverse events.

Study type: RCTs: Paracetamol versus NSAIDs				
Outcome	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Serum creatinine	1	66	The serum creatinine levels were increased by 0.2mg/decilitre in one participant in the paracetamol group and 4 subjects in the ibuprofen group.	
Study design: Observational studies (Cohort) **Outcome: Acute renal failure**				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Low MPR	1	423	RR	**1.16 (1.04, 1.29)**
Medium MPR		217		**1.27 (1.10, 1.47)**
High MPR		109		**1.44 (1.18, 1.75)**
Very high MPR		182		**1.34 (1.15, 1.57)**
Outcome: Chronic kidney disease (Glomerular filtration rate decreases 30ml/min/1.73m2)				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
12-1499 tablets during 14 years	1	4,494	OR*	0.53 (0.36, 0.78)
1500-2499 tablets during 14 years				0.65 (0.29, 1.46)
>2500 tablets during 14 years				1.28 (0.61, 2.69)
100-499g lifetime intake	1	1,697	OR*	**1·80 (1·02, 3·17)**
500-2999g lifetime intake				**2·23 (1·36, 3·63)**
>3000g lifetime intake				**2·04 (1·20, 3·24)**

Study type: Cohort				
Outcome: Chronic renal failure (Increased creatinine concentration of ≥ 0.3 mg/dL)				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
100-499g lifetime intake	1	21	OR*	**1.80 (1.02, 3.18)**
500-2999g lifetime intake		40		**2.23 (1.36, 3.66)**
>3000g lifetime intake		45		**2.04 (1.28, 3.25)**
Outcome: Chronic renal failure (differences in estimated progression rates (change in eGFR in mL/min/1.73 m2 per year))				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
<99g lifetime intake	1		Regression coefficient	-0·17 (-0·90, -0·60)
100-499g lifetime intake				0·60 (-0·30, -1·50)
500-2999g lifetime intake				0·65 (-0·70, -2·00)
>3000g lifetime intake				0·24 (-1·20, -1·70)
Outcome: Chronic renal failure (≥ 30% decrease in eGFR)				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
100-499g lifetime intake	1	1,697	OR*	1·40 (0·79, 2·49)
500-2999g lifetime intake				**1·64 (1·00, 2·69)**
>3000g lifetime intake				**2·19 (1·40, 3·45)**
Outcome: Time to renal replacement therapy				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
paracetamol twice a week for two months	1	801	HR	1·10 (0·90, 1·40)

Study type: Case-control **Outcome: Chronic renal failure**				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Regular use of paracetamol	1	1924	OR*	**2.50 (1.70, 3.60)**
>500g cumulative dose	1	1924	OR*	**3.30 (2.00, 5.50)**
Study type: Cohort **Outcome: End-stage kidney failure**				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
<0.568 DDD	1	19,163	HR	**1.43 (1.12, 1.82)**
>0.569DDD	1	19,163	HR	**5.21 (4.31, 6.29)**
Study type: Case-control **Outcome: End-stage kidney failure**				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
≥366 tablets	1	716	OR	**2.10 (1.10, 3.70)**
0-99g lifetime intake	1	51	OR	1.04 (0.58, 1.87)
100-499g lifetime intake	1	55	OR	1.63 (0.95, 2.80)
500-999g lifetime intake	1	13	OR	1.86 (0.60, 5.76)
1000-4999g lifetime intake	1	19	OR	**4.06 (1.32, 12.46)**
Regular exposure to paracetamol	1	325	OR	**2.66 (1.04, 6.82)**

Outcome: Newly diagnosed kidney disease				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Daily exposure to paracetamol	1	554	OR	**3.21 (1.05, 9.80)**
Outcome: Any renal disease				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
maximum daily dose of ≤4 gm 7 days before the index date	1	18,896	OR	**1.68 (1.38, 2.03)**

OR* - odds ratio was sub-optimally used in the cohort study by the original author, RR - risk ratio, HR - hazard ratio, CI - confidence interval, ml – millilitre, DDD - daily defined dose.

Table 2.4.5. Abnormal liver function.

Study design: RCTs				
Paracetamol versus placebo				
Outcome	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Liver	3	1,237	RR	**3.99 (2.05, 7.77)**
AST-level>3	3	1,535	RR	**7.42 (2.22, 24.77)**
Paracetamol versus NSAIDs				
Outcome	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
Aspartate aminotransferase level	1	204	Mean+/- SD	0.07+/-0.14 for paracetamol group and -0.01+/-0.16 for NSAIDs
Note: The aspartate aminotransferase level rose more than 0.17 µkat per litre (10 U per litre) in 11 participants in the paracetamol group compared to 4 participants in NSAIDs				

RCTs - randomised controlled trial, CI - confidence interval, RR - risk ratio, SD - standard deviation, AST - aspartate aminotransferase.

Table 2.4.6. Mortality.

Observational cohort study				
All-cause mortality				
Exposure	**No. of studies**	**No. of participants**	**Statistical measures**	**Effect size and 95%CI**
First prescription	1	382,404	RR	**1.95 (1.87, 2.04)**
Long gap	1		RR	**1.18 (1.14, 1.23)**
Low MPR	1		RR	0.95 (0.93, 0.98)
Medium MPR	1		RR	**1.08 (1.05, 1.12)**
High MPR	1		RR	**1.27 (1.21, 1.33)**
Very high MPR	1		RR	**1.63 (1.58, 1.68)**
Paracetamol users	1	49,890	SMR	**1.90 (1.88, 1.94)**

RR - risk ratio, SMR - standardised mortality rate, CI - confidence interval, MPR - medication possession rate.

2.5. Discussion

2.5.1. Key findings and interpretation

The main objective of this review was to synthesize the RCTs and observational evidence of adverse effects of long-term consumption of paracetamol. The valid estimates of adverse events for paracetamol usage are essential to make informed clinical decisions. To date, this is the most comprehensive SR, including both RCTs in OA and observational studies in the general population.

2.5.1.1. Gastrointestinal events

2.5.1.1.1. Paracetamol versus placebo in OA

This present SR/MA of 24 RCTs, including 7,299 participants with OA, suggested that paracetamol use is associated with an increased risk of diarrhoea compared to placebo (RR 2.12; 95%CI 1.36, 3.32). The findings of sensitivity analysis are also in line with these estimates, indicating no change in the increased risk for diarrhoea when studies with methodological limitations were excluded (RR 1.87; 95%CI 1.08, 3.22). In the absence of any clinical trial or observational evidence, these findings can be compared with a narrative review by Malar et al. (2012), signalling that paracetamol overdose might cause severe diarrhoea. Although the narrative information by Malar et al. (2012) was based on paracetamol overdose, whereas the current findings are estimated using its standard therapeutic dose. By contrast, these current SR/MA results do not support the previous SR/MA estimates, which reported that paracetamol is safe in people with OA (Leopoldino et al., 2019; Machado et al., 2015; Zhang et al., 2004). The discrepancy in the definitions of reported safety outcomes may most likely explain these differences in the results. Zhang et al (2004) defined their safety outcomes as GI discomfort, nausea, headache, and dizziness from 10 studies including 1,712 participants. Leopoldino et al. (2019) and Machado et al. (2015) analysed only composite outcomes such as the “total number of participants with adverse events” or the “number of withdrawals.” Using different operational definitions to classify the adverse effects in the SR/MA may explain why this is the first review to report an increased risk of diarrhoea in participants taking paracetamol when compared with placebo for OA.

Although there was an increased risk associated with paracetamol use and other GI-side-effects such as “GI events (any),” abdominal pain, dyspepsia, GI-upset, “nausea, and vomiting” compared to the placebo group in people with OA, with minimal or no heterogeneity, these findings lacked statistical significance. Few studies have analysed these outcomes therefore, these results may be compared with the reports of cumulative rates examining the toxicity profile of paracetamol and aspirin from the spontaneous reporting by the Spanish Drug Monitoring System 1981 in the general population. They reported that haematological and hepatic side effects were more significant with paracetamol than aspirin (Carvajal et al., 1996). However, the lack of statistical significance in the present SR/MA for these outcomes suggested that future work is still required to establish valuable information regarding paracetamol use and the increased risk of abdominal pain, dyspepsia, GI-upset, “nausea and vomiting” in people with OA.

2.5.1.1.2. Paracetamol versus NSAIDs and coxibs in OA

According to the best practice guidelines, paracetamol and NSAIDs are the two highly prescribed systemic analgesics and are popular OTC self-medication drugs. Both drugs are also part of the therapeutic management of OA. Furthermore, the comparative safety of paracetamol versus NSAIDs is important because NSAIDs are the next step of OA management after paracetamol in NICE guidelines. Therefore, this SR/MA also examined (i) paracetamol versus traditional NSAIDs and (ii) paracetamol versus Coxibs for GI events (any), abdominal pain, dyspepsia, constipation, “nausea and vomiting,” and diarrhoea. In head-to-head comparison trials, the present SR/MA suggested that paracetamol exposure was associated with an increased risk of diarrhoea and abdominal pain compared to traditional oral NSAIDs with a RR of 1.48 (95%CI 0.97, 2.25) and 1.31 (95%CI 0.78, 2.19), respectively with low heterogeneity, though the results were not statistically significant. These results are in line with RCTs reported by Rampal et al. (2002) with 8,633 participants and showed that the number of participants with diarrhoea was significantly higher in the paracetamol group (2.2%) in comparison to the ibuprofen group (1.3%). Similarly, in a large (n=8677) multicentre double-blinded study, paracetamol or ibuprofen was prescribed for musculoskeletal pain, back pain, sore throat, or common influenza (Moore et al., 1999). The total GI events, including dyspepsia and abdominal pain, were more frequently associated with paracetamol (3.9%) than Ibuprofen (2.8%) (Moore et al., 1999).

The results for abdominal pain may also be compared with an expert opinion by Bannwarth (2004), suggesting that paracetamol at its highest therapeutic dose may cause abdominal pain.

Although, the above discussion supports the findings of the SR/MA of this thesis, suggesting an indication of an increased risk associated with diarrhoea and abdominal pain with paracetamol use compared to conventional oral NSAIDs. However, the lack of statistical significance increases the imprecision of these estimates and recommends further studies for their confirmation and clinical relevance.

The GI toxicity of NSAIDs is well established therefore, health professionals might prefer paracetamol for OA pain. However, the above findings from the SR/MA of RCTs in people with OA suggested that paracetamol has a greater risk of diarrhoea than NSAIDs. Therefore, this may further question whether paracetamol is indeed relatively safer than NSAIDs and should it be considered as the first-line treatment for chronic painful conditions.

The previous SR/MA findings for the efficacy of paracetamol over NSAIDs also included safety estimates in people with OA, have contradictory estimates, and endorse the superior safety profile of paracetamol over traditional NSAIDs. They reported that conventional NSAIDs were associated with increased risk for GI discomfort compared to paracetamol, indicating the main reason for recommending paracetamol as the first-line treatment for OA pain (RR 1.47; 95%CI 1.08, 2.00 and 1.35; 95%CI 1.05, 1.75, respectively) (Towheed et al., 2006; Zhang et al., 2004). The variation in the study population, such as the inclusion of fewer trials with a small number of participants, may explain this disagreement in the findings (current MA: 24 studies, 7,299 participants; Towheed et al. (2006): 15 studies, 5986 participants; Zhang et al. (2004): 10 studies, 1,712 participants). It is because a small sample size might lead to biased estimates and reduce the chance of determining the true effect (Lin, 2018). Secondly, this inconsistency in the results could also be explained by differences in the outcome analysed. The present SR/MA used abdominal pain, GI-upset, diarrhoea, "nausea and vomiting," whilst Towheed et al. (2006) analysed composite "GI events," and Zhang et al. (2004) used only "GI discomfort" and "nausea" as an operational definition for their safety outcomes. Additionally, according to the modes of action, it was thought that paracetamol acts centrally therefore, it is less toxic than NSAIDs.

In contrast, recent studies have suggested that paracetamol can inhibit prostaglandin synthesis in the central nervous system and peripheral tissues indicating that paracetamol has analogous COX-inhibitory action similar to NSAIDs (Hinz et al., 2012).

Further examination indicated that paracetamol and coxibs have a similar risk associated with "GI events (any)" and "nausea and vomiting." The results are in line with the estimates of a previous SR, illustrating that coxibs share a similar safety profile to paracetamol with a RR of 0.98 (95%CI 0.80, 1.20) and RR of 0.65 (95%CI 0.17, 2.52) (Towheed et al., 2006; Zhang et al., 2004). On the contrary, there was an association between paracetamol use and dyspepsia, abdominal pain and diarrhoea compared with coxibs in OA patients. However, further investigation is required due to the lack of studies on these outcomes in this population.

2.5.1.1.3. Association of paracetamol exposure and GI-events irrespective of any underlying condition in the observational studies

The present SR/MA identified 16 cohorts and 26 case-control studies, more than the previous SR/MA. Lewis et al. (2002) meta-analysed three retrospective case-control studies, Roberts et al. (2016) evaluated eight cohort studies on the adverse profile of paracetamol, and Conaghan et al. (2019) only summarised the studies narratively for efficacy and toxicity for the long-term use of paracetamol.

The pooled estimates derived from twelve case-control studies demonstrated an increased risk for upper GI bleeding with paracetamol use in the previous week (OR 1.34; 95%CI 1.10, 1.63) with moderate heterogeneity. A significant dose-response relationship between paracetamol users and upper GI bleeding in the general population was observed in two cohort studies and one case-control study compared to non-users (De-Vries et al., 2010; Rahme et al., 2002; Rodriguez et al., 2001). These results align with previous reviews by Roberts et al. (2016) and Gonzalez-Perez et al. (2006). The current SR/MA findings are consistent with one cohort study that reported a dose-response relationship between paracetamol exposure and upper GI adverse events of gastroduodenal ulcers and complications compared with non-users in the general population (Gonzalez-Valcarcel et al., 2016). The MA of three case-control studies by Lewis et al. (2002) also suggested that the OR was 1.20 (95%CI 0.80, 1.70) for paracetamol users compared to non-users in the general population for UGIB, which was not significant.

This discrepancy in the estimates could be due to the small number of studies (only three case-control) included in the SR/MA by Lewis et al. (2002), which might not be enough to have an appropriate sample size to produce significant results for the therapeutic use of paracetamol in the general population.
Moreover, Lin (2018) suggested that the meta-analysis estimates of the underpowered studies need to be interpreted with caution as they might provide biased estimates due to sampling error.

The current SR/MA findings of the observational studies in the general population differ from the outcomes of the randomised placebo-controlled endoscopist-blinded three-way crossover study by Lanza et al. (1998). This RCT described that paracetamol might not induce any gastroduodenal injury, either clinical or statistically significant. However, the follow-up duration in this RCT was only seven days, and this trial was not designed to capture the long-term effects of paracetamol. The disagreement of the short-term follow-ups can be explained with the present SR/MA subgroup analysis for RCTs in people with OA (in the versus placebo trials) described in section 2.2.5.3.3 and observational data in section 2.3.7. The findings from this subgroup analysis indicate that the studies with a longer duration of follow-up were more homogenous than studies with short follow-up durations. The estimates from the subgroup analysis from the observational data stated that the longer durations had a significantly higher risk associated with paracetamol exposure than a shorter period suggesting that few detrimental effects might take longer to be discovered. A significant trend according to different durations of time was also apparent in the observational studies subgroup analysis.

Furthermore, the findings of the present SR/MA also suggested an increased risk was associated with paracetamol intake and peptic ulcers in one cohort and three case-control studies (Garcia-Rodriguez et al., 2004; González-Pérez et al., 2014; McIntosh et al., 1985; McIntosh et al., 1988). These findings are also reflected in a population-based large cohort study that signalled an increased risk associated with paracetamol use and hospitalisation due to perforation, ulceration, and bleeding in the general population (HR 1.20; 95%CI 1.03, 1.40) (Rahme et al., 2008).

2.5.1.2. Cardiovascular events

2.5.1.2.1. Paracetamol versus placebo in people with OA

Two placebos controlled RCTs were pooled together to determine cardiovascular risk in OA patients implying a small (5%) increased risk for cardiovascular adverse events with RR 1.05 (95%CI 0.07, 15.38) in paracetamol versus placebo RCTs with considerable heterogeneity. Due to a limited number of studies (only two), it was impossible to determine heterogeneity. There is low confidence in these estimates because of the small sample size, statistical non-significance, and wide confidence intervals. No direct quantitative evidence has been published previously regarding the relationship between paracetamol use and cardiovascular risks in people with OA. However, the observational data in the general population or biological plausibility or experimental studies may provide certain clues regarding the perceived safety of paracetamol in OA, which has been explained in this chapter at later stages.

2.5.1.2.2. Paracetamol versus (NSAIDs and Coxibs) in OA

The MA of 4 RCTs with the head-to-head comparison with traditional NSAIDs stated that the risk of any cardiac events was not significantly associated with paracetamol compared to NSAIDs in people with OA with a RR of 0.51 (95% 0.16, 1.64) with moderate heterogeneity. However, due to a lack of studies and moderate heterogeneity, it was not possible to assess the reasons for heterogeneity for the cardiovascular safety of paracetamol compared to NSAIDs in people with OA in the present SR/MA. These results are indirectly in line with a network meta-analysis with 116,429 participants comparing NSAIDs to other NSAIDs, or paracetamol or placebo for any underlying condition, which reported that ibuprofen was significantly associated with increased risk of stroke (RR 3.36; 95%CI 1.00, 11.6), etoricoxib and diclofenac were significantly associated with increased risk for cardiovascular mortality with RR 4.07 (95%CI 1.23, 15.7) and RR 3.98 (95%CI 1.48, 12.7), respectively, compared with paracetamol (Trelle et al., 2011).

There was insufficient data to analyse the risk between paracetamol and Coxibs in current SR/MA for cardiovascular outcomes.

2.5.1.2.3. Association of paracetamol exposure and cardiovascular events irrespective of any underlying condition in the observational studies

The pooled results from two cohort studies with similar doses of paracetamol have advocated a significant dose-response relationship between paracetamol intake and incident hypertension (Curhan et al., 2002; Dedier et al., 2002). On stratifying the dose of paracetamol, the results appeared to be more homogeneous only for 5-14 days/month use (I2 = 28.6%, p=0.237) compared to >22 days/month use of paracetamol (I2 = 91.5%, p=0.001). In the present SR/MA, there were two more studies that suggested a dose-response relationship between paracetamol exposure and hypertension. However, these were not included in the pooled analysis due to a different definition of paracetamol dosage regimen. Roberts et al. (2016) reported comparable results in their SR/MA, including three of these studies. Still, they did not mention if the dose-response was statistically significant for new cases of hypertension for those exposed to paracetamol compared to those unexposed. The literature supporting the association of paracetamol with hypertension is sparse. The RCTs are limited by sample size or study design to determine the impact of paracetamol on cardiovascular adverse events.

The present SR/MA findings show that paracetamol can increase the risk of hypertension, and these findings could be compared with the results of RCT by Sudano et al. (2010). They conducted a randomised, double-blind crossover study for two weeks, where 33 patients diagnosed with coronary artery disease were administered paracetamol 3g/day or a placebo. Although, they found a small yet significant increase in the mean systolic ambulatory blood pressure (from 122+/-12mmHg to 125+/-12 mm Hg) and diastolic ambulatory BP (73+/-7mmHg to 75+/-8mmHg). This modest change in the blood pressure may still cause a clinically significant impact on the individual participants with comorbid conditions such as myocardial infarction or stroke. Furthermore, a narrative review by McCrae et al. (2018) also reported that paracetamol intake is associated with a slight increase in BP.

Increased cardiovascular events were also detected in a cohort of 70,971 women reportedly on paracetamol (>15 tablets per week) with a RR of 1.68 (95%CI 1.10, 2.58) in comparison to non-users (Chan et al., 2006). This increased risk for paracetamol use was quite similar to that of NSAIDs (>15 NSAIDs tablets per week) with RR 1.86 (95%CI 1.27, 2.73) for the cardiovascular side effects. Four studies supported a significant dose-response relationship between paracetamol exposure and increased risk for cardiovascular adverse events. These results align with Gonzalez-Valcarcel et al. (2016), suggesting a dose-response relationship

between cardiovascular adverse events and paracetamol exposure in the general population. One case-control study indicated that daily use of paracetamol had a 21% elevated risk of having major cardiovascular events such as MI, stroke, or death (Gonzalez-Valcarcel et al., 2016).

However, the MA findings from three case-control studies are inconsistent, suggesting that paracetamol exposure defined as “current users” was not associated with MI with an OR of 0.93 (95%CI 0.80, 1.09) with moderate and non-significant heterogeneity. It was impossible to identify the reason for heterogeneity in these studies due to the limited number of studies. These results were in line with a cohort study by Fulton et al. (2015). They found no risk associated with paracetamol exposure and incidence of myocardial infarction, stroke, and other cardiovascular events. The study by Fulton and colleagues excluded the highly likely conditions for paracetamol prescriptions, such as renal impairment, asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis (Fulton et al., 2015). Therefore, selection bias might have affected the estimates of this study. A further investigation is advised to confirm the reliability of these results.

There is no direct biological plausibility for paracetamol exposure and myocardial infarction. However, Green et al. (1989) had advised the disadvantage of taking paracetamol if someone has myocardial infarction or deep vein thrombosis. These are the diseases where prostacyclin defence mechanisms are activated a priori. The biological explanation supports the cardiovascular findings of this SR. It is based on the proposed causal link between selective COX-2 inhibition and cardiovascular side effects. Paracetamol is thought to block COX-2 dependent prostaglandins such as prostacyclin and PGE2, resulting in pro-thrombotic and vasoconstriction outcomes (Hinz et al., 2006a). Prostacyclin is a potent vasodilator and platelet anti-aggregating compound (Green et al., 1989). During pregnancy, it is essential to mention that paracetamol exposure has been associated with an increased risk of developing pre-eclampsia and other thromboembolic disorders (Rebordosa et al., 2010). The reduction in prostacyclin has been assumed to play a role in these conditions (Rebordosa et al., 2010). It has been suggested that paracetamol inhibits prostacyclin production either due to a low concentration of peroxides or its effects on prostacyclin synthase by vascular endothelium metabolites, causing vasoconstriction resulting in hypertension (Graham et al., 2013).

Hence, the biological explanation and the observational evidence from this SR/MA suggested that long term exposure to paracetamol might increase blood pressure.
There was no association between the different doses of paracetamol and non-fatal ischaemic stroke compared to unexposed paracetamol in the general population (García-Poza et al., 2015). A large cohort study by Duong et al. (2016) with 342,494 participants suggested an increased risk of paracetamol exposure and acute coronary syndrome in the general population. Due to limited literature, the association between paracetamol use with acute coronary syndrome remains inconclusive.

2.5.1.3. Renal adverse events

2.5.1.3.1. Safety of paracetamol in RCTs in people with OA

There was insufficient data in RCTs to perform a MA for renal adverse effects, especially in placebo-controlled trials. Only one RCT reported renal side effects regarding serum creatinine. Due to the lack of enough information, it was only described narratively in the present SR/MA, suggesting a higher risk of increased serum creatinine with ibuprofen when compared to paracetamol in people with OA (Bradley et al., 1991).

2.5.1.3.2. Association of paracetamol exposure and renal events irrespective of any underlying condition in observational studies

Three cohort studies suggested that long-term paracetamol is associated with end-stage kidney failure. One of them also advocated a significant dose-response. These results align with a narrative review by McCrae et al. (2018), suggesting an association between paracetamol exposure and end-stage kidney failure in a dose-dependent manner compared with unexposed.

Furthermore, the results of this review have also highlighted: 1) acute renal failure (though no dose-response but a high risk associated with all doses of paracetamol), 2) Chronic renal failure (such as changes in GFR: 2 cohort studies suggesting a dose-response, case-control evidence suggesting regular usage was associated with two times higher risk in comparison to non-users of paracetamol and newly diagnosed cases, or any renal disorder). However, it was not possible to pool these results together due to different doses of paracetamol.

The association between paracetamol exposure and chronic renal disease in the general population is consistent with previous SR by Roberts et al. (2016), suggesting a dose-response relationship.

Paracetamol, being a derivative of phenacetin, is known to have renal complications due to overdose. However, long-term usage of paracetamol at its therapeutic dose may increase the risk of end-stage renal disease. The explanation for this could be the depletion of the antioxidant glutathione, which makes renal cells more sensitive and prone to oxidative damage (Sharma et al., 2013). Additionally, paracetamol has been considered a major metabolite of phenacetin that can cause analgesic nephropathy (Prescott, 2000). Therefore, this highlights the importance of considering its renal safety, especially in terms of long-term usage of paracetamol.

2.5.1.4. Abnormal liver function in people with OA

This SR/MA also explored liver side effects that were not listed as one of the outcomes of interest but identified three clinical trials examining the liver side effects of paracetamol at its therapeutic dose. They found a strong association with abnormal liver function and elevated serum aspartate transaminase levels with paracetamol use compared to placebo (RR 3.99; 95%CI 2.05, 7.77 and RR 7.42; 95%CI 2.22, 24.77, respectively). The relationship between liver toxicity with an overdose of paracetamol is well established. Therefore, it was worth highlighting abnormal liver function from the MA of clinical trials in people with OA associated with the standard dose of paracetamol. Although statistically significant, fewer trials and wide CIs generate uncertainty in these estimates. These results are consistent with a previous SR/MA (Leopoldino et al., 2019; Machado et al., 2015). Compared to previous reviews, the number of trials and participants in the present SR/MA is more than the last SR/MAs (current MA: 24 studies, 7,299 participants, Leopoldino et al. (2019): 10 studies, 3,541 participants; (Machado et al., 2015): 10 studies including 3541 participants for OA and three studies with 1825 participants for low back pain).

The present SR/MA also estimates risks for a range of aspartate transaminase levels that was not mentioned in previous SR/MAs. Due to the wide confidence interval, future studies are suggested to confirm these findings and their clinical relevance.

2.5.1.5. Mortality in the general population

There were insufficient data in RCTs concerning all-cause mortality. However, according to epidemiological studies, a dose-response relationship was observed for all-cause mortality in only two cohort studies (De-Vries et al., 2010; Lipworth et al., 2003). These results are consistent with a previous meta-analysis of observational studies (Roberts et al., 2016). According to the quality assessment of these two studies, they were both influenced by confounding by indication bias. The reduced baseline prognosis of participants might have made them more vulnerable to paracetamol toxicity.

2.5.1.6. Other secondary outcomes (RCTs) in people with OA

The findings of secondary outcomes suggested an association between paracetamol use and an increased risk of "treatment-related adverse events" with a RR of 1.37 (95%CI 1.06, 1.77) compared to placebo in people with OA. An increased risk was also ascertained for "serious adverse events" in the paracetamol group with RR 1.48 (95%CI 0.81, 2.73) than placebo in OA studies. It is in line with a previous SR/MA (Leopoldino et al., 2019) reporting a RR of 1.36 (95%CI 0.73, 2.53) in OA studies and (Machado et al., 2015) reported a RR of 1.20 (95%CI 0.70, 2.10) including studies with OA and back pain. The slight discrepancy in the estimates could be due to an increase in the number of studies and participants for this outcome in the present SR/MA (current MA: 24 studies, 7,299 participants, Leopoldino et al. (2019): 10 studies, 3,541 participants; Machado et al. (2015): 10 studies including 3541 participants for OA and three studies with 1825 participants for low back pain). Due to a lack of statistical significance, the quality of this evidence is downgraded because it may provide a biased estimate (Lin, 2018). However, high-quality evidence from ten trials suggested that there was a modest increase in the risk for "adverse events (any)" in the paracetamol group compared to placebo (RR 1.04; 95%CI 0.97, 1.11), 2). Comparable results were reported in a previous SR/MA with fewer trials (Leopoldino et al., 2019; Machado et al., 2015). The findings from the sensitivity analysis were also in line with these estimates suggesting a similar risk profile between both groups when the analysis was restricted to high-quality studies only.

The hypothesis that paracetamol can cause side effects similar to NSAIDs may also be linked to the present SR/MA results, especially those for paracetamol versus NSAIDs. For example, in the head-to-head comparison for "adverse events (any)," the risk was nearly similar in both groups with a borderline significance (RR 0.97; 95%CI 0.90, 1.04). The sensitivity estimates

were also consistent with these findings as there was no change indicated in the results when the analysis was restricted to only high-quality studies for any adverse events, including only large studies (n > 100) or excluding the cross-over trials (paracetamol versus placebo). Moreover, a significantly increased risk in people with OA was observed for the “number of withdrawals” in the paracetamol group compared to NSAIDs. Further investigation regarding withdrawals reported that “withdrawals related to adverse events” were higher in the paracetamol group, although this was not significant RR 1.08 (95%CI 0.87, 1.34). These results contrast with a previous SR/MA suggesting a better safety profile of paracetamol versus NSAIDs (Towheed et al., 2006). This may be because the present SR/MA has 24 studies with n=7299 compared to the previous review with 15 studies and 5986 participants.

The risk of withdrawals, adverse reactions, and severe negative reactions are similar in the paracetamol and Coxibs groups.

2.5.2. Strengths

It is the most comprehensive SR/MA, including ten placebo-controlled trials, 14 active head-to-head comparisons (NSAIDs and Coxibs) RCTs,16 cohort studies, and 26 case-control studies in contrast to previous reviews (Leopoldino et al., 2019; Machado et al., 2015; Roberts et al., 2016; Towheed et al., 2006; Zhang et al., 2004). In Leopoldino et al. (2019), there were ten studies with 3541 participants, Machado et al. (2015) included 13 studies with 3541 participants, Roberts et al. (2016) had eight observational studies, Towheed et al. (2006) included 15 studies with 5986 participants, and Zhang et al. (2004) 10 studies with 1712 participants. Different databases were combined to capture the maximum number of citations, and the combination of MEDLINE, Embase, Web of Science, and Google scholar is considered an optimum choice, with an overall recall rate of 98% to 100% in 72% of previous SRs (Bramer et al., 2017). One of the greatest strengths of this SR/MA is that it attempts to combine two study designs (RCTs, cohort and case-control studies), including non-English language studies.

Unlike other reviews, this review also included the crossover trials that might have the advantage of their cases acting as their controls. Although, Cochrane disregards the inclusion of the randomised crossover trials because it is assumed that the exposure to intervention in one phase might result in an adverse event in the second phase. Therefore, the results from

the first phase of the trials were only included. A sensitivity analysis was conducted by excluding the crossover trials, which suggested similar risks associated with paracetamol use, as shown in Appendix 3.4.

The use of a random effect model is not primarily to deal with heterogeneity, combined with careful assessment of clinical study differences such as prior stratification of studies according to comparison groups and study designs. It is considered a more robust approach than using a fixed-effect model. The present SR/MA did not pool across the study design, unlike SR by Kanchanasurakit et al. (2020). According to experimental evidence, the study designs themselves are associated with bias, with case-control studies design reporting an exaggerated effect compared to a cohort study (Lijmer et al., 1999).

Lastly, this current SR/MA included two different study designs: RCTs in people with OA and observational studies not restricted to participants with a specific underlying condition. The focus of this SR/MA was only on the adverse effects of paracetamol. The MA of RCTs in people with OA has shown that paracetamol use is significantly associated with an increased risk for diarrhoea than placebo. There were several other GI events where the risks were higher for paracetamol, including “GI events (any),” “abdominal pain,” “dyspepsia,” and “nausea and vomiting” compared to placebo but they lacked statistical significance. There was only one RCT by Doherty et al. (2011) that demonstrated an association of paracetamol with GI bleeding, suggesting that 3gm/day of paracetamol might cause a similar amount of asymptomatic blood loss as ibuprofen 1200mg/day. It was also found that both drugs together could induce occult GI bleeding in 38.4% of participants without providing any additional clinical analgesic benefit (Doherty et al., 2011). Thus, the concomitant use of paracetamol with ibuprofen might not be beneficial but perhaps hazardous. The clinical significance of these findings and identification of the GI bleeding site needs further investigation.

Similarly, the SR/MA of the observational data have also identified that more severe GI events such as “upper GI bleeding” and “peptic ulcers” were associated with paracetamol in the general population.

Furthermore, the MA of RCTs in people with OA indicated no significantly increased risk associated with the cardiovascular event but with small numbers and a very wide confidence interval (RR 1.05; 95%CI 0.07, 15.38). Even though the findings from the RCTs are not significant but in line with the increased risk associated with paracetamol use and cardiovascular outcomes from the SR/MA of the observational data in the general population. A possible explanation for the statistically non-significance in the MA of RCTs in people with OA might be the small sample size for cardiovascular events (n=1,011). The sample size and the follow-up duration were large in the SR/MA of observational studies in the general population. Therefore, the estimates either reached statistical significance or reported a dose-response relationship.

Thus, the GI events and cardiovascular events reported in the SR/MA of both study designs indicate almost similar findings implying that the mechanism of harm and the ability of paracetamol exposure to cause these side effects appeared similar across different disease groups, such as in people with OA (RCTs) and not restricted to people with a specific underlying condition (observational studies). Therefore, it was worth reviewing two different population groups for the adverse effects of paracetamol.

2.5.3. Caveats

2.5.3.1. Caveats in the SR/MA of RCTs (people with OA)

The present SR/MA is subject to some limitations. There was a varied duration of follow-up in the OA studies, from one week to 24 weeks. The short follow-up duration in the RCTs may only identify the adverse events with a higher incidence, such as skin reactions after intravenous or local administration of a drug which might occur in a short period after the intervention is delivered (Peryer et al., 2021). Other detrimental effects, such as serious GI, cardiovascular or renal events, might be rare or become apparent long after the first exposure to the intervention (Peryer et al., 2021). For example, only one study reported a severe GI event, i.e., 20% of the participants taking paracetamol had ≥1 g/dL drop in the haemoglobin levels, an indication of GI bleeding at 13 weeks, comparable to that from ibuprofen in people with OA.

The other limitation of the clinical trials in OA patients could be that they did not have enough sample size. It could be explained as follows:

Firstly, the inclusion criteria of primary studies were limited to only highly selected individuals. Sometimes they may not represent the people routinely seen in clinical practice, such as people with other diseases or living with frailty. Secondly, the number of participants who complete the study might not be enough to evaluate rare events. For example, the study with the longest follow-up duration of two years in the current MA of RCTs in people with OA reported that only 62 out of 178 participants completed the study (Williams et al., 1993). In addition, the present SR/MA findings suggested that the "number of withdrawals" was higher in the paracetamol arm than placebo. However, it is less likely that the symptoms in the placebo group will result in discontinuation from the study. It could be that the participants in the paracetamol arm that may experience adverse reactions were more likely to withdraw from the study. The other reason could be the operational definition of "number of withdrawals", which might have resulted from either safety or tolerability, mild side effects, lack of efficacy of the intervention, non-medical reasons, or a combination of two or more of these reasons, thus challenging its explanation and sometimes may not reflect the experience of side effects (Peryer et al., 2021).

Additionally, a considerable number of primary studies included in the present SR/MA used mixed terminology to define their safety outcomes. For example, 7 placebo trials and 3 head-to-head comparison trials suggested composite outcomes such as "serious events" in OA studies. The primary studies included in the present SR/MA did not explicitly mention in their text that there were no severe cardiovascular or renal events. Instead, they only reported it as a composite outcome such as "no serious adverse effects were found" or "serious events" only without providing details of diagnosis of those severe events. The primary threat for interpreting these mixed outcomes is that they are defined using diverse events, which might conceal an important rare event.

The other reason could be that all the included RCTs were primarily intended to assess the effectiveness of the interventions. Therefore, they had minimal uniform safety data to offer, and more details were given regarding the efficacy of the interventions. For example, only two clinical trials (paracetamol versus placebo) in the OA population reported cardiovascular events. There were no data on renal events in the clinical trials for OA except for a limited information on serum creatinine levels.

Another limitation could be publication bias. Although, there was no publication bias for "adverse events (any)" (paracetamol versus the comparison group (placebo or NSAIDs). However, it was impossible to determine publication bias for all the other primary outcomes because there were fewer trials, i.e., >10 studies. In addition, only published studies were included in the present SR/MA.

Kicinski and colleagues have highlighted that the trials showing no evidence of adverse effects or favouring the treatment are more likely to be published or included in the meta-analysis than those demonstrating adverse effects (Kicinski et al., 2015). Tang and colleagues have further reported 300 trials with "serious adverse events" mentioned in ClinicalTrials.gov. Furthermore, 26% of these trials did not have any corresponding publication. For the remaining 202, 13% of the published studies did not mention "any serious adverse events," and only 11% of the publications reported similar numbers of "severe events" and described the "type of serious events" (Tang et al., 2015). This could further explain the lack of significance for a small number of events, such as cardiovascular events (paracetamol versus placebo in OA studies), resulting from wide CIs due to the small sample size or lack of relevant studies with harmful effects. Therefore, limiting search strategies to published reports might have underestimated the long-term adverse effects of paracetamol in OA studies.
The information on serious adverse events such as GI bleeding or cardiovascular events is essential to determine the balance between benefits and risks. Cochrane recommends that reports from unpublished sources such as clinical study reports, trials registry, and regulatory agency websites should be included in the SR/MA to increase the robustness of the estimates (Peryer et al., 2021).

Although the estimated risks derived from RCTs are considered the least biased due to randomization. However, observational studies may reflect real-world practices and have better generalizability than RCTs in the current situation.

2.5.3.2. Caveats in SR/MA of observational data (general population)

Similar to RCTs in the OA population, observational studies have limitations. Firstly, the included studies had various definitions of paracetamol exposure with different doses or duration of exposure. This included lifetime intake of paracetamol or a number of tablets over many days and different sets of outcomes. Such variations did not support the quantitative pooling of study reports to make an informed decision regarding the safety of paracetamol.

It was impossible to analyse the publication bias for all the outcomes of the observational data in a similar context. Therefore, standardising the outcome reporting in studies might allow for clear interpretation and clinically relevant outcomes in the SR/MA.

Secondly, the confounding by indication bias was often observed in the observational studies due to non-randomisation, also called channelling bias. Channelling is a form of allocation bias that occurs when interventions with similar indications, either self-referred or clinically allocated, are favourably recommended to people with prognostic differences (Lobo et al., 2006). The adjusted confounders for each study can be found in Table 2.3.1 (P110-119) and Table 2.3.2 (120-128) for cohort and case-control studies, respectively: For example, Dedier et al. (2002) adjusted for age, BMI, intake of sodium, alcohol, history of diabetes and smoking; Evans et al. (2009) adjusted for gender, age, ACE-inhibitors, ARB use, mean arterial blood pressure and diabetic nephropathy; De-Vries et al. (2010) controlled for age, gender, BMI, calendar year, smoking history, ethanol use, general practitioner visits in previous 12 months, hospital admission in the last year, socioeconomic status in the location of practice and Kuo et al. (2010) accounted for age, gender diabetes, hypertension, hyperlipidaemia, atherosclerosis, coronary artery disease, cerebrovascular disease, transient ischaemic attack, peripheral vascular disease. The case-control studies such as Pommer et al. (1989) were age and gender-matched; Matikainen et al. (1996) and Holvoet et al. (1991) were age, gender and study site matched, and Steenland et al. (1990) had age, gender, lifestyle factors, non-occupational variables, missing data for lifestyle variable adjusted for in their analysis. These studies did not account for the use of oral NSAIDs. It could be that participants at higher risk of side effects were recognised to be unsuitable for NSAIDs therapy and were therefore given paracetamol. This indication or the choice of analgesic therapy by health professionals could be associated with future outcomes risks. This might lead to channelling and allocation bias when one intervention is preferred over the other and is given to a highly selected group who are at the potential of having higher risk of adverse events. Channelling occurs when

interventions with similar indications are preferred to a specific group of people with varied baseline prognosis, which can imbalance the underlying risk profile between the paracetamol exposed group and the unexposed, resulting in biased estimates.

Although the observational data included studies not restricted to participants with a specific underlying condition, this SR/MA found no longitudinal studies on the safety of adverse effects associated with paracetamol in people with OA. Except for Rahme et al. (2002), who reported that the estimates obtained from their sensitivity analysis based on paracetamol prescription by rheumatology were similar to those of the complete cohort. However, the information was not enough to be included in the meta-analysis.

Furthermore, Curhan et al. (2002) did not account for detection bias. Although the outcomes were recorded using biennial questionnaires and diagnosed by medical professionals. However, there was no record of follow-up of participants to record their respective blood pressure. Therefore, it is highly likely that the women taking pain relief were highly likely to visit health professionals to register their blood pressure, leading to detection bias. Moreover, two studies by De-Abajo et al. (2014) and García-Poza et al. (2015) reported an increased CV risk from paracetamol in people with already low CV risk but a decreased CV risk from paracetamol in people with high CV risk. This implausible finding might be explained by co-prescription of aspirin and other antiplatelet agents in those at higher initial risk. Still, such detail was not accounted for in these studies.

Lastly, most observational studies relied on self-reported usage of paracetamol or had only prescription-based data that might have underestimated the actual consumption of paracetamol (Chan et al., 2006; Curhan et al., 2004; Curhan et al., 2002; De-Vries et al., 2010; Dedier et al., 2002; Evans et al., 2009; Kurth et al., 2003). However, paracetamol is a prevalent over-the-counter drug. There is no provision to record over-the-counter non-prescription medicines. Similarly, the observational studies comparing paracetamol users with paracetamol-nonusers might also have been influenced by unaccounted additional analgesics OTC NSAIDs usage causing channelling bias. Therefore, the accuracy of paracetamol consumption is also open to question.

2.6. Summary

This SR/MA provides a comprehensive safety profile of paracetamol derived from clinical trials and real-world populations. While the RCTs evidence supports an association between the use of paracetamol and an increased incidence of “any treatment-related adverse events,” “diarrhoea,” and “liver function abnormality” in the short-term clinical trials. The observational data suggest an association between paracetamol and increased GI, CV, and renal adverse events; some are dose dependent. Despite this, the interpretation of the current evidence regarding the safety of paracetamol has been hampered by methodological limitations associated with RCTs and observational studies, such as selection bias and confounding by indication, respectively.

Thus, this SR/MA also highlights the gaps in the literature and warrants further research. Therefore, a large-scale, well-designed prospective study is required to ascertain the long-term safety of paracetamol.

Chapter 3: Cohort study using the UK Clinical Practice Research Datalink

3.0. Background

The results from the SR and MA of RCTs in OA and observational studies in the general population raised concerns over the safety of paracetamol associated with its therapeutic usage. Therefore, more research is required to answer the question, "What is the incidence of adverse effects related to the long-term use of paracetamol?" The notable issues for safety data in the selected RCTs are 1) Measured safety as a secondary outcome, i.e., not powered for and not appropriately measured 2) Short term: allowing insufficient time to capture a small number of the uncommon adverse effects such as renal and cardiac events 3) very selective, cannot represent the population of OA or the general population who are significant users of paracetamol. 4) RCTs reported mixed outcomes. Secondly, observational studies had methodological limitations such as confounding by indication (De-Vries et al., 2010).

Performing an RCT might have been challenging because it needs to be large to determine a slight increase in the observed risk. Secondly, there could be significant ethical issues regarding using a placebo in patients with pain, and the selection of highly vulnerable adults may cause an underrepresentation of particular patient groups.

Therefore, to address methodological limitations in the current literature, further research was conducted using a propensity score-matched cohort study using the UK Clinical Practice Research Dataset (CPRD).

Researchers wishing to analyse data from the CPRD need to comply with Medicines and Healthcare products Regulatory Agency (MHRA) policy and submit a protocol to the Independent Scientific Advisory Committee (ISAC) for approval. Consent from individuals involved in this study was not sought because this was a database research analysis. ISAC approved this cohort study with the protocol reference number 19_131R in September 2019 (Appendix: 4.1).

3.1. Objectives

Objective 1: The primary objective of this cohort study is to confirm the associations identified from the systematic review and examine the incidence of perforation ulcer bleeding (PUB), uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure in those exposed to paracetamol in the general population compared to unexposed people using electronic medical records of patients registered in CPRD

Objective 2: To examine the dose-response relationship between paracetamol and related adverse events.

3.2. Methods

3.2.1. Data source

For the last 25 years, the data collected on a routine basis from primary and secondary care are usually stored in extensive databases. For example, CPRD-database is an electronic record system that includes patient details recorded by general practitioners or paramedical staff from 736 primary care practices in the UK by the end of January 2018, including England, Scotland, Wales, and Northern Ireland. Data are entered electronically either during a consultation with a general practitioner (GP) or communicating with other health professionals. The details of the patients, medications and clinical outcomes, such as disease registries, subsequent referrals, health administrative data, surveillance databases, electronic health records, and pharmacy data, are recorded (Langan et al., 2018). Although not explicitly designed for survey or study, such standard health data are cost-effective for research purposes to examine the effectiveness and safety of interventions in the real world (Langan et al., 2018).

Data auditing is carried out to determine the data quality and ensure that every contributing practice has provided "up-to-standard" data (Herrett et al., 2010). The mandatory requirements included: 1) valid registration status and 2) recording basic demographic features such as age and gender. CPRD broadly represents the UK population in terms of age, gender, ethnicity, and BMI (Campbell et al., 2013; Herrett et al., 2015). The CPRD has linkage to other datasets such as hospital data, national cancer registration data, and national mortality records (Herrett et al., 2015). The data is updated every month while contributing to the CPRD (Herrett et al., 2015). This electronically based data is recorded prospectively when patients interact with their healthcare system. Therefore, it reduces the risk of recall bias if used for research purposes.

Researchers cannot identify individual patients as they have encrypted unique pseudo-identification. The identifiable information about the patients, such as their title, date of birth (DOB), name, address, or National Health Service (NHS) number, is not collected. CPRD has various data types such as structured codes, numerical measurements or tests, and free-text notes. The clinical information is coded using hierarchical Read codes. Read codes can be cross-referenced to the International Classification of Diseases (ICD-10) (Benson, 2011). The information on drug prescriptions and dosage are coded using a Vision-specific terminology (Gem script) reflecting those used in the British National Formulary (BNF). The free-text fields are not available in CPRD, although a certain amount of pre-extracted information is present for some areas, such as drug dosage. Table.3.1.1 explains the data extraction characteristics from the CPRD-dataset.

Table 3.1 Description of data-extraction files from CPRD.

Data file	Organisation of data	Description
Patient	multiple records of patients	basic demographic details of patients with their registration details
Clinical	multiple records of patients	the data were extracted for all clinical diagnoses, including med codes, terms, and event dates
Practice	multiple records of patients	details of data-collection and from which practice, including the region of the UK
Additional	multiple records of patients	the data regarding additional information that can be used to derive smoking, BMI, and alcohol status
Therapy	multiple records	all the prescriptions for drugs with dosage, number of days, number of packs, repeat medication, BNF-codes, strength, formulation, event date

The UK - United Kingdom, BNF - British national formulary, BMI - body mass index.

The CPRD data is linked to other data sources using the patient's unique identification, such as NHS number, date of birth and gender. These include practice level Index of Multiple Deprivation (IMD) scores for socio-economic status, Hospital Episodes Statistics (HES) data, and Office of National Statistics (ONS) death registration data. The HES is a warehouse of national data containing all NHS secondary care hospitalisations, procedures, and consultations in UK hospitals since 1989 (Thorn et al., 2016). HES use a modified version of the WHO ICD-10 standardised coding system, and any medical procedures are still identified through standard codes for hospital procedures (OPCS4). Access to this information is only available after approval of the protocol following the guidelines from research governance and ethics of research.

It is mandatory to document deaths occurring in England and Wales at the local registrar's office. Death registration is a complete source of death information, such as the date and place of death passed to ONS every week. The International Classification of Diseases coding system is used to code the cause of death. By the end of January 2018, there were more than 17 million people with anonymized data attributing to more than 26% of the total population of the UK (Herrett et al., 2015). The certainty and completeness of CPRD are high and validated in previous studies (Herrett et al., 2010; Jick et al., 2003). For example, Weinstein et al. (2017) had already used CPRD-dataset to investigate the challenging bias between paracetamol users and ibuprofen users and to which extent confounding adjustment can minimise this bias.

Although linkage data was requested for this study, only CPRD-data was used. The data was stored as CPRD-flat files and available for license holders from the Research-drive of the University of Nottingham. The study population was selected from the January 2018 version of the CPRD database.

3.2.2. Study design

In pharmacoepidemiology, cohort studies can produce data to make inferences at the population level. They may provide long follow-up periods to estimate the risk of long-term drug effects. Therefore, a cohort study design using the Cox proportional hazards model was considered the best choice to determine the incidence of adverse effects related to the long-term use of paracetamol in the elderly population.

3.2.3. Participants

The eligible participants were all 65 years or older and: (1) had at least 12 months of continuous registration within the database; (2) whose data were flagged as 'acceptable' and 'up to standard' within the CPRD database.

People with invalid gender details, age, and prescribed paracetamol on two or more occasions six months before the age of 65 were excluded from the study. This study did not define them as "new users" of paracetamol. People who developed an outcome of interest before the landmark date and participants with other data anomalies were excluded. A flow diagram of the included primary cohort is shown in Figure 3.4.

3.2.4. Exposure definition

The exposure of interest was paracetamol medication. Information was extracted for all paracetamol prescriptions that were a minimum of two prescriptions within six months during the study period. The participants needed to have 12 months gap from paracetamol before the index date to avoid prevalent bias (Danaei et al., 2012). The extracted information included the date of each prescription, dose, and total quantity prescribed. The CPRD product browser was used to search for product codes as it allows to search for therapeutic codes using different search terms. A British National Formulary (BNF) list was adapted according to inclusion and exclusion criteria used to define paracetamol exposures using read codes described in Appendix 5. The number of prescriptions during the exposure window was counted to analyse the dose-response between paracetamol exposure and the outcome of interest.

3.2.5. Comparators

The control group consisted of unexposed people aged 65 years old who had received less than two paracetamol prescriptions within six months. They did not have a paracetamol prescription during the study period. The controls (paracetamol-unexposed) were individually matched to paracetamol-exposed by year of birth, gender, and general practice to account for the differences in prescription policies and patient care management on a 1:4 ratio. Thus, making both exposed and unexposed groups more comparable at the start of follow-up and assigning the same index date to the non-exposed as their matched paracetamol exposed

3.2.6. Outcomes

The outcomes of interest were 1) PUB, uncomplicated ulcers –ulcers without bleeding or perforation, lower GI bleeding, 2) cardiovascular: hypertension, myocardial infarction, heart failure, and 3) chronic renal failure. Patients with these outcomes were identified using relevant Read codes or med codes if recorded on the general practice records (the med codes for PUB, uncomplicated ulcers, and lower GI bleeding are available in appendix 6.1, 6.2, 6.3). Previous studies had applied similar codes in their respective studies to extract data regarding GI, cardiovascular and renal events (De-Vries et al., 2010; Weinstein et al., 2017). The patients with a prior diagnosis, i.e., before the landmark date of an outcome, were excluded from the analysis.

Setting: The real-world primary care database CPRD January-2018 release was selected for the study cohort. This open cohort recruited all the elderly population 65 years or above from all 736 primary healthcare practices in the CPRD-electronic database during the study period (01/01/1998 to 31/01/2018). The people of this age group are eligible for free prescription of any medication.

Study entry date: 65th birthday during the study period 01/01/1998-31/01/2018

Study exit date: The earliest date of any adverse event occurring after landmark date, de-registration, death, date of last data collection, and end of the study period, i.e., 31/01/2018.

Index date: The date of the first paracetamol prescription of the two prescriptions within six months in the study period for the paracetamol exposure group, as shown in Figure 3.1.

Follow-up period: Each participant was followed from the landmark date until the occurrence of one of the following endpoints, whichever came first, (1) experience an outcome of interest, leave the practice, (2) date of death, (3) the last date of data collection from practice, or end of the study period, as shown in Figure 3.1.

Landmark date: a fixed time, i.e., a landmark date was assigned as the date one year after the index date, and it was selected a priori to conduct survival analysis. After the qualification of exposure, it provided an additional six months to an exposure window to accumulate the number of prescriptions for dose-response analysis. The visual summary of the landmark date is described in Figure 3.1.

Exposure window: The period between the index date and the landmark date is summarised in Figure 3.1. These extra six months provided an additional period after the exposure qualification to accumulate doses for dose-response analysis.

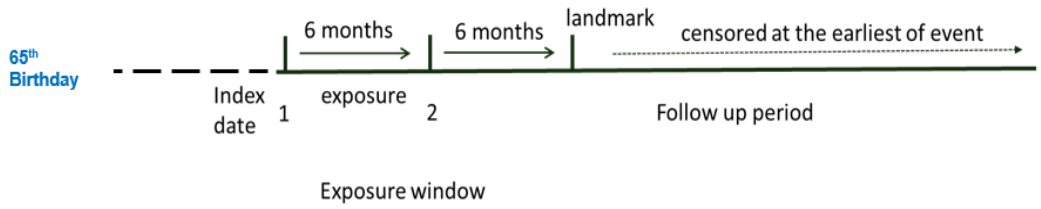


Figure 3.1. Visual interpretation of the timeline for this cohort study.

3.3. Confounders

The confounders were considered potential risk factors for the outcomes of the interest or associated with the likelihood of receiving paracetamol. Therefore, based on previous studies regarding the safety of paracetamol and clinical reasoning discussions with the supervisors, these were described as follows (De-Vries et al., 2010; Weinstein et al., 2017; Weinstein et al., 2020).

3.3.1. Age and gender

Although the literature regarding the safety of paracetamol with age and gender is sparse, these were considered significant potential confounding factors, as paracetamol is a highly preferred analgesic over its contemporary medications such as NSAIDs in the elderly age.

3.3.2. Charlson comorbidity index (CCI)

The comorbidity disease burden was measured and adapted using the Charlson co-morbidity index (Quan et al., 2011). It was first identified by Charlson et al. in 1987 and is a validated weighted comorbidity index. A weighted score was assigned to each comorbid condition based on RR of 1-year mortality to analyse the disease burden (Quan et al., 2011). The CCI considers myocardial infarction, congestive heart failure, cerebrovascular disease, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes, renal disease, hemiplegia, and acquired immunodeficiency syndrome (AIDS) and cancer. A weighted index was developed and assigned based on the severity and number of comorbid conditions. The codes for other comorbidities were obtained from the Primary Care Unit, University of Cambridge https://www.phpc.cam.ac.uk/pcu/cprd_cam/codelists/v11/ and updated using the CPRD code browser. The details regarding the comorbidities listed in the CCI are given in Appendix 4 (Tables 4.1, 4.2, 4.3).

In addition, other comorbid conditions such as OA were also considered. Firstly, OA is the main focus of this thesis. Secondly, it is also an indication for the long-term paracetamol prescription. The details regarding these confounders are given in section 3.6.2.

3.3.3. Other drugs

The other medications selected for each model were included: i) Gastrointestinal: NSAIDs, coxibs, aspirin, opioids, H2-receptor blockers, PPI-inhibitors, dipyridamole and clopidogrel (product codes are available to view in Appendix 5: 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 respectively), ii) heart failure: opioids, NSAIDs, coxibs, aspirin, clopidogrel, dipyridamole, statins, antihypertensives, anticoagulants, diuretics, cardiac glycosides, nitrates, glucocorticoids, iii) myocardial infarction: opioids, NSAIDs, coxibs, aspirin, clopidogrel, dipyridamole, statins, antihypertensives, anticoagulants, diuretics, cardiac glycosides, nitrates, glucocorticoids, iv) hypertension: opioids, NSAIDs, coxibs, aspirin, clopidogrel, dipyridamole, statins, anticoagulants, diuretics, cardiac glycosides, nitrates, glucocorticoids, v) chronic renal failure: opioids, NSAIDs, coxibs, aspirin, clopidogrel, dipyridamole, statins, aminosalicylates, diuretics, antibacterial, nitrates, glucocorticoids, antihypertensive, hypnotics, anxiolytics. Exposure to these drugs was defined if their prescription falls between one year before the index date and one year after (i.e., before the landmark date). These variables were dichotomised (0 = no use, 1 = user of drug), and the latest record was retained for the analysis before entering this cohort.

3.3.4. Lifestyle factors

The lifestyle factors such as BMI, smoking and alcohol intake were also considered potential confounders. The records of BMI before the landmark date were recorded from additional records data files. BMI was also calculated from weight and height records in the additional file if there was missing BMI data. If BMI, height, and weight were all missing, they were coded (missing=999). BMI-data were categorised according to WHO guidelines as underweight (17-18.5kg/m2), normal (18.5-24.9 kg/m2), overweight (24.9-29.9 kg/m2), obese (29.9-50.0 kg/m2) and missing(999 = missing) (Bhaskaran et al., 2013).The smoking and alcohol consumption were extracted using additional records data files before the landmark date. When there was more than one entry for smoking and alcohol status, the latest record before the landmark date was used for analysis. Participants were categorised as non-smokers (0), current smokers (1) and ex-smokers (2), and as non-drinkers (0), current drinkers (1) and ex-drinkers (2). In the case of missing data, an indicator category stating missing (.) was coded as “999.”

3.4. Feasibility counts and Sample size

According to a preliminary check, nearly 17 million people from 736 general practices in the CPRD. 2,026,929 people were aged ≥65 years between 1st Jan 1998 to 31st December 2017 (January 2018 data release). Of these, 1,192,435 patients, as given in Appendix 4.2, had at least two prescriptions for paracetamol in the study period with a gap of no more than six months, and they formed the source population of the exposure group for this study.

According to previous studies, the prevalence of upper GI, cardiovascular and renal adverse effects amongst non-users of paracetamol is 0.14%, 0.003% and 0.07%, respectively (Chan et al., 2006; Curhan et al., 2004; Garcia-Rodriguez et al., 2004; Kurth et al., 2003). The relative risk (RR) for each of the outcomes was estimated as 3.4 for GI, 1.35 for cardiovascular and 2.04 for renal (Chan et al., 2006; Curhan et al., 2004; Garcia-Rodriguez et al., 2004; Kurth et al., 2003). Therefore, to investigate a clinically significant HR for these safety outcomes with a power of 90% and significance level of 0.01, the required sample size was 1,025 participants for GI (205 paracetamol users and 820 non-users), 1,935 participants for cardiovascular (387 paracetamol users and 1548 non-users), and 825 (165 paracetamol users and 660 non-users) for renal adverse events. It was calculated using DuPont Power and the sample size program described by Dupont et al. (1990).

According to feasibility counting, more than 1m people aged 65 years or more had received at least two prescriptions within six months, suggesting that the study was powered enough to detect the assumed risk even after applying the exclusion criteria.

3.5. Data management

Data management is transforming raw data into a dataset suitable for analysis. It involves extraction of relevant information, data cleaning, generating new variables, and combining all these to create a final clean dataset. There are other core dimensions to consider regarding the quality of the CPRD-data. The first step in data preparation is identifying and pulling data from relevant fields within the CPRD dataset. The patient-ID for people over 65 years between January 1998 and January 2018 were extracted as a single (index) file. Those who had the first two prescriptions within 6 months for paracetamol were assigned as exposed. The participants who were not exposed to or were non-users of paracetamol were defined as unexposed. All this raw data was stored in a range of formats.

Therefore, an additional separate data file containing all patient demographic information, clinical diagnosis for other co-morbidities and outcomes (all linked by unique patient ID) were extracted and merged with the index file using Read codes. The next step was to identify and amend any errors through the data cleaning process. If there were any inaccuracies, such as date anomalies, duplicate records or implausible values, those were amended accordingly. The consistency level between the two datasets, such as coded smoking information in the clinical and additional files, was checked for any disagreement. Finally, the missing data were imputed using a multiple imputation approach, as explained in section 3.7.

The data management process is iterative, so data cleaning was performed before, during, or after defined variables. In case of further modifications, various stages were revisited to make necessary changes.

3.6. Statistical Analysis

Data were analysed using STATA S.E. version 16 (StataCorp). The initial step was to perform a descriptive analysis.

3.6.1. Age, gender, and practice matched

The exposure to paracetamol was defined as two prescriptions within six months. Age, gender, and practice matched paracetamol exposed, and unexposed participants aged 65 or over were identified with 1:4 matching and excluding those that did not match. This dataset was used to assign a matched index date to the matched control and to determine the population with comorbidities from the dataset. The unadjusted but age, gender, and practice matched HR was calculated using this dataset defined as Model 1.

3.6.2. Propensity score (PS)

Selection bias could affect the observational studies due to the non-random allocation of the intervention defined as “confounding by indication”(Okoli et al., 2014). The PS is being widely proposed as a statistical method to address the confounding by indication bias in observational studies (Rosenbaum et al., 1983; Signorello et al., 2002). Therefore, it was used in the present study to minimise the risk of “confounding by indication” bias by predicting the likelihood of paracetamol based on the study population's specified set of characteristics. Each paracetamol exposed was matched with the unexposed participant by PS to balance

both groups based on the observed attributes and calculate less biased estimates. Logistic regression was used to calculate PS, i.e., the probability of having paracetamol at the landmark date for each participant irrespective of their statistical significance or collinearity with over covariates (Elze et al., 2017). The PS combined the potential confounders into a single score for every person in the study. This score is equal to the probability of paracetamol exposure, given the characteristics measured at baseline (Kahlert et al., 2017).
PS methods involve the following four steps and assessment of the balance:

(i) Selection of the potential confounder included in the PS model: The PS primary analysis model included identifying the factors that may influence paracetamol prescriptions, including participants attributes and components of the intervention system. The selection of the covariates for the PS calculation was based on their association with the exposure and the outcome of interest and were as follows:

***GI events*:** age, gender, lifestyle factors (BMI, smoking, alcohol intake), OA, Charlson comorbidity index and other prescribed medications (NSAIDs, aspirin, coxibs, opioids, H2-receptor blockers, proton pump inhibitors (PPIs), clopidogrel and dipyridamole).
Cardiovascular events: Hypertension: age, gender, lifestyle factors (BMI, smoking, alcohol intake), Charlson comorbidity index, OA, hyperthyroidism, hypercholesterolemia, and other prescribed medications as explained in section 3.3.3.
Myocardial infarction: age, gender, lifestyle factors (BMI, smoking, alcohol intake), Charlson comorbidity index excluding myocardial infarction, hypertension, OA, hyperthyroidism, hyperlipidaemia, hypercholesterolemia, and other medications as described in section 3.3.3.
Heart failure*:* age, gender, lifestyle factors (BMI, smoking, alcohol intake), Charlson comorbidity index, OA, hyperthyroidism, hypertension, hypercholesterolemia, and other medications mentioned in section 3.3.3.
Renal Failure: age, gender, lifestyle factors (BMI, smoking, alcohol intake), OA, Charlson comorbidity index excluding chronic renal failure and other medications as presented in section 3.3.3.

(ii) Calculation of PS: 5 different PS models were created using the variables (selection was based on their association with exposure or outcome of interest) outlined above, along with paracetamol status in the propensity derivation model using logistic regression. The derived score becomes the estimated probability of being in one paracetamol exposed group or the unexposed.

(iii) Using PS to balance the two groups: The PS-matching was performed using the "greedy nearest neighbour matching" method without replacement, specifying a maximum calliper width of 0.001 (Geldof et al., 2020). This formed an algorithm where the X set of exposed was matched to the Y set of unexposed decisions (X) while excluding unmatched ones. The PS-matching started with assessing the imbalance of covariates between groups such as demographics, lifestyle factors, other drugs, and Charlson comorbidities. A well-validated standardised mean difference (*d*) was used to assess the imbalance between paracetamol exposed and unexposed groups (Austin, 2009; Qin et al., 2008).

For continuous variables, the standardised mean difference (*d*) was defined using the formula below in Figure 3.2.

$$d = \frac{(\bar{x}_{\text{treatment}} - \bar{x}_{\text{control}})}{\sqrt{\frac{s^2_{\text{treatment}} + s^2_{\text{control}}}{2}}}$$

Figure 3.2. The formula to calculate the standardised mean difference for continuous variables. Reference: (Austin, 2009). Reproduced with permission from John Wiley and Sons Ltd.

Here X-treatment and X-control signify the sample mean of the covariates for the paracetamol exposed and unexposed participants, respectively. However, S2-treatment and S2-control denote the sample variance for paracetamol exposed and unexposed participants. For categorical variables, this standardized difference (*d*) was characterised as described in Figure 3.3.

$$d = \frac{(\hat{p}_{\text{treatment}} - \hat{p}_{\text{control}})}{\sqrt{\frac{\hat{p}_{\text{treatment}}(1-\hat{p}_{\text{treatment}}) + \hat{p}_{\text{control}}(1-\hat{p}_{\text{control}})}{2}}}$$

Figure 3.3. The formula is used to calculate the standardised mean difference for categorical variables. Reference: (Austin, 2009). Reproduced with permission from John Wiley and Sons Ltd.

If imbalance defined as d >0.10 was present for any of the included covariates, it was included as an additional covariate in the COX regression model (Nguyen et al., 2017). The *d* was preferred over the significance test based on P-value. The latter is influenced by sample size, the area under the receiver operating curve (ROC) or c-statistic (Austin, 2009). For each variable in the model, the participants with similar PS should have approximately an equal distribution of that variable regardless of the intervention decision. The Kernel-density plot was used to check the covariate balance graphically.

iv) Assessing the association between paracetamol exposure and the outcome of interest: This was performed using the cox proportional hazards model described in section 3.6.3.

3.6.3. Time to event analysis

Participants entered the cohort on the entry date, and data were censored at the earliest event, study end date (31/01/2018), date of death, or transfer out of practices, whichever came first. For the primary analysis:

i) A landmark analysis was applied as a simple approach to minimise immortal time bias (Lévesque et al., 2010). The follow-up period started from the landmark date for both exposed and unexposed groups to avoid miscounting any outcome before the qualification as a paracetamol exposure (i.e., two or more prescriptions within six months).

ii) The checks for assumptions for proportional hazard (PH) were done using a log-log plot of survival for each outcome variable taking account of other covariates before any further analysis. These survival plots were examined to assure that they met the assumptions of the proportional hazard model before any further investigation. The Schoenfeld statistical test was also performed to check if the hazard ratio was constant over time (Corporation, 2003). The cumulative survival probability was estimated using the Kaplan Meier survival (Nelson-Aalen) Curve (Vinogradova et al., 2015). Cox proportional hazard model was used to determine the hazard ratio for paracetamol users and non-users for the outcomes of interests using i) Model 1: The age, gender and practice matched (non-PS-matched analysis ii) Model 2: conventional multivariable adjustment of the covariates as listed in the previous section 3.3 iii) Model 3: PS matched analysis including all the covariates iv) Model 4: PS matched analysis including the covariates, if they remained unbalanced (d >0.10) after PS-matching. When the hazard ratio was statistically significant at the 0.05 level, we considered that the effect of paracetamol was significant.

An initial dose-response relationship was assessed when the significant association was found within a predefined exposure window (one year between index and landmark dates). A dose-response was confirmed using P (P-trend) for the trend between paracetamol exposure and non-exposure by calculating the number of prescriptions with a significance level of < 0.01.

3.7. Managing Missing data

PS is an established tool to account for measured confounding in non-randomised studies and retain the balance between the two groups. However, these methods are sensitive to missing values. In order to use the entire cohort and reduce selection bias, two approaches were undertaken to manage missing values for BMI, smoking and alcohol. Firstly, missing indicator approach was used, and a dummy category was created for missing data such as: for BMI (normal weight (18.5/24.9) = baseline, underweight (17/18.5) =1, overweight (24.9/29.9) = 2, obese (29.9/50.0) = 3, missing =999) in the analyses, smoking (non-smoker = baseline, current smokers = 1, ex-smokers = 2, missing =999), alcohol intake (non-drinkers= baseline, current drinkers= 1, past drinkers =2, missing =999). This analysis then included all participants in calculating the hazard ratio (HR). However, matching can still discard many participants from the analysis (Austin, 2014).

Therefore, multiple imputations (MI) were conducted using Multivariate Imputation by Chained equation (MICE) for missing values for BMI (46.7%), smoking (34%), and alcohol intake (43.9%) based on all candidate predictors defined as Model 5. There were five imputed datasets created for further analysis. The comparison for distribution of observed data before performing multiple imputations and after was presented using midiagplots. Each of the five imputed datasets was analysed separately, and then the estimates were pooled using Rubin's rules.

Due to rare events and to adjust for confounding by indication appropriately, the inverse probability treatment weighting (IPTW) using the PS was used (Austin, 2009). The combination of MI and IPTW methods had been previously used in a cohort study to determine the incidence of GI-perforation associated with disease-modifying anti-rheumatic drugs (Barbulescu et al., 2020).

The IPTW were determined within each of the five imputed datasets for each participant. For each study participant within the dataset, formal weights were assigned, equal to the reciprocal of their probability of obtaining treatment in actual while taking account of their baseline covariates (Bolch et al., 2017; McCaffrey et al., 2013). During the calculation of formal weights, logistic regression calculated the probability of receiving paracetamol. The weights were further calculated from the predicted probability (propensity score (PS) of receiving paracetamol as if the participant received treatment (status=1). The calculated propensity score weight was 1/PS, and if there was no treatment received by the participant (status=0), then the formal weight was calculated as 1/(1-ps) (Mitchell et al., 2020).

Furthermore, HR was calculated using COX regression.

The absolute risk reduction for each outcome at one year from the landmark date was calculated using a published formula by Altman and Anderson (1999). In order to estimate the impact on public health and quantify the magnitude by which the incidence of outcomes could have been reduced if paracetamol exposure was eliminated, the attributable fraction (AF) and population attributable fraction (PAF) were calculated. The AF can be defined as proportion of disease in the exposed group that has contributed to the occurrence of disease in the exposed group. The PAF could be defined as the proportion of the incidence risk in the overall population associated with the particular exposure (or fraction of all the cases in the population that can be attributed to the exposure, i.e., paracetamol). The unadjusted number needed to harm (the inverse of the absolute risk increase) was also calculated.

3.8. Results

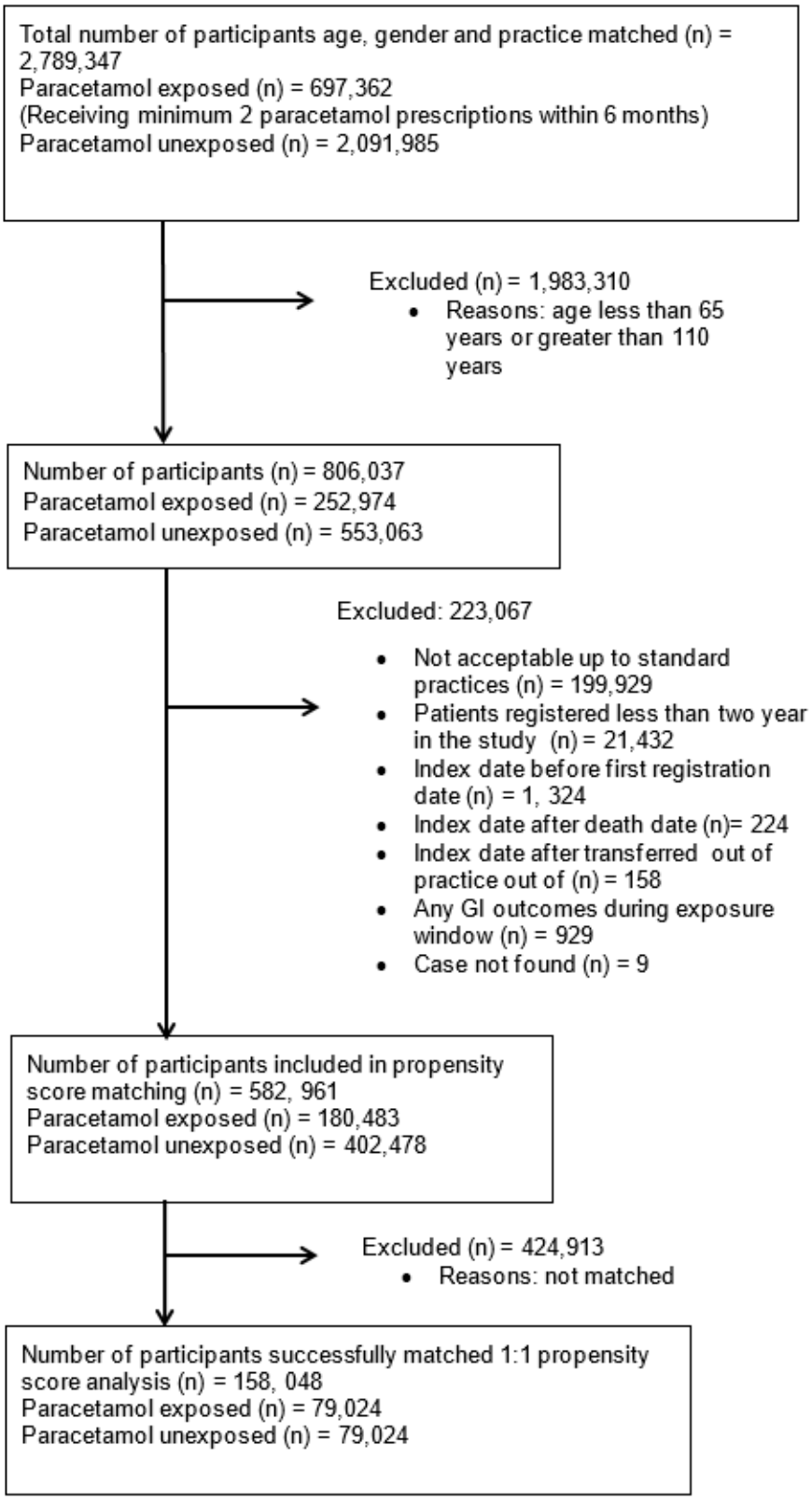


Figure 3.4. Participant selection process using propensity score matching.

3.8.1. Cohort description for gastrointestinal outcomes

The initial cohort included 2,789,347 participants aged ≥65 years with two paracetamol prescriptions within 6 months successfully matched for age, gender, and practice during the study period. Of these, 697,362 were paracetamol exposed, and 2,091,985 were unexposed. A further 223,067 participants were excluded for the reasons explained in Figure 3.4.

After inclusion and exclusion, the age, gender, and practice-matched dataset had 582,961 participants for propensity score matching. Table 3.2 presents age-gender practice matched dataset showing paracetamol exposed individuals were more likely to be female, had higher CCI scores, and had a significantly higher percentage of opioids-users (70%) and NSAIDs (31%) and PPI (35%) users compared to non-exposed group. The percentage of people with OA was higher in paracetamol-exposed in comparison with non-exposed (paracetamol exposed: 30% and paracetamol-unexposed: 15%) as given in Table 3.2. The maximum follow-up duration was 20 years in both groups. The mean duration of follow-up was one year (SD: 4.62) for paracetamol exposed and 3.4 years (SD: 4.98) for paracetamol unexposed.

Table 3.2 also demonstrates the PS-matched dataset, where 158,048 participants were successfully matched (79,024 paracetamol exposed, 79,024 unexposed) for gastrointestinal outcomes. Figure 3.4 depicts a drop of 424,913 individuals who did not find any suitable match during PS-match analysis. After PS-matching, the *d* was less than 0.1 for almost all the baseline covariates, indicating successful balancing of measured confounders except for Charlson co-morbidity index, OA, and aspirin users. Of note, the opioid users in the PS-matched dataset were 97% in both groups compared to the non-PS matching dataset. A detailed description of the characteristics of the participants is mentioned in Table 3.2 for age, gender and practice matched dataset and PS-matched dataset.

Table 3.2. Participants characteristics age-gender practice matched dataset and propensity score-matched for gastrointestinal.

Entire cohort (n=582,961)				**PS-matched sample (n=158,048)**		
Continuous variables, mean (S.D)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
age	74.88 (7.29)	74.99 (7.47)	-0.01	75.42 (7.51)	75.41 (7.75)	0.00
Charlson's co-morbidity index	0.43 (1.24)	0.24 (0.93)	0.15	0.53 (1.45)	0.36 (1.21)	**0.13**
Categorical covariates, n (%)						
Female	114,066 (63.20)	242,175 (60.17)	0.06	48,167 (60.95)	50,421 (63.80)	0.06
OA	55,038 (30.49)	60,349 (14.99)	0.38	28,356 (35.88)	24,391 (30.86)	**0.11**
BMI						
underweight	3,647 (2.02)	5,505 (1.37)	0.05	2,330 (2.95)	1,625 (2.06)	0.06
overweight	43,402 (24.02)	73,328 (18.22)	0.14	22,776 (28.82)	20,024 (25.34)	0.08
obese	22,163 (12.28)	29,131 (7.24)	0.17	12,363 (15.64)	9,761 (12.35)	0.09
missing	64,148 (35.54)	208,224 (51.74)	-0.33	19,101 (24.17)	25,648 (32.45)	-0.18
Smoking-status						
current	15,138 (8.39)	30,110 (7.48)	0.03	8,875 (11.23)	8,237 (10.42)	0.03
ex-smoker	44,190 (24.48)	63,636 (15.81)	0.21	21,471 (27.17)	18,347 (23.21)	0.09
missing	32,468 (17.99)	168,282 (41.81)	-0.54	9,208 (11.65)	14,680 (18.57)	-0.19

Entire cohort (n=582,961)				PS-matched sample (n=158,048)		
Categorical covariates, n (%)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
Alcohol						
current drinkers	79,661 (44.14)	144,373 (35.87)	0.17	40,956 (51.82)	38,149 (48.27)	0.07
past drinkers	4,448 (2.46)	4,767 (1.18)	0.10	2,180 (2.76)	1,493 (1.89)	0.06
missing	57,999 (32.14)	198,151 (49.23)	-0.35	16,978 (21.48)	22,904 (28.98)	-0.17
Other drug use						
Opioids	178,328 (69.87)	76,896 (30.13)	2.76	76,878 (97.27)	76,878 (97.27)	0.00
NSAIDS	55,559 (30.78)	48,061 (11.94)	0.47	26,635 (33.70)	24,385 (30.85)	0.06
Coxibs	10,077 (5.58)	5,965 (1.48)	0.22	5,208 (6.59)	3,621 (4.58)	0.09
Clopidogrel	10,183 (5.64)	7,658 (1.90)	0.20	4,073 (5.15)	2,983 (3.77)	0.07
Dipyridamole	5,255 (2.91)	4,947 (1.23)	0.12	2,771 (3.51)	1,835 (2.32)	0.07
H2-receptor blockers	18,745 (10.39)	17,714 (4.40)	0.23	10,914 (13.81)	8,213 (10.39)	**0.10**
Proton pump inhibitors	63,710 (35.30)	49,621 (12.33)	0.56	25,060 (31.71)	22,250 (28.15)	0.07
Aspirin	72,064 (39.93)	78,523 (19.51)	0.46	31,257 (39.55)	26,428 (33.44)	**0.13**

d - Standardized difference, PS - propensity score, NSAIDs - non-steroidal anti-inflammatory drugs, SD - standard deviation, OA - osteoarthritis, BMI - body mass index, significant values are in bold.

3.8.1.1. Assumptions of Cox-model for gastrointestinal outcomes

The proportional hazard assumption was measured before and after PS-matching. A visual inspection of the log-log plots given in Figure 3.5 indicated that the proportional hazards assumption was satisfied before and after PS-matching for GI outcomes. Figure 3.5 shows that log-log plots were parallel for almost all the outcomes suggesting no violation of this assumption. Table 3.3 illustrates the statistical Schoenfeld test results, indicating that the proportional hazards assumption was met as there was no evidence (P-value was not significant) to reject the hypothesis of proportional hazards for paracetamol exposed.

Table 3.3. A global test for proportional hazards assumption for gastrointestinal events.

Outcome	P-value (Schoenfeld)	
	Before PS-matching	After PS-matching
PUB	0.47	0.37
Uncomplicated ulcers	0.53	0.46
Lower GI bleeding	0.44	0.15

PUB - perforation ulcer bleeding PS - propensity score matching, GI – gastrointestinal.

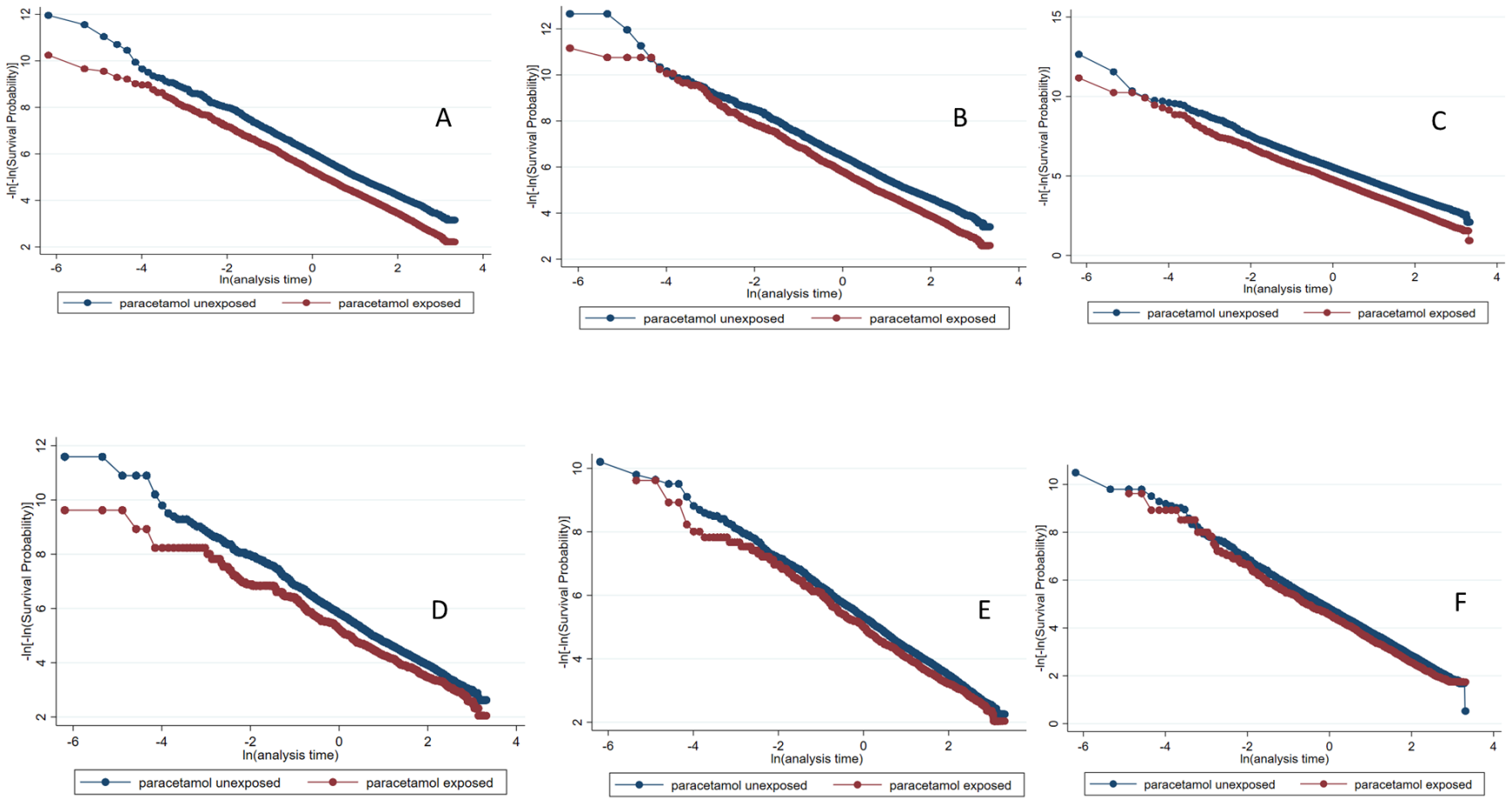


Figure 3.5. Log-log plots before PS-matching for outcomes for perforation ulceration and bleeding (PUB, image A), uncomplicated ulcers (image B) and lower gastrointestinal bleeding (image C) and after PS-matching for outcomes for perforation ulceration and bleeding (image D), uncomplicated ulcers (image E) and lower gastrointestinal bleeding (image F). All the Figures show lines parallel to each other and not crossing, which means that the proportional hazard assumption was not violated.

3.8.1.2. Kaplan Meier (Nelson-Aelon) for gastrointestinal outcomes

The Nelson-Aelon cumulative hazard estimates for paracetamol exposed compared to unexposed for PUBs, uncomplicated ulcers, and lower GI bleeding are given in Figures 3.6 (A), (B), and (C) before, and Figures 3.6 (D), (E), and (F) after PS-matching. These results indicated that the cumulative hazards for PUB, uncomplicated ulcers, and lower GI bleeding were higher in the paracetamol exposed compared to the unexposed group (in both the PS-unmatched and matched datasets).

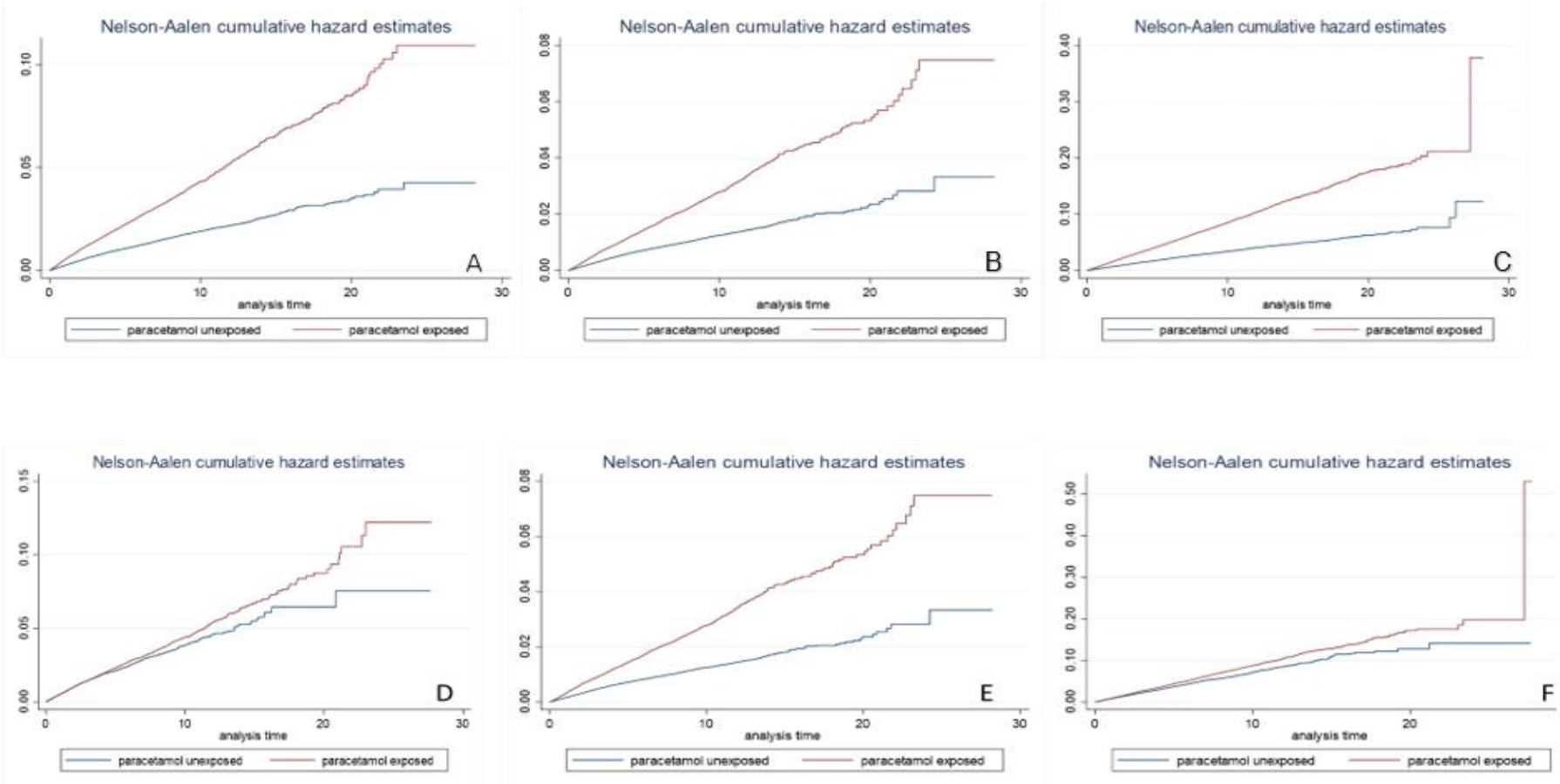


Figure 3.6. Cumulative hazards estimates before and after PS-matching for perforation ulcer bleeding image (A) and (D), uncomplicated ulcers image, (B) and (E) and lower gastrointestinal bleeding image (C) and (F). The red line represents that paracetamol exposure has higher hazards for gastrointestinal events than the unexposed group (represented by the blue line).

3.8.1.3. Incidence of gastrointestinal events

Any participants who had an outcome before the landmark period were excluded from this analysis, referring to the incident outcome. Table 3.4 shows the association between paracetamol exposure and gastrointestinal events. Table 3.4 indicates that the hazard ratio for Model 1 was two times greater in the paracetamol exposed group than the unexposed group for PUB with a HR of 2.21 (95%CI 2.10, 2.32), uncomplicated ulcers with a HR of 2.15 (95%CI 2.02, 2.29), and lower GI bleeding with a HR of 2.45 (95%CI 2.36, 2.54).

Further, a conventional multivariable-adjustment model (Model 2) was used to adjust all the baseline factors: specifically: OA, BMI, smoking, alcohol, CCI, NSAIDs, opioids, coxibs, aspirin, proton pump inhibitor, H2-receptor blockers, clopidogrel, and dipyridamole, reported a decreased HR to 1.01 (95%CI 0.94, 1.08), HR 0.97 (95%CI 0.89, 1.06) and HR 1.09 (95%CI 1.03, 1.15) for PUB, uncomplicated ulcers, and lower GI bleeding, respectively compared to Model 1 estimates. These findings suggested that a higher prevalence of other confounders might explain a small part of the excess risk. However, the results from Model 2 analysis could be affected by an overt bias as several of the observable factors such as co-morbidities, lifestyle factors, and other drugs had d >0.01, shown in Table 3.2 (before propensity score matching). Similarly, Figure 3.7 shows that the Kernel density plot, used to present the covariate balance between exposed and non-exposed to paracetamol before propensity score matching, suggested that both groups were not balanced.

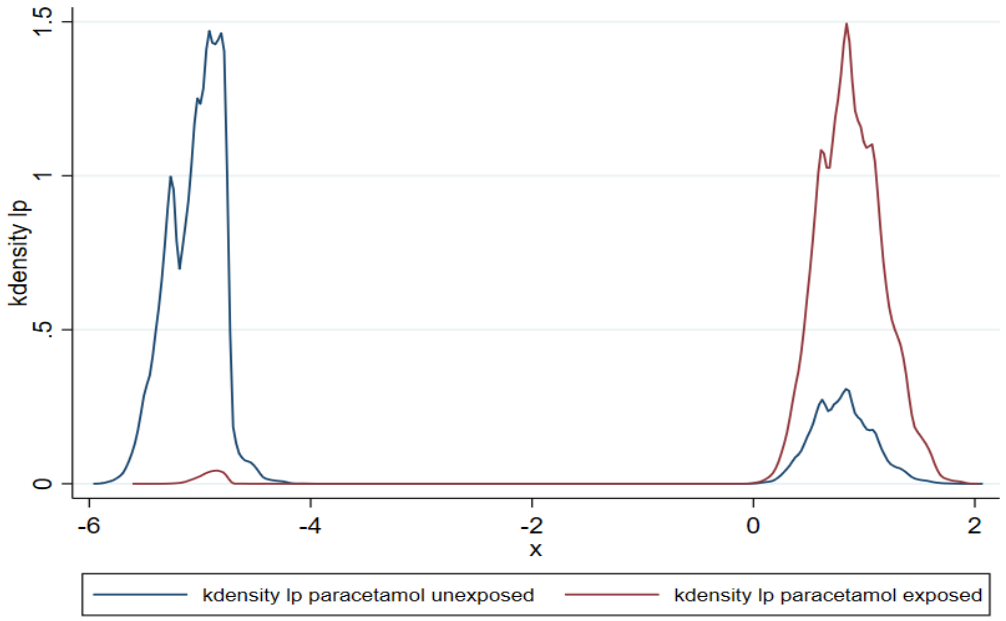


Figure 3.7. Kernel density plot presenting covariate balance between the unexposed and exposed to paracetamol before propensity score matching. The distribution of covariates varies over the treatment levels.

Therefore, to make both groups more comparable and account for confounding by indication bias, PS was calculated using logistic regression while incorporating all variables related to the outcome or treatment decision.

Table 3.4. Incidence of gastrointestinal outcomes between paracetamol exposed versus paracetamol non-exposed groups.

Outcomes	Paracetamol -exposed	Event rate (95%CI)/ 1,000 person-years (before matching)	Event rate (95%CI)/ 1,000 person-years (After matching)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)
PUB	No	5.51	11.54	1.00	1.00	1.00	1.00	1.00
	Yes	12.19	12.63	**2.21 (2.10, 2.32)**	1.01 (0.94, 1.08)	**1.10 (1.01, 1.19)**	**1.06 (1.00, 1.16)**	**1.24 (1.16, 1.34)**
Uncomplicated ulcers	No	3.65	7.72	1.00	1.00	1.00	1.00	1.00
	Yes	7.84	8.38	**2.15 (2.02, 2.29)**	0.97 (0.89, 1.06)	**1.09 (1.00, 1.21)**	1.04 (0.95, 1.16)	**1.20 (1.10, 1.31)**
Lower GI-bleed	No	9.53	19.87	1.00	1.00	1.00	1.00	1.00
	Yes	23.36	23.23	**2.45 (2.36, 2.54)**	**1.09 (1.03, 1.15)**	**1.20 (1.13, 1.28)**	**1.15 (1.09, 1.23)**	**1.36 (1.29, 1.45)**

Model 1 - age, gender and practice matched, Model 2 - age, gender, and practice-matched and adjusted for other covariates, Model 3 - propensity score-matched, Model 4 - propensity score-matched with further adjustments for the variables that were still not balanced after propensity score matching, i.e. Charlson co-morbidity index, OA, H2-receptor blockers, aspirin, Model 5 - Multiple imputations and Inverse probability treatment weighted method, CI - confidence interval, HR - hazard ratio, significant results are in bold.

Furthermore, the results from the PS-matching dataset (Model 3) given in Table 3.4 suggest a significantly increased incidence of PUB, uncomplicated ulcers, and lower GI bleeding (HR of 1.10; 95%CI 1.01, 1.19, HR 1.09; 95%CI 1.00, 1.21 and HR 1.20; 95%CI 1.13, 1.28, respectively) for paracetamol exposure compared to unexposed. Figure 3.8 shows the Kernel Density plot, indicating that the covariates were indistinguishable, implying that the baseline characteristics were now balanced for the paracetamol exposed and unexposed groups. The results from PS-matching were preferred over the conventional adjustment method.

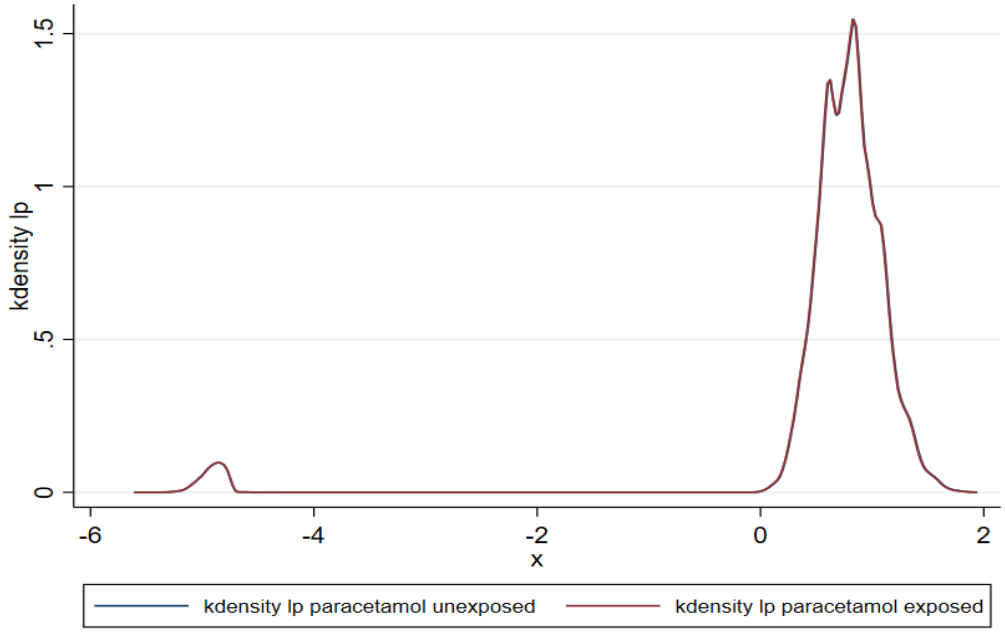


Figure 3.8. Kernel density plot shows covariate balance between the exposed and unexposed to paracetamol after propensity score matching, as both groups appeared similar. The Kernel density plot was nearly indistinguishable as the red line representing the exposed group overlaps the blue line representing the unexposed group.

A standardised mean difference was also estimated to assess the balance between both groups (paracetamol exposed and unexposed), as explained in section 3.6.2 (iii). Although, the Kernel Density plot in Figure 3.8 exhibits that the two groups are clinically similar. However, Table 3.2 (estimates from PS-matching dataset) illustrates that the standardised mean difference between paracetamol exposed and unexposed for H2-receptor blockers, aspirin-users, OA, and CCI was d >0.10, indicating that these few variables were still unbalanced.

Therefore, additional adjustment was conducted by adding these variables again into the analysis as Model 4 analysis. The results from this analysis presented in Table 3.4 as Model 4 suggested that even after further adjustments, there was an increased incidence of PUB and lower GI bleeding during the follow-up period from the landmark date with HR 1.09 (95%CI 1.00, 1.19) and 1.12 (95%CI 1.05, 1.19), respectively for paracetamol exposure compared to the unexposed group. A small increase in the hazards for uncomplicated ulcers was also noticed in the paracetamol exposed group compared to the unexposed (HR 1.05; 95%CI 0.96, 1.17). However, it did not reach statistical significance.

Furthermore, the missingness of values were high for BMI (n= 272,372), smoking (n=200,750) and alcohol consumption (n=256,150). Consequently, the PS-matching method might have dropped 424,913 observations due to missingness, as many participants might not have found a suitable match. Therefore, multivariate imputations by chained equation were performed to account for missing data. The MICE generated five imputed datasets for (missing values were assigned following guidelines in Stata using Multivariate imputation by chained equation (MICE). Figure 3.9 shows an excellent overlap between observed and imputed values of BMI using midiagplots.

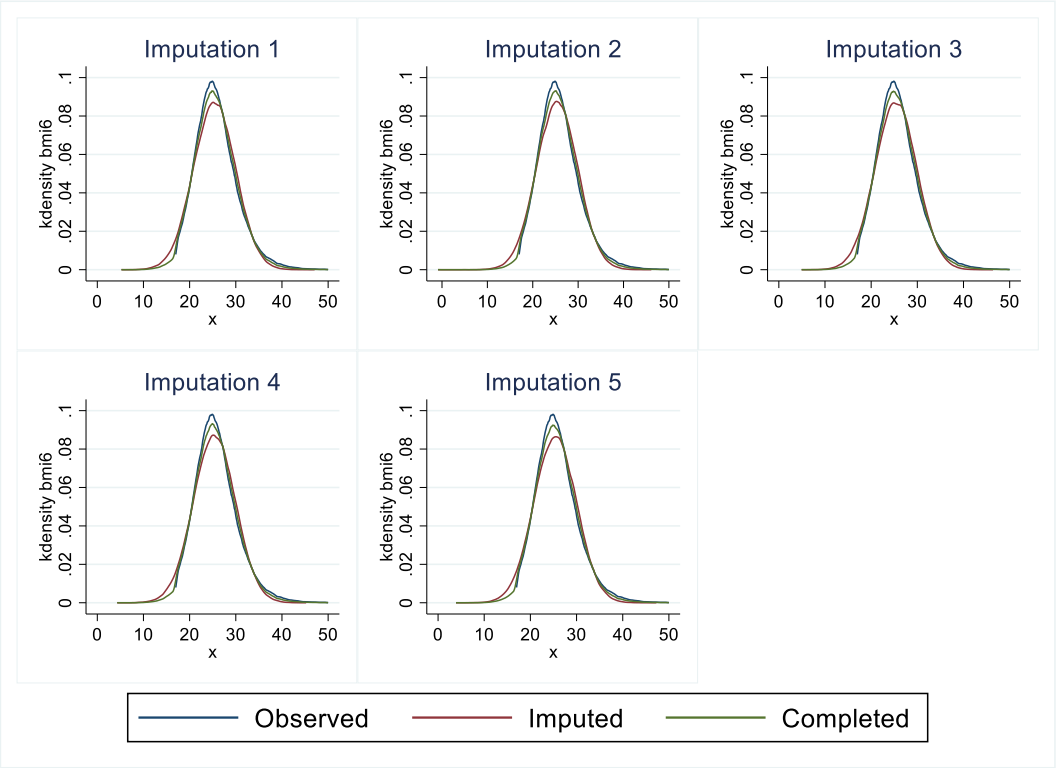


Figure 3.9. The distribution of observed, imputed, and completed dataset for BMI after five imputations for gastrointestinal outcomes.

Further, the inverse probability of treatment weighting (IPTW) method was applied to make both groups comparable. Table 3.4. Model 5 suggests that paracetamol exposure was significantly associated with increased hazards of PUB, uncomplicated ulcers, and lower GI bleeding (HR 1.24; 95%CI 1.15, 1.33, HR 1.20; 95%CI 1.10, 1.31 and HR 1.36; 95%CI 1.26, 1.41, respectively).

At one year from the landmark date, the unadjusted absolute risk was highest for lower GI bleeding (3.12%), followed by PUB (1.66 %) and uncomplicated ulcers (1.07 %) compared to the unexposed group with (1.35%, 0.78%, and 0.52%, respectively). Using the unadjusted risks, it was estimated that over a one-year follow-up, the number needed to harm was 114 (95%CI 107, 122) for PUB, 180 (95%CI 166.48, 196.57) for uncomplicated ulcers, and 56 (95%CI 54, 58) for lower GI bleeding. This indicates that an average of 114, 180, and 56 patients would need to receive paracetamol for one additional patient to have PUB, uncomplicated ulcers, and lower GI bleeding, respectively. Moreover, 52%, 51% and 56% of PUB, uncomplicated ulcers, and lower GI bleeding, respectively, in the population were attributable to paracetamol exposure. If paracetamol exposure was eliminated, then the unadjusted PAF of 26%, 25% and 29% for PUB, uncomplicated ulcers, and lower GI bleeding, respectively, could be reduced in the population.

3.8.1.4. Dose-response for gastrointestinal outcomes

In the PS-matched dataset, the sum of paracetamol prescriptions was calculated between the index date and the landmark period. No dose-response increase was observed for any outcome PUB, uncomplicated ulcers, and lower GI bleeding with P for trend >0.01, as summarised in Table 3.5. Table 3.6 illustrates similar results when the analysis was restricted to only paracetamol users.

Table 3.5. Dose-response for gastrointestinal outcomes with paracetamol exposure versus unexposed: using propensity score matching dataset.

Number of prescriptions	PUB HR (95%CI)	Uncomplicated ulcers HR (95%CI)	Lower gastro-intestinal bleed HR (95%CI)
Non-users	1	1	1
1-2 prescriptions	1.06 (0.93, 1.21)	1.13 (0.97, 1.32)	**1.13 (1.02, 1.25)**
3-4 prescriptions	1.06 (0.95, 1.19)	1.08 (0.94, 1.24)	**1.21 (1.12, 1.32)**
5-6 prescriptions	1.00 (0.87, 1.15)	1.00 (0.84, 1.18)	**1.29 (1.17, 1.42)**
7-8 prescriptions	**1.21 (1.04, 1.40)**	1.08 (0.89, 1.31)	1.12 (0.99, 1.26)
9 or more prescriptions	**1.30 (1.15, 1.46)**	**1.28 (1.11, 1.48)**	**1.16 (1.06, 1.28)**
	P > 0.01	P > 0.01	P > 0.01

PUB - perforation ulcer bleeding, HR - hazard ratio, CI - confidence interval, P – P for trend, and significant results are in bold.

Table 3.6. Dose-response for gastrointestinal outcomes with paracetamol exposure when restricted to exposed only using propensity score matching dataset.

Number of prescriptions	PUB HR (95%CI)	Uncomplicated ulcers HR (95%CI)	Lower gastrointestinal bleed HR (95%CI)
1-2 prescriptions	1	1	1
3-4 prescriptions	1.00 (0.86, 1.16)	0.95 (0.80, 1,14)	1.08 (0.96, 1.20)
5-6 prescriptions	0.95 (0.80, 1.12)	0.88 (0.72, 1.08)	**1.14 (1.01, 1.28)**
7-8 prescriptions	1.14 (0.96, 1.37)	0.95 (0.76, 1.19)	0.99 (0.87, 1.14)
9 or more prescriptions	**1.24 (1.06, 1.44)**	1.13 (0.94, 1.36)	1.03 (0.92, 1.16)
	P > 0.01	P > 0.01	P > 0.01

PUB - perforation ulcer bleeding, HR - hazard ratio, CI - confidence interval, P - P for trend, and significant results are in bold.

However, the chance of developing a PUB or uncomplicated ulcer increased with every increase in the paracetamol prescription using MI/IPTW analysis described in Table 3.7. A similar trend was observed in Table 3.8, when the analysis was restricted to paracetamol exposed only group with P for trend <0.01.

Table 3.7. Dose-response relationship between paracetamol exposure and gastrointestinal outcomes using multiple imputations and inverse probability treatment weighted method.

Number of prescriptions	PUB HR (95%CI)	Uncomplicated ulcers HR (95%CI)	Lower gastro-intestinal bleed HR (95%CI)
Non-users	1	1	1
1-2 prescriptions	**1.15 (1.02, 1.30)**	1.12 (0.97, 1.30)	**1.35 (1.14, 1.61)**
3-4 prescriptions	**1.17 (1.05, 1.29)**	**1.14 (1.01, 1.30)**	**1.34 (1.25, 1.44)**
5-6 prescriptions	**1.22 (1.08, 1.37)**	**1.15 (1.00, 1.33)**	**1.44 (1.32, 1.56)**
7-8 prescriptions	**1.28 (1.11, 1.47)**	**1.20 (1.01, 1.42)**	**1.33 (1.21, 1.47)**
9 or more prescriptions	**1.44 (1.29, 1.60)**	**1.39 (1.22, 1.58)**	**1.37 (1.26, 1.48)**
	P < 0.01	P < 0.01	P > 0.01

PUB - perforation ulcer bleeding, HR - hazard ratio, CI - confidence interval, P - P for trend, and significant results are in bold.

Table 3.8. Dose-response relationship between paracetamol exposure and gastrointestinal outcomes when restricted to exposed only using multiple imputations and inverse probability treatment weighted method.

Number of prescriptions	PUB HR (95%CI)	Uncomplicated ulcers HR (95%CI)	Lower gastrointestinal bleed HR (95%CI)
1-2 prescriptions	1	1	1
3-4 prescriptions	1.01 (0.88, 1.16)	1.02 (0.87, 1.21)	0.99 (0.83, 1.19)
5-6 prescriptions	1.06 (0.91, 1.23)	1.03 (0.85, 1.23)	1.06 (0.88, 1.28)
7-8 prescriptions	1.11 (0.94, 1.31)	1.07 (0.87, 1.31)	0.98 (0.81, 1.20)
9 or more prescriptions	**1.25 (1.09, 1.45)**	**1.24 (1.05, 1.47)**	1.02 (0.85, 1.22)
	P < 0.01	P < 0.01	P > 0.01

PUB - perforation ulcer bleeding, HR - hazard ratio, CI - confidence interval, P - P for trend, and significant results are in bold.

3.8.1.5. Sensitivity analysis

A sensitivity analysis was performed by restricting the investigation only to OA participants. Overall, 115,387 participants had OA in the entire cohort (non-PS-matching dataset), and there were 48,812 (24,406 paracetamol exposed and 24,406 unexposed) participants in the PS-matched dataset. The incidence was significantly high for PUB, uncomplicated ulcers, and lower GI bleeding only in the non-PS-matched analysis (Model 1) for paracetamol exposure in the OA population. Table 3.9 further describes that the incidence of PUB and lower GI bleeding was high in the PS-matched model (Model 3) when the analysis was restricted to OA patients. However, the results were not statistically significant. In PS-matched analysis, the HR for uncomplicated showed no increased risk associated with uncomplicated and paracetamol exposure in the OA population. Although a modest risk was associated with paracetamol exposure and PUB in people with OA, it failed to reach statistical significance (HR 1.13; 95%CI 0.99, 1.29) in MI/IPTW analysis. There was a significantly increased incidence observed with lower GI bleeding (HR 1.20; 95%CI 1.09, 1.33) in paracetamol exposed compared to non-exposed in MI/IPTW dataset when restricted to the OA population (Model 5) (Table 3.9).

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Table 3.9. Sensitivity analysis for gastrointestinal outcomes between paracetamol exposed versus non-exposed groups restricted the analysis to only those with osteoarthritis.

Outcomes	Paracetamol-exposed	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)
PUB	No	1.00	1.00	1.00	1.00	1.00
	Yes	**1.22 (1.10, 1.35)**	0.93 (0.82, 1.06)	1.08 (0.94, 1.26)	1.07 (0.92, 1.24)	1.13 (0.99, 1.29)
Uncomplicated ulcers	No	1.00	1.00	1.00	1.00	1.00
	Yes	**1.15 (1.01, 1.30)**	0.86 (0.73, 1.00)	0.97 (0.81, 1.16)	0.95 (0.79, 1.14)	1.04 (0.89, 1.22)
Lower GI- bleed	No	1.00	1.00	1.00	1.00	1.00
	Yes	**1.29 (1.19, 1.39)**	1.00 (0.91, 1.10)	1.09 (0.98, 1.22)	1.05 (0.94, 1.18)	**1.20 (1.09, 1.33)**

Model 1- age, gender and practice matched, Model 2 - age, gender, and practice-matched and adjusted for other covariates, Model 3 - propensity score-matched, Model 4 - propensity score-matched with further adjustments for the variables that were still not balanced after propensity score matching, i.e. Charlson co-morbidity index, aspirin, H2-receptors, Model 5 - Multiple imputations and Inverse probability treatment weighted method, HR - hazard ratio, CI - confidence interval, PUB - perforation ulcer bleeding, GI - gastrointestinal, significant results are in bold.

3.8.2. Cohort description for cardiovascular adverse events

The age, gender, and practice-matched dataset with 582,961 participants were used for propensity score matching. The details of inclusion and exclusion are mentioned in section 3.8.1 (GI outcomes). Tables 3.10, 3.11 and 3.12 indicate that in the age-gender and practice matched dataset, there was a higher percentage of females (62%), people with OA (30%), people with hypertension (40%) and the users of aspirin (40%), statin (45%), opioids (70%) and NSAIDs (31%) were also more significant in the paracetamol exposed group compared to the unexposed group. Further, the PS-matching was modified according to each cardiovascular outcome, i.e. heart failure, myocardial infarction and hypertension, as stated in a cohort study by De-Vries et al. (2010). This results in three different PS-matched datasets. Tables 3.10, 3.11, and 3.12 summarise the participant characteristics for the non-PS matched and PS-matched datasets for heart failure, myocardial infarction, and hypertension.

In the PS-matched datasets, heart failure: 172,690 participants (86,345 exposed and 86,345 unexposed); myocardial infarction n=172,592 (86,296 exposed and 86,296 unexposed); hypertension: 174,438 participants (87,219 paracetamol exposed 87,219 paracetamol unexposed) as presented in Table 3.10, 3.11 and 3.13. Of note the percentage of opioid users was 97% in both groups (paracetamol exposed and non-exposed) in all the three cardiovascular datasets (heart failure, myocardial infarction, and hypertension).

Table 3.10. Participant characteristics in the age-gender practice matched dataset, and propensity score matching for heart failure.

Entire cohort (n=582,961)				PS-matched sample (n=172,690)		
Continuous variables, mean (S.D)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
age	74.88 (7.29)	74.99 (7.47)	-0.01	75.42 (7.51)	75.41 (7.75)	-0.02
Charlson's co-morbidity index	0.37(1.24)	0.21 (0.93)	0.14	0.53 (1.45)	0.36 (1.21)	0.02
Categorical covariates n (%)						
female	114,066 (63.20)	242,175(60.17)	0.06	108,057 (62.57)	107,063 (62.00)	0.06
Other Co-morbidities						
OA	55,038 (30.49)	60,349 (14.99)	0.37	49,789 (28.83)	48,690 (28.20)	0.01
hypertension	71,525 (39.63)	105,410 (26.19)	0.30	11,921 (6.90)	10,314 (5.97)	-0.02
hyper cholesterol	14,974 (8.30)	21,463 (5.33)	0.12	14,460 (8.37)	14,093 (8.16)	0.00
hyperthyroidism	3,304 (1.83)	4,418 (1.10)	0.06	3,136 (1.82)	3,034 (1.76)	0.00
BMI						
underweight	3,647 (2.02)	5,505 (1.37)	0.05	3,524 (2.04)	3,711 (2.15)	0.00
overweight	43,402 (24.02)	73,328 (18.22)	0.15	42,029 (24.34)	44,253 (25.63)	-0.02
obese	22,163 (12.28)	29,131 (7.24)	0.18	20,804 (12.05)	20,965 (12.14)	0.00
missing	64,148 (35.54)	208,224 (51.74)	-0.35	60,075 (34.79)	55,041 (31.87)	0.06
Smoking-status						
current	15,138 (8.39)	30,110 (7.48)	0.04	14,954 (8.66)	16,238 (9.40)	-0.02
ex-smoker	44,190 (24.48)	63,636 (15.81)	0.23	42,458 (24.59)	42,666 (24.71)	0.00
missing	32,468 (17.99)	168,282 (41.81)	-0.5	30,380 (17.59)	26,899 (15.58)	0.05
Alcohol						
current drinkers	79,661 (44.14)	144,373 (35.87)	0.18	77,733 (45.01)	82,314 (47.67)	-0.05
past drinkers	4,448 (2.46)	4,767 (1.18)	0.10	4,112 (2.38)	3,732 (2.16)	0.01
missing	57,999 (32.14)	198,151 (49.23)	-0.38	54,037 (31.29)	49,111 (28.44)	0.06

Entire cohort (n=582,961)				PS-matched sample (n=172,690)		
Categorical covariates, n (%)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
Other drug use						
opioids	178,328 (69.87)	76,896 (30.13)	2.76	76,878 (97.27)	76,878 (97.27)	0.00
NSAIDs	55,559 (30.78)	48,061 (11.94)	0.47	26,635 (33.70)	24,385 (30.85)	0.06
coxibs	10,077 (5.58)	5,965 (1.48)	0.22	5,208 (6.59)	3,621 (4.58)	0.09
aspirin	72,064 (39.93)	78,523 (19.51)	0.46	66,616 (38.58)	65,519 (37.94)	0.01
clopidogrel	10,183 (5.64)	7,658 (1.90)	0.20	4,073 (5.15)	2,983 (3.77)	0.07
dipyridamole	5,255(2.91)	4,947(1.23)	0.12	2,771 (3.51)	1,835 (2.32)	0.07
statins	81,769 (45.31)	103,570 (25.73)	0.04	76,631 (43.89)	76,423 (43.77)	0.00
antihypertensive	384 (0.21)	517 (0.13)	0.02	362 (0.21)	326 (0.19)	0.00
anticoagulants	3,309 (1.83)	3,391 (0.84)	0.09	3,073 (1.76)	2,756 (1.58)	0.01
diuretics	14,154 (7.84)	18,704 (4.65)	0.13	13,497 (7.82)	13,677 (7.92)	0.00
cardiac glycosides	3,234 (1.79)	3,976 (0.99)	0.07	3,043 (1.76)	2,909 (1.68)	0.01
nitrates	5,054 (2.80)	5,637 (1.40)	0.10	4,757 (2.75)	4,376 (2.53)	0.01
glucocorticoids	2,397 (1.33)	2,143 (0.53)	0.08	2,158 (1.24)	1,786 (1.02)	0.02

d - standardized difference, PS - propensity score, NSAIDs - non-steroidal anti-inflammatory drugs, SD - standard deviation, OA - osteoarthritis, BMI - body mass index.

Table 3.11. Participant characteristics in the age-gender practice matched dataset, and propensity score-matched for myocardial infarction.

Entire cohort (n=582,961)				**PS-matched sample (n=172,592)**		
Continuous variables, mean (S.D)	Paracetamol-exposed	Paracetamol-unexposed	*d*	Paracetamol-exposed	Paracetamol-unexposed	*d*
age	74.88 (7.29)	74.99 (7.47)	-0.01	75.89 (7.32)	75.08 (7.47)	-0.03
Charlson's co-morbidity index	1.60 (1.73)	0.95 (1.48)	0.41	1.55 (1.69)	1.56 (1.72)	0.00
Categorical covariates, n (%)						
female	114,066 (63.20)	242,175 (60.17)	0.06	108,235 (62.71)	107,112 (62.06)	0.02
Other Co-morbidities						
OA	55,038 (30.49)	60,349 (14.99)	0.37	49,717 (28.81)	48,508 (28.11)	0.01
hypertension	71,525 (39.63)	105,410 (26.19)	0.30	68,005 (39.40)	70,137 (40.64)	-0.03
hyper cholesterol	14,974 (8.30)	21,463 (5.33)	0.12	14,343 (8.31)	14,083 (8.16)	0.01
hyperthyroidism	3,304 (1.83)	4,418 (1.10)	0.06	3,113 (1.80)	2,926 (1.70)	0.01
BMI						
underweight	3,647 (2.02)	5,505 (1.37)	0.05	3,518 (2.04)	3,446 (2.00)	0.00
overweight	43,402 (24.02)	73,328 (18.22)	0.15	41,999 (24.33)	45,116 (26.14)	-0.04
obese	22,163 (12.28)	29,131 (7.24)	0.18	20,868 (12.09)	21,176 (12.27)	0.01
missing	64,148 (35.54)	208,224 (51.74)	-0.35	60,374 (34.98)	53,868 (31.21)	0.08
Smoking-status						
current	15,138 (8.39)	30,110 (7.48)	0.04	14,887 (8.63)	16,238 (9.41)	-0.02
ex-smoker	44,190 (24.48)	63,636 (15.81)	0.23	42,126 (24.41)	42,467 (24.61)	0.00
missing	32,468 (17.99)	168,282 (41.81)	-0.57	30,375 (17.60)	26,253 (15.21)	0.06

Entire cohort (n=582,961)				PS-matched sample (n=172,592)		
Categorical covariates, n (%)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
Alcohol						
current drinkers	79,661 (44.14)	144,373 (35.87)	0.18	77,658 (45.00)	83,640 (48.46)	-0.07
past drinkers	4,448 (2.46)	4,767 (1.18)	0.10	4,073 (2.36)	3,578 (2.07)	0.02
missing	57,999 (32.14)	198,151 (49.23)	-0.38	54,185 (31.39)	47,726 (27.65)	0.08
Other drug use						
opioids	178,328 (69.87)	76,896 (30.13)	2.76	76,878 (97.27)	76,878 (97.27)	0.00
NSAIDs	55,559 (30.78)	48,061 (11.94)	0.47	26,635 (33.70)	24,385 (30.85)	0.06
coxibs	10,077 (5.58)	5,965 (1.48)	0.22	5,208 (6.59)	3,621 (4.58)	0.09
aspirin	72,064 (39.93)	78,523 (19.51)	0.47	66,772 (38.69)	65,582 (38.00)	0.02
clopidogrel	10,183 (5.64)	7,658 (1.90)	0.20	4,073 (5.15)	2,983 (3.77)	0.07
dipyridamole	5,255 (2.91)	4,947 (1.23)	0.12	2,771 (3.51)	1,835 (2.32)	0.07
statin users	81,769 (45.31)	103,570 (25.73)	0.41	75,894 (43.97)	75,526 (43.76)	0.01
anticoagulants	3,309 (1.83)	3,391 (0.84)	0.09	3,073 (1.76)	2,756 (1.58)	0.01
antihypertensive	384 (0.21)	517 (0.13)	0.02	362 (0.21)	326 (0.19)	0.00
diuretics	14,154 (7.84)	18,704 (4.65)	0.14	13,295 (7.70)	13,358 (7.74)	0.00
cardiac glycosides	3,234 (1.79)	3,976 (0.99)	0.07	2,999 (1.74)	2,912 (1.69)	0.00
nitrates	5,054 (2.80)	5,637 (1.40)	0.10	4,693 (2.72)	4,337 (2.51)	0.01
glucocorticoids	2,397 (1.33)	2,143 (0.53)	0.08	2,108 (1.22)	1,780 (1.03)	0.02

d - Standardized difference, PS - propensity score, NSAIDs - non-steroidal anti-inflammatory drugs, SD - standard deviation, OA - osteoarthritis, BMI - body mass index.

Table 3.12. Participant characteristics in the age-gender practice matched dataset, and propensity score-matched for hypertension.

Entire cohort (n=582,961)				**PS-matched sample (n=174,438)**		
Continuous variables, mean (S.D)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
age	74.88 (7.29)	74.99 (7.47)	-0.01	75.88 (7.32)	75.04 (7.43)	-0.02
Charlson's co-morbidity index	0.37 (1.24)	0.21 (0.93)	0.14	0.37 (1.24)	0.35 (1.17)	0.02
Categorical covariates, n (%)						
female	114,066 (63.20)	242,175 (60.17)	0.06	109,159 (62.58)	108,352 (62.11)	0.01
Other Co-morbidities						
OA	55,038 (30.49)	60,349 (14.99)	0.37	50,269 (28.82)	49,173 (28.19)	0.01
hyper cholesterol	14,974 (8.39)	21,463 (5.38)	0.11	14,420 (8.27)	14,322 (8.21)	0.00
hyperthyroidism	3,304 (1.85)	4,418 (1.11)	0.06	3,192 (1.83)	3,081 (1.77)	0.00
BMI						
underweight	3,647 (2.02)	5,505 (1.37)	0.05	3,514 (2.03)	3,586 (2.06)	0.00
overweight	43,402 (24.02)	73,328 (18.22)	0.14	42,060 (24.11)	44,094 (25.28)	-0.02
obese	22,163 (12.28)	29,131 (7.24)	0.17	21,125 (12.11)	21,367 (12.25)	0.00
missing	64,148 (35.54)	208,224 (51.74)	-0.33	62,081 (35.59)	57,217 (32.80)	0.06
Smoking-status						
current	15,138 (8.39)	30,110 (7.48)	0.03	14,982 (8.59)	15,989 (9.17)	-0.02
ex-smoker	44,190 (24.48)	63,636 (15.81)	0.22	42,821 (24.55)	43,179 (24.75)	0.00
missing	32,468 (17.99)	168,282 (41.81)	-0.54	32,466 (18.61)	28,908 (16.57)	0.05

Entire cohort (n=582,961)				PS-matched sample (n=174,438)		
Categorical covariates, n (%)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
Alcohol						
current drinkers	79,661 (44.14)	144,373 (35.87)	0.17	77,724 (44.56)	82,212 (47.13)	-0.05
past drinkers	4,448 (2.46)	4,767 (1.18)	0.09	4,197 (2.41)	3,774 (2.16)	0.02
missing	57,999 (32.14)	198,151 (49.23)	-0.35	55,657 (31.91)	50,879 (29.17)	0.06
Other drug use						
opioids	178,328 (69.87)	76,896 (30.13)	2.76	76,878 (97.27)	76,878 (97.27)	0.00
NSAIDs	55,559 (30.78)	48,061 (11.94)	0.47	26,635 (33.70)	24,385 (30.85)	0.06
coxibs	10,077 (5.58)	5,965 (1.48)	0.22	5,208 (6.59)	3,621 (4.58)	0.09
aspirin	72,064 (39.93)	78,523 (19.51)	0.46	66,382 (38.05)	65,609 (37.61)	0.01
clopidogrel	10,183 (5.64)	7,658 (1.90)	0.20	4,073 (5.15)	2,983 (3.77)	0.07
dipyridamole	5,255 (2.91)	4,947(1.23)	0.12	2,771 (3.51)	1,835 (2.32)	0.07
statin	81,769 (45.31)	103,570 (25.73)	0.42	76,599 (43.91)	76,355 (43.77)	0.00
anticoagulants	3,309 (1.83)	3,391 (0.84)	0.09	3,073 (1.76)	2,756 (1.58)	0.01
diuretics	14,154 (7.84)	18,704 (4.65)	0.13	13,443 (7.71)	13,766 (7.89)	0.00
cardiac glycosides	3,234 (1.79)	3,976 (0.99)	0.06	3,087 (1.77)	2,949 (1.69)	0.00
nitrates	5,054 (2.80)	5,637 (1.40)	0.10	4,761 (2.73)	4,400 (2.52)	0.01
glucocorticoids	2,397 (1.33)	2,143 (0.53)	0.08	2,153 (1.23)	1,814 (1.04)	0.02

d - Standardized difference, PS - propensity score, NSAIDs - non-steroidal anti-inflammatory drugs, SD - standard deviation, OA - osteoarthritis, BMI - body mass index.

3.8.2.1. Assumptions of Cox-model

Figure 3.10 shows that the PH assumption was met as the log-log plots look roughly parallel for hypertension, myocardial infarction, and heart failure. This was in line with the Schoenfeld statistical test presented in Table 3.13, suggesting that the PH assumption was not violated for all the cardiovascular outcomes.

Table 3.13. A global test for proportional hazards assumption.

Outcome	P-value (Schoenfeld) Before PS-matching	After PS-matching
Heart Failure	0.68	0.39
Myocardial Infarction	0.52	0.30
Hypertension	0.54	0.28

PS - propensity score matching.

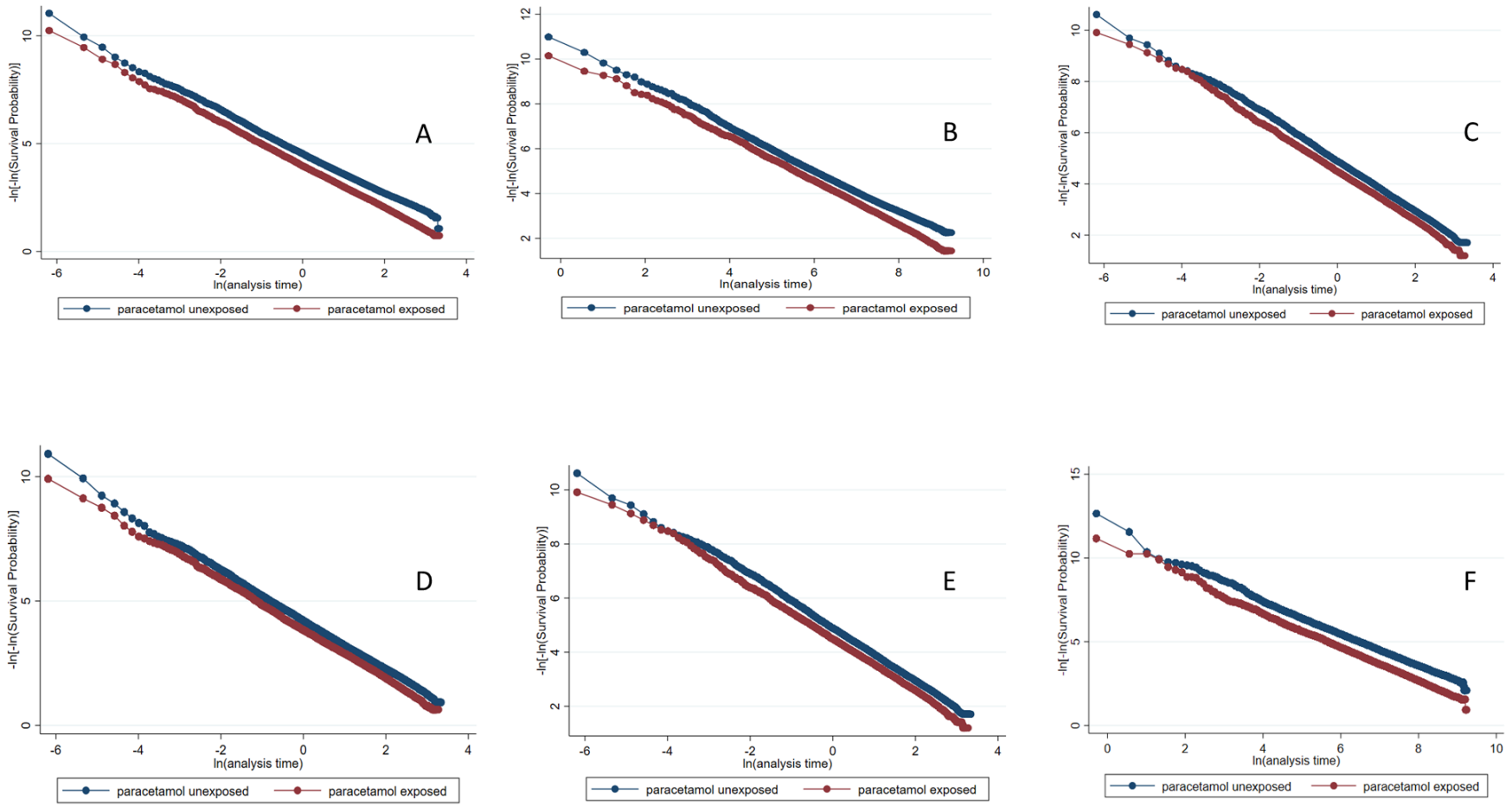


Figure 3.10. Log-log plots before PS-matching for outcomes of heart failure (image A), myocardial infarction (image B) and hypertension (image C) and after PS-matching for heart failure (image D), myocardial infarction (image E) and hypertension (image F). All the figures show lines parallel to each other and not crossing, which means that the proportional hazard assumption was not violated.

3.8.2.2. Kaplan Meier (Nelson-Aelon) for cardiovascular outcomes

The Nelson-Aelon cumulative hazard estimates for heart failure, myocardial infarction, and hypertension were higher in the paracetamol exposed than the unexposed group before PS-matching, as depicted in Figure 3.11 and after matching in Figure 3.11.

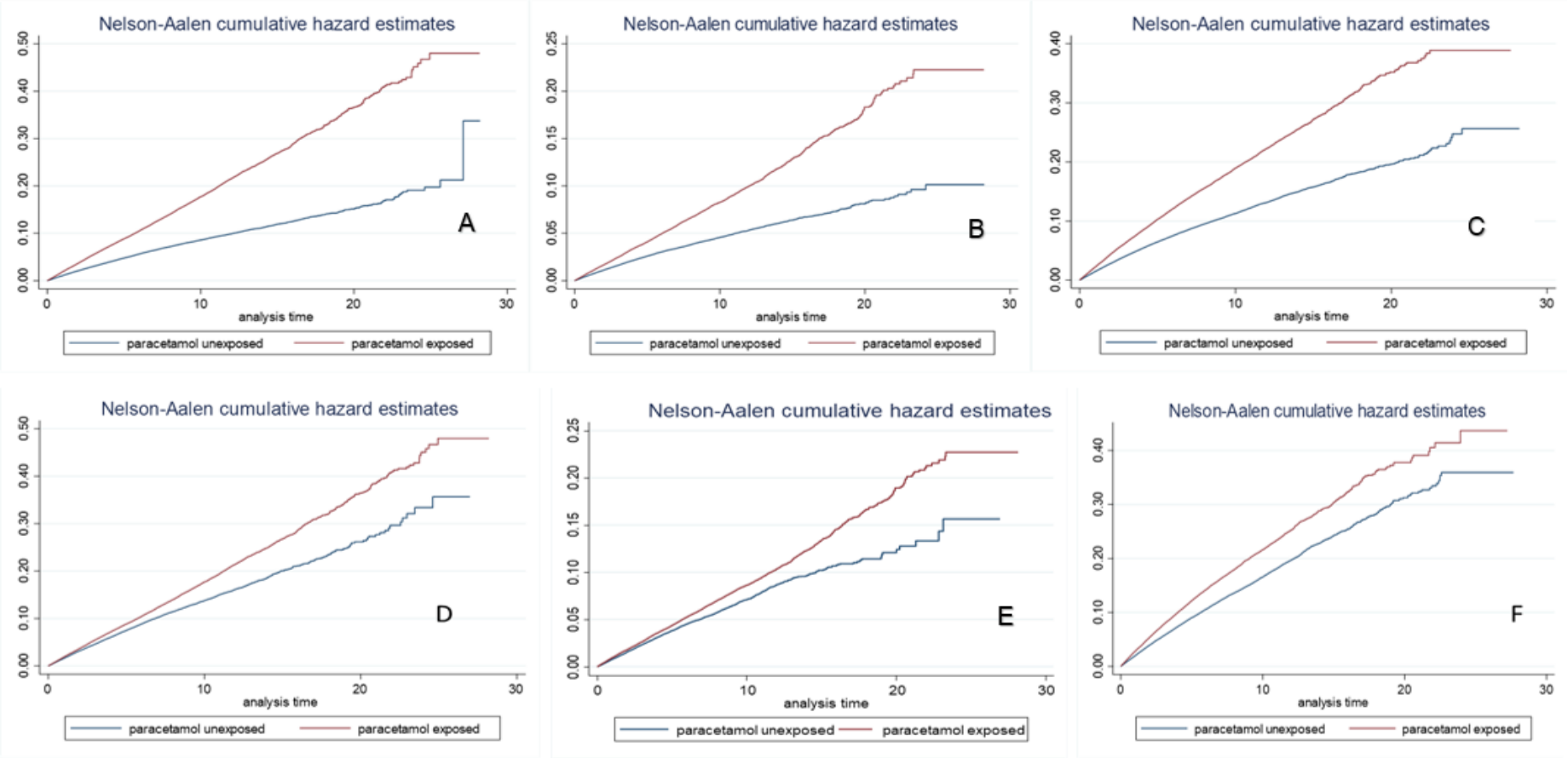


Figure 3.11 Cumulative hazards estimates before PS-matching for heart failure, myocardial infarction, and hypertension (image A, image B, and image C, respectively) and cumulative hazards estimates after PS-matching for heart failure, myocardial infarction, and hypertension (image D, image E and image F, respectively). The red line represents the paracetamol exposure group and shows higher hazards for heart failure, myocardial infarction, and hypertension than the unexposed group (represented by the blue line).

3.8.2.3. Incidence of cardiovascular adverse effects

In the unadjusted non-PS matched (model 1) in Table 3.14, there was an increased incidence of heart failure, MI, and hypertension in those exposed to paracetamol than unexposed (HR 1.98; 95%CI 1.93, HR 2.03, 1.73; 95%CI 1.67, 1.79 and HR 1.62; 95%CI 1.59, 1.66 respectively). After conventional adjustment of other covariates (model 2), the HR was lower than the unadjusted model shown in Table 3.14 for the paracetamol exposed group than the unexposed group for heart failure, MI, and hypertension with HRs of 1.40 (95%CI 1.37, 1.44), 1.12 (95%CI 1.09, 1.17) and 1.19 (95%CI 1.16, 1.22) respectively.

A Kernel Density plot for covariate adjustment indicated that both groups were still unbalanced before PS-matching, given in Figure 3.12. Three different propensity score models depending on each cardiovascular outcome, as explained in section 3.6.2, were conducted to balance the baseline characteristics between paracetamol exposed and unexposed for heart failure, myocardial infarction, and hypertension. Figure 3.13 shows that the Kernel density plots for the PS-matched sample become similar, suggesting that matching the estimated propensity score balanced the baseline covariates.

The results from PS matched (model 3) analysis suggested hazards were significantly higher in the paracetamol exposed than unexposed for heart failure (HR 1.24; 95%CI 1.20, 1.27), myocardial infarction (HR 1.04; 95%CI 1.00, 1.09) and hypertension (HR 1.10; 95%CI 1.07, 1.13). A *d* was also calculated to check the balance between both groups. After the PS-matching, the *d* for all the cardiovascular events was less than 0.1, as shown in Tables 3.10, 3.11 and 3.12. Therefore, no further adjustments were required. However, the PS-matching model dropped 408,378, 408428 and 410,271 participants for heart failure, myocardial infarction, and hypertension. Therefore, multiple imputations were conducted to account for missingness, followed by IPTW to make both groups clinically comparable. Table 3.14 illustrates increased heart failure and hypertension incidence in those exposed to paracetamol compared to the unexposed (HR 1.09; 95%CI 1.06, 1.13 and HR 1.07; 95%CI 1.04 1.11, respectively) for MI/IPTW dataset analysis (model 4). There was no increased risk associated with paracetamol exposure and myocardial infarction model 4 analysis, and the HR lacked statistical significance.

The unadjusted absolute risk was highest for hypertension (6.71%), heart failure (6.49%), and myocardial infarction (3.10%) in the paracetamol-exposed group versus the unexposed group (unadjusted absolute risk 4.49%, 3.59%, and 1.87%, respectively. The number needed to harm was 33 (95%CI 32, 34) for heart failure, 81 (95%CI 76, 87) for myocardial infarction, and 45 (95%CI 43, 48) for hypertension. This indicated that an average of 33, 81, and 45 people would have to be exposed to paracetamol for one additional patient to have heart failure, myocardial infarction, and hypertension, respectively. It was also observed that 47%, 39%, and 32% of heart failure, myocardial infarction and hypertension were attributable to paracetamol exposure.

According to unadjusted PAF, if paracetamol exposure is eliminated, there might be a 21%, 17%, and 13% reduction in the risk for heart failure, myocardial infarction, and hypertension in the entire population.

Table 3.14. Incidence of cardiovascular outcomes between the paracetamol exposed versus paracetamol non-exposed groups.

Outcomes	Paracetamol-exposed	Event rate (95%CI)/ 1,000 person-years (before matching)	Event rate (95%CI)/ 1,000 person-years (After matching)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)
Heart failure	No	24.67	40.94	1.00	1.00	1.00	1.00
	Yes	48.97	49.52	**1.98 (1.93, 2.03)**	**1.40 (1.37, 1.44)**	**1.24 (1.20, 1.27)**	**1.09 (1.06, 1.13)**
Myocardial Infarction	No	13.23	23.00	1.00	1.00	1.00	1.00
	Yes	22.95	23.13	**1.73 (1.67, 1.79)**	**1.12 (1.09, 1.17)**	**1.04 (1.00, 1.09)**	0.99 (0.94, 1.04)
Hypertension	No	33.20	50.16	1.00	1.00	1.00	1.00
	Yes	54.23	54.57	**1.62 (1.59, 1.66)**	**1.19 (1.16, 1.22)**	**1.10 (1.07, 1.13)**	**1.07 (1.04, 1.11)**

Model 1 - age, gender and practice matched, Model 2 - age, gender and practice matched and adjusted for other covariates Model 3 - propensity score-match, Model 4 - multiple imputations and inverse probability treatment weighted method, CI - confidence interval, HR - hazard ratio.

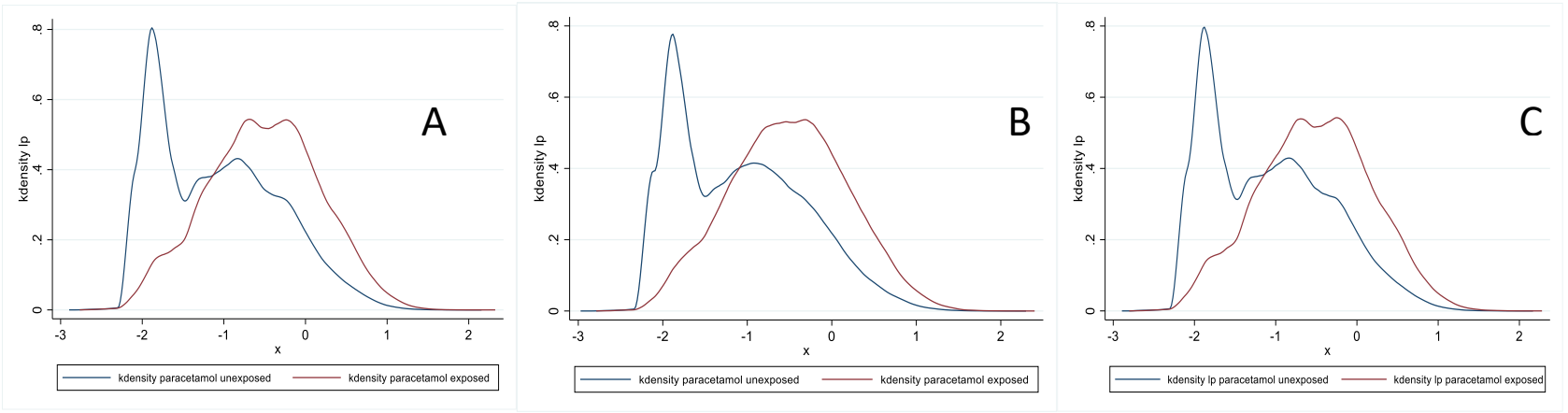


Figure 3.12. Kernel density plot presenting covariate balance between the exposed and unexposed to paracetamol before propensity score matching for heart failure (A), myocardial infarction (B) and hypertension (C). The distribution of covariates varies over the treatment levels (the red line represents the paracetamol exposure group, and the blue represents the unexposed group).

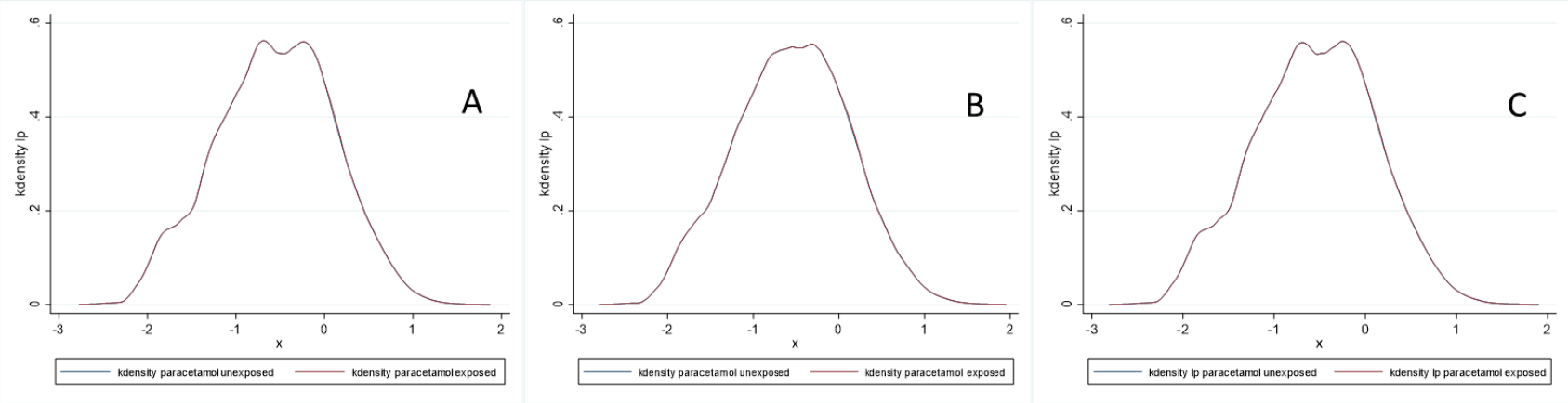


Figure 3.13. Kernel density plot presenting covariate balance between the exposed and unexposed to paracetamol after propensity score matching for heart failure (A), myocardial infarction (B) and hypertension (C). The distribution of covariates varies over the treatment levels. The Kernel density plot was indistinguishable as the red line representing the exposed group overlaps the blue line representing the unexposed group.

3.8.2.4. Dose-response

Tables 3.15 and 3.17 show no dose-response regarding heart failure, myocardial infarction, or hypertension in propensity score-matched analysis and MI/IPTW analysis. When the analysis was restricted to the exposed-only group, still there was no trend apparent, as shown in Tables 3.16 and 3.18.

Table 3.15. Dose-response for cardiovascular outcomes with paracetamol exposure versus unexposed: using propensity score matching dataset.

Number of prescriptions	Heart Failure HR (95%CI)	Myocardial infarction HR (95%CI)	HR (95%CI) hypertension
Non-users	1	1	1
1-2 prescriptions	**1.13 (1.07, 1.18)**	0.95 (0.90, 1.02)	**1.09 (1.05, 1.15)**
3-4 prescriptions	**1.20 (1.15, 1.25)**	1.03 (0.97, 1.10)	**1.21 (1.17, 1.26)**
5-6 prescriptions	**1.33 (1.26, 1.39)**	**1.10 (1.02, 1.17)**	**1.19 (1.14, 1.25)**
7-8 prescriptions	**1.31 (1.24, 1.38)**	1.06 (0.98, 1.15)	**1.17 (1.11, 1.23)**
9 or more prescriptions	**1.41 (1.35, 1.48)**	**1.08 (1.02, 1.16)**	0.98 (0.93, 1.02)
	P > 0.01	P > 0.01	P > 0.01

HR - hazard ratio, CI - confidence interval, P - P for trend, and significant values are in bold.

Table 3.16. Dose-response for cardiovascular outcomes with paracetamol exposure versus unexposed: using propensity score matching dataset when restricting population to paracetamol exposed only.

Number of prescriptions	Heart Failure HR (95%CI)	HR (95%CI) Myocardial infarction	HR (95%CI) hypertension
1-2 prescriptions	1	1	1
3-4 prescriptions	**1.06 (1.00, 1.12)**	1.08 (0.99, 1.17)	**1.11 (1.05, 1.17)**
5-6 prescriptions	**1.17 (1.10, 1.24)**	**1.14 (1.05, 1.26)**	**1.09 (1.03, 1.15)**
7-8 prescriptions	**1.16 (1.08, 1.24)**	**1.12 (1.01, 1.23)**	**1.07 (1.00, 1.14)**
9 or more prescriptions	**1.26 (1.19, 1.33)**	**1.14 (1.05, 1.24)**	0.89 (0.84, 0.95)
	P > 0.01	P > 0.01	P > 0.01

HR - hazard ratio, CI - confidence interval, P - P for trend, and significant values are in bold.

Table 3.17. Dose-response for cardiovascular outcomes with paracetamol exposure versus unexposed: using multiple imputations and inverse propensity treatment weighted dataset.

Number of prescriptions	Heart Failure HR (95%CI)	Myocardial infarction HR (95%CI)	HR (95%CI) hypertension
Non-users	1	1	1
1-2 prescriptions	1.01 (0.95, 1.07)	0.94 (0.86, 1.03)	**1.08 (1.02, 1.14)**
3-4 prescriptions	1.01 (0.96, 1.07)	0.97 (0.90, 1.04)	**1.13 (1.08, 1.18)**
5-6 prescriptions	**1.13 (1.07, 1.21)**	1.03 (0.94, 1.12)	**1.11 (1.05, 1.18)**
7-8 prescriptions	**1.10 (1.02, 1.19)**	1.03 (0.93, 1.14)	**1.10 (1.03, 1.18)**
9 or more prescriptions	**1.25 (1.18, 1.32)**	1.01 (0.93, 1.09)	0.95 (0.90, 1.00)
	P > 0.01	P > 0.01	P > 0.01

HR - hazard ratio, CI - confidence interval, p - p for trend, and significant results are in bold.

Table 3.18. Dose-response for cardiovascular outcomes with paracetamol exposure versus unexposed: using multiple imputations and inverse propensity treatment weighted dataset when restricting population to paracetamol exposed only.

Number of prescriptions	Heart Failure HR (95%CI)	HR (95%CI) Myocardial infarction	HR (95%CI) hypertension
1-2 prescriptions	1	1	1
3-4 prescriptions	1.00 (0.93, 1.08)	1.03 (0.93, 1.14)	1.05 (0.98, 1.12)
5-6 prescriptions	**1.12 (1.04, 1.22)**	1.09 (0.98, 1.22)	1.03 (0.96, 1.11)
7-8 prescriptions	**1.09 (1.00, 1.19)**	1.09 (0.97, 1.24)	1.02 (0.94, 1.10)
9 or more prescriptions	**1.24 (1.15, 1.34)**	1.08 (0.97, 1.20)	0.87 (0.81, 1.00)
	P > 0.01	P > 0.01	P > 0.01

HR - hazard ratio, CI - confidence interval, P - P for trend, and significant results are in bold.

3.8.2.5. Sensitivity analysis

Paracetamol is the most prescribed medication for the OA subpopulation. Therefore, a sensitivity analysis was performed only on individuals having this condition. Table 3.19 suggested an increased risk associated with paracetamol exposure and heart failure in models 1, 2 and 3 but not for model 4.

Table 3.19 illustrates that the estimates from models 1, 2, 3 and 4 showed no increased incidence of myocardial infarction and hypertension in the paracetamol exposed group when the analysis was restricted only to participants with OA. However, there was a significantly increased risk of hypertension among those exposed to paracetamol in the MI/IPTW dataset (model 4) than the unexposed (HR 1.06, 95%1.00, 1.13) when the analysis was restricted to only the OA population.

Table 3.19. Sensitivity analysis for cardiovascular outcomes between paracetamol exposed versus paracetamol non-exposed groups when restricting the analysis to only the osteoarthritis population.

Outcomes	Paracetamol-exposed	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)
Heart failure	No	1.00	1.00	1.00	1.00
	Yes	**1.08 (1.03, 1.14)**	**1.06 (1.00, 1.11)**	**1.07 (1.02, 1.13)**	0.98 (0.92, 1.04)
Myocardial Infarction	No	1.00	1.00	1.00	1.00
	Yes	1.00 (0.93, 1.07)	0.96 (0.90, 1.03)	0.96 (0.88, 1.03)	0.82 (0.75, 1.04)
Hypertension	No	1.00	1.00	1.00	1.00
	Yes	0.96 (0.91, 1.01)	0.97 (0.93, 1.02)	0.99 (0.94, 1.05)	**1.06 (1.00, 1.13)**

Model 1 - age, gender and practice matched, Model 2 - age, gender and practice-matched and adjusted for other covariates, Model 3 - propensity score-matched, Model 4 - multiple imputations and Inverse probability treatment weighted method, HR - hazard ratio, CI - confidence interval, significant results are in bold.

3.8.3. Chronic renal failure

The original cohort comprised 582,961 participants, with 63% females, 30% having OA, and 40% having hypertension in the paracetamol exposed group. Table 3.20 illustrates that 98% and 31% in the paracetamol exposed group also received co-prescription of opioids and NSAIDs. 158,336 were successfully matched using propensity score, comprising (79,168 exposed and 79,168 unexposed groups.

Table 3.20. Participant characteristics in the age-gender practice matched dataset, and the propensity score-matched for chronic renal failure.

Entire cohort (n=582,961)				PS-matched sample (n=158,336)		
Continuous variables, mean (S.D)	**Paracetamol-exposed**	**Paracetamol-unexposed**	**d**	**Paracetamol-exposed**	**Paracetamol-unexposed**	**d**
Age	74.88 (7.29)	74.99 (7.47)	-0.01	75.52 (7.61)	75.41 (7.76)	-0.03
Charlson's Co-Morbidity Index	0.43 (1.24)	0.24 (0.93)	0.15	0.48 (1.29)	0.33 (1.10)	**0.13**
Categorical covariates, n (%)						
female	114,066 (63.20)	242,175 (60.17)	0.06	46,680 (60.56)	49,016 (63.59)	-0.17
Other Co-morbidities						
OA	55,038 (30.49)	60,349 (14.99)	0.37	27,009 (35.04)	23,755 (30.82)	0.07
hypertension	71,693 (39.65)	105,645 (26.20)	0.29	33,143 (43.00)	30,296 (39.30)	0.08
hyper cholesterol	14,974 (8.30)	21,463 (5.33)	0.12	14,343 (8.31)	14,083 (8.16)	0.01
hyperthyroidism	3,304 (1.83)	4,418 (1.10)	0.06	3,113 (1.80)	2,926 (1.70)	0.01
BMI						
underweight	3,647 (2.02)	5,505 (1.37)	0.05	2,253 (2.92)	1,624 (2.11)	0.05
overweight	43,402 (24.02)	73,328 (18.22)	0.14	19,675 (25.52)	20,026 (25.98)	-0.01
obese	22,163 (12.28)	29,131 (7.24)	0.17	10,834 (14.05)	9,763 (12.67)	0.04
missing	64,148 (35.54)	208,224(51.74)	-0.33	21,155 (27.44)	23,669 (30.71)	-0.07
Smoking-Status						
current	15,138 (8.39)	30,110 (7.48)	0.03	8,433 (10.94)	8,245 9(10.70)	0.01
ex-smoker	44,190 (24.48)	63,636 (15.81)	0.21	21,975 (28.51)	18,357 (23.81)	**0.11**
missing	32,468 (17.99)	168,282 (41.81)	-0.54	9,800 (12.71)	12,686 (16.46)	-0.10

Entire cohort (n=582,961)				PS-matched sample (n=158,336)		
Categorical covariates, n (%)	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***	**Paracetamol-exposed**	**Paracetamol-unexposed**	***d***
Alcohol						
current drinkers	79,661 (44.14)	144,373(35.87)	0.17	37,939 (49.22)	38,177 (49.53)	-0.06
past drinkers	4,448 (2.46)	4,767(1.18)	0.09	2,179 (2.83)	1,490 (1.93)	0.06
missing	57,999 (32.14)	198,151 (49.23)	-0.35	18,731 (24.30)	20,916 (27.13Z	-0.06
Other Drug Use						
opioids	178,664 (98.81)	77,033 (19.11)	2.76	77,016 (99.91)	77,016 (99.91)	0
NSAIDs	55,659 (30.78)	48,139 (11.94)	0.47	27,191 (35.27)	24,429 (31.69)	0.08
coxibs	10,102 (5.59)	5,970 (1.48)	0.22	5,060 (6.56)	3,617 (4.69)	0.08
aspirin	72,064(39.93)	78,523 (19.51)	0.47	66,772 (38.69)	65,582 (38.00)	0.02
clopidogrel	10,183 (5.64)	7,658 (1.90)	0.20	4,073 (5.15)	2,983 (3.77)	0.07
dipyridamole	5,255 (2.91)	4,947 (1.23)	0.12	2,771 (3.51)	1,835 (2.32)	0.07
statin users	81,769 (45.31)	103,570 (25.73)	0.41	75,894 (43.97)	75,526 (43.76)	0.01
amino salicylates	370 (0.20)	379 (0.09)	0.46	251 (0.33)	202 (0.26)	0.01
diuretics	14,154 (7.84)	18,704 (4.65)	0.13	8,791 (11.40)	7,026 (9.11)	0.08
antibacterial	16,766 (9.27)	23,104 (5.73)	0.13	10,415 (13.51)	8,609 (11.17)	0.07
nitrates	5,066 (2.80)	5,645 (1.40)	0.10	3,324 (4.31)	2,320 (3.01)	0.07
glucocorticoids	2,403 (1.33)	2,144 (0.53)	0.08	1,742 (2.26)	1,187 (1.54)	0.05
antihypertensive	384 (0.21)	517 (0.13)	0.02	275 (0.36)	180 (0.23)	0.02
hypnotics	7,072 (3.91)	6,816 (1.69)	0.13	4,514 (5.86)	3,108 (4.03)	0.08
anxiolytics	362 (0.20)	394 (0.10)	0.03	260 (0.34)	181 (0.23)	0.01

d - Standardized difference, PS - propensity score, NSAIDs - non-steroidal anti-inflammatory drugs, SD - standard deviation, OA - osteoarthritis, BMI - body mass index.

3.8.3.1. Assumptions of cox proportional hazards for chronic renal failure

A visual inspection of the log-log plots for paracetamol exposure and the unexposed group appeared parallel, as presented in Figure 3.14 (image A - before PS-matching and B - after PS-matching), indicating that the proportional hazard assumption was satisfied. The findings from the global statistical test given in Table 3.21 are in line with these assumptions. There was no evidence (P-value not significant) to reject the hypothesis of proportional hazards for paracetamol exposed.

Table 3.21. A global test for proportional hazards assumption for chronic renal impairment.

Outcome	P-value (Schoenfeld) Before PS-matching	After PS-matching
Chronic renal failure	0.94	0.47

PS - propensity score matching.

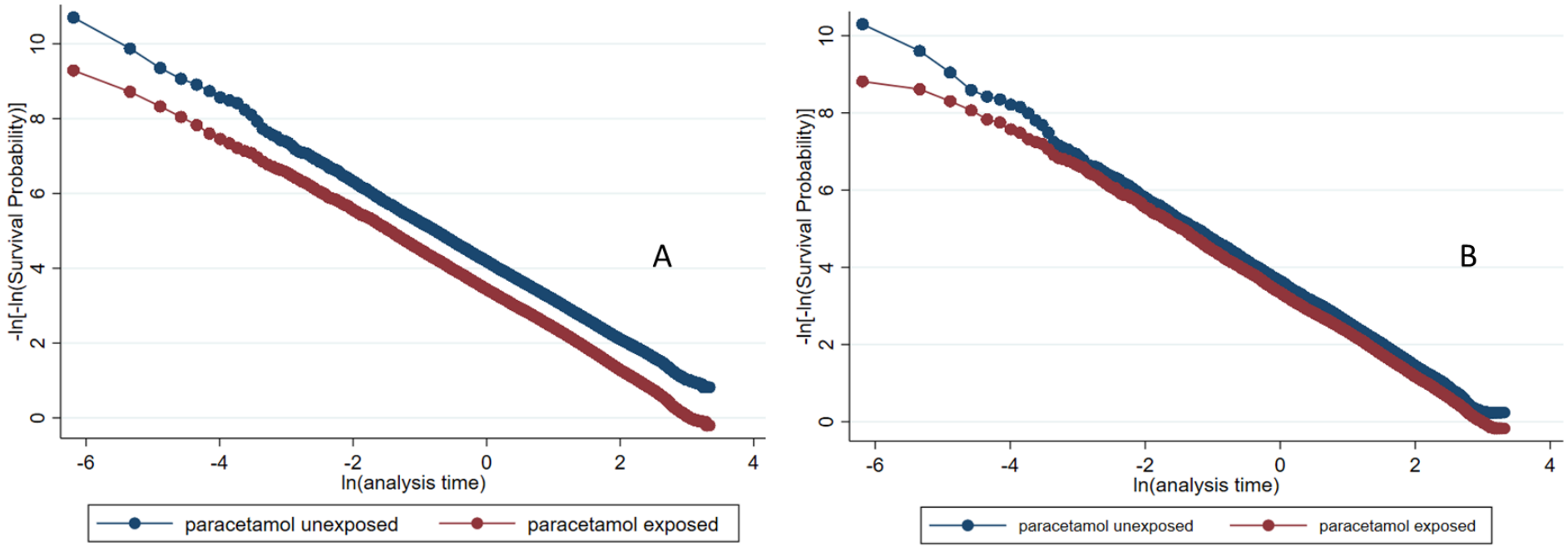


Figure 3.14. Log-log plots before PS-matching (A) and after PS-matching (B) for chronic renal failure. All the Figures show lines parallel to each other and not crossing, which means that the proportional hazard assumption was not violated.

3.8.3.2. Kaplan Meier survival curves (Nelson-Aelon) for chronic renal impairment

Figure 3.15 shows that the Nelson-Aelon cumulative hazard estimates for paracetamol exposure were higher than in the unexposed group for chronic renal impairment in both before PS-matching (A) and after PS-matching (B) dataset analysis.

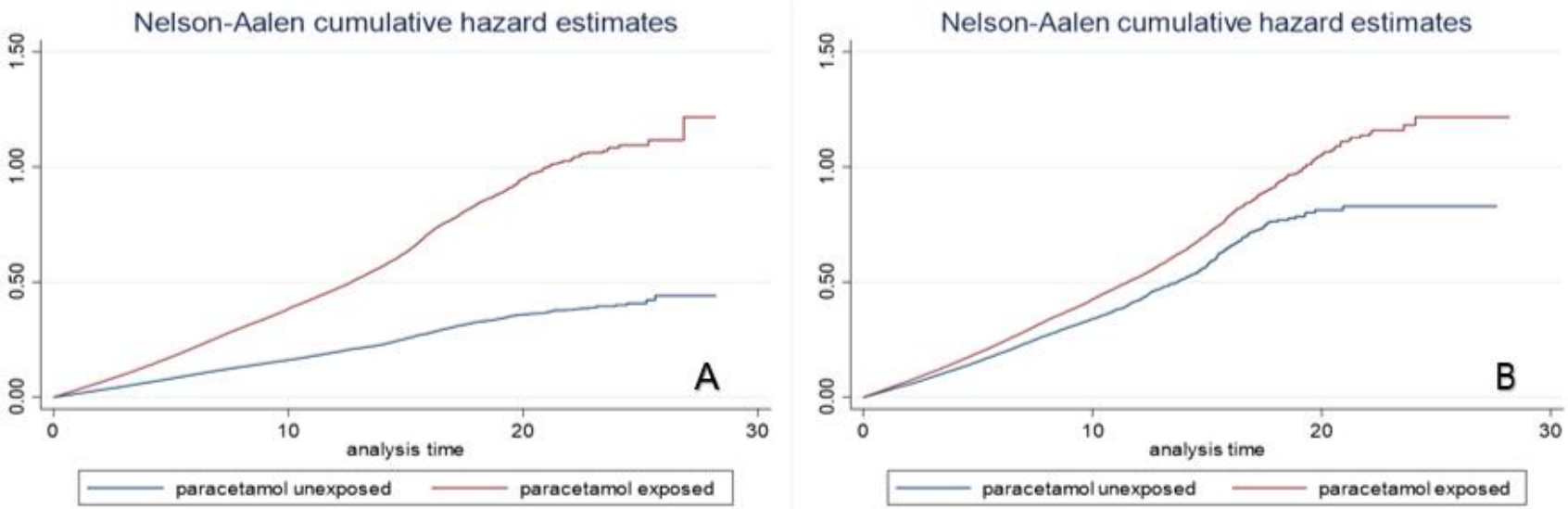


Figure 3.15. Cumulative hazards estimate paracetamol exposure compared to the unexposed group before PS-matching image (A) and after PS-matching image (B) for chronic renal impairment. The red line represents the paracetamol exposure group with higher hazards for chronic renal impairment than the unexposed group (represented by the blue line).

3.8.3.3. Incidence of Chronic renal disease adverse effects

Table 3.22 shows HRs from Model 1: The unadjusted non-PS-matched analysis obtained using the standard Cox model indicated that the incidence of chronic renal failure was two folds higher in the paracetamol group than in the unexposed (HR 2.29; 95%CI 2.25, 2.33). This incidence decreased after conventional adjustment for other covariates using the multivariable Cox model with a HR of 1.09 (95%CI 1.06, 1.12).

The Kernel density plot in Figure 3.16 suggested that the baseline covariates were not balanced in both groups after conventional adjustment for other covariates. The standardised mean difference was >0.1 for a few covariates, as detailed in Table 3.20, indicating an imbalance between the covariates in both groups. Therefore, a PS-matched analysis was performed to balance both groups. In the PS-matched model 3, an increased incidence was still observed for chronic renal failure in the paracetamol exposed with HR of 1.31 (95%CI 1.27, 1.35) compared to the unexposed group. Although the Kernel density plot in Figure 3.17 showed that both groups appeared to be in clinical equipoise on visual inspection, the standardised mean difference for CCI and ex-smoker was still >0.10 as given in Table 3.20, suggesting that it was still not balanced. Therefore, model 4 analysis was performed, including further adjustment for these two variables. According to model 4 analysis after further adjustment, the HR for chronic renal failure was still high in the paracetamol exposed group than the unexposed for chronic renal failure (HR 1.22; 95%CI 1.18, 1.25).

The unadjusted absolute risk calculated one year from the landmark date in the paracetamol-exposed group for chronic renal failure was 12.43% compared to 6% in the unexposed in the whole population. For every 16 people prescribed paracetamol, one additional chronic renal failure could be expected with NNH 16 (95%CI 15, 16). Moreover, 49% of the chronic renal failure cases were attributable to paracetamol exposure. According to unadjusted PAF, 23% of chronic renal failure cases could be reduced if paracetamol exposure were eliminated in the entire population.

Table 3.22. Incidence of chronic renal failure between paracetamol exposed versus paracetamol non-exposed groups.

Outcomes	Paracetamol-exposed	Event rate (95%CI)/ 1,000 person-years (before matching)	Event rate (95%CI)/ 1,000 person-years (After matching)	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 MI/IPTW
Chronic renal	No	16.24	30.77	1.00	1.00	1.00	1.00	1.00
failure	Yes	37.08	40.90	**2.29 (2.25, 2.33)**	**1.09 (1.06, 1.12)**	**1.31 (1.27, 1.35)**	**1.22 (1.18, 1.25)**	**1.19 (1.13, 1.24)**

Model 1 - age, gender and practice matched, Model 2 - age, gender, and practice-matched and adjusted for other covariates, Model 3 - propensity score-matched, Model 4 - propensity score-matched with further adjustments for the variables that were still not balanced after propensity score matching, i.e., Charlson co-morbidity index, ex-smokers, Model 5 - multiple imputations and Inverse probability treatment weighted method, CI - confidence interval, HR - hazard ratio, significant results are in bold.

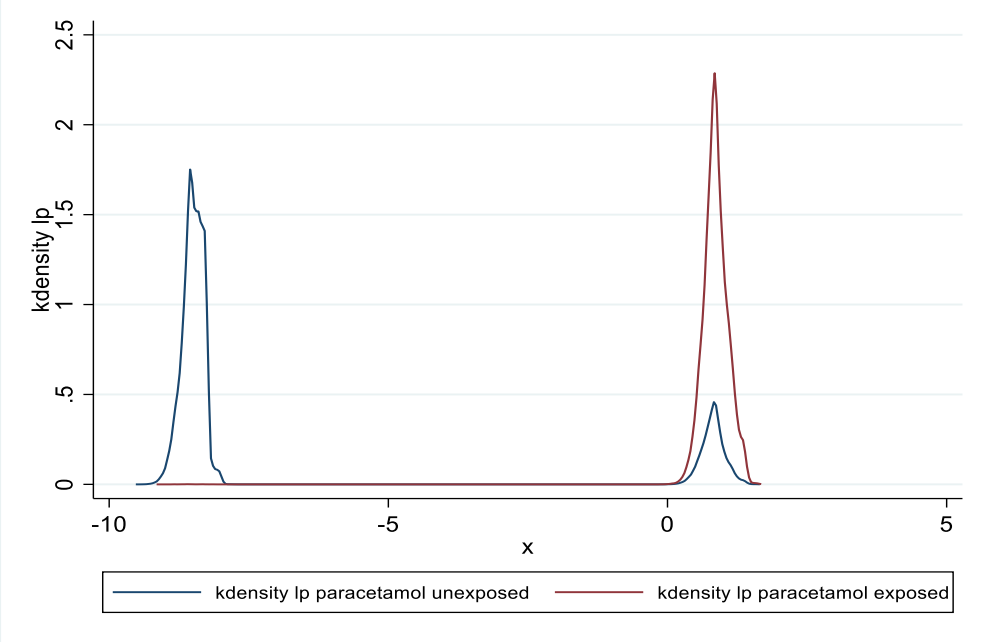


Figure 3.16. Kernel density plot showing covariate imbalance between the unexposed and exposed to paracetamol after propensity score matching (red line represents the paracetamol exposure group, and the blue line represents the unexposed group).

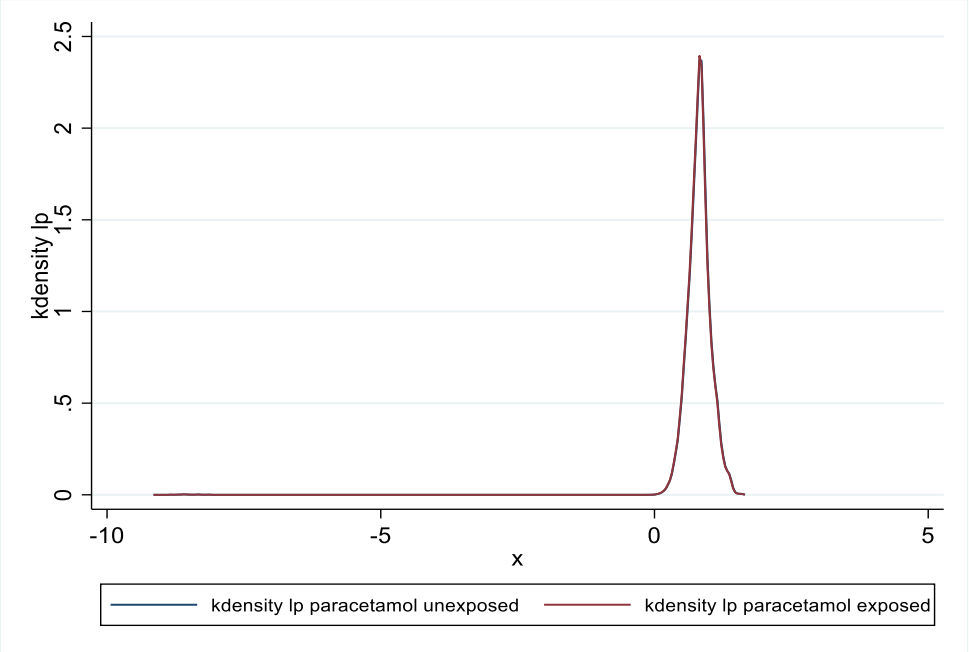


Figure 3.17. The Kernel density plot shows that the paracetamol exposed, and unexposed groups are similar. The Kernel density plot was indistinguishable as the red line representing the exposed group overlaps the blue line representing the unexposed group.

The missingness of values for BMI, smoking, and alcohol consumption was high (n=64,148, n=32,468, and n=57,999 respectively). As a result, the PS-matching method might have dropped 424,915 observations due to missingness, as many participants might not have found a suitable match. Therefore, multiple imputations were conducted to impute the missing values. The MICE generated five imputed datasets. Figure 3.18 describes the midiagplots with excellent overlap between observed and imputed datasets while comparing their distribution for BMI. IPTW was used to achieve a balanced distribution of covariates across both groups.

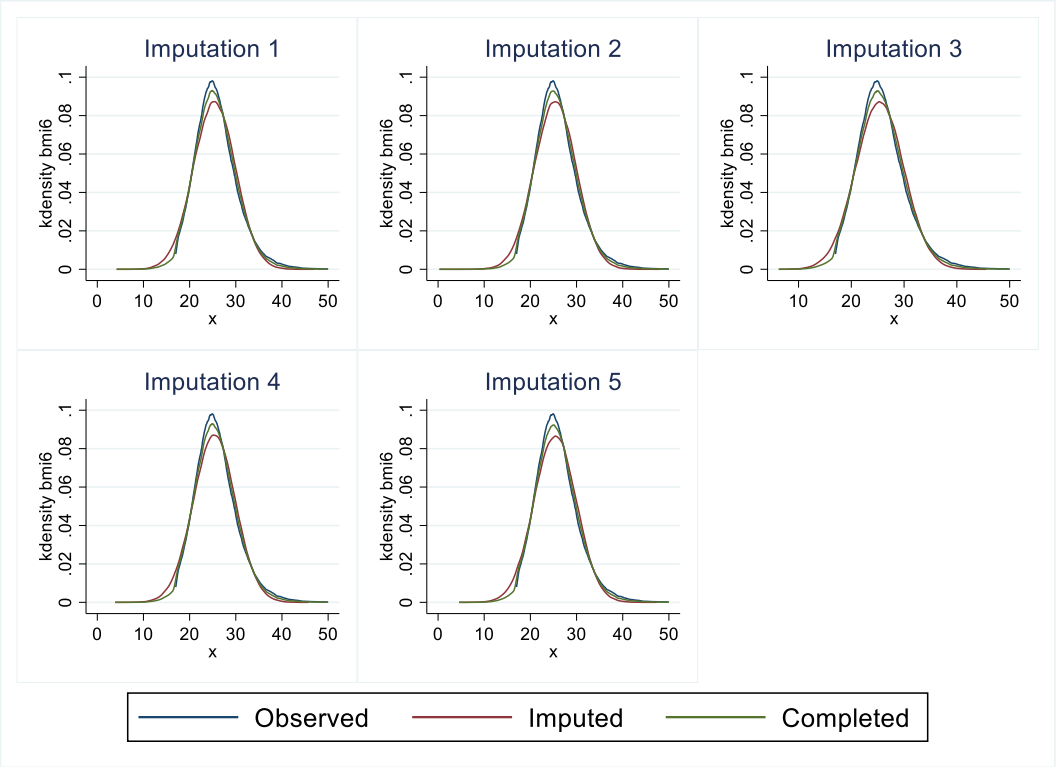


Figure 3.18. The distribution of observed imputed and complete datasets for BMI after five imputations for chronic renal failure.

According to Table 3.22, Model 5 analysis estimates suggested a significantly increased incidence of chronic renal failure with paracetamol exposure compared to those unexposed (HR 1.19; 95%CI 1.13, 1.24).

3.8.3.4. Dose-response

A dose-response for risk of chronic renal failure was apparent with paracetamol exposure (Table 3.23: PS-matched and MI/IPTW), with significant P for trend in the PS-matched and MI/IPTW datasets for the entire population. The dose-response trend was also apparent when the analysis was restricted to the paracetamol exposed only group in both datasets, as shown in Table 3.24 (PS-matched and MI/IPTW).

Table 3.23. Dose-response for chronic renal failure with paracetamol exposure versus unexposed for the entire population.

Number of prescriptions	After PS-matching	MI/IPTW
Non-users	1	1
1-2 prescriptions	**1.27 (1.21, 1.34)**	**2.15 (2.08, 2.22)**
3-4 prescriptions	**1.31 (1.25, 1.37)**	**2.18 (2.12, 2.25)**
5-6 prescriptions	**1.37 (1.30, 1.44)**	**2.36 (2.84, 2.44)**
7-8 prescriptions	**1.52 (1.43, 1.61)**	**2.54 (2.44, 2.63)**
9 or more prescriptions	**1.55 (1.48, 1.63)**	**2.55 (2.48, 2.63)**
	P < 0.01	**P < 0.01**

PS - propensity score, MI - multiple imputations, IPTW - inverse probability treatment weighted, P - P for trend, significant values are bold.

Table 3.24. Dose-response for chronic renal failure when the analysis was restricted to paracetamol exposed only group.

Number of prescriptions	After PS-matching	MI/IPTW
1-2 prescriptions	1.00	1.00
3-4 prescriptions	**1.03 (0.97, 1.09)**	**1.02 (0.98, 1.06)**
5-6 prescriptions	**1.07 (1.01, 1.15)**	**1.10 (1.06, 1.15)**
7-8 prescriptions	**1.19 (1.11, 1.27)**	**1.19 (1.13, 1.24)**
9 or more prescriptions	**1.22 (1.15, 1.29)**	**1.20 (1.16, 1.25)**
	P < 0.01	**P < 0.01**

PS - propensity score, MI - multiple imputations, IPTW - inverse probability treatment weighted, P - P for trend, significant values are bold.

3.8.3.5. Sensitivity analysis

The sensitivity analysis restricted only to OA participants demonstrated that the incidence of chronic renal failure was significantly higher in the paracetamol-exposed group than in the unexposed group in all the models, as given in Table 3.25.

Table 3.25. Sensitivity analysis for chronic renal failure between paracetamol exposed versus paracetamol non-exposed groups when the analysis was restricted to only people with osteoarthritis.

Outcomes	Paracetamol-exposed	Model 1 HR (95%CI)	Model 2 HR (95%CI)	Model 3 HR (95%CI)	Model 4 HR (95%CI)	Model 5 HR (95%CI)
Chronic renal failure	No	1.00	1.00	1.00	1.00	1.00
	Yes	**1.26 (1.22, 1.31)**	**1.09 (1.04, 1.15)**	**1.21 (1.15, 1.28)**	**1.16 (1.10, 1.22)**	**1.15 (1.09, 1.22)**

Model 1 - age, gender and practice matched, Model 2 - age, gender, and practice-matched and adjusted for other covariates, Model 3 - propensity score-matched, Model 4 - propensity score-matched with further adjustments for the variables that were still not balanced after propensity score matching, i.e., Charlson co-morbidity index, ex-smokers, Model 5 - multiple imputations and Inverse probability treatment weighted method, CI - confidence interval, HR - hazard ratio, significant results are in bold.

3.9. Discussion

3.9.1. Summary of main findings

Despite being widely recommended for pain at an early stage of OA, evidence suggests the efficacy of paracetamol for OA pain is modest, and concerns have been raised regarding its safety in the present SR/MA. Therefore, this study was designed to examine the incidence of GI, cardiovascular and chronic renal adverse events in those exposed to paracetamol than unexposed in the population derived from the UK primary care centres. Table 3.26 presents the key findings of this observational study based on PS-matching analysis and MI/IPTW analysis. The significant results are highlighted in bold.

Table 3.26. Summary of the findings using propensity score-matched and multiple imputations and inverse propensity treatment weighted methods.

Outcomes	HR (95%CI) PS-matched	HR (95%CI) MI/IPTW
PUB	**1.06 (1.00, 1.16)**	**1.24 (1.16, 1.34)**
Uncomplicated ulcer	1.04 (0.95, 1.16)	**1.20 (1.10, 1.31)**
Lower GI bleeding	**1.15 (1.09, 1.23)**	**1.36 (1.29, 1.45)**
Heart Failure	**1.24 (1.20, 1.27)**	**1.09 (1.06, 1.13)**
Myocardial Infarction	**1.04 (1.00, 1.09)**	0.99 (0.94, 1.04)
Hypertension	**1.10 (1.07, 1.13)**	**1.07 (1.04, 1.11)**
Chronic Renal Failure	**1.22 (1.18, 1.25)**	**1.19 (1.13, 1.24)**

PS - propensity score, GI- gastrointestinal, MI - multiple imputation and inverse probability treatment weighting, CI - confidence interval, and significant results are in bold.

A dose-response relationship was observed for PUB and uncomplicated ulcers in MI/IPTW analysis and chronic renal disease in both PS-matched analysis and MI/IPTW analysis. Given the similar risk susceptibility, while restricting analysis only to the paracetamol-exposed group, the trend was still apparent for PUB, uncomplicated ulcers in the MI/IPTW analysis and chronic renal disease in PS-matching and MI/IPTW analysis. Care was taken to avoid multiple consultations for the same outcome of interest by analysing the first documented event during the study period.

3.9.2. Placing findings into the context of previous studies

There are limited studies on the association between paracetamol use and the risk of PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure. In the absence of long term RCTs, the overall results are compared to the current SR/MA (Chapter 2 of this thesis), SR/MA of 8 observational studies by Roberts et al. (2016) and other observational studies in the literature.

3.9.2.1. Gastrointestinal events

The evidence from the current observational study findings based on MI/IPTW analysis suggested that paracetamol exposure at its standard therapeutic dose can cause uncomplicated ulcers (HR of 1.20; 95%CI 1.10, 1.31). The PS-matched findings of the current cohort study have also shown a small increased incidence of uncomplicated ulcers with a HR of 1.04 (95%CI 0.95, 1.16) but failed to reach statistical significance. This could be explained by the loss of unmatched participants in the PS-matched cohort impacting the statistical power. The MI/IPTW analysis findings are consistent with the current SR/MA of the observational studies (Chapter 2) (Garcia-Rodriguez et al., 2004; González-Pérez et al., 2014; McIntosh et al., 1985; McIntosh et al., 1988). For example, according to Chapter 2 of this thesis, Garcia-Rodriguez et al. (2004) found an association between current intake of paracetamol and risk of gastric ulcer compared to non-use, with a RR of 1.90 (95%CI 1.50, 2.30) in 458,840 participants using GPRD-data (also known as CPRD-data). Additionally, another cohort study that used a different longitudinal database, The Health Improvement Network database (THIN) with 3,914 participants, also included in the current SR/MA, reported that current use (7 days before the index date) of paracetamol is associated with an increased risk of uncomplicated ulcers (OR 1.56; 95%CI 1.38, 1.78) (González-Pérez et al., 2014). An explanation for the slight discrepancy between the estimates from the present study and the other two observational studies included in the SR/MA of Chapter 2 could be due to variation in the list of confounders included in the model and using a different statistical methodology. Garcia-Rodriguez et al. (2004) adjusted for age, gender, study calendar year, study cohort, history of GI symptoms, smoking (current, past, or never), use of corticosteroids, gastro protective drugs, NSAIDs and further adjustment for BMI, alcohol intake, anticoagulants, cardiovascular disease, RA, and OA. Whereas González-Pérez et al. (2014)

accounted for age, gender, year of the index date, number of primary care physician visits in the year before the index date, smoking, PPIs, acetylsalicylic acid and NSAIDs.
In contrast, the present study adjusted for age, gender, smoking, alcohol, BMI, Charlson co-morbidity index, OA, aspirin, opioids, NSAIDs, coxibs, dipyridamole, clopidogrel, PPIs, and H2-receptor blockers. Additionally, Garcia-Rodriguez et al. (2004) used the conventional multivariable regression methods to adjust for the listed confounders compared to PS-matched and MI/IPTW methodology used in the present analysis. However, when the exposure (paracetamol) is common, outcomes are rare, then the PS-matching and MI/IPTW are considered robust methods to control several confounders compared to traditional multivariable adjustment methods which were applied in previous studies (Arbogast et al., 2009).

The findings of this observational study also indicated an increased incidence of PUB associated with paracetamol exposure compared to non-exposed (HR 1.06; 95%CI 1.00, 1.16 in PS-matched dataset and 1.24; 95%CI 1.16, 1.34 in MI/IPTW-dataset, respectively). These findings corroborate with the SR/MA of the observational studies of this thesis, where the pooled estimates from 12 case-control studies reported a higher risk of developing UGIB and other complications in paracetamol users compared to non-users (RR 1.34; 95%CI 1.10, 1.63). These outcomes could also be indirectly compared with a cohort study by Rahme et al. (2008). This study used the Quebec-health-insurance agency database, including 644,183 participants aged >65years and informed that the hospitalisation rate due to GI complications was high in the people taking >3g/day of paracetamol (HR 1.20; 95%CI 1.03, 1.40).

Unlike most studies, only the present study has measured the increased hazards of lower GI bleeding with long-term paracetamol exposure. These results indirectly agree with the estimates of a case-control study by Imhof et al. (1997) that shows a significant association between paracetamol exposure and peptic ulcer bleeding (OR 3.29; 1.17, 8.73). The discrepancy in the estimates could be explained due to their study designs (i.e., cohort versus case-control). These findings are also in line with a cohort study stating a dose-response relationship between paracetamol exposure and GI complications or bleeding (De-Vries et al., 2010). The safety outcomes definition in these two studies differed from that of the current observational study. Therefore, the recent findings add to the growing body of literature. However, further research is required using lower GI bleeding as an operational definition to confirm the results of this study.

The estimates from the current cohort differ from a few published clinical trials (Hoftiezer et al., 1982; Lanza et al., 1998; Lanza et al., 2018). The healthy subjects were assessed endoscopically in these clinical trials for the GI events for a low dose of paracetamol, i.e., <2g/day compared to placebo and showed no significant difference between both groups (Hoftiezer et al., 1982; Lanza et al., 1998; Lanza et al., 2018). Based on such findings, paracetamol might have been considered a safer analgesic option so far, especially for the long-term treatment of chronic illnesses such as OA. However, these trials focused solely on short-term acute effects, were less powered, and studied a healthy early age group compared to the long term effects of paracetamol examined using a longitudinal database in the age group ≥65 years for the present cohort study (Hoftiezer et al., 1982; Lanza et al., 1998; Lanza et al., 2018). Considering these factors in the present cohort study was of foremost importance because the risk of GI injury increases with age, other comorbidities, and previous history of GI injury (Dumic et al., 2019). Therefore, the estimates of the present study question the findings of these short clinical trials and signal that paracetamol is not safe as it was thought previously.

Furthermore, the present study demonstrated a significant dose-response relationship, suggesting an increased risk associated with paracetamol exposure and PUB for every increase in prescriptions. It aligns with findings of a nested case-control study that suggested an elevated risk for UGIB and other complications of 1.30 (95%CI 1.10, 1.50), the risk being three times higher in those who had received >2g/day of paracetamol with RR 3.6 (95%CI 2.6, 5.1) (Garcia-Rodriguez et al., 2001). The dose-response estimates in the current study are low compared to that study by Garcia-Rodriguez et al. (2001). This may be explained in part by the number of confounders listed (age, gender, practice, BMI, smoking, alcohol, Charlson comorbidity index, OA, NSAIDs, opioids, aspirin, clopidogrel, dipyridamole, PPIs, H2-receptor blockers) in the present study compared to age, gender, calendar year, smoking, prior history of UGI complications, anticoagulants, misoprostol, H2-receptor blockers, omeprazole and nitrates listed in the study by Garcia-Rodriguez et al. (2001). The other reason could be due to a difference in study design, the present study being a cohort study, whereas Garcia-Rodriguez et al. (2001) used a case-control study design. It is well known that risk estimates may be exaggerated in case-control studies compared to cohort studies, which may explain the higher risk reported in the study by Garcia-Rodriguez et al. (2001).

A dose-response was also observed for uncomplicated ulcers in the MI/IPTW matched dataset for paracetamol exposed compared to the unexposed group with HR varying from 1.12 (95%CI 0.97, 1.30) for 1-2 prescriptions to 1.39 (95%CI 1.22, 1.58) for 9 or more prescriptions. These findings match with those observed in the earlier study stating a dose-response relationship between paracetamol exposure and GI complications or bleeding with RR 1.11 (95%CI 1.04, 1.18) to 1.49 (95%CI 1.34, 1.66) (De-Vries et al., 2010).

Besides this, people with OA are the highest paracetamol users. Therefore, a sensitivity analysis was conducted by restricting analysis only to OA patients. The estimates from the sensitivity analysis varied according to each outcome. For example, the HR for PUB was 1.07 (95%CI 0.92, 1.24) in the propensity score model and HR 1.13 (95%CI 0.99, 1.29) for MI/IPTW analysis with paracetamol exposure. However, these results were not significantly associated with paracetamol exposure compared to unexposed in both datasets. No increased incidence was found for uncomplicated ulcers in the PS-matched analysis for the paracetamol exposed group compared to the unexposed; however, the MI/IPTW analysis found a small incidence that lacked statistical significance. The lack of statistical significance could be explained as a drop in the sample size after PS-matching when the data was restricted only to the OA population. Secondly, those at risk of GI, CV or renal are more likely to be given paracetamol, which leads to the crude HR significance. However, it became insignificant after controlling this bias (confounding by indication) either using PS-matching or MI/IPTW adjustment. The lower GI bleeding estimates are in agreement with the original cohort stating a significantly increased risk in MI/IPTW analysis HR 1.20 (95%CI 1.09, 1.33). These estimates could be compared with RCTs by Doherty et al. (2011) that analysed the effects of paracetamol 3g/day and ibuprofen 1.2g/day. It also investigated the combination of paracetamol and ibuprofen with low and high doses (0.6 ibuprofen and 1.5g paracetamol, and 1.2g ibuprofen and 3g paracetamol every day) for chronic knee pain in a clinical trial with 892 participants with a mean age of 61. The study was designed and powered to analyse the effectiveness of both drugs. It also reported adverse effects with a follow-up of 13 weeks. The study found that 3g/day of paracetamol monotherapy could cause a similar reduction in haemoglobin levels (i.e., ≥10g/l) as 1.2 g/day of ibuprofen single therapy (20.3% and 19.6% reduction, respectively). There was an additive effect with the combination of paracetamol and ibuprofen (low dose 24.1% and high dose combination 38.4% reduction, respectively) (Doherty et al., 2011).

The results for paracetamol administration were significantly different from the other intervention groups. Additionally, the authors observed a significant elevation of platelets and lower mean cell volume, which supports the occult GI bleeding as the cause of the haemoglobin reductions (Doherty et al., 2011). Notably, in the absence of any other study, the findings of this RCT can indirectly correspond to the results of the current cohort study; however, the drop in haemoglobin results in this RCT did not discriminate between upper and lower GI bleeding. Future studies are, therefore, recommended to confirm these results. A similar risk profile was observed in this study for paracetamol to that of NSAIDs for GI bleeding. Apart from this study, there has been only one long-term trial (maximum duration of 2 years) in OA patients that compared paracetamol and naproxen for knee OA (Williams et al., 1993). It suggested that GI events were higher with naproxen use than with paracetamol. This inconsistency could be due to different comparison groups. However, the rate of withdrawals in that study was significant, specifically in the paracetamol group, which might have biased the results. In addition, the GI events reported in the present sensitivity analysis are serious compared to those by Williams et al. (1993), such as dyspepsia or GI upset and had an active comparison group. Thus, in the absence of any specific long term observational study on paracetamol exposure in the OA population, the findings of lower GI bleeding may be indirectly accorded with the sensitivity analysis of Rahme et al. (2002). It demonstrated that the rate of GI events was still high in the paracetamol group even when they restricted the analysis to a prescription written by the rheumatologist. Future studies are therefore recommended to confirm these findings.

3.9.2.2. Cardiovascular events

The evidence that two paracetamol prescriptions within 6 months have a higher incidence of heart failure corresponds with a cohort study by Chan et al. (2006), where they examined the frequency of use of paracetamol, NSAIDs and aspirin and increased risk of cardiovascular events, including nonfatal MI, nonfatal stroke, fatal coronary heart disease and fatal stroke using NHS data. The participants who used paracetamol less than 22 days/month demonstrated an increased risk of cardiovascular events with a RR of 1.44 (95%CI 1.27, 1.65). A slight discrepancy in the estimates could firstly be due to differences in the operational definition of the outcome for the present study (heart failure) compared to Chan et al. (2006), who defined their outcome as nonfatal MI, nonfatal fatal coronary heart disease,

and fatal stroke. Secondly, it could be due to selecting the covariates and the conventional regression method to adjust various confounders. Chan and colleagues used the Cox proportional regression method to adjust the baseline characteristics: age, parental history of myocardial infarction, history of diabetes mellitus, hypercholesterolemia, diabetes mellitus, BMI, exercise, postmenopausal hormone use, multivitamin use, and energy-adjusted energy quintiles of folate, omega-3 fatty acids, saturated fat, alcohol, and other analgesics to obtain the estimates (Chan et al., 2006). The present cohort study performed various analyses based on four different methods. One of the methods also used the traditional adjustment of the covariates that generated an almost similar HR of 1.40 (95%CI 1.37, 1.44). However, PS-matching was applied to account for "confounding by indication bias" and calculated a HR of 1.24 (95%CI 1.20, 1.27). The SR of 43 studies by Shah et al. (2005) suggested that PS-matching might give slightly weaker associations than the conventional regression analysis. Also, in the case of rare events, the results from PS analysis are highly preferred over the regression analysis (Cepeda et al., 2003).

Furthermore, according to the PS-matched analysis, there is evidence that exposure to paracetamol with a minimum of two prescriptions within six months has an increased incidence of myocardial infarction. Although it was a small risk, it can still not be ignored as PS analysis is considered one of the best approaches to investigate rare outcomes. These findings support the results from the SR/MA of the observational studies (Chapter 2) included in the thesis that suggested a dose-response relationship between paracetamol exposure and myocardial infarction. However, the MI/IPTW analysis cohort study results contrast with the PS-matching estimates, indicating no significant risk associated with paracetamol exposure and myocardial infarction. The results from MI/IPTW corroborate with the pooled estimates from the case-control studies of present SR/MA in Chapter 2 of this thesis, demonstrating that there is no significant risk associated with paracetamol use and myocardial infarction (OR 0.93, 95%CI 0.80, 1.09). These rather contradictory results from two statistical models may be partly explained due to the weighting of stratum specific effect estimates (effect measure modification) (Stürmer et al., 2006). For example, in the PS-matching model, weights are assigned according to the distribution of the effect-measure modifier of the exposed group only. Whereas, in IPTW-model, weights are set according to the whole study population (Stürmer et al., 2006).

In pharmacology, the contraindications to the intervention that also influence the effect might be predominant in the entire study population but rare in the exposed group.

In this context, estimating the impact of exposure in the exposed group is highly preferred compared to the whole population. The second possible explanation could be that using only measured confounding might not be sufficient to reduce the `confounding by indication bias' for PS-matching or IPTW adjustment. It is more likely that due to unmeasured confounding, the results from the cohort study are not in agreement with both datasets. Therefore, it further requires a large-scale PS-matching investigation, including the negative control confounders, to mitigate the impact of channelling bias to investigate further that paracetamol tends to increase the risk of myocardial infarction at its usual therapeutic dose (Weinstein et al., 2017).

Moreover, the evidence that paracetamol exposure may increase the risk of hypertension supports the findings of Chapter 2 SR/MA suggesting a dose-response relationship between paracetamol exposure and hypertension pooled from two studies (Curhan et al., 2002; Dedier et al., 2002). These present findings also correlate with the conclusions of the previous SR that included seven prospective observational studies, 6 RCTs, one commentary and two reviews suggesting an increased risk associated with paracetamol use for hypertension (Turtle et al., 2013). Comparable results were found from three RCTs with 104 patients included in that same review and showed an increase in blood pressure by 4mm Hg. In addition, Gualtierotti et al. (2013) explained that paracetamol might adversely affect the efficacy of the antihypertensive such as ramipril or valsartan in their double-blind crossover trial. In contrast, the Dawson et al. (2013) PS matched study found no impact of paracetamol exposure on blood pressure in a cohort of 2754 participants with treated hypertension aged 65 years using the GPRD-dataset. Their estimates were only based on a single blood pressure measurement at baseline and during drug administration. In addition, Dawson et al. (2013) did not consider comorbid renal impairment, asthma, chronic obstructive pulmonary disease, OA, or rheumatoid arthritis. However, these confounders are essential to study in an observational study, where these conditions might lead to an analgesic preference for paracetamol over NSAIDs. Unlike the model used by Dawson et al. (2013), all these confounders were considered in the cohort study of Chapter 3 of this thesis. It is important to mention that OA pain might increase blood pressure. Therefore, patients with OA and hypertension as a comorbidity need careful evaluation for drug preference.

The sensitivity analysis estimates are consistent with the original cohort for two outcomes: heart failure in PS-matched analysis with a HR of 1.07 (95%CI 1.02, 1.13) and hypertension in MI/IPTW analysis with a HR of 1.06 (95%CI 1.00, 1.13). These estimates agree with the findings of a recent MA for people with OA from Chapter 2 of this thesis. The MA of two placebo-controlled trials showed a small increased risk associated with paracetamol compared to placebo in people with OA (RR 1.05; 95%CI 0.07, 15.38). The differences in the estimates and the reason it could not reach statistical significance were due to the small size (paracetamol n=9/619; placebo n=5/392), and these trials analysed the short-term effects. Therefore, this is the first longitudinal study to investigate the long-term adverse effects of paracetamol in the OA population. The knowledge regarding the side effects of paracetamol in different population groups is still evolving. These results, therefore, need to be interpreted with caution.

3.9.2.3. Chronic renal failure

Prior studies had described that 1-2% of people might develop poor renal function with an overdose of paracetamol (Mazer et al., 2008). Interestingly, the present cohort study identified that paracetamol exposure, even at its standard therapeutic dose, can be unsafe and has a higher incidence of chronic renal failure (HR 1.22; 95%CI 1.18, 1.25 from PS-matched and 1.19; 95%CI 1.13, 1.24 from MI/IPTW analysis). These estimates also align with recent SR investigating the association between paracetamol and renal impairment in adults (Kanchanasurakit et al., 2020). It meta-analysed five studies with 13,114 participants and found that paracetamol use was significantly associated with renal impairment with an adjusted OR of 1.23 (95%CI 1.07, 1.40) (Kanchanasurakit et al., 2020).
Furthermore, a dose-response relationship was observed in both PS-matched and MI/IPTW analysis for chronic kidney disease. These estimates seem consistent with the current SR/MA of observational studies (Chapter 2). For example, a significant dose-response relationship was observed between paracetamol use and a decrease in the >30mL/min/1.73m2 in eGFR, by Curhan et al. (2004) and an increase in the OR of >0.3 mg/dL increase in serum creatinine and a decrease of >30ml/min/1.73m2 in eGFR by Kurth et al. (2003).

In addition, a sensitivity analysis restricted only OA participants and produced comparable results for the increased incidence of chronic renal failure to the original cohort in both analyses, with the HRs of 1.21 (95%CI 1.15, 1.28) and 1.15 (95%CI 1.09, 1.22), respectively. The unadjusted PAF calculations suggest that if paracetamol exposure was eliminated, then 26%, 25%, 29%, 21%, 17%, 13% and 23% of PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction and hypertension and chronic renal failure could be reduced in the population. NNH findings illustrated that for every 114, 180, 56, 33, 81, 45, and 15 people receiving paracetamol, one additional case could be expected for PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure, respectively. However, these results should be interpreted cautiously as these estimates are based on unadjusted risks.

Overall, prospective clinical trials using standard therapeutic doses of paracetamol and addressing its gastrointestinal, cardiovascular, and renal safety are still lacking, especially in individuals at increased risk of GI, cardiovascular or renal events. Therefore, the findings were compared to the best available evidence, i.e., observational data.

3.9.3. Interpretation of findings: Biological explanation

Minimal experimental evidence is available to support the impact of paracetamol on the human gastric mucosa. According to Konturek et al. (1981), paracetamol can significantly decrease the synthesis of prostaglandin E-2 by 50%, which is considered cytoprotective (jointly synthesized by COX-1 and COX-2 to protect gastric mucosa). However, it is not associated with mucosal damage (Cryer et al., 1998; Konturek et al., 1981). In addition, the consumption of paracetamol for more prolonged periods might consistently inhibit the synthesis of prostacyclin in humans, which further leads to gastrointestinal lesions, and high-grade inhibition might cause bleeding (Green et al., 1989; Prescott, 2000). This is in line with an endoscopic study on 27 healthy subjects that suggested a significant PGE-2 inhibitory action of paracetamol on the GI- mucosa after oral intake of paracetamol (Konturek et al., 1981). The degree of reduction in PGE-2 activity was 40% at the fundus and 60% at the antrum following 2.5 grams of oral intake of paracetamol in divided doses compared to 2.5 grams of aspirin (Konturek et al., 1981). Therefore, an imbalance between acid secretion and gastric mucosa interference may damage the gastric mucosa. This finding reinforces the concern over the GI safety of paracetamol (Cannon et al., 2006; Hinz et al., 2006b). Hinz et al.

(2006b) and Cannon et al. (2006) had suggested that the long-term use of traditional NSAIDs and coxibs could cause permanent blockade of COX-2 dependent prostaglandin and PGE-2, causing high blood pressure, which could further result in cardiovascular hazards. Boutaud et al. (2002) explained further that the endothelial cells possess low peroxide levels, making an undisturbed COX-2 inhibition by paracetamol compared to inflamed tissue. Paracetamol was also found to suppress cyclooxygenase activity in the human umbilical vein endothelial cells.

An oral administration of 500 mg paracetamol decreases the urinary excretion of 2-3-dinor 6 keto prostaglandin F1alpha (PGF1-alpha), a stable, inactive metabolite of major endothelium-derived COX-2 prostacyclin (Green et al., 1989). It can cause a marked reduction in prostacyclin synthesis for a minimum of 6-8 hours without affecting thromboxane production. Therefore, Green et al. (1989) suggested that paracetamol could be disadvantageous to people suffering from initial conditions where prostacyclin mediated vascular defence mechanisms are pronounced, such as myocardial infarction, deep vein thrombosis and after surgery.

In a similar context, Rebordosa et al. (2010) and Walsh (1985) demonstrated that paracetamol use during pregnancy is associated with an increased risk of pre-eclampsia and thromboembolic disorders. In these conditions, prostacyclin is hypothesized to play a role. O'Brien et al. (1993) explained that 1 gram of paracetamol reduces PGF1-alpha in the urine by up to 50% in pregnant women. Additional to these reports, inhibition of lipopolysaccharide induced PGE2 production has been observed in whole blood in an experimental setting. This correlates with the inhibition of urinary excretion of PGF1-alpha. These studies and experimental findings suggested that the COX-2 measurement in the whole blood function as a potential substitute to evaluate the cardiovascular risk with a specific cyclooxygenase inhibition. An experimental study suggested that paracetamol can cause 80% COX-2 inhibition in endothelium, further supporting the concerns over cardiovascular risk (Hinz et al., 2012).

Furthermore, the causes of renal toxicity due to paracetamol are still debatable. The biological explanation for the association of paracetamol and renal side effects could be tubular necrosis. It has been estimated that 5% of paracetamol is metabolised in the phase 1 metabolism (cytochrome P-450 pathway) to form N-acetyl-p-benzoquinone imine.

The cytochrome P-450 pathway is evident in both the kidney and liver. They differ in these organs and result in lipid peroxidation accompanying cell apoptosis commencing to programmed cell death, resulting in further tissue necrosis and organ damage (Bessems et al., 2001; Mazer et al., 2008). This hypothesis has been supported by an experimental study by Lorz et al. (2004), which signalled that acute tubular necrosis might be responsible for renal impairment in people taking paracetamol. It may be described due to the involvement of prostaglandin synthase, N-deacetylase, cytochrome p450 and glutathione S-transferase (Bessems et al., 2001).

Another explanation could be that paracetamol is considered a major metabolite of phenacetin which is associated with nephropathy. Being a product of phenacetin, the safety of paracetamol for renal adverse effects remains in question.

3.9.4. Strengths and limitations

All the mild to moderate pain-related conditions are initially managed in the community. The clinical practice data allowed access to an extensive, well-validated, primary care-based database with a sample of 582,961 participants that also have prescribed medication records. The main strength of the CPRD is its size, and it stores information from 736 practices that include over 17 million people. Therefore, there is a provision to apply complex epidemiological relationships with significantly higher statistical precision than small database sources.

Secondly, it offered an opportunity to include a range of participants that might be excluded from clinical trials with restricted inclusion criteria. The CPRD-database has been well validated and has been used successfully for various observational studies. It is advantageous when studying rare exposures and diseases, and reusing such datasets is comparatively cheaper than planning a bespoke cohort study (Herrett et al., 2015). According to Crooks et al. (2013), the anticipated median duration of follow-up was 9.4 years for all active participants (interquartile range (IQR) 3.4-13.9) and 5.1 years (IQR 1.8-11.1 years) overall for CPRD-studies (Crooks et al., 2013). Due to the cohort study design, the temporal biases associated with the timing of exposure were minimal.

Additionally, the statistical analysis included in this study is based on 4 different models to estimate the adverse effects of paracetamol exposure compared to non-exposure, specifically: (i) age, gender, and practice matched analysis; (ii) conventional multivariable Cox regression; (iii) PS-matching and Cox proportional hazards analysis; (iv) MI/IPTW analysis. Clinicians prescribe paracetamol to older individuals, or those at elevated risk or who take multiple medications. Therefore, valid estimates regarding the safety of paracetamol are vital for informing treatment decisions. The present cohort study included people who were 65 years or older. It is likely that these participants might have other comorbidities and could be on other concomitant medications.

The unadjusted rates for PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal disease were exaggerated in the paracetamol-exposed group than the unexposed analysis because it did not control for these confounders. However, the conventionally adjusted results from Cox proportional hazards multivariable model suggested a downward change in the HRs for the paracetamol exposed group, indicating the importance of taking confounding into account. Although, the conventional multivariate analysis and PS-matching cannot account for unmeasured confounding. The estimates of PS-matching are theoretically more advantageous than traditional multivariable analysis in pharmaco-epidemiology for the following reasons (Austin, 2009; Weinstein et al., 2017).

Firstly, the observational study design involved non-random allocation of paracetamol; therefore, it is prone to 'confounding by indication' bias (Okoli et al., 2014). A careful study design and appropriate interpretation of results are required to mitigate the biased conclusions. The baseline characteristics such as lifestyle factors and other comorbidities that may be associated with paracetamol intake might influence the study outcomes. For example, people with peptic ulcers or GI bleeding may be offered paracetamol over NSAIDs. Although the inherent characteristics may not imply an absolute contraindication for NSAIDs, clinicians may be more likely to be extra cautious while prescribing any medication due to the risk associated with those drugs (Okoli et al., 2014). The recognition of various markers of frailty and co-morbidities such as congestive heart failure, dementia, COPD, OA, and their inclusion in the PS might have improved control for confounding compared to an analysis that does not account for these factors (Glynn et al., 2006).

The confounding by indication is a significant challenge to validity in pharmaco-epidemiologic studies when the entire previous history of the patient is unclear to the investigators. (Glynn et al., 2006). In this context, RCTs are considered the gold standard for the causal effects of an intervention.

Nevertheless, it might not be possible to conduct RCTs for adverse outcomes due to ethical reasons, expensive or duration. Therefore, observational, or non-randomised data may also provide causal effects if designed to match the properties of RCTs, such as using PS methods. This can also assign the exposed and unexposed groups with an equal distribution of baseline factors (Bijan et al., 2014).

Secondly, unlike conventional cox regression analysis, the PS creates a `single' covariable that summarises all the confounding factors used in the model, implying the propensity (probability) to be exposed. This reduces the issue of having too many confounders in the model in relation to the number of events (Cepeda et al., 2003). PS directly aims at the indications for using the study intervention and its non-use (Austin, 2011; Glynn et al., 2006). The individuals with either absolute indications or contraindications for using a specific intervention might find comparable exposed or unexposed participants to accurately determine the effect size for the outcome (Glynn et al., 2006). Compared with the conventional multivariate Cox modelling, these individuals remain unrecognised, which could be influential due to model misspecification (Glynn et al., 2006).

Further, the Kernel density plots graphically represent the comparison of PS in paracetamol exposed and unexposed groups to identify the areas of non-overlap. This could be challenging to demonstrate using the multivariate approach such as cox regression adjustment, where many attributes may influence the treatment decisions (Glynn et al., 2006). Moreover, previous studies have also validated the use of PS-matching to examine if evidence of confounding by indication exists in an observational study that compared paracetamol with ibuprofen and the extent to which this confounding adjustment can minimise this bias (Weinstein et al., 2017). The balanced PS between the paracetamol users and nonusers suggested that confounding by indication was reduced to a minimum according to known reasons. However, it is evident from the results that the reduction of hazard ratio (HR) from age, gender and practice matched dataset to PS-matched dataset indicated that the direction of the confounding by indication is towards an HR of more than 1 (HR>1, not HR<1).

Bearing this potential underestimation bias in mind helps to interpret the results correctly. This further indicates that the PS-matching for GI, cardiovascular and renal events is justified.

However, the results from the PS-matched analysis provide slightly weaker associations, as explained earlier in section 3.9.2.2 (P278). Few variables in the PS model for GI events and chronic renal disease were still not balanced, indicating the residual difference in the data even after PS-matching on selected covariates. Therefore, the analysis was repeated using the unbalanced variables again in the model.

Besides, the PS-matching and IPTW aim to achieve a similar objective to balance the inherent difference between the intervention and comparison group. However, the two statistical methods produced different treatment effect estimates, therefore need to be interpreted accordingly. For example, the IPTW analysis findings were significantly higher than PS-matched research for PUB, uncomplicated and lower GI bleeding. King et al. (2019) explained that PS matching with the nearest neighbour matching without replacement with a calliper width of 0.001 ensured a more closely match based on PS value. However, it might lead to few matches as the distance is too narrow, resulting in a reduced sample size. Therefore, matching might have dropped many paracetamol-exposed participants if the proper match was not found. In comparison, the IPTW-analysis kept all the eligible participants without losing the unmatched individual who may differ systematically from its matched participant, thus increasing the precision of estimates.

The other strength of this cohort study was that a landmark analysis was applied to control "immortal time bias" to avoid miscounting the outcome before fulfilling the exposure definition. The outcomes occurring before the landmark date were excluded to prevent `prevalent user' bias and capture the whole course of the exposure. This study controlled for a wide variety of covariates. The confounding by co-morbidity was accounted for using a robust measure, i.e., the Charlson co-morbidity index. It is a well-validated comorbidity measure that is also used in morbidity studies.

Paracetamol is widely available as an over the counter (OTC) medication which might have significantly influenced this study as the CPRD does not have a provision for recording over the counter prescriptions. Therefore, to have enough data, the age was limited to ≥65 years in the study, i.e., when people can receive a free prescription. This age group is highly prone to consume paracetamol for more extended periods due to chronic pain conditions such as OA.

A retrospective cohort study with 644,183 participants aged 65 years or older concluded that GI events were relatively higher in paracetamol users than in traditional NSAIDs (Rahme et al., 2002). However, OTC usage might have affected both the exposure and non-exposure groups. It was assumed that the distribution would be random for other OTC analgesics but slightly more towards the non-exposure as those being prescribed paracetamol may be less likely to buy it independently. This imbalance was expected to underestimate rather than overestimate the HR. If we have an HR of more than 1 and it is significant, the true HR is more likely to be greater. Bearing this potential underestimation bias in mind further helps interpret the results correctly. However, it was assumed to be a differential bias whose impact would be considered towards unity. In addition, the patients taking paracetamol may also be taking ibuprofen, primarily OTC. The adverse events may be contaminated by ibuprofen, resulting in overestimating adverse events. Again, the study was matched for age, gender, and practice to account for bias.

The other rationale for selecting this age group was that they are considered the highest users of analgesics, especially for pain associated with the musculoskeletal system. According to SR, of 83 clinical trials, including >10,000 participants, only 2.3% of those were over 65 years (Rochon et al., 1993). Therefore, it can be concluded that this group was considered highly selective for the clinical trials and may have ethical implications. Additionally, there is limited clinical evidence regarding the safety of these interventions in this population subgroup (McLachlan et al., 2011).

Alongside these advantages, the observational study design and reuse of routinely collected health data have caveats. These issues arise because electronic datasets such as CPRD were not generated for research purposes. Studies collecting data specifically for research purposes may standardise the data collection to minimise the error and maximise the completeness of the data. In comparison, the completeness of the real-world data is based on many factors such as patients presenting to their practitioners, time pressure faced by clinicians, the primary purpose of recording the data, completeness of the patient's history, diagnostic accuracy and any incentives involved for recording data (Taggar et al., 2012). The mandatory data mining, cleaning and preparation are laborious tasks in electronically based datasets, and it is challenging to report transparently. For example, recording of lifestyle factors such as BMI, smoking and alcohol consumption was less populated than prescription data (Thiru et al., 2003). Although the smoking codes were used in addition to additional

information, data mining using more fields (e.g., clinical entities as 'health advice on smoking') might have improved the completeness of lifestyle data rather than imputation. Sometimes practices in the CPRD leave and stop contributing data. Therefore, the stability of CPRD-practices remains in question.

Secondly, the observational research design has faced criticism due to conflicting findings or estimates that are not reproducible. GI, cardiovascular, and chronic renal disease events were ascertained using read codes that are highly prone to misclassification bias. However, it was unlikely to be a differential bias. Due to read codes overlapping, it was impossible to measure individual results such as upper GI bleeding or perforation; therefore, mixed codes were used. Epidemiological research is susceptible to other biases such as protopathic bias, selection bias, information, and confounding bias. In the context of adverse drug reactions, there was potential for protopathic bias, which may occur when the disease is at its initial stage before the drug administration. When the drug is prescribed in an early phase of the symptoms of any disease, the entire clinical presentation of the disease may later be thought to be associated with the use of the drug (Graham et al., 2005). Similarly, paracetamol may be used to treat GI pain and discomfort in the early phase of GI disease before being diagnosed (Graham et al., 2005). However, later, the GI disease, once it is diagnosed, is assumed to be associated with paracetamol (Graham et al., 2005; Langman et al., 1983b).

Although PS-matching is widely used to estimate treatment effects, as it is complicated to determine the exposure-outcome association for all the potential confounders, the selection of covariates for the propensity score model is still debatable (Brookhart et al., 2006). There is no well-developed tool to select potential variables for PS-modelling (Ali et al., 2019). Therefore, covariates for the propensity score were based on "subject matter knowledge" or their relationship with either exposure or outcome (Patrick et al., 2011). The covariates used in the previous studies and advice from all supervisors (Professor Weiya Zhang, Professor Michael Doherty, Professor Abhishek, and Dr Georgina Nakafero) were used to identify co-variates. It also depends upon the probability that participants would receive paracetamol (exposure intervention) based on their characteristics, comorbidities, and usage of other painkillers (Haukoos et al., 2015; Patrick et al., 2011). In addition, any adjustment/matching in such an observational study can only control known confounders (Streeter et al., 2017). Therefore, an attempt was made to incorporate a detailed number of variables in the PS-matching model. However, this study might still be prone to confounding bias by

unknown/unmeasured confounders (Streeter et al., 2017; Weinstein et al., 2017). Therefore, a large-scale propensity score analysis to examine the association between paracetamol prescription and unrelated conditions such as open-angle glaucoma is warranted (Weinstein et al., 2017). It might be based on the assumption that the association would be neutral if there is no unmeasured confounding by indication. However, due to time constraints, this analysis was postponed until after completion of the PhD and might be included in the eventual publication of the study.

Restricting the age at which free prescriptions occur, the study population was skewed toward older subjects with chronic conditions. This may limit the generalizability of the results to the entire population.

Unlike other drugs, paracetamol is an analgesic often used episodically, challenging to define paracetamol users and non-users. The present study determined that paracetamol exposure as two or more prescriptions within 6 months is minimal. Similarly, immortal time bias will not just occur within the exposure window but during the entire follow-up period. Therefore, a time-varying exposure analysis is required to cope with the dynamic changes of paracetamol use, depending on this primary propensity-score matched landmark analysis. Furthermore, an exposure window of one year was also provided to calculate the cumulative doses during that period aiming to catch some longer-term dose-response relationships. However, the use of paracetamol and its amounts may change during the follow-up, not just in the exposure window. Therefore, future studies need to calculate dose-response after the landmark date using time-varying exposure analysis to count all paracetamol prescriptions after the landmark date to determine the dose-response relationship between paracetamol and adverse effects as GI bleeding.

3.10. Summary

This study shows a significant association between paracetamol use and increased incidence of gastrointestinal (GI) adverse events such as PUB, uncomplicated ulcers and lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure. A dose-response trend was also observed for PUB, uncomplicated ulcer, and chronic renal failure, with significant P for the trend. However, further research is required to investigate the long-term use of paracetamol and all-cause mortality.

Chapter 4: General discussion and conclusion

4.1. Summary of main thesis findings

After a thorough investigation of existing literature and analysis undertaken in the UK adult general population, this PhD thesis builds on the previous evidence from clinical and observational studies, suggesting the detrimental side effects of long-term usage of paracetamol. The findings from the SR/MA of Chapter 2 of this thesis were confirmed in the current propensity score-matched observational study for GI complications and cardiovascular and renal adverse events as described in Chapter 3. Because people with OA are the highest paracetamol users, a sensitivity analysis was conducted by restricting the investigation only to people with OA. This provided a greater insight by comparing the estimates between the general adult population and people with OA.

Key findings are:

1) The SR/MA of this thesis has shown that in people with OA, the risk of diarrhoea is two folds and abnormal liver function is three times more likely to be associated with paracetamol intake when compared to placebo in the RCTs in people with OA.
2) In the short-term trials, no conclusions could be drawn about the incidence of adverse events with paracetamol versus NSAIDs and paracetamol versus Coxibs in people with OA. Many of the estimates failed to meet the requirement of statistical significance, such as diarrhoea (RR 1.48; 95%CI 0.97, 2.25 in paracetamol versus oral NSAIDs).
3) The SR/MA of observational studies showed that paracetamol exposure was associated with upper GI bleeding, peptic ulcer, hypertension, chronic kidney failure, end-stage kidney disease and increased mortality in the general adult population. A dose-response relationship was observed for the increased incidence of hypertension, myocardial infarction, and chronic renal failure.
4) The results from Chapter 3: a cohort study of this thesis, underpin the findings of SR/MA written in Chapter 2 and the other epidemiological evidence to date. An assessment of the first two prescriptions of paracetamol within six months after their 65th birthday using two models i.e., PS-matching dataset, MI/IPTW-dataset with landmark analysis, indicated a significantly increased incidence of PUB and the lower GI bleeding in the general adult population. An increased incidence was also

observed for uncomplicated ulcers in those exposed to paracetamol compared to those unexposed was estimated using MI/IPTW analysis in those aged 65 years or older. The sensitivity analysis results are consistent for lower GI bleeding in the MI/IPTW dataset.

5) Paracetamol exposure compared to the unexposed group has an increased incidence of heart failure and hypertension using PS and MI/IPTW analysis, but for myocardial infarction only in a PS-matched dataset. The sensitivity analysis estimates only accord for heart failure in PS-matched and hypertension for MI/IPTW dataset with the original cohort.
6) An exposure to paracetamol also suggested an increased incidence of chronic renal failure. While restricting only to the OA population, the sensitivity analysis results were in line with the original cohort.
7) A dose-response relationship was found only in the MI/IPTW dataset for PUB and uncomplicated ulcers. A dose-response trend was apparent for chronic renal failure in both datasets (PS-matching and MI/IPTW). Given the similar risk susceptibility, the dose-response trend did not change even when the analysis was restricted to paracetamol users only.

4.2. Implications of not restricting observational studies to people with OA

The potential advantages of observational studies in the general population included in the present SR/MA had a large sample size that better represented the entire population than RCTs and had a longer follow-up time (up to lifetime). The reason to evaluate the side effects of paracetamol regardless of any condition for which it was delivered in the observational data was justified. It was based on the assumption that the susceptibility of adverse effects due to paracetamol, such as pronounced cyclooxygenase inhibition and causing side effects analogous to NSAIDs, is expected to be similar in different populations and settings (Peryer et al., 2021). For example, the SR/MA results of RCTs in people with OA also correlate with the estimates from the SR/MA of the observational studies in the general population (such as GI and CV risks), as described in detail in section 2.5.2 (Strengths).

Additionally, most of the findings from the sensitivity analysis (restricting the cohort only to people with OA) for the current observational study agree with the original cohort, lower GI bleeding, heart failure, hypertension, and chronic renal failure. Only a few estimates from the sensitivity analysis remained inconclusive as they either failed to meet the statistical significance requirement or were marginally significant. The incidence reported in those outcomes was small but still on the higher side that needs to be notified, such as HR for PUB was 1.13 (95%CI 0.99, 1.29) in the sensitivity analysis for the present cohort study. The reason explained by Hackshaw et al. (2011) is that the marginal significant results might lose the opportunity to present the likelihood of the small risk associated with an exposure that is common but may have rare outcomes. Therefore, they suggested that estimates with borderline significance still needed to be addressed as an "indication" or `suggestion' in case of rare events. Therefore, even the estimates that were not statistically significant were on the higher side with borderline 95%CI and in agreement with the original cohort.

Thus, these findings further support the assumption stated earlier that the likelihood of paracetamol having the side effects is similar irrespective of the underlying condition for which it was prescribed. Therefore, the observational cohort study designed in the general population provided an overall estimate of side effects related to paracetamol exposure that could further be generalised to the broader population. This work will help clinicians and their patients can make an evidence-based informed decision regarding their chronic pain management based on the likelihood of a clinically relevant adverse effect.

The other reason is that the adverse effect is often not a disease-specific outcome. The investigations such as analysing the general population and analysing specific subgroups by restricting the analysis to OA people as it was done for the sensitivity analysis in the present study would allow us to understand the differences between the different populations in a better way. Hence, provide the best care accordingly.

4.3. Comprehensive description of Bradford Hill criteria

Despite the Evidence grading, systems consider RCTs to provide a higher level of certainty compared to observational studies (Atkins et al., 2004). However, Vandenbroucke's eloquent arguments published in The Lancet in 2004 drew attention to the strengths of pharmacoepidemiology in detecting the side effects of drugs (Vandenbroucke, 2004). Firstly, it was noted that RCTs are often too small. Secondly, it may not have sufficient follow-up time to detect the rare side effects or those that develop after one year. For example, according to Chapter 2 (SR/MA) of this thesis, there was only one RCT by Williams et al. (1993) that had a follow-up of 2 years. Therefore, these small scale RCTs might be insufficient or have misleading estimates for the long-term side effects of any intervention. In this context, it is suggested that an observational study, either a large-scale cohort or case control, might be beneficial for studying the long-term impacts of an intervention.

Furthermore, establishing an argument of causality plays a vital role in healthcare while reinforcing good clinical practice. Sometimes, it might require multiple longitudinal studies because the ability to interpret the current literature and apply criteria for causation accurately makes it particularly important for clinicians to improve population health. It is worth reviewing the observed associations identified in this thesis using Bradford hill criteria for causation as a framework to scrutinise this association further. The Bradford hill criteria are widely accepted and applied in the healthcare field, which might increase the rigour in establishing causation through their tools. These are the strength of an association, consistency, specificity, temporality, biological gradient, plausibility, coherence, experimental evidence, and analogy. A brief description of each aspect of the observed association between paracetamol and the outcome of interest in the current research has been presented as follows:

Strength of association

It is generally accepted that the larger the association, the more likely it is to be less biased and to reflect a causal relationship (Shimonovich et al., 2020). The magnitude of the association and statistical significance is interpreted with statistical advancement and improved computational processing power strength. In pharmacoepidemiology, the effect size of <2 suggested a weak association (Strom, 2019). The results from Chapter 2 of this thesis reported that the RR of diarrhoea was >2 for paracetamol use compared to placebo, indicating a strong association. However, it is quite challenging to find out RR >2 for side effects of intervention, especially for serious adverse effects when that marketed intervention is compared with a placebo. An explanation for this could be that the interventions with a significantly high incidence of severe adverse reactions would not be safe to be marketed (Shakir et al., 2002). The latter might be the case for having a small HR (<2) for all the outcomes in the observational study of this thesis (Chapter 3). It has also been acknowledged that a true causal factor might also be associated with a small risk increase in cases when that factor is one of those many factors operating to cause an outcome (Elwood, 2007). In pharmacoepidemiologic studies, if the RR is relatively modest for adverse drug reactions, then the second Bradford hill criteria, the consistency of findings, becomes highly important (Shakir et al., 2002).

Consistency:

Traditionally, the Bradford hill consistency criterion is upheld when multiple epidemiological studies use various locations, populations, and methods to show a consistent association or comparable results that can be reproduced. However, it is also considered that lack of consistency might not rule out a causal relationship because few of the outcomes are assumed to be produced under certain circumstances. Bradford hill highlighted the importance of repetitive findings compared to a single study that may be statistically robust but cannot expect to prove causality due to ever-present threats to internal validity. Combining the evidence from molecular experimental studies can also strengthen the epidemiological findings by providing supportive evidence for a mechanistic hypothesis by data integration. Thus, reducing the need for repetitive observational studies.

The current research findings from Chapter 3 for the safety of paracetamol for PUB, Uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, chronic renal impairment, abnormal liver function, and all-cause mortality are in line with the results from the SR/MA of Chapter 2 and the two experimental studies by Hinz et al. (2008) and Huntjens et al. (2005) and observational studies in the literature that have suggested that paracetamol has selective COX-2 inhibitory action analogous to that of NSAIDs and causing similar side effects. Additionally, the sensitivity analysis results from the current observational study are in line with its original cohort for lower GI bleeding, heart failure, hypertension, and chronic renal failure. Although the increased risk of diarrhoea is a recent new finding with sparse knowledge, the risk associated with this outcome is >2 and meets the first causal Bradford hill criteria. Additionally, the sensitive analysis of diarrhoea, including only the high-quality studies in the current SR/MA, still reported a higher risk in the paracetamol group than placebo (RR 1.86; 95%CI 1.08, 3.22). Thus, showing consistency in the causal relationship by considering several factors alongside the "exposure-to-effect" paradigm.

Specificity

This argues that the association is more likely to be causal if it is more specific, for example, if an exposure can only cause one disease and acknowledges that it might not be accurate in every situation. Because the original specificity criterion may be irrelevant from an epidemiological standpoint and may mislead the pharmacovigilance studies as certain drugs can have multiple side-effects. The latter is true for the cohort study of this thesis, as paracetamol can produce several side effects. Therefore, the cohort study of this thesis presumably did not score well for this Bradford hill specificity criterion.

Temporality

This is the only criterion where epidemiologists have a universal agreement that it is crucial for causal relationships. Bradford hill demonstrated that the exposure must precede the onset of the outcome for an exposure-outcome relationship. This criterion was met in both studies, such as diarrhoea, treatment-related adverse effects, liver function complications, GI bleeding, peptic ulcer, hypertension, chronic kidney failure as described in SR/MA Chapter 2 and PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure in Chapter 3.

Biological gradient

Bradford hill described that if a dose-response is shown in the study, the relationship is more likely to be causal (Rothman et al., 2005). The epidemiological studies included in the SR/MA of Chapter 2 supported a dose-response for GI, CV, and renal side effects. In contrast, no dose-response was observed in the observational research (Chapter 3) for PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, and hypertension in the PS-matched dataset. A dose-response was only observed for PUB, uncomplicated ulcers, and chronic renal disease in MI/IPTW dataset.

Plausibility

Sir Austin Bradford Hill had mentioned that plausibility is quite an important aspect that might be complex to understand if the mechanism is unclear (Shakir et al., 2002). In this case, he suggested considering the plausibility of the hypothesis for causal inference. Therefore, in the absence of any direct biological evidence, the biological plausibility of paracetamol exposure and the risk of diarrhoea may be hypothesized. In the traditional NSAIDs, it was thought that there is an alteration of the intestinal barrier causing increased permeability by oxidative phosphorylation inhibition in the enterocytes in the animal models (Somasundaram et al., 1997; Thiéfin et al., 2005). Hinz et al. (2012) explained that the side effects of paracetamol could be analogous to NSAIDs, such as selective COX-2 inhibition and increased permeability may cause diarrhoea. Therefore, paracetamol acts like a weak NSAID, so its side effects are credible. Malar et al. (2012) suggested that paracetamol overdose could cause severe diarrhoea in a review article. The biological plausibility of other outcomes such as GI, CV and renal events has been explained in Chapter 3, section 3.9.3 of this thesis.

Coherence

Coherence can be theoretically viewed as similar to biological plausibility. It can be considered an aspect of causal inference that indicates that the conclusion drawn from the observed association between exposure and the disease, or the outcome should correspond to the available knowledge. It should be noted that the current research area of long-term paracetamol exposure and its side effects is relatively new. Therefore, the knowledge against the observed associations evaluated is still developing. However, the current research findings agree with the expected direction of association illustrated by a few epidemiological studies for the long-term safety of paracetamol

Experiment

According to this factor, causation is more likely to be causal if the findings are based on experiments on animals or humans. The results from both studies included in this thesis are in line with two experimental studies by Hinz et al. (2008) and Huntjens et al. (2005), stating that paracetamol may have side effects similar to that of NSAIDs (also explained in Bradford hill criteria of consistency in this section previously).

In addition, large RCTs still need to ascertain the long-term paracetamol exposure and observed associations, specifically GI complications and cardiovascular and renal events. In the absence of RCTs or if RCTs are not ethically possible, prospective cohort studies may be considered the highest level of evidence. The observational cohort study included in this thesis also used the PS-matching approach to minimise the confounding by indication and MI/IPTW analysis. The PS-matched research is considered a quasi-experimental design where the baseline characteristics were clinically equipoised in both groups. Therefore, it may be viewed as the latest evidence on paracetamol safety.

Analogy

When one causal agent is unknown, the standard of evidence can be lowered for a second causal agent, which may be similar in some manner (Susser, 1991). The GI complications, cardiovascular and renal are known side effects of traditional NSAIDs. However, it is also important to note that paracetamol is also a selective inhibitor of COX-2 dependent prostaglandin PGE-2 and can cause similar adverse effects observed with NSAIDs (Hinz et al., 2012).

The Bradford hill criteria are flexible recommendations to guide epidemiological research and augment causal inference. With advancements in understanding and technology methods, any epidemiological study of causal inference needs to evolve to reflect data integration concepts. It involves incorporating traditional epidemiological evidence and conclusion, literature derived from molecular biology, toxicology other disciplines into the evaluation of causation. Bradford hill is one of the most cited concepts in health research and still upholds valid standard tools to aid causal inference (Phillips et al., 2004).

Thus, except for the specificity, both studies scored reasonably well for almost all the other measures of Bradford hill criteria. In order to demonstrate an association between an exposure and the outcome, the consistency of the findings, biological gradient and temporal sequence is mandatory and were likely to have been achieved for the research carried out for this thesis. Additionally, the biological gradient, coherence and analogy also add to the causation argument. The experimental evidence also seemed compelling; however, being an observational study design of Chapter 3 might raise minor concerns.

Lastly, the systematic application of the Bradford hill criteria adds robustness to the findings of this research.

4.4. Clinical implications and recommendations for clinicians and groups developing and updating OA guidelines

According to the existing guidelines for OA, high-risk groups such as older people are encouraged to use paracetamol due to its perceived safety. The health professional decision is largely based on calculating risk, efficacy, and tolerability. If paracetamol provides adequate pain relief, patients may be willing to accept the risk of adverse effects demonstrated in this research. However, according to previous SRs, its analgesic benefit is not clinically significant, so adverse effects may outweigh its benefits. The recent SR/MA of RCT in people with OA and observational studies (irrespective of any underlying condition) described in Chapter 2 of this thesis and the population-based propensity score-matched cohort study written as Chapter 3 of this thesis have indicated the high incidence of adverse effects, where the likelihood of confounding by indication has been minimised. It has identified an increased risk of diarrhoea, treatment-related effects, abnormal liver function, PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal failure. Therefore, there is a great need to make clinicians aware of the adverse effects of paracetamol at its standard therapeutic dose. A dose-response relationship was observed for GI events, cardiovascular and renal adverse events in present SR/MA (Chapter 2) and the observational study (Chapter 3) for PUBs and renal events.

Clinicians who participate in prescribing paracetamol need to limit the dose (not to exceed 3.25 g/day) and duration (not more than 5 days), because its most prolonged prescription was with a mean duration of 84 months, according to a cross-sectional survey from five European countries (Kingsbury et al., 2014; Lacy et al., 2007). Notably, certain health authorities have already altered their guidelines based on preliminary findings of a few narrative reviews and epidemiological studies. The ACR, OARSI, and European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) recommend a conditional use of paracetamol as a single intervention. According to Zeng et al. (2021) report on analgesics prescriptions in the UK, there was a high incidence of paracetamol prescriptions reported in OA patients with a history of GI-event. Therefore, paracetamol should be restricted or occasionally used in patients with contraindications for traditional NSAIDs and COX-2 inhibitors. According to recent updates in the pharmacology of paracetamol, its side effects such as PUB, uncomplicated ulcers, lower GI bleeding, heart failure, myocardial infarction, hypertension, and chronic renal disease are analogous to those of NSAIDs.

This could be further explained by providing an example from the present SR/MA of RCTs in people with OA. The risk of diarrhoea was higher in the participants in the paracetamol group in a head-to-head comparison with oral NSAIDs in people with OA (RR 1.48, 95%CI 0.97, 2.25). Although the estimates are borderline significant, they still have clinical importance and could be used to address the concerns regarding the relative safety of paracetamol to that of NSAIDs.

The guidelines also need to consider the over-the-counter availability of paracetamol and oral NSAIDs because the over-the-counter usage of these analgesics was 15-30% (Kingsbury et al., 2014). According to one RCTs by Doherty et al. (2011) included in the SR/MA of this thesis examined, the effects of paracetamol 3g/day and ibuprofen 1200mg/day were associated with a similar amount of occult blood loss. It indicates that guidelines need to revise the over-the-counter use of such drugs. Therefore, over-the-counter buying of paracetamol is required to be restricted to up to 1-2 packs of 16 tablets.

Dagli et al. (2014) stated that ageing is a public health issue worldwide. According to WHO (2021), one in every six will be an older person by 2030, i.e., aged 60 or above, increasing from 1 billion in 2020 to 1.4 billion. By 2050, this number would be doubled and increase to 2.1 billion. This demographic transition in the elderly population constitutes a significant challenge to the health authorities in the world due to an increase in multiple chronic diseases such as hypertension, diabetes mellitus, arthritis, chronic heart failure, and renal impairment. As a result, older adults tend to take plenty of medications, referred to as polypharmacy. Older people are among the highest users of analgesics. According to a prospective cohort study (n=149) of the prescribed pain reliefs for the older population aged >75 years in France. 96% of participants received paracetamol, 66% at least any other analgesic, and the reason for the pain was predominantly OA (Chevé et al., 2018). Paracetamol is the most commonly used standard first-line treatment for different painful conditions. The efficacy of paracetamol is relatively poor. Due to the lack of adequate or tolerant alternatives, its use is driven by the perceived belief of relative safety. This research suggests an increased risk of adverse events with long-term paracetamol use. Although there are few limitations to interpreting the results, this study challenges the perceived safety of paracetamol. It may even be that the true risk of paracetamol may be higher than that determined in the current study.

However, the findings from this research might modify the current recommendations and guidelines for chronic pain conditions such as OA and help clinicians discuss these side effects with patients when considering treatment with paracetamol.

4.5. Future recommendations for further research

This research has only investigated the GI, cardiovascular, and renal side effects. There is still a need to identify all cause-mortality with long-term use of paracetamol. For mortality, this will require additional data from ONS. In addition, the cardiovascular outcome such as myocardial infarction needs to be examined again, as the estimates were inconsistent in both statistical analyses. More information regarding the relative safety of paracetamol to NSAIDs and Coxibs would help us establish safer treatment options as they are considered as primary treatment options to manage OA pain. In the cohort study, a sensitivity analysis was performed for the OA population therefore, future work would be needed to identify the safety of paracetamol in different population groups.

Few estimates in the SR/MA lacked statistical significance, which could be due to a lack of appropriate sample size or the operational definition of adverse events. Therefore, there is a need to increase the awareness and interest regarding the operational definitions, monitoring, and reporting of the adverse events in the RCTs. It will further increase the confidence of review authors to ascertain the presence of outcomes if they are pre-specified properly. By contrast, review authors might restrain to report from the incidental findings or composite definitions (serious adverse events, treatment-related effects) findings regarding lack of harm unless there is robust evidence to capture any event of interest. They are a valuable resource for assessing the risk-benefit ratio of any intervention but might go unreported due to composite operational definitions.

Future research is required to address some of the limitations encountered during this research, specifically in the cohort study. This study used prescription data to define paracetamol exposure, similar to other previous observational studies. However, this limits the impact of overall usage of paracetamol since it is an over-the-counter drug. In the UK, there is no provision to calculate the effect of non-prescribed paracetamol.

However, the health authorities should revise their over-the-counter availability of the drugs or may start to reimburse for the prescribed drugs such as paracetamol and NSAIDs that are widely available over the counter. It might improve the records of the over-the-counter availability of such drugs and help the researchers estimate the adverse events associated with these drugs. Secondly, there is a need for a validation study using large-scale PS-matching that could incorporate unmeasured confounders such as open-angle glaucoma and using another population-based database such as The Health Improvement Network.

Lastly, unlike other drugs, paracetamol is an analgesic often used episodically. It is challenging to define paracetamol users and non-users. The current cohort study defined the paracetamol exposure as two or more prescriptions within 6 months. This provided an exposure window of one year to calculate the cumulative doses during that period aiming to catch some longer-term dose-response relationships. However, the use of paracetamol and its doses may change during the follow-up, not just in the exposure window. Immortal time bias will not just occur within the exposure window but during the entire follow-up period. Therefore, there is a need to use time-varying exposure analysis to cope with the dynamic changes in paracetamol use, depending on the paracetamol prescriptions after the landmark date.

4.6. Conclusion

This thesis includes a comprehensive evaluation of literature SR/MA (RCTs and observational studies) and a quasi-experimental propensity score matched cohort study using a large population-based CPRD-data. It has provided the best evidence-based estimates regarding the risk of important adverse effects associated with paracetamol with a detailed assessment of paracetamol safety in the people with OA and the general population aged 65 years and above. The estimates presented in this thesis from both studies (SR/MA and cohort study of this thesis), including two statistical approaches used in the cohort study of this thesis, produced consistent results, which adds further reliability to the estimates. Although, the findings from an observational study design might be susceptible to residual confounding. However, these findings do indicate a potential increased risk for most of the adverse outcomes associated with paracetamol and add on to the argument led by NICE guidelines in 2014 that paracetamol is not as safe as it was thought.

Therefore, it becomes important to highlight that every prescription decision should depend on the risk and benefit ratio and the trade-off between effectiveness and safety. Given the uncertain analgesic benefit of paracetamol, careful consideration of the long-term use of paracetamol is warranted, especially in older people, and its over-the-counter usage should be limited.

Lastly, the guidelines supporting paracetamol as a standard treatment for OA and other musculoskeletal pain also need further modifications.

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Appendix 1: Systematic review and meta-analysis (methods)

1.1. Search Strategy for Medline for randomised controlled trial for Paracetamol: searched on OVID interface: Randomized Controlled trials

1. Paracetamol.mp
2. Paracetamol.mp.
3. Panadol.mp
4. Tylenol.mp.
5. Acetaminophen.mp.
6. Analgesic
7. Acamol.mp
8. Acephen.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. randomized controlled trial.pt.
11. randomised controlled trial.pt
12. random allocation.pt
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo. ab
16. drug therapy.fs.
17. randomly. ab
18. trial.ab.
19. groups.ab.
20. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. Osteoarthritis or osteoarthrosis
24. knee osteoarthritis or hip osteoarthritis or hand osteoarthritis
25. (osteoarthr* or OA or arthritis or Degenerative arthritis or degenerative joint disease or arthrosis or osteoarthrosis).af.
26. 24 or 25
27. 9 and 22 and 26

1.2. Search Strategy for Paracetamol for Observational studies (Medline): searched on OVID interface

1. Paracetamol.mp.
2. Panadol.mp.
3. Tylenol.mp.
4. Acetaminophen.mp.
5. Acamol.mp.
6. 1 or 2 or 3 or 4 or 5 or 6
7. exp cohort analysis/
8. cohort$.tw.
9. exp longitudinal study/
10. exp prospective study/
11. exp case-control studies/
12. (case$ and control$).tw.
13. case control. ti, ab.
14. (cohort adj (study or studies or analys*)). ti, ab.
15. exp follow up/
16. ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)). ti, ab.
17. ((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort*)). ti, ab.
18. or/7-17
19. cross sectional studies.mp.
20. cross-sectional studies/
21. observational studies.mp.
22. 18 or 19 or 20 or 21
23. exp animals/ not humans.sh.
24. 22 not 23
25. (gastrointestinal bleeding or duodenal ulcer or peptic ulcer).mp.
26. (heart failure or cardiovascular diseases or cardiovascular failure or myocardial infarction).mp.
27. (acute renal failure or kidney failure or renal failure).mp.
28. 25 or 26 or 27
29. 6 and 22 and 28

1.3. Search strategies for Embase search terms: searched on OVID interface

1. exp paracetamol/
2. (paracetamol or acetaminophen or panadol or tylenol or acetominophen or acamol or acephen). ti, ab.
3. or/1-2
4. (gastrointestinal bleeding or duodenal ulcer or peptic ulcer).mp.
5. (heart failure or cardiovascular diseases or cardiovascular failure or myocardial infarction).mp.
6. (acute renal failure or kidney failure or renal failure).mp.
7. or/4-6
8. 3 and 7
9. clinical study/
10. exp case control study/
11. family study/
12. longitudinal study/
13. retrospective study
14. prospective study/
15. cross-sectional study/
16. cohort analysis/
17. follow-up/
18. cohort*. ti, ab.
19. 9 and 10
20. case control. ti, ab.
21. (cohort adj (study or studies or analys*)). ti, ab.
22. ((follow up or observational or uncontrolled or non randomi#ed or nonrandomi#ed or epidemiologic*) adj (study or studies)). ti, ab.
23. ((longitudinal or retrospective or prospective or cross sectional) and (study, studies, or review
24. or analys* or cohort*)). ti, ab.
25. or/9-23
26. 8 and 24

Appendix 2: Data extraction and Quality assessment forms

2.1. Appendix: Data-extraction form Paracetamol – Systematic review - Data Extraction (RCTs).

Report ID:		Date form completed:
First author:	Year of study:	Review Author:

1. General Information

Country:	
Source of funding: Public □ Commercial □ Not mentioned □	
Language:	Setting: Hospital □ Community □ unclear □
Disease: Osteoarthritis Site Knee □ Hip □ Hand □ Other □	
Diagnosis: Clinical □ Radiological □ Other/Unclear □ Pain □ Physical function □ Stiffness □ American college of Rheumatology criteria □ Patient Global Assessment □	

2. Study Methods

A) Study Characteristics
Efficacy Adverse Effects Both

Study type Randomised
Blinding Single Double Triple
Placebo-controlled Comparative-study
Study Centres: Multi/Single
Study design Cross Over Parallel other
Washout period/ Run in – Yes/No
Rescue medicine use during wash out period – Yes/NO
Name/ dose and duration of Rescue medication

Number of arms

	Arm-1	Arm- 2	Arm- 3	Arm-4
Drug				
Formulation	Tablets capsules Instant release Extended Sustained Effervescent Caplets	Tablets capsules Instant release Extended Sustained Effervescent Caplets	Tablets capsules Instant release Extended Sustained Effervescent Caplets	Tablets capsules Instant release Extended Sustained Effervescent Caplets
Dose	Number of times/day that treatment is taken			
Frequency –Number of times /day treatment taken	Number of times/day that treatment is taken			
Duration of intervention in weeks	Number of weeks treatment is prescribed for participant			
Time of follow up in weeks	The timing, in weeks after baseline, when outcome measures are assessed			

3. Participant's characteristics:

Total patients randomised to the trial -

Demographics	Arm-1	Arm2	Arm-3	Arm-4
Age (mean +/- SD)				
Female %				
Mean BMI				
Number of withdrawals				

4. Quality

Domain	Review authors' judgement	Reasons	Instructions
Random sequence generation1	High risk Unclear Low risk		Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment	High risk Unclear Low risk		Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	High risk Unclear Low risk		Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Note that the impact of performance bias must be considered and reported even if blinding of participants and/or personnel is not possible for the type of intervention being evaluated2,3
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	High risk Unclear Low risk		1. Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. 2. Provide any information relating to whether the intended blinding was effective. Blinding of outcome assessment can be feasible even if blinding of participants and personnel is not.
Incomplete outcome data Assessments should be made for each main outcome (or	High risk Unclear Low risk		Describe the completeness of outcome data for each main outcome, including attrition (loss to follow up, withdrawn) and exclusions from the analysis. Note that the participant numbers and reasons reported in the 'Participants'

class of outcomes)			section of this form (below) should be used as a basis for making these decisions. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Conduct			
Are definitions of reported adverse effects given	High risk □ Unclear □ Low risk □		
Were the methods used for monitoring adverse effects reported?	High risk □ Unclear □ Low risk □		Use of prospective or routine monitoring; spontaneous reporting; patient-checklist, questionnaire, or diary. Systematic survey of patients
Selective reporting	High risk □ Unclear □ Low risk □		State how the review authors examined the possibility of selective outcome reporting, and what was found.
Reporting			
Were any patients excluded from the adverse effects analysis?	High risk □ Unclear □ Low risk □		
Does the report provide numerical data by intervention group?	High risk □ Unclear □ Low risk □		
Did investigators report on all important or serious adverse effects?	High risk □ Unclear □ Low risk □		
Other sources of bias	High risk □ Unclear □ Low risk □		State any important concerns about bias not addressed in the other domains in the tool.

5. Other Outcomes				
Extract all the outcomes at all durations of follow-up presented in the study.				
Analysis – Intention to treat per-protocol population values Unclear				
Treatment compliance Yes No				
Rescue medication or any other treatment related to disease considered in analysis Yes No Unclear				
List of concomitant drugs related to disease if any -				
6. Adverse effects				
Which categories of adverse effects do the investigators report?				
Please indicate the type of adverse events (AEs) and numbers affected by in each group.				
Number of adverse events after randomisation				
Number of adverse events Number of patients				
Systematic				
Gastrointestinal				
Upper – Nausea/				
Vomiting				
Pain				
Discomfort/				
Dyspepsia				
Bleeding				
Perforation				
Lower – Diarrhoea				
Rectal bleeding				
Others				
Cardiovascular				
Hypertension				
Cardiac attack				
Heart failure				
Others				
Renal -				
Chronic renal failure				
Acute renal failure				

2.2. Modified Risk of bias assessment for RCTs Guide.

Domain	Review authors' judgement	Instructions
Random sequence generation1	High risk Unclear Low risk	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation concealment	High risk Unclear Low risk	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	High risk Unclear Low risk	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Note that the impact of performance bias must be considered and reported even if blinding of participants and/or personnel is not possible for the type of intervention being evaluated2,3
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	High risk Unclear Low risk	1. Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. 2. Provide any information relating to whether the intended blinding was effective. Blinding of outcome assessment can be feasible even if blinding of participants and personnel is not.
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	High risk Unclear Low risk	Describe the completeness of outcome data for each main outcome, including attrition (loss to follow up, withdrawn) and exclusions from the analysis. Note that the participant numbers and reasons reported in the 'Participants' section of this form (below) should be used as a basis for making these decisions. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
Selective reporting	High risk Unclear Low risk	State how the review authors examined the possibility of selective outcome reporting, and what was found.
Other sources of bias	High risk Unclear Low risk	State any important concerns about bias not addressed in the other domains in the tool.

2.3. Modified Newcastle -Ottawa Scale for cohort studies

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

No.	Criterion	Decision rule	Score (*=1, no*=0)	Location in text
SELECTION				
1	Representativeness of the exposed cohort	a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population* b) Not satisfying requirements in part (a), or not stated.		
2	Selection of the non-exposed cohort	a) Selected from the same source population* b) Selected from a different source population c) No description		
3	Ascertainment of exposure	a) Structured injury data (e.g. record completed by medical staff)* b) Structured interview* c) Written self-report d) No description		
4	Demonstration that outcome of interest was not present at the start of the study	a) Yes* b) No or not explicitly stated		
COMPARABILITY				
1	Comparability of cohorts on the basis of the design or analysis	a) Study controls for previous injury* b) Study controls for age* *Note:* Exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for in the analysis. Alone statements of no differences between groups or that differences were not statistically significant are not sufficient.		
OUTCOME				
1	Assessment of outcome	a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records (e.g. imaging, structured injury data, etc.)* b) record linkage (e.g. identified through ICD codes on database records)* c) Self-report with no reference to original structured injury data or imaging d) No description		
2	Was follow-up long enough for outcomes to occur?	a) Yes (≥3 months)* b) No (<3 months)		
3	Adequacy of follow up of cohorts	a) Complete follow up – all participants accounted for* b) Subjects lost to follow up unlikely to introduce bias (<15% lost to follow up, or description provided of those lost*) c) Follow up rate <85% and no description of those lost provided d) No statement		
		SCORE:		

2.4. Modified Newcastle Ottawa Scale for case-control studies

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

CASE-CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

No.	Criterion	Decision rule	Score: (*=1 no*=0)	Location in text
SELECTION				
1	Is the case definition adequate?	a) Yes, with independent validation (>1 person/record/time/process to extract information, or reference to primary record source such as x-rays or structured injury data)* b) Yes, based on self-reports c) No description		
2	Representativeness of the cases	a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined team/competition/sport, or a random sample of those cases* b) Not satisfying requirements in part (a), or not stated.		
3	Selection of controls	a) Controls were selected from the same source population as the cases* b) controls were selected from a different source population c) no description		
4	Definition of controls	a) If cases are first occurrence of injury of interest, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of specific injury, then controls with previous occurrences of outcome of interest should not be excluded* b) No description of injury history		
COMPARABILITY				
1	Comparability of cases and controls on the basis of the design or analysis	a) Study controls for previous injury* b) Study controls for age* *Note:* Cases and controls must be matched in the design and/or confounders must be adjusted for in the analysis. Alone statements of no differences between groups or that differences were not statistically significant are not sufficient.		
EXPOSURE				
1	Ascertainment of exposure	a) Structured injury data (e.g. record completed by medical staff)* b) Structured interview where blinded to case/control status* c) Interview not blinded to case/control status d) Written self-report or medical record (unstructured data) only e) No description		
2	Same method of ascertainment for cases and controls	a) Yes* b) No		
3	Non-response rate	a) Same for both groups* b) Non-respondents described c) Rate different and no designation		
		SCORE:		

Appendix 3: Systematic review and meta-analysis (Results)

Table 3.1. Characteristics of the included studies.

Study	Year	No of the participants In intervention group (n)	Paracetamol dose (gm)	Duration of follow up (weeks)
Amadio	1983	25	4	6
Bradley	1991	66	4	4
Williams	1993	88	2.6	104
March	1994	25	2	12
Zoppi	1995	30	1.5	1
Lequesne	1997	192	3	1.5
Lee	1998	52	3.9	8
Pincus	2001	227	4	12
Geba	2002	94	4	6
Richard	2004	405	4	6
Boureau	2004	111	3	2
Golden	2004	148	4	1
Pincus PACES-I	2004	300	1	6
Pincus PACES-II	2004	331	1	6
Altman	2006	318	1.95+3.9*	12
Temple	2006	290	4	52
Beaumont	2007	108	3	24
Gualda	2007	86	3	6
Yelland	2007	59	3.9	12
Schnitzer	2008	136	3.9	4
Doherty	2011	222	3	13
Prior	2014	267	3.9	12
Verkleji	2014	52	3	2
Reed	2018	471	4+3.9*	12

The studies with * denote a combination of two arms.

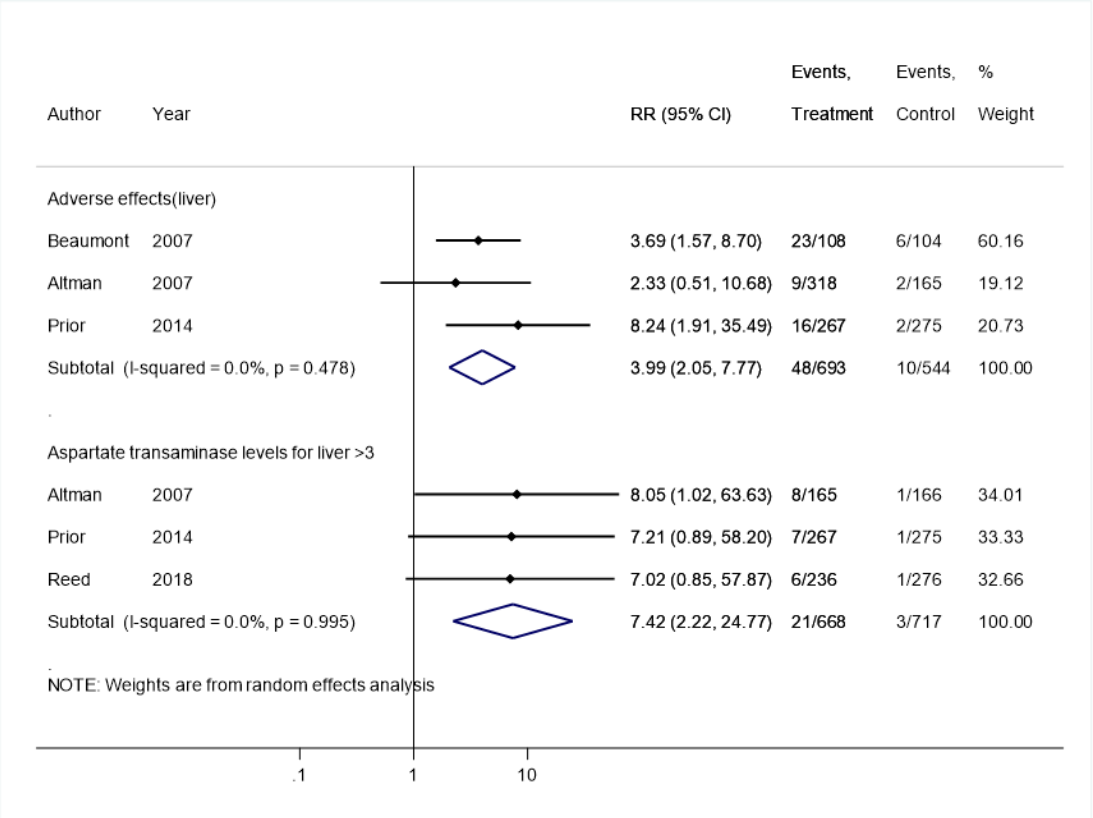


Figure 3.2. Forest plot for paracetamol exposure association with adverse liver effects in comparison to placebo for randomised controlled trials.

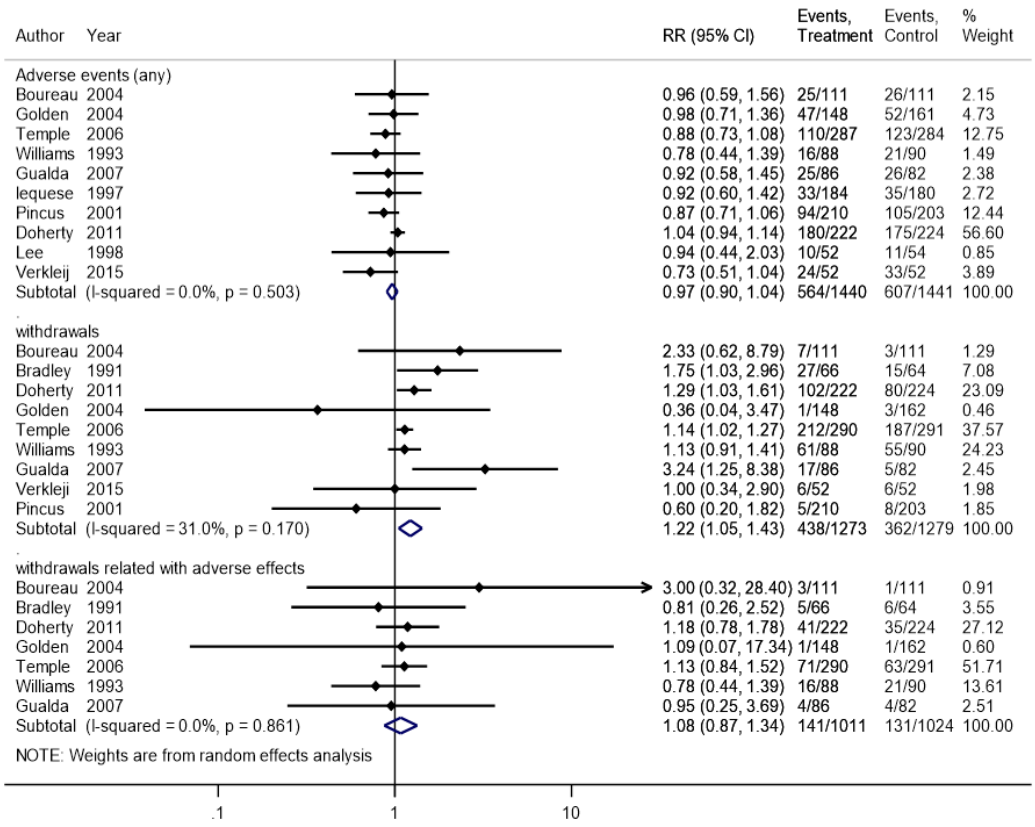


Figure 3.3. Forest plot for secondary outcomes for paracetamol exposure versus NSAIDs.

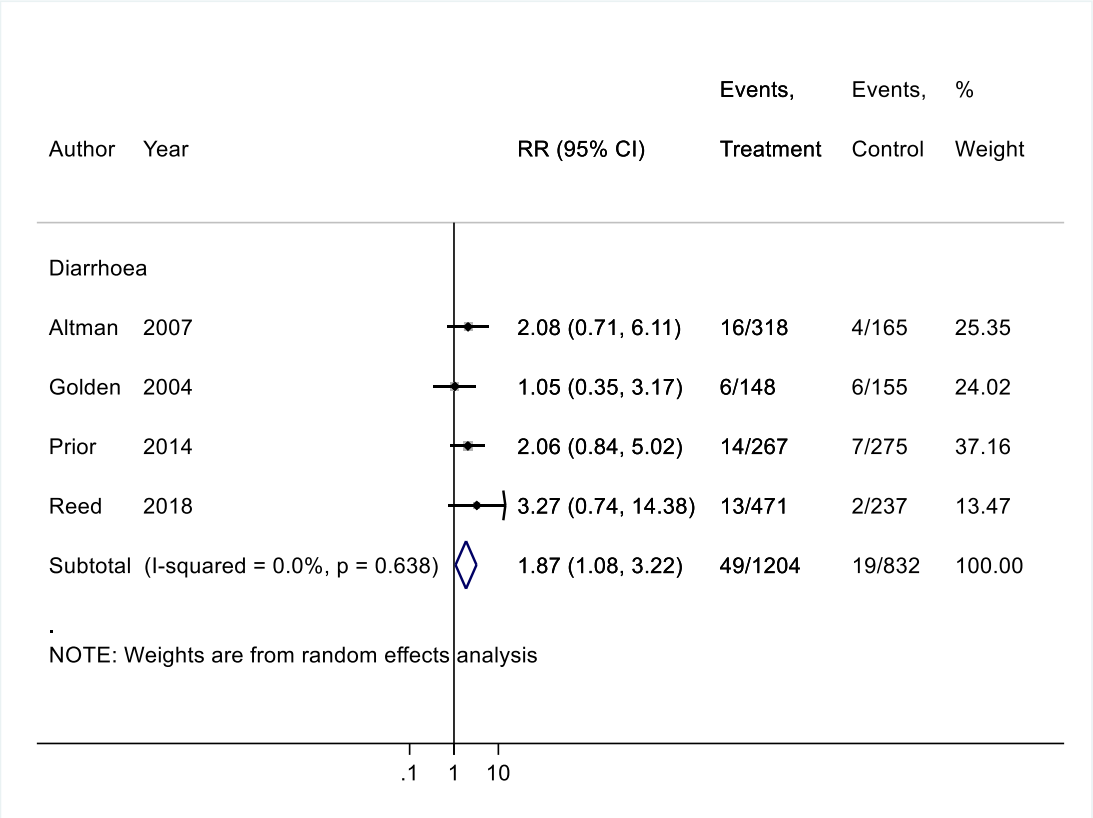


Figure 3.4. Sensitivity analysis for Diarrhoea excluding cross-over trials. RR= risk ratio, CI= confidence interval.

Appendix 4: Cohort Study

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING CPRD DATA

FEEDBACK TO APPLICANTS

CONFIDENTIAL			***by e-mail***
PROTOCOL NO:	19_131R		
PROTOCOL TITLE:	Incidence of adverse effects related with long-term use of paracetamol: a propensity score matched cohort study		
APPLICANT:	Prof Weiya Zhang University of Nottingham weiya.zhang@exmail.nottingham.ac.uk		
APPROVED ☐	**APPROVED WITH COMMENTS (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐

INSTRUCTIONS:

Protocols with an outcome of 'Approved' or 'Approved with comments' do not require resubmission to the ISAC.

REVIEWER COMMENTS:

Please address the following comments, revising the protocol as necessary and highlighting all changes:

The definitions around index date/inclusion criteria/exposure window/landmark date seem to increase the potential for bias in this study. The use of a landmark date a year after index date leave a window of a year during which patients cannot have an outcome (immortal time) and the inclusion criteria is for two prescriptions but the index date is listed as the date of the first prescription. Additionally, the use of the new user design and the limitations around OTC medication that have been previously discussed will complicate things further.

There are some tricky decisions to make around the study design and I would urge the applicants to think through their approach carefully and interpret any results with a great deal of caution as these may be challenged due to the definitions mentioned.

APPLICANT FEEDBACK:

Dear Reviewers

Many thanks indeed for your suggestions to improve this protocol. We very much appreciate your valuable feedback. We have made the changes according to your comments and highlighted them in yellow in the attached file.

The following are brief responses to your comments:

Figure 4.1. ISAC approval for propensity score-matched cohort study.

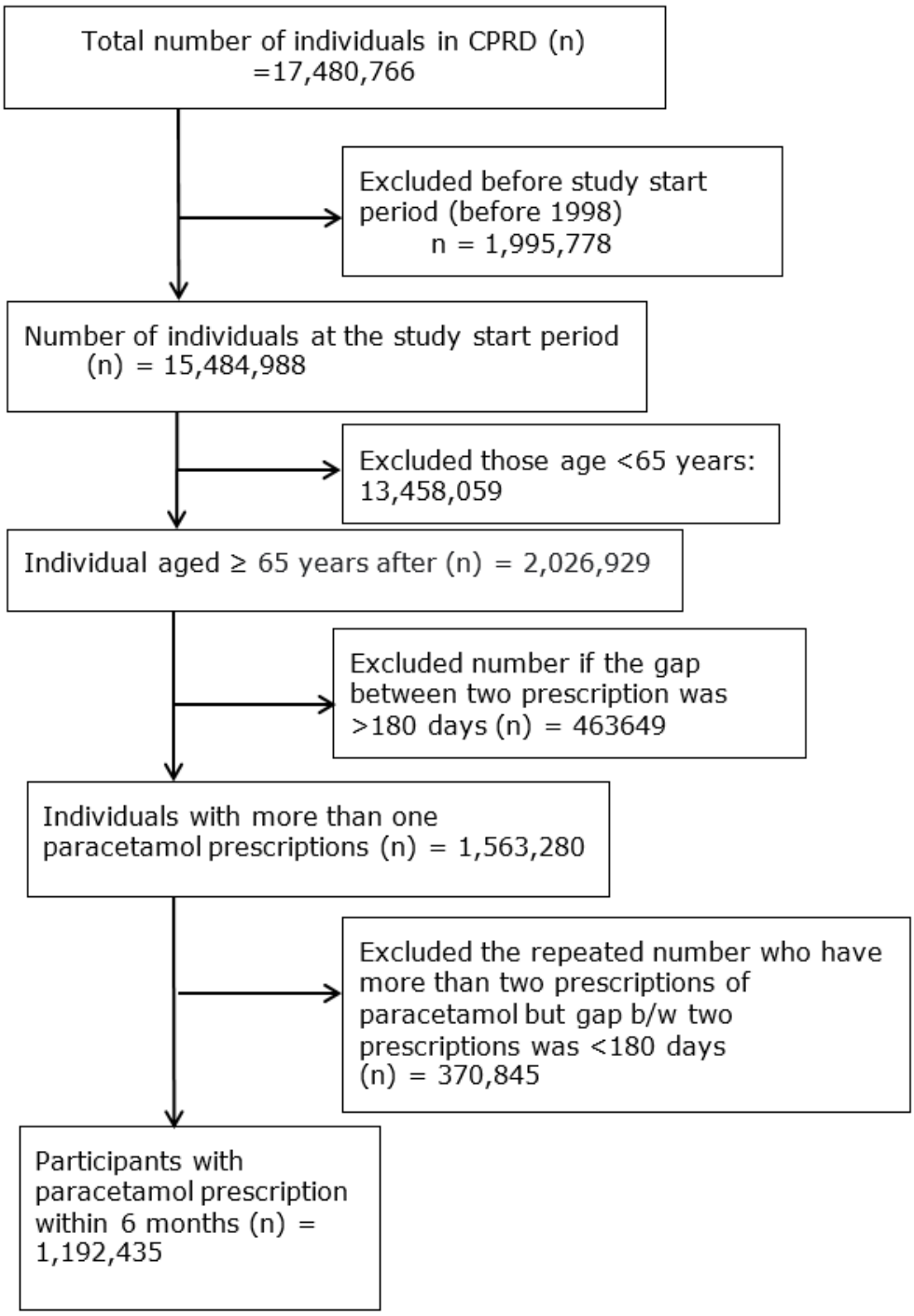


Figure 4.2. Feasibility count.

Table 4.1. List of co-morbidities included in Charlson Comorbidity Index for Gastrointestinal events.

Co-morbidities	Before PS-matching		After PS-matching	
	Paracetamol exposed	Paracetamol unexposed	Paracetamol exposed	Paracetamol unexposed
Cardiovascular	33,443 (18.53)	43,376 (10.78)	15,049 (19.04)	12,719 (16.09)
Rheumatic	11,957 (6.63)	12,692 (3.15)	5,553 (7.03)	5,248 (6.64)
Peripheral vascular diseases	10,736 (5.95)	14,497 (3.60)	5,278 (6.68)	5,227 (6.61)
Peptic ulcer	11,018 (6.10)	14,187 (3.52)	5,404 (6.84)	4,887 (6.18)
Metastatic cancer	1,946 (1.08)	2,874 (0.71)	857 (1.08)	1,165 (1.47)
Moderate liver disease	462 (0.26)	685 (0.17)	210 (0.27)	217 (0.27)
Mild liver disease	226 (0.13)	317 (0.08)	105 (0.13)	107 (0.14)
Myocardial infarction	15,849 (73.74)	22,431 (74.87)	9,872 (74.79)	6,839 (65.55)
Hemplagia	1,240 (0.69)	1,532 (0.38)	540 (0.68)	472 (0.60)
Diabetes no complications	20,627 (11.43)	29,006 (7.21)	9,462 (11.97)	8,670 (10.97)
Diabetes end complications	2,998 (1.66)	4,242 (1.05)	1,393 (1.76)	1,328 (1.68)
COPD	27,302 (15.13)	43,924 (10.91)	13,549 (17.14)	14,717 (18.62)
Congestive heart failure	40,567 (22.48)	56,443 (14.02)	20,673 (26.16)	17,790 (22.51)
Chronic kidney disease	21,803 (12.08)	25,683 (6.38)	9,531 (12.06)	8,069 (10.21)
Cancer	23,608 (13.08)	32,587 (8.10)	10,635 (13.46)	10,787 (13.65)
AIDS	6 (0.00)	9 (0.00)	2 (0.00)	4 (0.01)
Dementia	20,406 (11.31)	17,527 (4.35)	6,791 (8.59)	4,483 (5.67)

PS - propensity score, AIDS - Acquired Immuno Deficiency Syndrome.

Table 4.2. List of co-morbidities included in Charlson Comorbidity Index for cardiovascular events.

Co-morbidities	Before PS-matching		After PS-matching	
	Paracetamol exposed	Paracetamol unexposed	Paracetamol exposed	Paracetamol unexposed
Cardiovascular	33,443 (18.53)	43,376 (10.78)	15,049 (19.04)	12,719 (16.09)
Rheumatic	11,957 (6.63)	12,692 (3.15)	5,553 (7.03)	5,248 (6.64)
Peripheral vascular diseases	10,736 (5.95)	14,497 (3.60)	5,278 (6.68)	5,227 (6.61)
Peptic ulcer	11,018 (6.10)	14,187 (3.52)	5,404 (6.84)	4,887 (6.18)
Metastatic cancer	1,946 (1.08)	2,874 (0.71)	857 (1.08)	1,165 (1.47)
Moderate liver disease	462 (0.26)	685 (0.17)	210 (0.27)	217 (0.27)
Mild liver disease	226 (0.13)	317 (0.08)	105 (0.13)	107 (0.14)
Myocardial infarction*	15,849 (73.74)	22,431 (74.87)	9,872 (74.79)	6,839 (65.55)
Hemplagia	1,240 (0.69)	1,532 (0.38)	540 (0.68)	472 (0.60)
Diabetes no complications	20,627 (11.43)	29,006 (7.21)	9,462 (11.97)	8,670 (10.97)
Diabetes end complications	2,998 (1.66)	4,242 (1.05)	1,393 (1.76)	1,328 (1.68)
COPD	27,302 (15.13)	43,924 (10.91)	13,549 (17.14)	14,717 (18.62)
Congestive heart failure	40,567 (22.48)	56,443 (14.02)	20,673 (26.16)	17,790 (22.51)
Chronic kidney disease	21,803 (12.08)	25,683 (6.38)	9,531 (12.06)	8,069 (10.21)
Cancer	23,608 (13.08)	32,587 (8.10)	10,635 (13.46)	10,787 (13.65)
AIDS	6 (0.00)	9 (0.00)	2 (0.00)	4 (0.01)
Dementia	20,406 (11.31)	17,527 (4.35)	6,791 (8.59)	4,483 (5.67)

PS - propensity score, AIDS - Acquired Immuno Deficiency Syndrome, COPD - Chronic Obstructive Pulmonary Disease, (*) myocardial infarction was excluded in myocardial infarction as an outcome from this index.

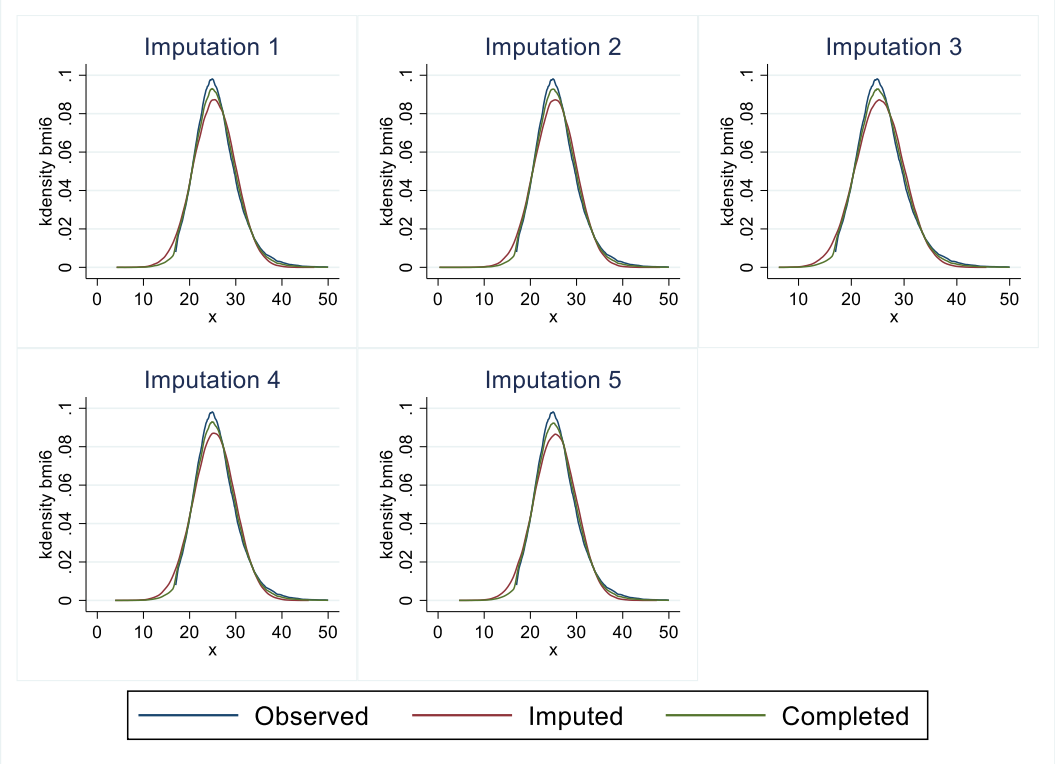


Figure 4.3. The distribution of observed, imputed, and completed dataset for BMI after five imputations for heart failure.

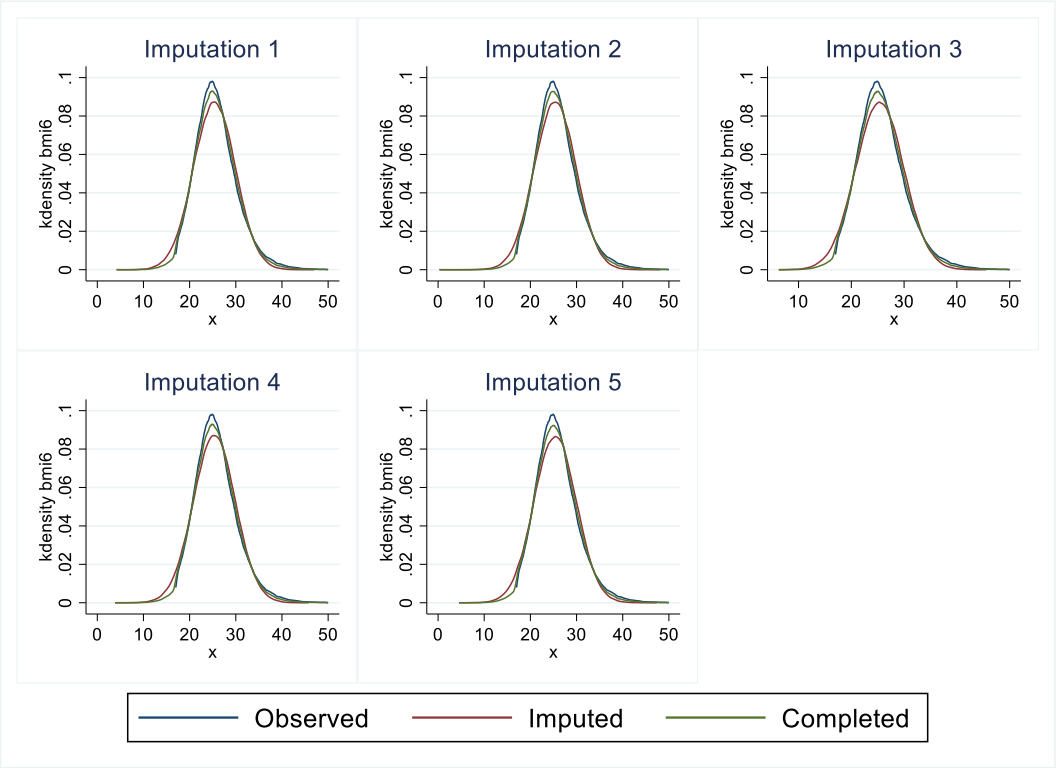


Figure 4.4. The distribution of observed, imputed, and completed dataset for BMI after five imputations for myocardial infarction.

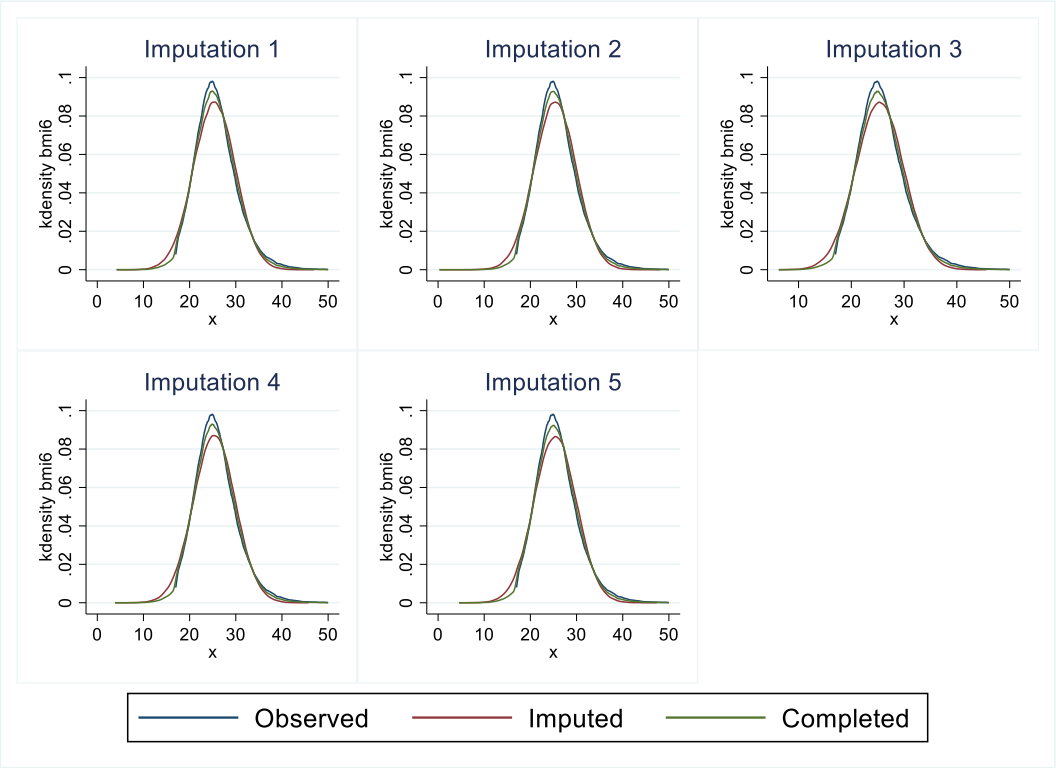


Figure 4.5. The distribution of observed, imputed, and completed dataset for BMI after five imputations for hypertension.

Table 4.3. List of co-morbidities included in Charlson Comorbidity Index for chronic renal events.

Comorbidities included in CCI	Paracetamol exposed	Paracetamol unexposed	Paracetamol exposed	Paracetamol unexposed
Cerebrovascular disease	33,519 (18.54)	43,477 (10.78)	14,740 (19.12)	12,597 (16.34)
Rheumatological conditions	11,982 (6.63)	12,725 (3.16)	5,427 (7.04)	5,207 (6.75)
Peripheral vascular disease	10,756 (5.95)	14,520 (3.60)	5,233 (6.79)	5,175 (6.71)
Peptic ulcer	11,035 (6.10)	14,213 (3.52)	5,171 (6.71)	4,836 (6.27)
Metastatic tumour	1,953 (1.08)	2,877 (0.71)	930 (1.21)	1,154 (1.50)
Myocardial infarction	15,873 (73.73)	22,479 (74.89)	9,988 (76.47)	6,729 (75.55)
Moderate liver disease	463 (0.26)	687 (0.17)	223 (0.29)	215 (0.28)
Mild liver disease	226 (0.12)	318 (0.08)	96 (0.12)	105 (0.14)
Hemiplegia	1,240 (0.69)	1,534 (0.38)	552 (0.72)	461 (0.60)
Dementia	20,470 (11.32)	17,560 (4.36)	7,454 (9.67)	4,421 (5.74)
Diabetes with no complications	20,653 (11.42)	29,053 (7.21)	9,261 (12.01)	8,603 (11.16)
Diabetes with end stage complications	3,001 (1.66)	4,248 (1.05)	1,409 (1.83)	1,319 (1.71)
COPD	27,345 (15.12)	43,999 (10.91)	13,181 (17.10)	14,573 (18.91)
Congestive heart failure	40,637 (22.47)	56,541 (14.02)	20,919 (27.14)	17,587 (22.82)
Cancer	23,648 (13.08)	32,638 (8.09)	10,618 (13.77)	10,675 (13.85)
AIDS	6 (0.00)	9 (0.00)	2 (0.00)	4 (0.01)

PS - propensity score, AIDS - Acquired Immuno Deficiency Syndrome, COPD - Chronic Obstructive Pulmonary disease.

Appendix 5: Product Codes

5.1. Exposure variable paracetamol.

prodcode	product name	drug substance	strength
7	Paracetamol 500mg Tablets	Paracetamol	500mg
139	Paracetamol 500mg capsules	Paracetamol	500mg
258	Panadol 500mg Tablets (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
1609	Paracetamol 500mg soluble Tablets	Paracetamol	500mg
1862	Paracetamol 500mg/5ml oral suspension sugar free	Paracetamol	500mg/5ml
2800	Panadol 500mg Soluble Tablet (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
3313	Calpol six plus 250mg/5ml Oral suspension sugar free (McNeil Products Ltd)	Paracetamol	250mg/5ml
4186	Paracetamol 250mg/5ml oral suspension sugar free	Paracetamol	250mg/5ml
5239	Paracetamol 1g oral powder sachets	Paracetamol	1gram
6571	Paracetamol 240mg oral powder sachets sugar free	Paracetamol	240mg
7205	Panadol 500mg capsules (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
9712	Paracetamol 250mg or dispersible Tablets sugar free	Paracetamol	250mg
9914	Calpol Six Plus Fast melts 250mg Tablets (McNeil Products Ltd)	Paracetamol	250mg
10748	Tramil 500mg Capsule (Wyeth Consumer Healthcare)	Paracetamol	500mg
15238	Paracetamol 500mg Tablets (Zentiva)	Paracetamol	500mg
18799	Flu strength hot lemon 1g Powder (A H Pharmaceuticals Ltd)	Paracetamol	1gram
20068	Paracetamol 250mg/5ml oral suspension sugar free	Paracetamol	250mg/5ml
20116	Paradote 100mg/500mg Tablets (Sinclair IS Pharma Plc)	Paracetamol	500mg
22288	Medinol 250mg/5ml Oral suspension (SSL International Plc)	Paracetamol	250mg/5ml
23716	Paracetamol 500mg caplets (IVAX Pharmaceuticals UK Ltd)	Paracetamol	500mg
23840	Panasorb 500mg Tablet (Sanofi-Synthelabo Ltd)	Paracetamol	500mg
24000	Mandanol 500mg Tablets (M & A Pharmachem Ltd)	Paracetamol	500mg
24075	Mandanol 500mg caplets (M & A Pharmachem Ltd)	Paracetamol	500mg

24534	Anadin Paracetamol 500mg Tablets (Pfizer Consumer Healthcare Ltd)	Paracetamol	500mg
24947	Co-methiamol 100mg/500mg Tablets	Paracetamol	500mg
25895	Hedex 500mg Tablets (Omega Pharma Ltd)	Paracetamol	500mg
26988	Paracets 500mg Tablet (Sussex Pharmaceutical Ltd)	Paracetamol	500mg
27452	Paracetamol 500mg soluble Tablets (Zentiva)	Paracetamol	500mg
27459	Paracetamol 500mg caplets (Zentiva)	Paracetamol	500mg
28211	Paracetamol 250mg/5ml oral suspension sugar free	Paracetamol	250mg/5ml
28344	Paracetamol 500mg caplets (Wockhardt UK Ltd)	Paracetamol	500mg
28346	Paracetamol 500mg Tablet (M & A Pharmachem Ltd)	Paracetamol	500mg
28955	Panadol ActiFast 500mg Tablets (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
31196	Paracetamol 500mg Tablets (IVAX Pharmaceuticals UK Ltd)	Paracetamol	500mg
31257	Paracetamol 500mg caplets (Galpharm International Ltd)	Paracetamol	500mg
32163	Paracetamol 500mg Tablets (Vantage)	Paracetamol	500mg
32839	Paracetamol 500mg Tablets (A H Pharmaceuticals Ltd)	Paracetamol	500mg
32970	Paracets 500mg capsules (Sussex Pharmaceutical Ltd)	Paracetamol	500mg
32993	Children's Lemsip Cold & Flu Blackcurrant oral powder sachets (Reckitt Benckiser Healthcare (UK) Ltd)	Paracetamol	240mg
33104	Paraclear 500mg Soluble Tablet (Roche Consumer Health)	Paracetamol	500mg
33614	Obimol 500mg Tablet (Ayrton Saunders Ltd)	Paracetamol	500mg
33666	Paracetamol 500mg Tablets (Actavis UK Ltd)	Paracetamol	500mg
33710	Paracetamol 500mg caplets (A H Pharmaceuticals Ltd)	Paracetamol	500mg
33826	Paracetamol 500mg Tablet (Teva UK Ltd)	Paracetamol	500mg
34164	Paracetamol 500mg soluble Tablets (Fannin UK Ltd)	Paracetamol	500mg
34209	Paracetamol 500mg/5ml Oral suspension sugar free (Rosemont Pharmaceuticals Ltd)	Paracetamol	500mg/5ml
34305	Paracetamol 500mg Tablet (M & A Pharmachem Ltd)	Paracetamol	500mg
34350	Paracetamol 500mg Tablet (Celltech Pharma Europe Ltd)	Paracetamol	500mg
34396	Paracetamol 500mg Tablet (Family Health)	Paracetamol	500mg
34409	Paracetamol 500mg Tablet (Co-operative)	Paracetamol	500mg
34500	Paracetamol 500mg Tablets (Kent Pharmaceuticals Ltd)	Paracetamol	500mg
34669	Paracetamol 500mg capsules (Zentiva)	Paracetamol	500mg

34858	Paracetamol Capsule (Co-operative)	Paracetamol	500mg
34954	Paracetamol 500mg Tablets (Aspar Pharmaceuticals Ltd)	Paracetamol	500mg
35679	Paracetamol 500mg Tablet (Nucare Plc)	Paracetamol	500mg
36754	Paracetamol 500mg soluble Tablets (A H Pharmaceuticals Ltd)	Paracetamol	500mg
38032	Paracetamol 500mg capsules (Teva UK Ltd)	Paracetamol	500mg
38984	Paracetamol 500mg capsules (Actavis UK Ltd)	Paracetamol	500mg
39333	Paracetamol 500mg Tablet (Aspar Pharmaceuticals Ltd)	Paracetamol	500mg
39481	Panadol Advance 500mg Tablets (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
39934	Paracetamol 500mg caplets (Almus Pharmaceuticals Ltd)	Paracetamol	500mg
39940	Panadol ActiFast Soluble Tablets (GlaxoSmithKline Consumer Healthcare)	Paracetamol	500mg
40107	Paracetamol 500mg soluble Tablets (Kent Pharmaceuticals Ltd)	Paracetamol	500mg
40158	Paracetamol 500mg Capsule (A H Pharmaceuticals Ltd)	Paracetamol	500mg
42201	Paracetamol 500mg capsules (A H Pharmaceuticals Ltd)	Paracetamol	500mg
42371	Paracetamol 1g Tablets	Paracetamol	1gram
42514	Paracetamol oral liquid	Paracetamol	
42834	Panadol OA 1000mg Tablets (GlaxoSmithKline Consumer Healthcare)	Paracetamol	1gram
43028	Paracetamol 650mg oral powder sachets	Paracetamol	650mg
43233	Paracetamol 500mg capsules (Kent Pharmaceuticals Ltd)	Paracetamol	500mg
43252	Paracetamol 500mg capsules (Aspar Pharmaceuticals Ltd)	Paracetamol	500mg
43479	Paracetamol 500mg caplets (Actavis UK Ltd)	Paracetamol	500mg
45259	Paracetamol 500mg Tablet (OBG Pharmaceuticals Ltd)	Paracetamol	500mg
45298	Paracetamol 500mg Tablets (Galpharm International Ltd)	Paracetamol	500mg
46544	Paracetamol 500mg capsules (Wockhardt UK Ltd)	Paracetamol	500mg
47116	Paracetamol 500mg soluble Tablets (Almus Pharmaceuticals Ltd)	Paracetamol	500mg
47211	Paracetamol 500mg capsules (Focus Pharmaceuticals Ltd)	Paracetamol	500mg
47834	Paracetamol 500mg soluble Tablets (Actavis UK Ltd)	Paracetamol	500mg
48535	Paracetamol 500mg caplets (Rusco Ltd)	Paracetamol	500mg
48597	Paracetamol 500mg caplets (Alliance Healthcare (Distribution) Ltd)	Paracetamol	500mg

49096	Paracetamol 500mg caplets (Lloyds Pharmacy Ltd)	Paracetamol	500mg
49105	Paracetamol 500mg caplets (Teva UK Ltd)	Paracetamol	500mg
49417	Paracetamol 500mg caplets (Kent Pharmaceuticals Ltd)	Paracetamol	500mg
49575	Paracetamol 500mg caplets (Vantage)	Paracetamol	500mg
49849	Paracetamol 500mg caplets (Phoenix Healthcare Distribution Ltd)	Paracetamol	500mg
50482	Paracetamol 500mg Tablets (DE Pharmaceuticals)	Paracetamol	500mg
50504	Numark Paracetamol 500mg capsules (Numark Ltd)	Paracetamol	500mg
53952	Paracetamol 500mg capsules (Lloyds Pharmacy Ltd)	Paracetamol	500mg
54179	Paracetamol 500mg Tablets (The Boots Company Plc)	Paracetamol	500mg
55129	Paracetamol 500mg caplets (Waymade Healthcare Plc)	Paracetamol	500mg
55418	Paracetamol 500mg Tablet (Almus Pharmaceuticals Ltd)	Paracetamol	500mg
56046	Paracetamol 500mg capsules (Waymade Healthcare Plc)	Paracetamol	500mg
56566	Paracetamol 500mg caplets (J M McGill Ltd)	Paracetamol	500mg
56945	Paracetamol 500mg soluble Tablets (Waymade Healthcare Plc)	Paracetamol	500mg
57650	Paracetamol 500mg capsules (Sigma Pharmaceuticals Plc)	Paracetamol	500mg
58526	Paracetamol 500mg caplets (AM Distributions (Yorkshire) Ltd)	Paracetamol	500mg
58582	Paracetamol 500mg Tablets (Teva UK Ltd)	Paracetamol	500mg
58743	Paracetamol 500mg Tablets (Accord Healthcare Ltd)	Paracetamol	500mg
59599	Paracetamol 500mg Tablets (Wockhardt UK Ltd)	Paracetamol	500mg
60378	Flu Strength Hot Lemon Powders 1g oral powder sachets (Bell, Sons & Co (Druggists) Ltd)	Paracetamol	1gram
60442	Paracetamol 500mg Tablets (Alliance Healthcare (Distribution) Ltd)	Paracetamol	500mg
60812	Paracetamol 500mg caplets (Ethigen Ltd)	Paracetamol	500mg
61124	Paracetamol 500mg caplets (Bristol Laboratories Ltd)	Paracetamol	500mg
61522	Paracetamol 500mg caplets (Numark Ltd)	Paracetamol	500mg
61963	Paracetamol 500mg caplets (Ennogen Healthcare Ltd)	Paracetamol	500mg
62088	Paracetamol 500mg caplets (Icarus Pharmaceuticals Ltd)	Paracetamol	500mg

62743	Boots Paracetamol 500mg capsules (The Boots Company Plc)	Paracetamol	500mg
63543	Paracetamol 500mg Tablets (Sigma Pharmaceuticals Plc)	Paracetamol	500mg
63943	Paracetamol 500mg caplets (Crescent Pharma Ltd)	Paracetamol	500mg
63962	Paracetamol 500mg soluble Tablets (Teva UK Ltd)	Paracetamol	500mg
65107	Paracetamol 500mg capsules (Bristol Laboratories Ltd)	Paracetamol	500mg
65239	Paracetamol 500mg caplets (Mawdsley-Brooks & Company Ltd)	Paracetamol	500mg
65299	Paracetamol 500mg caplets (Sigma Pharmaceuticals Plc)	Paracetamol	500mg
65330	Paracetamol 500mg capsules (DE Pharmaceuticals)	Paracetamol	500mg
66097	Paracetamol 500mg capsules (Almus Pharmaceuticals Ltd)	Paracetamol	500mg
67086	Paracetamol 500mg capsules (Galpharm International Ltd)	Paracetamol	500mg
67784	Paracetamol 500mg capsules (Almus Pharmaceuticals Ltd)	Paracetamol	500mg
68070	Paracetamol 500mg Tablets (Zanza Laboratories Ltd)	Paracetamol	500mg
70018	Boots Paracetamol 500mg caplets (The Boots Company Plc)	Paracetamol	500mg
70326	Paravict 500mg Tablets (Ecogen Europe Ltd)	Paracetamol	500mg
71270	Paracetamol 500mg effervescent Tablets sugar free	Paracetamol	500mg
72131	Paracetamol 500mg capsules (Mawdsley-Brooks & Company Ltd)	Paracetamol	500mg
72288	Paracetamol 500mg caplets (Accord Healthcare Ltd)	Paracetamol	500mg

5.2. Covariates: Non-steroidal anti-inflammatory drugs.

prodcode	drug substance	BNF code
15	Ibuprofen	10010100
40	Diclofenac sodium	10010100
120	Indomethacin	10010100
126	Mefenamic acid	10010100
129	Naproxen	10010100
140	Naproxen	4070100
141	Piroxicam	10010100
156	Diclofenac diethylammonium	10010100
157	Diclofenac sodium	10010100
162	Diclofenac sodium/Misoprostol	10010100
177	Indometacin	7010300
259	Mefenamic acid	10010100
296	Mefenamic acid	10010100
341	Piroxicam	10010100
344	Acemetacin	10010100
360	Ibuprofen	10010100
389	Ketoprofen	10010100
392	Ibuprofen	10010100
402	Ibuprofen	10010100
407	Ibuprofen	10010100
416	Ibuprofen	10010100
417	Diclofenac sodium	10010100
447	Diclofenac sodium	10010100
474	Celecoxib	10010100
497	Diclofenac sodium	10010100
499	Diclofenac sodium	10010100
526	Aceclofenac	10010100
560	Diflunisal	10010100
580	Diclofenac sodium	10010100
586	Ibuprofen	10010100
589	Diclofenac sodium	10010100
597	Diclofenac potassium	10010100
612	Diclofenac sodium	10010100
628	Diclofenac potassium	10010100
647	Ibuprofen	10010100
649	Diclofenac sodium	10010100
650	Etoricoxib	10010100
661	Naproxen	4070100
676	Diclofenac sodium	10010100
736	Indometacin	7010300
754	Meloxicam	10010100
784	Ibuprofen	10010100

807	Naproxen	4070100
827	Diclofenac diethylammonium	10010100
838	Ketoprofen	10010100
849	Ibuprofen	10010100
850	Meloxicam	10010100
917	Diclofenac Sodium	10010100
919	Indometacin	7010300
920	Indometacin	7010300
928	Diclofenac Sodium	10010100
1043	Naproxen sodium	4070100
1073	Mefenamic acid	10010100
1075	Diclofenac Sodium	10010100
1086	Ibuprofen	10010100
1096	Diclofenac Sodium	10010100
1115	Diclofenac sodium	10010100
1116	Diclofenac sodium	10010100
1139	Diclofenac sodium	10010100
1210	Indometacin	10010100
1231	Ketoprofen	10010100
1233	Diclofenac Sodium	10010100
1246	Mefenamic Acid	10010100
1392	Ibuprofen	10010100
1446	Diclofenac sodium	10010100
1468	Ibuprofen	10010100
1469	Meloxicam	10010100
1470	Meloxicam	10010100
1496	Indometacin	10010100
1544	Piroxicam	10010100
1571	Ketoprofen	10010100
1688	Indometacin	10010100
1692	Diclofenac sodium/Misoprostol	10010100
1739	Ibuprofen	10010100
1755	Piroxicam	10010100
1757	Magnesium Trisilicate	10010100
1766	Diclofenac sodium	10010100
1778	Tiaprofenic acid	10010100
1866	Naproxen	4070100
1983	Mefenamic Acid	10010100
1984	Diclofenac Sodium	10010100
2129	Ibuprofen	10010100
2197	Naproxen	10010100
2234	Nabumetone	10010100
2235	Nabumetone	10010100
2243	Meloxicam	10010100

2258	Acemetacin	10010100
2288	Naproxen	4070100
2293	Diclofenac sodium	10010100
2366	Flurbiprofen	10010100
2386	Diclofenac sodium	10010100
2387	Diclofenac sodium/Misoprostol	10010100
2606	Ketoprofen	10010100
2858	Piroxicam	10010100
2863	Tiaprofenic acid	10010100
2904	Diclofenac sodium	10010100
3043	Ketoprofen	10010100
3053	Naproxen	4070100
3077	Ketoprofen	10010100
3170	Meloxicam	10010100
3182	Flurbiprofen	10010100
3266	Flurbiprofen	10010100
3326	Ketoprofen	10010100
3409	Piroxicam	10010100
3416	Diclofenac sodium	10010100
3421	Diclofenac sodium	10010100
3431	Naproxen	4070100
3432	Naproxen	4070100
3496	Naproxen	4070100
3597	Ibuprofen	10010100
3599	Ibuprofen	10010100
3710	Piroxicam	10010100
3817	Naproxen sodium	4070100
3852	Diclofenac sodium	10010100
3897	Sulindac	10010100
3901	Naproxen	4070100
3935	Piroxicam	10010100
3958	Diclofenac sodium	10010100
3972	Naproxen	4070100
3974	Tenoxicam	10010100
4043	Flurbiprofen	10010100
4045	Naproxen	4070100
4095	Diclofenac sodium	10010100
4216	Ibuprofen	10010100
4298	Ibuprofen	10010100
4309	Ibuprofen lysine	10010100
4368	Etodolac	10010100
4469	Fenoprofen calcium	10010100
4506	Diclofenac sodium	10010100
4564	Fenoprofen Calcium	10010100

4625	Diclofenac sodium	10010100
4631	Diclofenac sodium	10010100
4692	Diclofenac sodium	10010100
4710	Mefenamic acid	10010100
4713	Diclofenac sodium	10010100
4806	Diclofenac sodium	10010100
4880	Diclofenac sodium/Misoprostol	10010100
4911	Ibuprofen	10010100
4965	Piroxicam	10010100
5080	Celecoxib	10010100
5085	Diclofenac potassium	10010100
5173	Dexketoprofen trometamol	10010100
5175	Celecoxib	10010100
5200	Diclofenac sodium	10010100
5254	Celecoxib	10010100
5266	Etodolac	10010100
5268	Naproxen sodium	10010100
5401	Diclofenac potassium	10010100
5407	Naproxen	4070100
5455	Etodolac	10010100
5482	Sulindac	10010100
5648	Ibuprofen	10010100
5812	Etoricoxib	10010100
5938	Etoricoxib	10010100
6208	Diclofenac diethylammonium	10010100
6249	Flurbiprofen	10010100
6464	Etoricoxib	10010100
6498	Etoricoxib	10010100
7426	Fenbufen	10010100
7432	Ketoprofen	10010100
7481	Fenbufen	10010100
7483	Phenylbutazone	10010100
7522	Fenbufen	10010100
7535	Ibuprofen	10010100
7667	Diclofenac sodium	10010100
7840	Ketoprofen	10010100
8062	Diclofenac sodium	10010100
8385	Ketoprofen	10010100
8451	Etodolac	10010100
8663	Naproxen sodium	10010100
8789	Diclofenac sodium	10010100
8969	Etodolac	10010100
9222	Diclofenac sodium	10010100
9421	Ketoprofen	10010100

9439	Flurbiprofen	10010100
9465	Diclofenac sodium	10010100
9474	Aceclofenac	10010100
9500	Diclofenac sodium	10010100
9630	Piroxicam	10010100
9637	Dexketoprofen trometamol	10010100
9688	Diclofenac sodium	10010100
9822	Etoricoxib	10010100
9886	Diclofenac sodium	10010100
10033	Etodolac	10010100
10149	Ibuprofen	10010100
10169	Piroxicam betadex	10010100
10209	Ibuprofen	10010100
10325	Dexibuprofen	10010100
10336	Ketoprofen	10010100
10481	Fenbufen	10010100
10678	Fenoprofen calcium	10010100
10711	Tolmetin Sodium	10010100
10785	Ibuprofen	10010100
10792	Diclofenac sodium	10010100
10917	Diclofenac sodium	10010100
10978	Diclofenac sodium	10010100
11168	Diclofenac sodium	10010100
11215	Diclofenac sodium	10010100
11322	Diclofenac sodium	10010100
11495	Piroxicam betadex	10010100
11550	Ibuprofen	10010100
11907	Dexibuprofen	10010100
11970	Meloxicam	10010100
11980	Ibuprofen	10010100
11995	Ketoprofen	10010100
11999	Ketoprofen	10010100
12000	Ketoprofen	10010100
12075	Tenoxicam	10010100
12122	Ketoprofen	10010100
12188	Magnesium Trisilicate	10010100
13347	Ketoprofen	10010100
13459	Mefenamic acid	10010100
13627	Meloxicam	10010100
13818	Nabumetone	10010100
14084	Diclofenac sodium	10010100
14085	Diclofenac sodium	10010100
14333	Ibuprofen	10010100
14385	Ibuprofen	10010100

14422	Fenbufen	10010100
14476	Indometacin	10010100
14672	Diclofenac sodium	10010100
14678	Diclofenac sodium	10010100
14707	Diclofenac sodium	10010100
14776	Tiaprofenic acid	10010100
14884	Diclofenac epolamine	10010100
14901	Diclofenac epolamine	10010100
15023	Naproxen	10010100
15104	Naproxen	10010100
15159	Tolfenamic Acid	4070401
15180	Naproxen/Misoprostol	1030400
15201	Diclofenac sodium	10010100
15286	Ketoprofen	10010100
15732	Diclofenac sodium	10010100
16001	Ibuprofen	10010100
16192	Ibuprofen	10010100
16194	Etodolac	10010100
16221	Diclofenac sodium	10010100
16222	Diclofenac sodium	10010100
16225	Diclofenac sodium	10010100
16272	Diclofenac sodium	10010100
16286	Diclofenac sodium	10010100
17029	Diclofenac sodium	10010100
17030	Diclofenac sodium	10010100
17124	Diclofenac sodium	10010100
17126	Diclofenac sodium	10010100
17128	Diclofenac sodium	10010100
17165	Naproxen	4070100
17491	Diclofenac sodium	10010100
17525	Diclofenac sodium	10010100
17532	Diclofenac sodium	10010100
17572	Tenoxicam	10010100
17680	Indometacin	10010100
17733	Naproxen/Misoprostol	1030400
17750	Indometacin	10010100
17754	Fenoprofen Calcium	10010100
17818	Ketoprofen	10010100
18151	Diclofenac diethylammonium	10010100
18234	Indometacin	10010100
18364	Ibuprofen	10010100
18371	Diclofenac sodium	10010100
18448	Diclofenac sodium	10010100
18527	Ibuprofen	10010100

18640	Tolmetin Sodium	10010100
18647	Ketoprofen	10010100
18662	Indometacin	10010100
18798	Diclofenac sodium	10010100
18812	Ibuprofen	10010100
18921	Diclofenac sodium	10010100
19007	Naproxen	10010100
19046	Ibuprofen	10010100
19320	Piroxicam	10010100
19322	Salsalate	10010100
19382	Diclofenac sodium	10010100
19575	Ibuprofen	10010100
20016	Tolmetin Sodium	10010100
20036	Tolfenamic Acid	4070401
20059	Tiaprofenic Acid	10010100
20105	Diclofenac sodium	10010100
20230	Salsalate	10010100
20384	Diclofenac sodium	10010100
20385	Naproxen	4070100
20386	Etodolac	10010100
20395	Diclofenac sodium	10010100
20442	Ibuprofen	10010100
20621	Diclofenac sodium	10010100
20805	Diclofenac sodium	10010100
20978	Ibuprofen	10010100
21045	Ibuprofen	10010100
21050	Ketoprofen	10010100
21123	Piroxicam	10010100
21387	Diclofenac sodium	10010100
21419	Dexibuprofen	10010100
21421	Dexibuprofen	10010100
21444	Diclofenac sodium	10010100
21610	Diclofenac sodium	10010100
21807	Diclofenac sodium	10010100
21811	Ibuprofen	10010100
21813	Ibuprofen	10010100
21816	Naproxen sodium	10010100
21821	Ibuprofen	10010100
21824	Diclofenac sodium	10010100
21831	Mefenamic acid	10010100
21840	Naproxen	4070100
21843	Naproxen	10010100
21846	Piroxicam	10010100
21864	Piroxicam	10010100

21955	Ketoprofen	10010100
22230	Mefenamic acid	10010100
23026	Indometacin	10010100
23121	Naproxen	10010100
23204	Indometacin	10010100
23323	Naproxen	10010100
23795	Indometacin	10010100
24007	Naproxen	10010100
24020	Naproxen	10010100
24121	Diclofenac sodium	10010100
24122	Diclofenac sodium	10010100
24128	Diclofenac sodium	10010100
24137	Indometacin	7010300
24193	Indometacin	10010100
24212	Indometacin	10010100
24236	Diclofenac sodium	10010100
24305	Ibuprofen	10010100
24308	Indometacin	10010100
24320	Indometacin	10010100
24356	Etodolac	10010100
24469	Ibuprofen	10010100
24531	Tenoxicam	10010100
24617	Ketoprofen	10010100
24682	Tenoxicam	10010100
25283	Diclofenac sodium	10010100
25329	Diclofenac sodium	10010100
25341	Naproxen	4070100
25342	Naproxen	4070100
25358	Diclofenac sodium	10010100
25361	Diclofenac sodium	10010100
25362	Diclofenac sodium	10010100
25619	Ibuprofen	10010100
25643	Tiaprofenic Acid	10010100
25701	Ketoprofen	10010100
25750	Naproxen	10010100
25790	Diclofenac sodium	10010100
25794	Ibuprofen	10010100
26083	Indometacin	10010100
26095	Ibuprofen lysine	10010100
26165	Diclofenac sodium	10010100
26205	Fenbufen	10010100
26214	Fenbufen	10010100
26216	Naproxen	10010100
26231	Naproxen	10010100

26234	Piroxicam	10010100
26242	Naproxen	10010100
26247	Mefenamic acid	10010100
26351	Diclofenac sodium	10010100
26404	Tolmetin Sodium	10010100
26522	Mefenamic acid	10010100
26575	Flurbiprofen	10010100
26631	Diclofenac sodium	10010100
26888	Diclofenac sodium	10010100
26970	Ibuprofen	10010100
26994	Fenbufen	10010100
27013	Ketoprofen	10010100
27055	Diclofenac sodium	10010100
27082	Ketoprofen	10010100
27200	Diclofenac sodium	10010100
27362	Diclofenac sodium	10010100
27366	Naproxen	4070100
27677	Diclofenac sodium	10010100
27723	Phenylbutazone	10010100
27782	Ibuprofen	10010100
27968	Ibuprofen	10010100
28255	Naproxen	4070100
28256	Diclofenac sodium	10010100
28348	Ibuprofen	10010100
28390	Diclofenac sodium	10010100
28479	Ibuprofen	10010100
28553	Diclofenac sodium	10010100
28695	Piroxicam	10010100
28764	Diclofenac sodium	10010100
28816	Naproxen	10010100
28888	Ibuprofen	10010100
28900	Indometacin	10010100
29010	Phenylbutazone	10010100
29037	Diclofenac sodium	10010100
29181	Diclofenac sodium	10010100
29316	Ibuprofen	10010100
29330	Diclofenac sodium	10010100
29332	Ibuprofen	10010100
29345	Ibuprofen	10010100
29352	Ibuprofen	10010100
29455	Diclofenac sodium	10010100
29465	Piroxicam	10010100
29524	Ibuprofen	10010100
29587	Ibuprofen	10010100

29674	Phenylbutazone	10010100
29704	Ibuprofen	10010100
29772	Ketoprofen	10010100
30122	Lornoxicam	10010100
30168	Naproxen	10010100
30243	Ibuprofen	10010100
30282	Diclofenac sodium	10010100
30297	Diclofenac sodium	10010100
30327	Ketoprofen	10010100
30382	Ibuprofen	10010100
30389	Mefenamic acid	10010100
30391	Mefenamic acid	10010100
30790	Diclofenac sodium	10010100
30806	Diclofenac sodium	10010100
30811	Ibuprofen	10010100
30849	Diclofenac sodium	10010100
30892	Ibuprofen	10010100
30923	Diclofenac sodium	10010100
30942	Diclofenac sodium	10010100
30982	Naproxen	4070100
31064	Tenoxicam	10010100
31178	Ketoprofen	10010100
31383	Diclofenac sodium	10010100
31429	Naproxen	10010100
31469	Ibuprofen	10010100
31482	Ibuprofen	10010100
31589	Diclofenac sodium	10010100
31787	Diclofenac sodium	10010100
31916	Ketoprofen	10010100
31944	Diclofenac sodium	10010100
31945	Naproxen	10010100
31950	Diclofenac sodium	10010100
31959	Indometacin	7010300
31962	Ketoprofen	10010100
32090	Mefenamic acid	10010100
32097	Indometacin	10010100
32100	Ibuprofen	10010100
32105	Mefenamic acid	10010100
32108	Diclofenac sodium	10010100
32136	Ibuprofen	10010100
32227	Ketoprofen	10010100
32234	Mefenamic acid	10010100
32366	Ibuprofen	10010100
32509	Ibuprofen	10010100

32536	Diclofenac sodium	10010100
32601	Diclofenac sodium	10010100
32641	Indometacin	7010300
32854	Diclofenac sodium	10010100
32862	Ibuprofen	10010100
32916	Diclofenac sodium	10010100
33111	Naproxen	10010100
33113	Indometacin	10010100
33180	Ketoprofen	10010100
33308	Phenylbutazone	10010100
33318	Indometacin	10010100
33321	Indometacin	7010300
33457	Diclofenac sodium	10010100
33559	Diclofenac sodium	10010100
33568	Ketoprofen	10010100
33589	Ibuprofen	10010100
33645	Diclofenac sodium	10010100
33669	Diclofenac sodium	10010100
33704	Ibuprofen	10010100
33801	Mefenamic acid	10010100
33935	Ibuprofen lysine	4070100
33994	Diclofenac sodium	10010100
34091	Diclofenac sodium	10010100
34143	Naproxen	10010100
34190	Indometacin	10010100
34199	Indometacin	7010300
34212	Diclofenac sodium	10010100
34218	Diclofenac sodium	10010100
34271	Diclofenac sodium	10010100
34289	Naproxen	4070100
34290	Naproxen	4070100
34354	Ibuprofen	10010100
34359	Ibuprofen	10010100
34362	Diclofenac sodium	10010100
34425	Ibuprofen	10010100
34438	Mefenamic acid	10010100
34447	Ibuprofen	10010100
34487	Diclofenac sodium	10010100
34550	Ibuprofen	10010100
34595	Mefenamic acid	10010100
34610	Naproxen	4070100
34616	Piroxicam	10010100
34621	Ibuprofen	10010100
34663	Ibuprofen	10010100

34670	Naproxen	10010100
34725	Flurbiprofen	10010100
34738	Naproxen	4070100
34743	Naproxen	4070100
34744	Diclofenac sodium	10010100
34757	Ibuprofen	10010100
34769	Naproxen	4070100
34793	Mefenamic acid	10010100
34850	Ibuprofen	10010100
34889	Ibuprofen	10010100
34898	Mefenamic acid	10010100
34910	Mefenamic acid	10010100
34911	Ibuprofen	10010100
34922	Naproxen	10010100
34923	Naproxen	10010100
34924	Mefenamic acid	10010100
34931	Ibuprofen	10010100
34977	Naproxen	10010100
35292	Ibuprofen	10010100
35653	Etodolac	10010100
35711	Diclofenac sodium	10010100
35890	Ibuprofen	10010100
35893	Diclofenac sodium	10010100
35935	Meloxicam	10010100
36260	Mefenamic acid	10010100
36486	Diclofenac sodium	10010100
36577	Indometacin	10010100
36597	Ibuprofen	10010100
36606	Ibuprofen	10010100
36650	Ibuprofen	10010100
36787	Ibuprofen lysine	4070100
37002	Ibuprofen	10010100
37094	Ibuprofen	10010100
37253	Ibuprofen	10010100
37553	Ibuprofen	10010100
37562	Etoricoxib	10010100
37587	Etoricoxib	10010100
37648	Ibuprofen	10010100
37750	Piroxicam	10010100
37763	Diclofenac sodium	10010100
38332	Ibuprofen	10010100
38493	Ibuprofen	10010100
38511	Naproxen	4070100
38770	Etodolac	10010100

38817	Diclofenac potassium	10010100
38881	Diclofenac sodium	10010100
38944	Flurbiprofen	10010100
38948	Diclofenac sodium	10010100
38992	Diclofenac sodium	10010100
39019	Ibuprofen	10010100
39085	Naproxen	4070100
39109	Piroxicam	10010100
39264	Diclofenac sodium	10010100
39317	Naproxen	4070100
39502	Ibuprofen sodium dihydrate	10010100
39722	Diclofenac potassium	10010100
39758	Ibuprofen sodium dihydrate	4070100
39823	Diclofenac sodium	10010100
39873	Ibuprofen	10010100
40083	Ibuprofen	10010100
40086	Diclofenac sodium	10010100
40141	Ketoprofen	10010100
40185	Ketoprofen	10010100
40215	Ketoprofen	10010100
40253	Ibuprofen	10010100
40336	Ketoprofen	10010100
40394	Ibuprofen	10010100
40401	Naproxen	4070100
40484	Ketoprofen	10010100
40516	Ibuprofen	10010100
40664	Ketoprofen	10010100
40756	Diclofenac sodium	10010100
41364	Ketoprofen/Omeprazole	1030500
41365	Ketoprofen/Omeprazole	1030500
41366	Ketoprofen/Omeprazole	1030500
41367	Ketoprofen/Omeprazole	1030500
41450	Ketoprofen	10010100
41521	Indometacin	10010100
41524	Mefenamic acid	10010100
41615	Indometacin	10010100
41621	Piroxicam	10010100
41622	Piroxicam	10010100
41623	Piroxicam	10010100
41624	Piroxicam	10010100
41677	Mefenamic acid	10010100
41817	Indometacin	10010100
41823	Indometacin	10010100
42003	Indometacin	10010100

42397	Ibuprofen sodium dihydrate	4070100
42406	Diclofenac sodium	10010100
42455	Diclofenac sodium	10010100
42500	Ketoprofen	10010100
42604	Tenoxicam	10010100
42793	Diclofenac sodium	10010100
42821	Nabumetone	10010100
42905	Diclofenac sodium	10010100
43032	Ibuprofen	10010100
43045	Diclofenac potassium	10010100
43456	Ibuprofen	10010100
43541	Piroxicam	10010100
43616	Celecoxib	10010100
43904	Ibuprofen lysine	4070100
43911	Ibuprofen	10010100
44112	Diclofenac potassium	10010100
44313	Indometacin	10010100
44703	Piroxicam	10010100
44800	Esomeprazole magnesium trihydrate/Naproxen	1030500
44986	Esomeprazole magnesium trihydrate/Naproxen	1030500
45213	Diclofenac sodium	10010100
45216	Ibuprofen	10010100
45256	Indometacin	10010100
45262	Naproxen	10010100
45320	Ibuprofen	10010100
45331	Ibuprofen	10010100
45814	Diclofenac potassium	10010100
45842	Ibuprofen	10010100
46440	Naproxen	10010100
46844	Diclofenac sodium	10010100
46848	Naproxen	10010100
46860	Ibuprofen	10010100
46919	Ketoprofen	10010100
46920	Ketoprofen	10010100
46940	Ketoprofen	10010100
46967	Mefenamic acid	10010100
46968	Mefenamic acid	10010100
47501	Diclofenac sodium	10010100
47816	Tenoxicam	10010100
47820	Diclofenac potassium	10010100
47994	Naproxen	10010100
48059	Diclofenac potassium	10010100
48062	Ibuprofen	10010100
48138	Ibuprofen	10010100

48161	Naproxen	10010100
48218	Diclofenac sodium	10010100
48326	Ibuprofen	10010100
48546	Ibuprofen	10010100
48562	Ibuprofen	10010100
48568	Ibuprofen lysine	10010100
48644	Ibuprofen	10010100
48738	Ibuprofen	10010100
48810	Mefenamic acid	10010100
48871	Diclofenac potassium	10010100
49059	Diclofenac sodium	10010100
49132	Diclofenac diethylammonium	10010100
49133	Ibuprofen	10010100
49266	Ibuprofen	10010100
49277	Ibuprofen	10010100
49432	Ibuprofen	10010100
49788	Diclofenac diethylammonium	10010100
49862	Diclofenac diethylammonium	10010100
50058	Diclofenac sodium	10010100
50059	Celecoxib	10010100
50117	Ibuprofen	10010100
50266	Ibuprofen	10010100
50269	Diclofenac sodium/Misoprostol	10010100
50314	Ibuprofen	10010100
50317	Diclofenac sodium	10010100
50343	Piroxicam	10010100
50363	Ibuprofen	10010100
50602	Diclofenac potassium	10010100
50628	Ibuprofen	10010100
50652	Ibuprofen	10010100
50785	Diclofenac sodium	10010100
51099	Diclofenac potassium	10010100
51237	Diclofenac diethylammonium	10010100
51242	Naproxen	4070100
51284	Etoricoxib	10010100
51293	Diclofenac potassium	10010100
51339	Indometacin	7010300
51343	Diclofenac potassium	10010100
51360	Naproxen	4070100
51614	Ibuprofen	10010100
51769	Ibuprofen	10010100
51827	Mefenamic acid	10010100
51828	Ibuprofen	10010100
51829	Naproxen	4070100

51874	Etoricoxib	10010100
51943	Ibuprofen	10010100
52009	Ibuprofen	10010100
52141	Indometacin	10010100
52154	Ibuprofen	10010100
52229	Diclofenac diethylammonium	10010100
52338	Diclofenac potassium	10010100
52389	Diclofenac sodium	10010100
52420	Celecoxib	10010100
52617	Ibuprofen	10010100
52714	Etodolac	10010100
52931	Naproxen	4070100
52956	Diclofenac diethylammonium	10010100
53164	Diclofenac sodium	10010100
53331	Ibuprofen	10010100
53345	Diclofenac potassium	10010100
53384	Diclofenac sodium	10010100
53397	Ibuprofen	10010100
53576	Etoricoxib	10010100
53604	Ibuprofen	10010100
53626	Naproxen	4070100
53700	Naproxen	4070100
53803	Ibuprofen	10010100
53980	Naproxen	4070100
54021	Diclofenac sodium	10010100
54075	Diclofenac sodium	10010100
54137	Ibuprofen	10010100
54304	Naproxen	4070100
54463	Diclofenac sodium	10010100
54476	Naproxen	4070100
54514	Ibuprofen lysine	10010100
54518	Diclofenac sodium	10010100
54660	Diclofenac Sodium	10010100
54783	Naproxen	4070100
54870	Piroxicam	10010100
55009	Ibuprofen	10010100
55099	Diclofenac sodium	10010100
55153	Ibuprofen lysine	10010100
55233	Ibuprofen	10010100
55313	Ibuprofen	10010100
55434	Ibuprofen	10010100
55454	Naproxen	4070100
55486	Naproxen	4070100
55505	Naproxen	4070100

55582	Celecoxib	10010100
55894	Naproxen	4070100
55913	Diclofenac sodium	10010100
56039	Ibuprofen	10010100
56078	Diclofenac sodium	10010100
56213	Ibuprofen	10010100
56275	Meloxicam	10010100
56282	Diclofenac diethylammonium	10010100
56441	Ibuprofen	10010100
56554	Naproxen	4070100
56558	Diclofenac diethylammonium	10010100
56584	Etoricoxib	10010100
56651	Piroxicam	10010100
56762	Naproxen	4070100
56898	Diclofenac sodium	10010100
56925	Naproxen	4070100
57006	Diclofenac sodium	10010100
57007	Mefenamic acid	10010100
57045	Diclofenac sodium	10010100
57112	Ibuprofen	10010100
57162	Diclofenac sodium	10010100
57297	Mefenamic acid	10010100
57370	Meloxicam	10010100
57475	Meloxicam	10010100
57523	Piroxicam	10010100
57545	Diclofenac diethylammonium	10010100
57943	Ketoprofen	10010100
58048	Diclofenac sodium	10010100
58071	Diclofenac potassium	10010100
58213	Naproxen	4070100
58221	Naproxen	4070100
58298	Piroxicam	10010100
58415	Diclofenac sodium/Misoprostol	10010100
58523	Indometacin	7010300
58572	Diclofenac potassium	10010100
58652	Ibuprofen	10010100
58708	Naproxen	4070100
58842	Diclofenac sodium/Misoprostol	10010100
59067	Ibuprofen	10010100
59203	Ibuprofen	10010100
59246	Naproxen	4070100
59289	Diclofenac sodium	10010100
59502	Ibuprofen	10010100
59553	Ibuprofen	10010100

59562	Ibuprofen	10010100
59595	Diclofenac sodium	10010100
59878	Naproxen	4070100
59880	Diclofenac sodium	10010100
60035	Ibuprofen	10010100
59878	Naproxen	4070100
60368	Diclofenac sodium	10010100
60408	Naproxen	4070100
60443	Diclofenac sodium	10010100
60510	Ibuprofen	10010100
60666	Diclofenac sodium	10010100
60705	Meloxicam	10010100
60772	Indometacin	7010300
60786	Diclofenac sodium	10010100
60916	Indometacin	10010100
60930	Indometacin	7010300
61235	Meloxicam	10010100
61314	Piroxicam	10010100
61581	Mefenamic acid	10010100
61596	Diclofenac sodium	10010100
61695	Naproxen	4070100
61715	Piroxicam	10010100
61762	Diclofenac sodium	10010100
61878	Ibuprofen	10010100
61953	Ibuprofen	10010100
62238	Ibuprofen	10010100
62251	Etoricoxib	10010100
62375	Piroxicam	10010100
62615	Ketoprofen	10010100
62636	Diclofenac sodium	10010100
62643	Indometacin	10010100
62658	Etoricoxib	10010100
62840	Celecoxib	10010100
62843	Etoricoxib	10010100
62851	Diclofenac diethylammonium	10010100
62892	Ibuprofen	10010100
63036	Ibuprofen	10010100
63079	Ibuprofen	10010100
63357	Naproxen	4070100
63843	Naproxen	4070100
64103	Mefenamic acid	10010100
64245	Celecoxib	10010100
64297	Nabumetone	10010100
64303	Diclofenac sodium	10010100

64521	Etoricoxib	10010100
64595	Diclofenac sodium/Misoprostol	10010100
64935	Celecoxib	10010100
65016	Celecoxib	10010100
65025	Ibuprofen	10010100
65121	Ibuprofen	10010100
65348	Naproxen	4070100
65471	Ibuprofen	10010100
65514	Ibuprofen	10010100
65528	Diclofenac sodium/Misoprostol	10010100
65591	Ibuprofen	10010100
65594	Piroxicam	10010100
65783	Diclofenac potassium	10010100
65862	Naproxen	10010100
65877	Diclofenac sodium	10010100
65952	Naproxen	4070100
66123	Diclofenac sodium	10010100
66194	Ibuprofen	10010100
66247	Ibuprofen	10010100
66323	Etodolac	10010100
66364	Meloxicam	10010100
66452	Mefenamic acid	10010100
66486	Etoricoxib	10010100
66544	Ibuprofen	10010100
66567	Ibuprofen sodium dihydrate	10010100
66571	Celecoxib	10010100
66577	Diclofenac sodium	10010100
66648	Ibuprofen	10010100
66757	Celecoxib	10010100
66993	Naproxen	4070100
67117	Naproxen	10010100
67220	Diclofenac sodium	10010100
67363	Naproxen	4070100
67594	Ibuprofen	10010100
67740	Ibuprofen	10010100
67756	Indometacin	7010300
67768	Naproxen	4070100
67803	Ketoprofen	10010100
67815	Piroxicam	10010100
68018	Ibuprofen	10010100
68097	Naproxen	4070100
68220	Ibuprofen	10010100
68354	Diclofenac sodium	10010100
68470	Naproxen	4070100

68582	Ibuprofen	10010100
68685	Naproxen	4070100
68708	Indometacin	10010100
68932	Meloxicam	10010100
69018	Ibuprofen sodium dihydrate	10010100
69477	Diclofenac potassium	10010100
69582	Diclofenac sodium	10010100
69584	Diclofenac sodium	10010100
69645	Naproxen	4070100
69683	Diclofenac diethylammonium	10010100
69828	Naproxen	4070100
70145	Diclofenac potassium	10010100
70221	Mefenamic acid	10010100
70299	Ibuprofen	10010100
70393	Naproxen	4070100
70438	Diclofenac sodium/Misoprostol	10010100
70468	Diclofenac potassium	10010100
70698	Naproxen	4070100
70828	Naproxen	4070100
70878	Ibuprofen	10010100
70904	Indometacin	7010300
71027	Piroxicam	10010100
71041	Ibuprofen	10010100
71064	Diclofenac sodium	10010100
71072	Ibuprofen	10010100
71088	Diclofenac sodium/Misoprostol	10010100
71100	Diclofenac sodium	10010100
71104	Ketoprofen	10010100
71117	Diclofenac sodium	10010100
71127	Ketoprofen	10010100
71307	Diclofenac sodium	10010100
71314	Ibuprofen	10010100
71362	Diclofenac sodium	10010100
71364	Diclofenac diethylammonium	10010100
71374	Ibuprofen	10010100
71376	Ketoprofen	10010100
71584	Ibuprofen	10010100
71709	Naproxen	4070100
71779	Ibuprofen	10010100
71908	Etodolac	10010100
71949	Ibuprofen	10010100
71968	Ibuprofen	10010100
71989	Meloxicam	10010100
72030	Naproxen	4070100

72047	Naproxen	4070100
72293	Celecoxib	10010100
72396	Diclofenac sodium	10010100
72546	Diclofenac sodium	10010100
140	Naproxen	10010100
156	Diclofenac diethylammonium	10030250
157	Diclofenac sodium	10010450
177	Indometacin	10010100
661	Naproxen	10010100
736	Indometacin	10010100
807	Naproxen	10010100
838	Ketoprofen	10010450
917	Diclofenac Sodium	10010450
928	Diclofenac Sodium	10010450
1043	Naproxen sodium	10010100
1075	Diclofenac Sodium	10010450
1096	Diclofenac Sodium	10010450
1139	Diclofenac sodium	10010450
1233	Diclofenac Sodium	10010450
1446	Diclofenac sodium	10010450
1766	Diclofenac sodium	10010450
1866	Naproxen	10010100
1984	Diclofenac Sodium	10010450
2197	Naproxen	10010450
2288	Naproxen	10010100
3053	Naproxen	10010100
3326	Ketoprofen	10010450
3421	Diclofenac sodium	10010450
3431	Naproxen	10010100
3432	Naproxen	10010100
3496	Naproxen	10010100
3817	Naproxen sodium	10010100
3852	Diclofenac sodium	10010450
3901	Naproxen	10010100
3972	Naproxen	10010100
4045	Naproxen	10010100
5407	Naproxen	10010100
7840	Ketoprofen	10010450
8789	Diclofenac sodium	10010450
9465	Diclofenac sodium	10010450
9886	Diclofenac sodium	10010450
11322	Diclofenac sodium	10010450
11999	Ketoprofen	10010450
12122	Ketoprofen	10010450

13347	Ketoprofen	10010450
14678	Diclofenac sodium	10010450
15023	Naproxen	10010450
15104	Naproxen	10010450
15159	Tolfenamic Acid	10010100
15180	Naproxen/Misoprostol	10010100
16225	Diclofenac sodium	10010450
17124	Diclofenac sodium	10010450
17165	Naproxen	10010100
17491	Diclofenac sodium	10010450
17733	Naproxen/Misoprostol	10010100
17750	Indometacin	10010450
18371	Diclofenac sodium	10010450
19007	Naproxen	10010450
20036	Tolfenamic Acid	10010100
20105	Diclofenac sodium	10010450
20385	Naproxen	10010100
21050	Ketoprofen	10010450
21816	Naproxen sodium	10010450
21840	Naproxen	10010100
21843	Naproxen	10010450
23026	Indometacin	10010450
23121	Naproxen	10010450
23323	Naproxen	10010450
24007	Naproxen	10010450
24020	Naproxen	10010450
24137	Indometacin	10010100
24193	Indometacin	10010450
24212	Indometacin	10010450
24236	Diclofenac sodium	10010450
24320	Indometacin	10010450
25283	Diclofenac sodium	10010450
25341	Naproxen	10010100
25342	Naproxen	10010100
25750	Naproxen	10010450
25790	Diclofenac sodium	10010450
26216	Naproxen	10010450
26231	Naproxen	10010450
26242	Naproxen	10010450
26575	Flurbiprofen	12030300
26888	Diclofenac sodium	10010450
27013	Ketoprofen	10010450
27362	Diclofenac sodium	10010450
27366	Naproxen	10010100

28255	Naproxen	10010100
28256	Diclofenac sodium	10010450
28390	Diclofenac sodium	10010450
28764	Diclofenac sodium	10010450
28816	Naproxen	10010450
28900	Indometacin	10010450
30168	Naproxen	10010450
30282	Diclofenac sodium	10010450
30297	Diclofenac sodium	10010450
30790	Diclofenac sodium	10010450
30806	Diclofenac sodium	10010450
30942	Diclofenac sodium	10010450
30982	Naproxen	10010100
31429	Naproxen	10010450
31945	Naproxen	10010450
31959	Indometacin	10010100
32097	Indometacin	10010450
32536	Diclofenac sodium	10010450
32641	Indometacin	10010100
32916	Diclofenac sodium	10010450
33111	Naproxen	10010450
33113	Indometacin	10010450
33180	Ketoprofen	10010450
33318	Indometacin	10010450
33321	Indometacin	10010100
33457	Diclofenac sodium	10010450
33559	Diclofenac sodium	10010450
33568	Ketoprofen	10010450
33645	Diclofenac sodium	10010450
33669	Diclofenac sodium	10010450
33935	Ibuprofen lysine	10010100
34143	Naproxen	10010450
34212	Diclofenac sodium	10010450
34218	Diclofenac sodium	10010450
34289	Naproxen	10010100
34290	Naproxen	10010100
34362	Diclofenac sodium	10010450
34610	Naproxen	10010100
34670	Naproxen	10010450
34738	Naproxen	10010100
34743	Naproxen	10010100
34744	Diclofenac sodium	10010450
34769	Naproxen	10010100
34922	Naproxen	10010450

34923	Naproxen	10010450
34977	Naproxen	10010450
36577	Indometacin	10010450
36787	Ibuprofen lysine	10010100
38511	Naproxen	10010100
39085	Naproxen	10010100
39317	Naproxen	10010100
39758	Ibuprofen sodium dihydrate	10010100
40401	Naproxen	10010100
41364	Ketoprofen/Omeprazole	10010100
41365	Ketoprofen/Omeprazole	10010100
41366	Ketoprofen/Omeprazole	10010100
41367	Ketoprofen/Omeprazole	10010100
41521	Indometacin	10010450
41615	Indometacin	10010450
41817	Indometacin	10010450
41823	Indometacin	10010450
42003	Indometacin	10010450
42397	Ibuprofen sodium dihydrate	10010100
42406	Diclofenac sodium	10010450
42500	Ketoprofen	10010450
42793	Diclofenac sodium	10010450
42905	Diclofenac sodium	10010450
43904	Ibuprofen lysine	10010100
44313	Indometacin	10010450
44800	Esomeprazole magnesium trihydrate/Naproxen	10010100
44986	Esomeprazole magnesium trihydrate/Naproxen	10010100
45256	Indometacin	10010450
45262	Naproxen	10010450
46440	Naproxen	10010450
46848	Naproxen	10010450
46919	Ketoprofen	10010450
46920	Ketoprofen	10010450
47994	Naproxen	10010450
48161	Naproxen	10010450
48218	Diclofenac sodium	10010450
49132	Diclofenac diethylammonium	10030250
49788	Diclofenac diethylammonium	10030250
49862	Diclofenac diethylammonium	10030250
51237	Diclofenac diethylammonium	10030250
51242	Naproxen	10010100
51339	Indometacin	10010100
51360	Naproxen	10010100
51829	Naproxen	10010100

52141	Indometacin	10010450
52229	Diclofenac diethylammonium	10030250
52931	Naproxen	10010100
52956	Diclofenac diethylammonium	10030250
53626	Naproxen	10010100
53700	Naproxen	10010100
53980	Naproxen	10010100
54304	Naproxen	10010100
54463	Diclofenac sodium	10010450
54476	Naproxen	10010100
54660	Diclofenac Sodium	10010450
54783	Naproxen	10010100
55454	Naproxen	10010100
55486	Naproxen	10010100
55505	Naproxen	10010100
55894	Naproxen	10010100
56282	Diclofenac diethylammonium	10030250
56554	Naproxen	10010100
56558	Diclofenac diethylammonium	10030250
56762	Naproxen	10010100
56925	Naproxen	10010100
57545	Diclofenac diethylammonium	10030250
58213	Naproxen	10010100
58221	Naproxen	10010100
58523	Indometacin	10010100
58708	Naproxen	10010100
59246	Naproxen	10010100
59878	Naproxen	10010100
60408	Naproxen	10010100
60772	Indometacin	10010100
60930	Indometacin	10010100
61695	Naproxen	10010100
62643	Indometacin	10010450
62851	Diclofenac diethylammonium	10030250
63357	Naproxen	10010100
63843	Naproxen	10010100
65348	Naproxen	10010100
65952	Naproxen	10010100
66993	Naproxen	10010100
67363	Naproxen	10010100
67756	Indometacin	10010100
67768	Naproxen	10010100
68097	Naproxen	10010100
68470	Naproxen	10010100

68685	Naproxen	10010100
69645	Naproxen	10010100
69683	Diclofenac diethylammonium	10030250
69828	Naproxen	10010100
70393	Naproxen	10010100
70698	Naproxen	10010100
70828	Naproxen	10010100
70904	Indometacin	10010100
71364	Diclofenac diethylammonium	10030250
71709	Naproxen	10010100
72030	Naproxen	10010100
72047	Naproxen	10010100

5.3. Covariates: Coxibs.

prodcode	Drug substance	BNF code
474	Celecoxib	10010100
518	Rofecoxib	0
538	Rofecoxib	0
570	Parecoxib Sodium	15010402
613	Rofecoxib	0
637	Rofecoxib	0
640	Rofecoxib	0
650	Etoricoxib	10010100
666	Rofecoxib	0
706	Rofecoxib	0
723	Valdecoxib	0
5080	Celecoxib	10010100
5175	Celecoxib	10010100
5254	Celecoxib	10010100
5695	Rofecoxib	0
5739	Rofecoxib	0
5812	Etoricoxib	10010100
5841	Rofecoxib	0
5938	Etoricoxib	10010100
6460	Rofecoxib	0
6464	Etoricoxib	10010100
6498	Etoricoxib	10010100
6663	Valdecoxib	0
7118	Lumiracoxib	0
9822	Etoricoxib	10010100
9899	Valdecoxib	0
9912	Valdecoxib	0
9978	Valdecoxib	0
10212	Lumiracoxib	0
18066	Valdecoxib	0
19975	Parecoxib Sodium	15010402
28171	Lumiracoxib	0
28383	Lumiracoxib	0
37562	Etoricoxib	10010100
37587	Etoricoxib	10010100
43616	Celecoxib	10010100
50059	Celecoxib	10010100
50080	Parecoxib sodium	15010402
51284	Etoricoxib	10010100
51306	Parecoxib sodium	15010402
51874	Etoricoxib	10010100
52420	Celecoxib	10010100

53145	Rofecoxib	0
53576	Etoricoxib	10010100
54760	Parecoxib sodium	15010402
55582	Celecoxib	10010100
56584	Etoricoxib	10010100
58644	Parecoxib sodium	15010402
62251	Etoricoxib	10010100
62658	Etoricoxib	10010100
62840	Celecoxib	10010100
62843	Etoricoxib	10010100
64245	Celecoxib	10010100
64521	Etoricoxib	10010100
64935	Celecoxib	10010100
65016	Celecoxib	10010100
66486	Etoricoxib	10010100
66571	Celecoxib	10010100
66757	Celecoxib	10010100
67786	Rofecoxib	0
72293	Celecoxib	10010100

5.4. Covariates: Aspirin.

prodcode	Drug substance	BNF code
2607	Aspirin	02090000/04070100
29759	Aspirin	02090000/04070100
9301	Aspirin	02090000
17704	Aspirin	02090000
17920	Aspirin	02090000
36543	Aspirin	02090000
15364	Aspirin	02090000/04070100
49799	Aspirin	02090000/04070100
51474	Aspirin	02090000/04070100
53791	Aspirin	02090000/04070100
68051	Aspirin	02090000/04070100
66171	Aspirin	04070100
39738	Aspirin	02090000
43679	Aspirin	02090000
10305	Aspirin	02090000/04070100
31858	Aspirin	02090000/04070100
37541	Aspirin	02090000/04070100
254	Aspirin	02090000/04070100
377	Aspirin	02090000/04070100
393	Aspirin	02090000/04070100
434	Aspirin	02090000/04070100
645	Aspirin	02090000/04070100
1137	Aspirin	02090000/04070100
2105	Aspirin	02090000/04070100
6007	Aspirin	02090000/04070100
7516	Aspirin	02090000/04070100
8185	Aspirin	02090000/04070100
8186	Aspirin	02090000/04070100
8645	Aspirin	02090000/04070100
18217	Aspirin	02090000/04070100
21921	Aspirin	02090000/04070100
22232	Aspirin	02090000/04070100
23488	Aspirin	02090000/04070100
23932	Aspirin	02090000/04070100
24025	Aspirin	02090000/04070100
24960	Aspirin	02090000/04070100
30920	Aspirin	02090000/04070100
31210	Aspirin	02090000/04070100
32210	Aspirin	02090000/04070100
33662	Aspirin	02090000/04070100
33668	Aspirin	02090000/04070100
34309	Aspirin	02090000/04070100

34386	Aspirin	02090000/04070100
34666	Aspirin	02090000/04070100
34762	Aspirin	02090000/04070100
40144	Aspirin	02090000/04070100
41569	Aspirin	02090000/04070100
41594	Aspirin	02090000/04070100
43060	Aspirin	02090000/04070100
43434	Aspirin	02090000/04070100
43806	Aspirin	02090000/04070100
44639	Aspirin	02090000/04070100
45840	Aspirin	02090000/04070100
45851	Aspirin	02090000/04070100
48000	Aspirin	02090000/04070100
48165	Aspirin	02090000/04070100
49220	Aspirin	02090000/04070100
50555	Aspirin	02090000/04070100
52044	Aspirin	02090000/04070100
52280	Aspirin	02090000/04070100
52905	Aspirin	02090000/04070100
53622	Aspirin	02090000/04070100
53711	Aspirin	02090000/04070100
53804	Aspirin	02090000/04070100
53816	Aspirin	02090000/04070100
54526	Aspirin	02090000/04070100
54734	Aspirin	02090000/04070100
55230	Aspirin	02090000/04070100
56007	Aspirin	02090000/04070100
56736	Aspirin	02090000/04070100
58331	Aspirin	02090000/04070100
60278	Aspirin	02090000/04070100
62334	Aspirin	02090000/04070100
62430	Aspirin	02090000/04070100
63603	Aspirin	02090000/04070100
67160	Aspirin	02090000/04070100
67362	Aspirin	02090000/04070100
67754	Aspirin	02090000/04070100
55579	Aspirin	00000000
28810	Aspirin	02090000/04070100
29848	Aspirin	02090000/04070100
31870	Aspirin	02090000/04070100
22138	Aspirin	02090000
3	Aspirin	02090000
16	Aspirin	02090000
34	Aspirin	02090000

2628	Aspirin	02090000
19189	Aspirin	02090000
22618	Aspirin	02090000
23878	Aspirin	02090000
31211	Aspirin	02090000
31938	Aspirin	02090000
31953	Aspirin	02090000
31954	Aspirin	02090000
31956	Aspirin	02090000
32036	Aspirin	02090000
32992	Aspirin	02090000
33293	Aspirin	02090000
33320	Aspirin	02090000
33656	Aspirin	02090000
33676	Aspirin	02090000
34385	Aspirin	02090000
34434	Aspirin	02090000
34485	Aspirin	02090000
34611	Aspirin	02090000
34796	Aspirin	02090000
34797	Aspirin	02090000
34942	Aspirin	02090000
40381	Aspirin	02090000
41512	Aspirin	02090000
43709	Aspirin	02090000
45643	Aspirin	02090000
47992	Aspirin	02090000
48021	Aspirin	02090000
48974	Aspirin	02090000
49060	Aspirin	02090000
49685	Aspirin	02090000
50926	Aspirin	02090000
50949	Aspirin	02090000
51561	Aspirin	02090000
52618	Aspirin	02090000
53178	Aspirin	02090000
54284	Aspirin	02090000
54430	Aspirin	02090000
54565	Aspirin	02090000
54997	Aspirin	02090000
56883	Aspirin	02090000
56995	Aspirin	02090000
56996	Aspirin	02090000
57057	Aspirin	02090000

59021	Aspirin	02090000
59253	Aspirin	02090000
59728	Aspirin	02090000
59791	Aspirin	02090000
60127	Aspirin	02090000
60777	Aspirin	02090000
66345	Aspirin	02090000
66546	Aspirin	02090000
66563	Aspirin	02090000
66861	Aspirin	02090000
68752	Aspirin	02090000
6006	Aspirin	02090000/04070100
6696	Aspirin	02090000/04070100
9144	Aspirin	02090000/04070100
18329	Aspirin	02090000/04070100
23593	Aspirin	02090000/04070100
25335	Aspirin	02090000/04070100
25718	Aspirin	02090000/04070100
47937	Aspirin	00000000

5.5. Covariates: Opioids.

prodcode	drug substance	BNF code
4	Morphine sulphate	04070200
7	Diamorphine Hydrochloride	04070200
11	Dihydrocodeine tartrate	04070200
53	Tramadol hydrochloride	04070200
86	Oxycodone hydrochloride	04070200
96	Morphine Sulphate	04070200
123	Tramadol hydrochloride	04070200
124	Meptazinol hydrochloride	04070200
139	Tramadol hydrochloride	04070200
158	Codeine phosphate	01040200/03090100/04070200
187	Codeine phosphate	04070200
191	Morphine sulphate	04070200
213	Codeine phosphate	01040200/03090100/04070200
258	Tramadol hydrochloride	04070200
262	Dihydrocodeine tartrate	04070200
306	Fentanyl citrate	04070200
328	Tramadol hydrochloride	04070200
354	Oxycodone hydrochloride	04070200
381	Dihydrocodeine tartrate	04070200
382	Codeine phosphate	01040200/03090100/04070200
395	Morphine sulphate	04070200
430	Dextromoramide tartrate	04070200
458	Tramadol hydrochloride	04070200
462	Fentanyl	04070200
483	Fentanyl citrate	04070200
484	Tramadol hydrochloride	04070200
495	Diamorphine hydrochloride	04070200
539	Codeine phosphate	01040200/03090100/04070200
570	Morphine Sulphate	04070200
607	Oxycodone hydrochloride	04070200
620	Oxycodone hydrochloride	04070200
625	Fentanyl	04070200
635	Fentanyl	04070200
656	Fentanyl	04070200
659	Dihydrocodeine tartrate	04070200
661	Pentazocine Lactate	04070200
687	Oxycodone hydrochloride	04070200
701	Oxycodone hydrochloride	04070200
715	Tramadol hydrochloride	04070200
748	Dihydrocodeine tartrate	04070200
759	Tramadol hydrochloride	04070200
767	Fentanyl	04070200

800	Pethidine Hydrochloride	04070200
807	Pethidine Hydrochloride	04070200
810	Tramadol hydrochloride	04070200
826	Oxycodone hydrochloride	04070200
855	Dextromoramide tartrate	04070200
899	Morphine sulfate	04070200
901	Morphine sulfate	04070200
1043	Tramadol hydrochloride	04070200
1068	Morphine sulfate	04070200
1147	Morphine sulfate	04070200
1404	Fentanyl	04070200
1503	Tramadol hydrochloride	04070200
1609	Morphine sulfate	04070200
1640	Diamorphine hydrochloride	04070200
1689	Dihydrocodeine tartrate	04070200
1762	Fentanyl Citrate	04070200
1862	Tramadol hydrochloride	04070200
1866	Fentanyl	04070200
1999	Tramadol Hydrochloride	04070200
2034	Tramadol Hydrochloride	04070200
2040	Fentanyl	04070200
2041	Morphine Sulphate	04070200
2047	Tramadol hydrochloride	04070200
2055	Fentanyl	04070200
2211	Methadone Hydrochloride	04070200
2288	Fentanyl	04070200
2344	Diamorphine Hydrochloride	04070200
2450	Buprenorphine	04070200
2462	Morphine sulfate	04070200
2555	Tramadol hydrochloride	04070200
2586	Hydromorphone hydrochloride	04070200
2794	Fentanyl Citrate	04070200
2800	Hydromorphone hydrochloride	04070200
2846	Morphine sulfate	04070200
2917	Morphine sulfate	04070200
2957	Oxycodone hydrochloride	04070200
2966	Oxycodone hydrochloride	04070200
2986	Tramadol hydrochloride	04070200
2997	Oxycodone hydrochloride	04070200
3053	Fentanyl	04070200
3074	Tramadol Hydrochloride	04070200
3156	Tramadol hydrochloride	04070200
3165	Diamorphine hydrochloride	04070200
3185	Fentanyl	04070200

3239	Buprenorphine	04070200
3309	Morphine sulfate	04070200
3313	Morphine Sulphate	04070200
3316	Oxycodone hydrochloride	04070200
3431	Dihydrocodeine tartrate	04070200
3432	Tramadol hydrochloride	04070200
3435	Fentanyl	04070200
3496	Fentanyl	04070200
3644	Tramadol hydrochloride	04070200
3653	Oxycodone hydrochloride	04070200
3713	Pentazocine lactate	04070200
3724	Fentanyl Citrate	04070200
3794	Oxycodone hydrochloride	04070200
3817	Tramadol hydrochloride	04070200
3901	Tramadol hydrochloride	04070200
3919	Oxycodone hydrochloride	04070200
3972	Dihydrocodeine tartrate	04070200
3990	Buprenorphine	04070200
4016	Fentanyl citrate	04070200
4045	Fentanyl	04070200
4114	Tramadol hydrochloride	04070200
4115	Tramadol hydrochloride	04070200
4186	Morphine Sulphate	04070200
4196	Fentanyl	04070200
4236	Fentanyl	04070200
4266	Tramadol hydrochloride	04070200
4280	Tramadol hydrochloride	04070200
4369	Codeine Phosphate	03090100/04070200
4476	Buprenorphine	04070200
4477	Fentanyl	04070200
4556	Pethidine Hydrochloride	04070200
4600	Morphine hydrochloride	04070200
4607	Fentanyl Citrate	04070200
4633	Diamorphine Hydrochloride	04070200
4671	Fentanyl	04070200
4691	Oxycodone hydrochloride	04070200
4693	Fentanyl	04070200
4805	Codeine phosphate	03090100/04070200
4823	Pethidine hydrochloride	04070200
4834	Tramadol hydrochloride	04070200
4950	Fentanyl	04070200
4999	Fentanyl	04070200
5028	Diamorphine hydrochloride	04070200
5079	Buprenorphine	04070200

5137	Buprenorphine	04070200
5138	Buprenorphine	04070200
5239	Diamorphine Hydrochloride	04070200
5243	Morphine sulfate	04070200
5257	Fentanyl	04070200
5288	Fentanyl citrate	04070200
5322	Methadone hydrochloride	03090100/04070200/04105200
5323	Fentanyl citrate	04070200
5407	Fentanyl	04070200
5555	Tramadol hydrochloride	04070200
5563	Buprenorphine	04070200
5585	Buprenorphine	04070200
5599	Tramadol hydrochloride	04070200
5651	Buprenorphine	04070200
5652	Buprenorphine	04070200
5657	Buprenorphine	04070200
5668	Buprenorphine	04070200
5670	Oxycodone hydrochloride	04070200
5681	Tramadol hydrochloride	04070200
5696	Buprenorphine	04070200
5697	Buprenorphine	04070200
5714	Buprenorphine	04070200
5833	Buprenorphine	04070200
5840	Fentanyl	04070200
5843	Hydromorphone hydrochloride	04070200
5936	Buprenorphine	04070200
5955	Fentanyl citrate	04070200
5991	Buprenorphine	04070200
6040	Oxycodone hydrochloride	04070200
6153	Oxycodone hydrochloride	04070200
6181	Buprenorphine	04070200
6215	Tramadol hydrochloride	04070200
6232	Alfentanil hydrochloride	15010403
6234	Alfentanil Hydrochloride	15010403
6269	Alfentanil Hydrochloride	15010403
6298	Alfentanil hydrochloride	15010403
6366	Alfentanil hydrochloride	15010403
6414	Alfentanil hydrochloride	15010403
6441	Methadone hydrochloride	03090100/04070200/04105200
6458	Remifentanyl hydrochloride	15010403
6459	Alfentanil hydrochloride	15010403
6557	Alfentanil Hydrochloride	15010403
6558	Alfentanil hydrochloride	15010403
6571	Morphine sulfate	04070200

6608	Alfentanil hydrochloride	15010403
6609	Remifentanyl hydrochloride	15010403
6699	Morphine tartrate/Cyclizine tartrate	04070200
6708	Morphine Sulphate/Atropine Sulphate	04070200/15010300
6736	Papaveretum/Hyoscine hydrobromide	04070200/15010300
6769	Hyoscine Hydrobromide/Papaveretum	04070200/15010300
6790	Buprenorphine hydrochloride	04070200/04105200
6879	Methadone hydrochloride	04070200/04105200
6886	Morphine sulfate	04070200
6892	Buprenorphine hydrochloride	04070200/04105200
6917	Buprenorphine hydrochloride	04070200/04105200
6948	Buprenorphine hydrochloride	04070200/04105200
7063	Oxycodone hydrochloride	04070200
7072	Oxycodone hydrochloride	04070200
7082	Buprenorphine hydrochloride	04070200/04105200
7104	Morphine sulfate	04070200
7107	Buprenorphine hydrochloride	04070200/04105200
7114	Buprenorphine hydrochloride	04070200/04105200
7126	Methadone hydrochloride	04070200/04105200
7167	Buprenorphine hydrochloride	04070200/04105200
7197	Buprenorphine hydrochloride	04070200/04105200
7205	Oxycodone hydrochloride	04070200
7236	Methadone Hydrochloride	04070200/04105200
7238	Methadone hydrochloride	04070200/04105200
7275	Methadone Hydrochloride	04070200/04105200
7334	Methadone hydrochloride	04070200/04105200
7372	Methadone hydrochloride	04070200/04105200
7389	Methadone hydrochloride	04070200/04105200
7397	Methadone hydrochloride	04070200/04105200
7406	Methadone hydrochloride	04070200/04105200
7450	Oxycodone hydrochloride	04070200
7457	Methadone hydrochloride	04070200/04105200
7469	Methadone hydrochloride	04070200/04105200
7489	Buprenorphine	04070200
7499	Oxycodone hydrochloride	04070200
7517	Methadone hydrochloride	04070200/04105200
7518	Tapentadol hydrochloride	04070200
7539	Morphine sulfate	04070200
7542	Tapentadol hydrochloride	04070200
7555	Methadone hydrochloride	04070200/04105200
7729	Methadone hydrochloride	04070200/04105200
7800	Buprenorphine hydrochloride	04070200/04105200
7849	Methadone hydrochloride	04070200/04105200
7875	Methadone hydrochloride	04070200/04105200

7999	Methadone hydrochloride	04070200/04105200
8039	Methadone hydrochloride	04070200/04105200
8040	Buprenorphine Hydrochloride/Naloxone Hydrochloride	04070200/04105200
8075	Methadone hydrochloride	04070200/04105200
8139	Morphine sulfate	04070200
8246	Oxycodone hydrochloride	04070200
8329	Oxycodone hydrochloride	04070200
8335	Fentanyl Citrate	04070200
8375	Buprenorphine hydrochloride	04070200/04105200
8416	Buprenorphine hydrochloride	04070200/04105200
8447	Buprenorphine hydrochloride	04070200/04105200
8456	Methadone hydrochloride	04070200/04105200
8723	Buprenorphine	04070200
8735	Methadone hydrochloride	04070200/04105200
8740	Buprenorphine Hydrochloride/Naloxone Hydrochloride	04070200/04105200
8822	Methadone hydrochloride	04070200/04105200
8866	Methadone hydrochloride	04070200/04105200
8876	Buprenorphine hydrochloride	04070200/04105200
9001	Methadone hydrochloride	04070200/04105200
9012	Buprenorphine hydrochloride	04070200/04105200
9044	Tramadol hydrochloride	04070200
9053	Buprenorphine hydrochloride	04070200/04105200
9129	Buprenorphine	04070200
9163	Oxycodone hydrochloride	04070200
9183	Buprenorphine hydrochloride	04070200/04105200
9193	Tramadol hydrochloride	04070200
9209	Buprenorphine hydrochloride	04070200/04105200
9231	Morphine sulfate	04070200
9239	Dihydrocodeine tartrate	04070200
9271	Morphine sulfate	04070200
9275	Buprenorphine hydrochloride	04070200/04105200
9313	Buprenorphine hydrochloride	04070200/04105200
9325	Buprenorphine hydrochloride	04070200/04105200
9330	Buprenorphine hydrochloride	04070200/04105200
9331	Buprenorphine hydrochloride	04070200/04105200
9337	Buprenorphine hydrochloride	04070200/04105200
9371	Buprenorphine hydrochloride	04070200/04105200
9389	Buprenorphine hydrochloride	04070200/04105200
9396	Buprenorphine hydrochloride	04070200/04105200
9432	Tapentadol hydrochloride	04070200
9457	Tapentadol hydrochloride	04070200
9460	Tapentadol Hydrochloride	04070200
9462	Tapentadol Hydrochloride	04070200

9484	Methadone hydrochloride	04070200/04105200
9516	Tapentadol Hydrochloride	04070200
9557	Methadone hydrochloride	04070200/04105200
9562	Tapentadol Hydrochloride	04070200
9581	Oxycodone hydrochloride	04070200
9602	Methadone hydrochloride	04070200/04105200
9615	Methadone hydrochloride	04070200/04105200
9672	Buprenorphine hydrochloride	04070200/04105200
9712	Fentanyl	04070200
9742	Tapentadol hydrochloride	04070200
9785	Tapentadol Hydrochloride	04070200
9855	Oxycodone Hydrochloride	04070200
9874	Morphine sulfate	04070200/50030000
9914	Morphine sulfate	04070200
9927	Morphine hydrochloride/Cocaine hydrochloride/Syrup/Ethanol 90%	04070200/15020000
10023	Tramadol hydrochloride	04070200
10122	Fentanyl citrate	04070200
10123	Morphine sulfate	04070200
10176	Tapentadol hydrochloride	04070200
10178	Fentanyl citrate	04070200
10196	Oxycodone Hydrochloride	04070200
10226	Fentanyl	04070200
10239	Fentanyl Citrate	04070200/15010403
10293	Tramadol hydrochloride	04070200
10309	Fentanyl Citrate	04070200/15010403
10509	Fentanyl	04070200
10582	Tramadol Hydrochloride	04070200
10583	Fentanyl citrate	04070200/15010403
10602	Tramadol hydrochloride	04070200
10631	Fentanyl citrate	04070200/15010403
10730	Fentanyl citrate	04070200/15010403
10748	Diamorphine Hydrochloride	04070200
10769	Fentanyl citrate	04070200/15010403
10922	Fentanyl citrate	04070200/15010403
10925	Fentanyl citrate	04070200/15010403
10939	Tramadol hydrochloride	04070200
10993	Diamorphine Hydrochloride	04070200
11009	Fentanyl	04070200
11101	Alfentanil hydrochloride	04070200/15010403
11129	Fentanyl citrate	04070200/15010403
11250	Fentanyl	04070200
11325	Tapentadol hydrochloride	04070200
11326	Oxycodone hydrochloride	04070200

11584	Morphine anhydrous/Peppermint oil	01020200/04070200
11665	Fentanyl	04070200
11698	Morphine anhydrous/Peppermint oil	01020200/04070200
11734	Pethidine Hydrochloride/Promethazine Hydrochloride	03040102/04070200
11807	Papaveretum	04070200
11925	Fentanyl	04070200
11986	Oxycodone hydrochloride	04070200
12364	Oxycodone hydrochloride	04070200
12394	Oxycodone hydrochloride	04070200
12964	Morphine sulfate	04070200
12976	Oxycodone hydrochloride	04070200
12992	Oxycodone hydrochloride	04070200
14251	Morphine Sulphate	04070200
14517	Oxycodone hydrochloride	04070200
14627	Buprenorphine	04070200
14655	Pentazocine Lactate	04070200
14676	Morphine sulfate	04070200
14688	Tapentadol Hydrochloride	04070200
14785	Fentanyl	04070200
14829	Morphine Sulphate	04070200
14899	Buprenorphine	04070200
14912	Tapentadol hydrochloride	04070200
14964	Morphine sulfate	04070200
15198	Diamorphine Hydrochloride	04070200
15238	Oxycodone hydrochloride	04070200
15779	Diamorphine Hydrochloride	04070200
15831	Morphine sulfate	04070200
15845	Fentanyl	04070200
16039	Fentanyl Citrate	04070200
16076	Tramadol Hydrochloride	04070200
16096	Codeine phosphate	01040200/03090100/04070200
16106	Fentanyl	04070200
16112	Diamorphine Hydrochloride	04070200
16184	Fentanyl	04070200
16205	Oxycodone hydrochloride	04070200
16467	Morphine sulfate	04070200
16592	Morphine sulfate	04070200
16611	Morphine Sulphate	04070200
16637	Fentanyl	04070200
16818	Morphine sulfate	04070200
17158	Tramadol hydrochloride	04070200
17165	Fentanyl	04070200

17412	Buprenorphine	04070200
17490	Cyclizine Tartrate/Morphine Tartrate	03040103/04070200
17563	Pethidine hydrochloride	04070200
17773	Tramadol hydrochloride	04070200
17845	Buprenorphine	04070200
17917	Dihydrocodeine tartrate	04070200
17926	Pethidine hydrochloride	04070200
17998	Oxycodone hydrochloride	04070200
18221	Diamorphine hydrochloride	04070200
18261	Diamorphine hydrochloride	04070200
18441	Buprenorphine	04070200
18482	Diamorphine hydrochloride	04070200
18675	Oxycodone hydrochloride	04070200
18799	Oxycodone hydrochloride	04070200
18840	Fentanyl	04070200
18922	Oxycodone hydrochloride	04070200
19139	Buprenorphine Hydrochloride	04070200
19206	Diamorphine hydrochloride	04070200
19255	Dihydrocodeine tartrate	04070200
19626	Dihydrocodeine tartrate	04070200
19975	Fentanyl	04070200
20068	Morphine sulfate	04070200
20127	Diamorphine hydrochloride	04070200
20385	Dextromoramide tartrate	04070200
20565	Fentanyl	04070200
20646	Pethidine Hydrochloride	04070200
20650	Buprenorphine	04070200
20840	Morphine Hydrochloride	04070200
21067	Dextromoramide Tartrate	04070200
21113	Morphine sulfate	04070200
21229	Diamorphine Hydrochloride	04070200
21251	Paracetamol/Codeine phosphate/Caffeine	04070000/04070200
21673	Diamorphine hydrochloride	04070200
21770	Morphine sulfate	04070200
21840	Fentanyl citrate	04070200
21880	Diamorphine hydrochloride	04070200
21949	Pethidine hydrochloride	04070200
22014	Diamorphine Hydrochloride	04070200
22073	Oxycodone hydrochloride	04070200
22288	Morphine sulfate	04070200
22305	Diamorphine Hydrochloride	04070200
22380	Morphine Sulphate	04070200
22988	Pethidine Hydrochloride	04070200

23077	Pentazocine hydrochloride	04070200
23108	Buprenorphine Hydrochloride	04070200
23114	Tramadol Hydrochloride	04070200
23420	Tramadol hydrochloride	04070200
23425	Meptazinol hydrochloride	04070200
23617	Dihydrocodeine tartrate	04070200
23716	Diamorphine hydrochloride	04070200
23840	Morphine hydrochloride	04070200
23841	Morphine sulfate	04070200
23952	Tramadol hydrochloride	04070200
24000	Diamorphine hydrochloride	04070200
24075	Morphine sulfate	04070200
24111	Morphine sulfate	04070200
24125	Ethylmorphine hydrochloride	03090100/04070200
24133	Cyclizine hydrochloride/Dipipanone hydrochloride	04070200
24283	Codeine Phosphate	04070200
24309	Morphine tartrate/Cyclizine tartrate	04070200
24534	Diamorphine Hydrochloride	04070200
24828	Oxycodone hydrochloride	04070200
24947	Morphine sulfate	04070200
25109	Oxycodone hydrochloride	04070200
25211	Morphine sulfate	04070200
25316	Dipipanone Hydrochloride/Cyclizine Hydrochloride	03040103/04070200
25341	Naloxone Hydrochloride/oxycodone Hydrochloride	04070200
25342	Naloxone Hydrochloride/oxycodone Hydrochloride	04070200
25514	Oxycodone hydrochloride	04070200
25529	Oxycodone hydrochloride	04070200
25607	Dihydrocodeine tartrate	04070200
25895	Dihydrocodeine tartrate	04070200
26133	Dihydrocodeine tartrate	04070200
26746	Hydromorphone hydrochloride	04070200
26988	Hydromorphone hydrochloride	04070200
27064	Hydromorphone hydrochloride	04070200
27197	Hydromorphone hydrochloride	04070200
27366	Naloxone hydrochloride/Oxycodone hydrochloride	04070200
27435	Morphine sulfate	04070200
27446	Morphine sulfate	04070200
27452	Morphine sulfate	04070200
27459	Morphine sulfate	04070200
27492	Pentazocine hydrochloride	04070200

27784	Morphine sulfate	04070200
27785	Oxycodone hydrochloride	04070200
27856	Morphine sulfate	04070200
28211	Tramadol hydrochloride	04070200
28253	Morphine sulfate	04070200
28255	Naloxone hydrochloride/Oxycodone hydrochloride	04070200
28344	Tramadol hydrochloride	04070200
28346	Morphine Sulphate	04070200
28598	Dihydrocodeine tartrate	04070200
28636	Morphine sulfate	04070200
28712	Morphine sulfate	04070200
28780	Fentanyl	04070200
28784	Oxycodone hydrochloride	04070200
28878	Hydromorphone hydrochloride	04070200
28937	Morphine Sulphate	04070200
28955	Morphine sulfate	04070200
29054	Oxycodone hydrochloride	04070200
29342	Oxycodone hydrochloride	04070200
29373	Tramadol hydrochloride	04070200
29375	Oxycodone hydrochloride	04070200
29488	Fentanyl	04070200
29670	Pethidine Hydrochloride	04070200
30021	Oxycodone hydrochloride	04070200
30022	Oxycodone Hydrochloride	04070200
30070	Diamorphine hydrochloride	04070200
30123	Tramadol hydrochloride	04070200
30165	Fentanyl	04070200
30295	Oxycodone hydrochloride	04070200
30444	Morphine Sulphate	04070200
30556	Oxycodone hydrochloride	04070200
30590	Oxycodone hydrochloride	04070200
30954	Buprenorphine	04070200
30958	Morphine sulfate	04070200
30966	Oxycodone hydrochloride	04070200
30982	Tramadol hydrochloride	04070200
30984	Morphine sulfate	04070200
31001	Dihydrocodeine tartrate	04070200
31151	Pentazocine Lactate	04070200
31155	Oxycodone hydrochloride	04070200
31196	Morphine Anhydrous	04070200
31257	Morphine sulfate	04070200
31452	Codeine phosphate	01040200/03090100/04070200
31488	Pentazocine hydrochloride	04070200

31499	Fentanyl	04070200
31577	Oxycodone hydrochloride	04070200
31700	Codeine phosphate	01040200/03090100/04070200
31871	Oxycodone hydrochloride	04070200
31894	Meptazinol hydrochloride	04070200
31943	Codeine phosphate	01040200/03090100/04070200
32093	Tramadol hydrochloride	04070200
32154	Papaveretum	04070200
32163	Tramadol hydrochloride	04070200
32178	Morphine sulfate	04070200
32314	Oxycodone hydrochloride	04070200
32554	Tramadol hydrochloride	04070200
32626	Buprenorphine	04070200
32692	Oxycodone hydrochloride	04070200
32728	Morphine Sulphate	04070200
32766	Tramadol hydrochloride	04070200
32839	Tramadol hydrochloride	04070200
32926	Oxycodone hydrochloride	04070200
32942	Morphine Sulphate	04070200
32970	Tramadol hydrochloride	04070200
32993	Meptazinol hydrochloride	04070200
33060	Morphine sulfate	04070200
33104	Fentanyl citrate	04070200
33139	Fentanyl	04070200
33260	Codeine phosphate	04070200
33317	Cyclizine hydrochloride/Dipipanone hydrochloride	04070200
33340	Pethidine hydrochloride	04070200
33386	Dextropropoxyphene Napsylate	04070200
33614	Morphine sulfate	04070200
33643	Tramadol hydrochloride	04070200
33647	Morphine sulfate	04070200
33653	Morphine sulfate	04070200
33666	Morphine sulfate	04070200
33679	Oxycodone hydrochloride	04070200
33687	Morphine sulfate	04070200
33688	Morphine sulfate	04070200
33710	Fentanyl citrate	04070200
33743	Tramadol hydrochloride	04070200
33826	Morphine sulfate	04070200
33838	Morphine sulfate	04070200
33935	Fentanyl citrate	04070200
33961	Morphine sulfate	04070200
33995	Oxycodone hydrochloride	04070200

34022	Morphine sulfate	04070200
34073	Codeine phosphate	03090100/04070200
34090	Codeine phosphate	03090100/04070200
34152	Codeine phosphate	03090100/04070200
34164	Morphine sulfate	04070200
34172	Codeine phosphate	03090100/04070200
34176	Codeine phosphate	03090100/04070200
34209	Buprenorphine	04070200
34229	Tramadol hydrochloride	04070200
34233	Diamorphine hydrochloride	04070200
34235	Morphine Sulphate	04070200
34257	Tramadol hydrochloride	04070200
34264	Morphine Sulphate	04070200
34266	Morphine Sulphate	04070200
34289	Dihydrocodeine tartrate	04070200
34290	Fentanyl citrate	04070200
34305	Morphine Sulphate	04070200
34319	Morphine sulfate	04070200
34348	Codeine phosphate	01040200/03090100/04070200
34349	Morphine sulfate	04070200
34350	Morphine sulfate	04070200
34373	Codeine phosphate	03090100/04070200
34383	Codeine phosphate	01040200/03090100/04070200
34396	Phenazocine Hydrobromide	04070200
34397	Hydromorphone hydrochloride	04070200
34409	Tramadol hydrochloride	04070200
34437	Codeine phosphate	03090100/04070200
34444	Codeine phosphate	01040200/03090100/04070200
34468	Fentanyl	04070200
34495	Fentanyl citrate	04070200
34497	Morphine sulfate	04070200
34500	Diamorphine Hydrochloride	04070200
34518	Oxycodone hydrochloride	04070200
34546	Oxycodone hydrochloride	04070200
34552	Codeine phosphate	01040200/03090100/04070200
34554	Diamorphine hydrochloride	04070200
34597	Papaveretum	04070200
34610	Tramadol hydrochloride	04070200
34667		04070200
34669	Morphine Sulphate	04070200
34678	Hydromorphone hydrochloride	04070200
34700	Diamorphine hydrochloride	04070200
34718	Hydromorphone hydrochloride	04070200
34737	Diamorphine hydrochloride	04070200

34738	Fentanyl Citrate	04070200
34743	Fentanyl citrate	04070200
34761	Morphine sulfate	04070200
34769	Tramadol hydrochloride	04070200
34784	Morphine sulfate	04070200
34789	Codeine phosphate	01040200/03090100/04070200
34815	Morphine sulfate	04070200
34840	Pethidine Hydrochloride	04070200
34845	Morphine sulfate	04070200
34858	Morphine sulfate	04070200
34861	Morphine Sulphate	04070200
34865	Pethidine hydrochloride	04070200
34920	Morphine Sulphate	04070200
34939	Tramadol hydrochloride	04070200
34954	Tramadol hydrochloride	04070200
34968	Pethidine Hydrochloride	04070200
35679	Morphine sulfate	04070200
35792	Codeine phosphate	01040200/03090100/04070200
35798	Cyclizine Tartrate/Morphine Tartrate	03040103/04070200
35800	Morphine tartrate/Cyclizine tartrate	04070200
35965	Tramadol hydrochloride	04070200
36019	Dihydrocodeine tartrate	04070200
36472	Morphine sulfate	04070200
36488	Fentanyl	04070200
36608	Morphine Sulphate	04070200
36754	Nalbuphine Hydrochloride	04070200
36787	Fentanyl citrate	04070200
36929	Pethidine hydrochloride	04070200
36945	Phenazocine Hydrobromide	04070200
36993	Oxycodone hydrochloride	04070200
37291	Pethidine hydrochloride	04070200
37411	Morphine tartrate/Cyclizine tartrate	04070200
37904	Pethidine hydrochloride	04070200
37979	Dextromoramide Tartrate	04070200
38032	Morphine sulfate	04070200
38085	Buprenorphine	04070200
38088	Fentanyl	04070200
38122	Morphine sulfate	04070200
38299	Morphine sulfate	04070200
38301	Codeine phosphate	01040200/03090100/04070200
38323	Morphine sulfate	04070200
38363	Diamorphine hydrochloride	04070200
38511	Tramadol hydrochloride	04070200
38943	Morphine Sulphate	04070200

38984	Fentanyl citrate	04070200
39085	Fentanyl citrate	04070200
39317	Tramadol hydrochloride	04070200
39333	Pethidine hydrochloride/Promethazine hydrochloride	04070200
39340	Fentanyl	04070200
39481	Morphine sulfate	04070200
39647	Morphine sulfate	04070200
39656	Morphine sulfate	04070200
39693	Meptazinol hydrochloride	04070200
39758	Fentanyl citrate	04070200
39934	Diamorphine hydrochloride	04070200
39940	Morphine sulfate	04070200
40107	Morphine sulfate	04070200
40158	Morphine Sulphate	04070200
40385	Morphine sulfate	04070200
40401	Fentanyl citrate	04070200
40422	Pethidine Hydrochloride	04070200
40662	Pethidine Hydrochloride	04070200
40663	Pethidine hydrochloride	04070200
41214	Codeine phosphate	03090100/04070200
41259	Codeine phosphate	04070200
41275	Morphine Sulphate	04070200
41278	Pethidine hydrochloride/Promethazine hydrochloride	04070200
41407	Nalbuphine Hydrochloride	04070200
41409	Morphine sulfate	04070200
41414	Codeine Phosphate/Papaverine Hydrochloride/Morphine Hydrochloride	04070200
41416	Codeine phosphate	01040200/03090100/04070200
41523	Codeine phosphate	03090100/04070200
41535	Codeine phosphate	01040200/03090100/04070200
41599	Codeine phosphate	01040200/03090100/04070200
41680	Morphine sulfate	04070200
41682	Tramadol hydrochloride	04070200
42101	Morphine sulfate	04070200
42125	Morphine sulfate	04070200
42201	Codeine Phosphate/Papaverine Hydrochloride/Morphine Hydrochloride	04070200
42213	Hydromorphone hydrochloride	04070200
42218	Hydromorphone hydrochloride	04070200
42371	Tramadol hydrochloride	04070200
42397	Fentanyl citrate	04070200
42514	Morphine sulfate	04070200
42706	Levorphanol Tartrate	04070200

42791	Tramadol hydrochloride	04070200
42792	Dihydrocodeine Tartrate	03090100/04070200
42834	Morphine sulfate	04070200
42915	Morphine sulfate	04070200
43028	Hydromorphone hydrochloride	04070200
43199	Hydromorphone hydrochloride	04070200
43233	Tramadol hydrochloride	04070200
43238	Tramadol hydrochloride	04070200
43252	Tramadol hydrochloride	04070200
43414	Alfentanil Hydrochloride	04070200
43441	Oxycodone hydrochloride	04070200
43447	Cocaine/Diamorphine Hydrochloride	04070200
43479	Tramadol hydrochloride	04070200
43504	Codeine phosphate	01040200/04070200
43536	Fentanyl	04070200
43550	Codeine phosphate	01040200/03090100/04070200
43554	Morphine sulfate	04070200
43891	Morphine sulfate	04070200
43904	Tramadol hydrochloride	04070200
44159	Buprenorphine	04070200
44210	Morphine sulfate	04070200
44258	Fentanyl	04070200
44924	Pethidine hydrochloride	04070200
45231	Oxycodone hydrochloride	04070200
45259	Morphine Sulphate	04070200
45276	Oxycodone hydrochloride	04070200
45298	Morphine sulfate	04070200
45348	Morphine sulfate	04070200
45349	Dextromoramide Tartrate	04070200
45645	Pethidine hydrochloride	04070200
45649	Tramadol hydrochloride	04070200
46141	Tramadol hydrochloride	04070200
46511	Morphine sulfate	04070200
46544	Diamorphine Hydrochloride	04070200
46633	Morphine sulfate	04070200
46638	Morphine Sulphate	04070200
46729	Oxycodone hydrochloride	04070200
46763	Diamorphine Hydrochloride	04070200
46846	Hydromorphone hydrochloride	04070200
46898	Oxycodone hydrochloride	04070200
46904	Morphine Sulphate	04070200
46906	Tramadol hydrochloride	04070200
46925	Pethidine Hydrochloride/levallorphan	04070200
46987	Pethidine hydrochloride	04070200

47003	Codeine phosphate	01040200/03090100/04070200
47071	Oxycodone hydrochloride	04070200
47081	Diamorphine hydrochloride	04070200
47116	Fentanyl citrate	04070200
47211	Fentanyl citrate	04070200
47508	Morphine sulfate	04070200
47834	Morphine Anhydrous	04070200
47847	Tramadol hydrochloride	04070200
47919	Codeine phosphate	01040200/04070200
47952	Codeine phosphate	01040200/04070200
48004	Codeine phosphate	01040200/03090100/04070200
48129	Dextromoramide Tartrate	04070200
48153	Codeine phosphate	01040200/03090100/04070200
48157	Dextropropoxyphene napsylate	04070200
48178	Fentanyl citrate	04070200
48295	Morphine sulfate	04070200
48301	Morphine sulfate	04070200
48311	Oxycodone hydrochloride	04070200
48330	Tramadol hydrochloride	04070200
48354	Fentanyl citrate	04070200
48444	Tramadol hydrochloride	04070200
48526	Morphine sulfate	04070200
48535	Tramadol hydrochloride	04070200
48561	Morphine Sulphate	04070200
48597	Fentanyl	04070200
48622	Morphine Sulphate	04070200
48775	Diamorphine hydrochloride	04070200
48816	Diamorphine Hydrochloride	04070200
49096	Tramadol hydrochloride	04070200
49105	Dextromoramide Tartrate	04070200
49219	Diamorphine Hydrochloride	04070200
49314	Morphine sulfate	04070200
49417	Pethidine Hydrochloride	04070200
49524	Diamorphine hydrochloride	04070200
49575	Fentanyl citrate	04070200
49849	Tramadol hydrochloride	04070200
50009	Morphine Sulphate	04070200
50080	Dihydrocodeine tartrate	04070200
50232	Morphine Anhydrous	04070200
50421	Codeine phosphate	01040200/04070200
50468	Codeine phosphate	01040200/03090100/04070200
50482	Diamorphine Hydrochloride	04070200
50504	Levorphanol Tartrate	04070200
50659	Codeine phosphate	01040200/03090100/04070200

50881	Diamorphine Hydrochloride	04070200
50984	Diamorphine Hydrochloride	04070200
51084	Morphine sulfate	04070200
51242	Tramadol hydrochloride	04070200
51306	Pentazocine hydrochloride	04070200
51327	Codeine phosphate	01040200/03090100/04070200
51360	Tramadol hydrochloride	04070200
51381	Pethidine hydrochloride	04070200
51595	Diamorphine Hydrochloride	04070200
51644	Codeine phosphate	01040200/03090100/04070200
51819	Buprenorphine	04070200
51829	Fentanyl Citrate	04070200
51937	Codeine phosphate	01040200/03090100/04070200
52455	Fentanyl	04070200
52856	Tramadol hydrochloride	04070200
52888	Codeine phosphate	01040200/03090100/04070200
52889	Codeine phosphate	01040200/03090100/04070200
52929	Codeine phosphate	01040200/03090100/04070200
52931	Fentanyl Citrate	04070200
52948	Tramadol hydrochloride	04070200
52966	Oxycodone hydrochloride	04070200
53079		04070200
53208	Pethidine Hydrochloride	04070200
53287	Fentanyl citrate	04070200
53600	Codeine phosphate	01040200/03090100/04070200
53626	Dihydrocodeine tartrate	04070200
53700	Tramadol hydrochloride	04070200
53702	Buprenorphine	04070200
53952	Pentazocine lactate	04070200
53961	Pentazocine lactate	04070200
53980	Pethidine hydrochloride	04070200
53984	Morphine Sulphate	04070200
53999	Codeine phosphate	01040200/04070200
54179	Tramadol hydrochloride	04070200
54304	Tramadol hydrochloride	04070200
54476	Tramadol hydrochloride	04070200
54760	Pethidine hydrochloride	04070200
54783	Fentanyl citrate	04070200
54853	Pethidine hydrochloride	04070200
55044	Buprenorphine	04070200
55129	Pethidine hydrochloride	04070200
55245	Diamorphine hydrochloride	04070200
55301	Tramadol hydrochloride	04070200
55309	Codeine phosphate	01040200/03090100/04070200

55418	Oxycodone hydrochloride	04070200
55425	Methadone hydrochloride	03090100/04070200/04105200
55454	Fentanyl citrate	04070200
55486	Morphine sulfate	04070200
55505	Fentanyl Citrate	04070200
55530	Fentanyl	04070200
55817	Tramadol hydrochloride	04070200
55828	Diamorphine Hydrochloride	04070200
55894	Naloxone Hydrochloride/oxycodone Hydrochloride	04070200
56006	Morphine sulfate	04070200
56046	Pethidine Hydrochloride	04070200
56106	Naloxone Hydrochloride/oxycodone Hydrochloride	04070200
56171	Buprenorphine	04070200
56205	Oxycodone hydrochloride	04070200
56266	Dihydrocodeine tartrate	04070200
56340	Dihydrocodeine tartrate	04070200
56549	Tramadol hydrochloride	04070200
56554	Oxycodone Hydrochloride	04070200
56559	Codeine phosphate	01040200/03090100/04070200
56565	Oxycodone hydrochloride	04070200
56566	Diamorphine hydrochloride	04070200
56762	Tramadol hydrochloride	04070200
56817	Codeine phosphate	01040200/03090100/04070200
56925	Oxycodone hydrochloride	04070200
56945	Dihydrocodeine tartrate	04070200
57097	Oxycodone hydrochloride	04070200
57197	Buprenorphine	04070200
57353	Oxycodone hydrochloride	04070200
57381	Codeine phosphate	01040200/03090100/04070200
57433	Dihydrocodeine tartrate	04070200
57465	Fentanyl	04070200
57487	Codeine phosphate	01040200/03090100/04070200
57650	Tramadol Hydrochloride	04070200
57752	Codeine phosphate	01040200/03090100/04070200
57929	Diamorphine hydrochloride	04070200
58213	Oxycodone hydrochloride/Naloxone hydrochloride	04070200
58221	Tramadol hydrochloride	04070200
58288	Tramadol hydrochloride	04070200
58526	Tramadol hydrochloride	04070200
58582	Tramadol Hydrochloride	04070200
58636	Fentanyl	04070200
58644	Morphine sulfate	04070200

58708	Tramadol hydrochloride	04070200
58743	Tramadol hydrochloride	04070200
58848	Buprenorphine	04070200
59139	Pethidine Hydrochloride	04070200
59246	Tramadol hydrochloride	04070200
59479	Morphine sulfate	04070200
59599	Dihydrocodeine tartrate	04070200
59705	Tramadol hydrochloride	04070200
59773	Morphine sulfate	04070200
59878	Fentanyl Citrate	04070200
59986	Fentanyl	04070200
60115	Fentanyl citrate	04070200
60378	Diamorphine Hydrochloride	04070200
60408	Oxycodone hydrochloride/Naloxone hydrochloride	04070200
60442	Tramadol hydrochloride	04070200
60517	Morphine sulfate	04070200
60640	Codeine phosphate	01040200/03090100/04070200
60812	Tramadol hydrochloride	04070200
60883	Dihydrocodeine tartrate	04070200
60944	Dihydrocodeine tartrate	04070200
60958	Codeine phosphate	01040200/03090100/04070200
61091	Codeine phosphate	01040200/03090100/04070200
61124	Tramadol hydrochloride	04070200
61372	Morphine sulfate	04070200
61406	Dihydrocodeine tartrate	04070200
61485	Dihydrocodeine tartrate	04070200
61522	Morphine Sulphate	04070200
61647	Morphine sulfate	04070200
61695	Fentanyl citrate	04070200
61963	Diamorphine hydrochloride	04070200
62088	Diamorphine hydrochloride	04070200
62169	Tramadol hydrochloride	04070200
62228	Codeine phosphate	01040200/03090100/04070200
62323	Oxycodone hydrochloride	04070200
62635	Tramadol hydrochloride	04070200
62743	Oxycodone hydrochloride	04070200
63357	Fentanyl	04070200
63543	Morphine Sulphate	04070200
63683	Tapentadol hydrochloride	04070200
63843	Fentanyl Citrate	04070200
63900	Tramadol hydrochloride	04070200
63943	Oxycodone hydrochloride	04070200
63962	Tramadol Hydrochloride	04070200

64073	Tramadol hydrochloride	04070200
64074	Oxycodone hydrochloride	04070200
64108	Codeine phosphate	01040200/03090100/04070200
64154	Tramadol hydrochloride	04070200
64313	Tramadol hydrochloride	04070200
64368	Oxycodone hydrochloride	04070200
64387		04070200
64545	Oxycodone hydrochloride	04070200
64726	Oxycodone hydrochloride	04070200
64752	Codeine phosphate	01040200/03090100/04070200
65035	Morphine sulfate	04070200
65080	Tramadol hydrochloride	04070200
65092	Oxycodone hydrochloride	04070200
65107	Fentanyl	04070200
65118	Codeine phosphate	01040200/03090100/04070200
65239	Tramadol hydrochloride	04070200
65245	Codeine phosphate	01040200/03090100/04070200
65269	Codeine phosphate	01040200/03090100/04070200
65299	Fentanyl	04070200
65308	Fentanyl	04070200
65330	Tramadol hydrochloride	04070200
65348	Fentanyl Citrate	04070200
65440	Tramadol Hydrochloride	04070200
65683	Tramadol hydrochloride	04070200
65806	Tramadol hydrochloride/Paracetamol	04070200
65904	Tramadol hydrochloride	04070200
65952	Pethidine Hydrochloride	04070200
66097	Tramadol hydrochloride	04070200
66115	Codeine phosphate	01040200/03090100/04070200
66171	Tramadol hydrochloride	04070200
66481	Tramadol hydrochloride	04070200
66538	Pethidine hydrochloride	04070200
66553	Oxycodone hydrochloride	04070200
66602	Oxycodone hydrochloride	04070200
66664	Alfentanil hydrochloride	04070200
66814	Pethidine hydrochloride	04070200
66893	Codeine phosphate	01040200/03090100/04070200
66904	Morphine sulfate	04070200
66993	Morphine hydrochloride	04070200
67086	Fentanyl	04070200
67106	Codeine phosphate	04070200
67363	Morphine sulfate	04070200
67751		01040200/03090100/04070200
67753	Morphine sulfate	04070200

67755	Fentanyl	04070200
67768	Morphine sulfate	04070200
67779	Oxycodone hydrochloride	04070200
67887	Tramadol hydrochloride	04070200
68070	Tramadol Hydrochloride	04070200
68097	Diamorphine hydrochloride	04070200
68252	Tramadol hydrochloride	04070200
68271	Fentanyl	04070200
68434	Fentanyl	04070200
68470	Morphine sulfate	04070200
68509	Codeine phosphate	03090100/04070200
68538	Codeine phosphate	01040200/03090100/04070200
68685	Tramadol hydrochloride	04070200
68738	Fentanyl	04070200
68861	Codeine phosphate	01040200/03090100/04070200
69006	Fentanyl	04070200
69043	Fentanyl	04070200
69066	Codeine phosphate	01040200/03090100/04070200
69259	Pethidine hydrochloride	04070200
69304	Dihydrocodeine tartrate	04070200
69534	Fentanyl	04070200
69576	Codeine phosphate	01040200/04070200
69645	Fentanyl	04070200
69828	Pentazocine lactate	04070200

5.6. Covariates: H2-receptors.

prodcode	drug substance	BNF code
225	Nizatidine	1030100
690	Nizatidine	1030100
4742	Nizatidine	1030100
4885	Nizatidine	1030100
13579	Nizatidine	1030100
16195	Nizatidine	1030100
19277	Nizatidine	1030100
27288	Nizatidine	1030100
28509	Nizatidine	0
34321	Nizatidine	1030100
34511	Nizatidine	1030100
42088	Nizatidine	1030100
67812	Nizatidine	1030100
71082	Nizatidine	1030100
4485	Famotidine	0
8388	Famotidine	1030100
8389	Famotidine	1030100
10555	Famotidine	1030100
10746	Famotidine	1030100
13592	Famotidine	0
23132	Famotidine	1030100
25404	Famotidine	1030100
68	Cimetidine	1030100
181	Cimetidine	0
446	Cimetidine	1030100
1230	Cimetidine	1030100
2057	Cimetidine	1030100
3086	Cimetidine	1030100
3276	Cimetidine	1030100
3367	Cimetidine	0
3857	Cimetidine	1030100
3968	Cimetidine	0
4451	Cimetidine	1030100
7848	Cimetidine	1030100
8030	Cimetidine	0
9472	Cimetidine	1030100
11283	Cimetidine	0
12025	Cimetidine	0
12725	Cimetidine	0
17162	Cimetidine	1030100
18426	Cimetidine	1030100
20011	Cimetidine	1030100

20360	Cimetidine	1030100
21823	Cimetidine	1030100
21825	Cimetidine	1030100
21853	Cimetidine	1030100
21871	Cimetidine	1030100
21988	Cimetidine	1030100
21991	Cimetidine	1030100
22037	Cimetidine	1030100
22635	Cimetidine	1030100
22643	Cimetidine	1030100
24092	Cimetidine	1030100
24301	Cimetidine	1030100
25271	Cimetidine	1030100
26208	Cimetidine	1030100
26699	Cimetidine	1030100
27024	Cimetidine	1030100
27465	Cimetidine	1030100
27808	Cimetidine	1030100
28047	Cimetidine	1030100
28050	Cimetidine	1030100
28787	Cimetidine	1030100
29048	Cimetidine	1030100
29148	Cimetidine	1030100
31846	Cimetidine	1030100
32747	Cimetidine	1030100
33088	Cimetidine	1030100
33325	Cimetidine	1030100
33667	Cimetidine	1030100
34556	Cimetidine	1030100
34788	Cimetidine	1030100
40430	Cimetidine	1030100
41534	Cimetidine	1030100
41568	Cimetidine	1030100
41587	Cimetidine	1030100
41588	Cimetidine	1030100
41589	Cimetidine	1030100
41631	Cimetidine	1030100
41648	Cimetidine	1030100
41684	Cimetidine	1030100
41895	Cimetidine	1030100
47934	Cimetidine	1030100
56686	Cimetidine	0
57236	Cimetidine	1030100
63641	Cimetidine	1030100

71057	Cimetidine	1030100
21	Ranitidine hydrochloride	1030100
801	Ranitidine hydrochloride	1030100
1229	Ranitidine hydrochloride	1030100
1367	Ranitidine hydrochloride	1030100
1394	Ranitidine hydrochloride	1030100
1556	Ranitidine hydrochloride	1030100
1963	Ranitidine hydrochloride	1030100
3967	Ranitidine Hydrochloride	1030100
3970	Ranitidine bismuth citrate	0
4468	Ranitidine hydrochloride	1030100
7666	Ranitidine hydrochloride	1030100
9174	Ranitidine hydrochloride	1030100
9433	Ranitidine hydrochloride	1030100
9795	Ranitidine hydrochloride	1030100
9904	Ranitidine hydrochloride	1030100
13378	Ranitidine hydrochloride	1030100
15277	Ranitidine hydrochloride	1030100
15724	Ranitidine bismuth citrate	0
16034	Ranitidine hydrochloride	1030100
16092	Ranitidine hydrochloride	1030100
16619	Ranitidine hydrochloride	1030100
17108	Ranitidine hydrochloride	1030100
18489	Ranitidine hydrochloride	1030100
19249	Ranitidine hydrochloride	1030100
19272	Ranitidine hydrochloride	1030100
21544	Ranitidine hydrochloride	1030100
21565	Ranitidine hydrochloride	1030100
21602	Ranitidine hydrochloride	1030100
21893	Ranitidine hydrochloride	1030100
21894	Ranitidine hydrochloride	1030100
21901	Ranitidine hydrochloride	1030100
24302	Ranitidine hydrochloride	1030100
25360	Ranitidine hydrochloride	1030100
26170	Ranitidine hydrochloride	1030100
26949	Ranitidine hydrochloride	1030100
27698	Ranitidine hydrochloride	1030100
30241	Ranitidine Hydrochloride	1030100
30863	Ranitidine hydrochloride	1030100
31492	Ranitidine hydrochloride	1030100
31533	Ranitidine hydrochloride	1030100
32342	Ranitidine hydrochloride	1030100
32859	Ranitidine hydrochloride	1030100
34276	Ranitidine hydrochloride	1030100

34295	Ranitidine hydrochloride	1030100
34301	Ranitidine hydrochloride	1030100
34403	Ranitidine hydrochloride	1030100
34433	Ranitidine hydrochloride	1030100
34450	Ranitidine hydrochloride	1030100
34480	Ranitidine hydrochloride	1030100
34531	Ranitidine hydrochloride	1030100
34708	Ranitidine hydrochloride	1030100
34886	Ranitidine hydrochloride	1030100
40152	Ranitidine hydrochloride	1030100
41536	Ranitidine hydrochloride	1030100
43529	Ranitidine hydrochloride	1030100
45214	Ranitidine hydrochloride	1030100
45232	Ranitidine hydrochloride	1030100
45294	Ranitidine hydrochloride	1030100
45322	Ranitidine hydrochloride	1030100
51549	Ranitidine hydrochloride	1030100
51801	Ranitidine hydrochloride	1030100
52691	Ranitidine hydrochloride	1030100
53317	Ranitidine hydrochloride	1030100
53333	Ranitidine hydrochloride	1030100
53335	Ranitidine hydrochloride	1030100
53947	Ranitidine hydrochloride	1030100
54101	Ranitidine hydrochloride	1030100
54135	Ranitidine hydrochloride	1030100
54253	Ranitidine hydrochloride	1030100
54539	Ranitidine hydrochloride	1030100
54746	Ranitidine hydrochloride	1030100
54784	Ranitidine hydrochloride	1030100
55647	Ranitidine hydrochloride	1030100
55665	Ranitidine hydrochloride	1030100
55857	Ranitidine hydrochloride	1030100
55936	Ranitidine hydrochloride	1030100
55991	Ranitidine hydrochloride	1030100
56414	Ranitidine hydrochloride	1030100
56569	Ranitidine hydrochloride	1030100
56614	Ranitidine hydrochloride	1030100
56816	Ranitidine hydrochloride	1030100
57909	Ranitidine hydrochloride	1030100
58244	Ranitidine hydrochloride	1030100
58334	Ranitidine hydrochloride	1030100
58447	Ranitidine hydrochloride	1030100
58711	Ranitidine hydrochloride	1030100
60964	Ranitidine hydrochloride	1030100

61094	Ranitidine hydrochloride	1030100
61188	Ranitidine hydrochloride	1030100
61720	Ranitidine hydrochloride	1030100
62000	Ranitidine hydrochloride	1030100
62063	Ranitidine hydrochloride	1030100
62296	Ranitidine hydrochloride	1030100
62625	Ranitidine hydrochloride	1030100
62641	Ranitidine hydrochloride	1030100
62666	Ranitidine hydrochloride	1030100
62741	Ranitidine hydrochloride	1030100
63294	Ranitidine hydrochloride	1030100
63468	Ranitidine hydrochloride	1030100
63568	Ranitidine hydrochloride	1030100
63764	Ranitidine hydrochloride	1030100
63997	Ranitidine hydrochloride	1030100
64230	Ranitidine hydrochloride	1030100
64770	Ranitidine hydrochloride	1030100
64963	Ranitidine hydrochloride	1030100
65166	Ranitidine hydrochloride	1030100
65770	Ranitidine hydrochloride	1030100
66576	Ranitidine hydrochloride	1030100
66805	Ranitidine hydrochloride	1030100
67682	Ranitidine hydrochloride	1030100
67763	Ranitidine hydrochloride	1030100
69010	Ranitidine hydrochloride	1030100
69017	Ranitidine hydrochloride	1030100
69368	Ranitidine hydrochloride	1030100
69551	Ranitidine hydrochloride	1030100
69664	Ranitidine hydrochloride	1030100
70121	Ranitidine hydrochloride	1030100
70169	Ranitidine hydrochloride	1030100
70825	Ranitidine hydrochloride	1030100
71043	Ranitidine hydrochloride	1030100
71567	Ranitidine hydrochloride	1030100
71643	Ranitidine hydrochloride	1030100
3970	Ranitidine bismuth citrate	0
15724	Ranitidine bismuth citrate	0

5.7. Covariates: Proton pump inhibitors.

prodcode	Drug substance	BNF code
5178	Esomeprazole magnesium trihydrate	1030500
5269	Esomeprazole magnesium trihydrate	1030500
5604	Esomeprazole magnesium trihydrate	1030500
6490	Esomeprazole magnesium trihydrate	1030500
18225	Esomeprazole sodium	1030500
25596	Esomeprazole sodium	1030500
41454	Esomeprazole magnesium trihydrate	1030500
41501	Esomeprazole magnesium trihydrate	1030500
43948	Esomeprazole magnesium dihydrate	1030500
43995	Esomeprazole magnesium dihydrate	1030500
46744	Esomeprazole magnesium dihydrate	1030500
46745	Esomeprazole magnesium dihydrate	1030500
51548	Esomeprazole magnesium trihydrate	1030500
53843	Esomeprazole magnesium trihydrate	1030500
57311	Esomeprazole magnesium dihydrate	1030500
61504	Esomeprazole magnesium trihydrate	1030500
61669	Esomeprazole magnesium dihydrate	1030500
64332	Esomeprazole magnesium trihydrate	1030500
65142	Esomeprazole magnesium dihydrate	1030500
65719	Esomeprazole magnesium trihydrate	1030500
69714	Esomeprazole magnesium trihydrate	1030500
69798	Esomeprazole magnesium trihydrate	1030500
70964	Esomeprazole magnesium dihydrate	1030500
71678	Esomeprazole magnesium dihydrate	1030500
1986	Pantoprazole sodium sesquihydrate	1030500
5419	Pantoprazole sodium sesquihydrate	1030500
6165	Pantoprazole sodium sesquihydrate	1030500
6727	Pantoprazole sodium sesquihydrate	1030500
17111	Pantoprazole sodium sesquihydrate	1030500
44023	Pantoprazole sodium sesquihydrate	1030500
44700	Pantoprazole sodium sesquihydrate	1030500
49375	Pantoprazole sodium sesquihydrate	1030500
51804	Pantoprazole sodium sesquihydrate	1030500
54693	Pantoprazole sodium sesquihydrate	1030500
59390	Pantoprazole sodium sesquihydrate	1030500
59711	Pantoprazole sodium sesquihydrate	1030500
64750	Pantoprazole sodium sesquihydrate	1030500
65710	Pantoprazole sodium sesquihydrate	1030500
67327	Pantoprazole sodium sesquihydrate	1030500
68430	Pantoprazole	1030500
70804	Pantoprazole sodium sesquihydrate	1030500
1941	Rabeprazole sodium	1030500

1977	Rabeprazole sodium	1030500
2151	Rabeprazole sodium	1030500
5834	Rabeprazole sodium	1030500
58030	Rabeprazole sodium	1030500
58475	Rabeprazole sodium	1030500
59296	Rabeprazole sodium	1030500
60588	Rabeprazole sodium	1030500
60590	Rabeprazole sodium	1030500
71666	Rabeprazole sodium	1030500
30	Lansoprazole	1030500
39	Lansoprazole	1030500
519	Lansoprazole	1030500
1947	Lansoprazole	1030500
5358	Lansoprazole	1030500
6063	Lansoprazole	1030500
6245	Lansoprazole	1030500
6291	Lansoprazole	1030500
6300	Lansoprazole	1030500
10098	Lansoprazole	1030500
37815	Lansoprazole	1030500
39904	Lansoprazole	1030500
40759	Lansoprazole	1030500
40896	Lansoprazole	1030500
42382	Lansoprazole	1030500
42532	Lansoprazole	1030500
42730	Lansoprazole	1030500
43057	Lansoprazole	1030500
44753	Lansoprazole	1030500
47909	Lansoprazole	1030500
48063	Lansoprazole	1030500
49209	Lansoprazole	1030500
50492	Lansoprazole	1030500
51290	Lansoprazole	1030500
53616	Lansoprazole	1030500
53871	Lansoprazole	1030500
54121	Lansoprazole	1030500
54188	Lansoprazole	1030500
54939	Lansoprazole	1030500
55439	Lansoprazole	1030500
57158	Lansoprazole	1030500
57504	Lansoprazole	1030500
57572	Lansoprazole	1030500
58679	Lansoprazole	1030500
59106	Lansoprazole	1030500

59404	Lansoprazole	1030500
59586	Lansoprazole	1030500
60537	Lansoprazole	1030500
60615	Lansoprazole	1030500
60900	Lansoprazole	1030500
62031	Lansoprazole	1030500
62549	Lansoprazole	1030500
63125	Lansoprazole	1030500
63831	Lansoprazole	1030500
64445	Lansoprazole	1030500
66348	Lansoprazole	1030500
67270	Lansoprazole	1030500
67385	Lansoprazole	1030500
67577	Lansoprazole	1030500
67811	Lansoprazole	1030500
68305	Lansoprazole	1030500
68873	Lansoprazole	1030500
69314	Lansoprazole	1030500
69769	Lansoprazole	1030500
70649	Lansoprazole	1030500
71087	Lansoprazole	1030500
72144	Lansoprazole	1030500
18	Omeprazole	1030500
89	Omeprazole	1030500
276	Omeprazole	1030500
1232	Omeprazole	1030500
1451	Omeprazole	1030500
4654	Omeprazole	1030500
4921	Omeprazole magnesium	1030500
4955	Omeprazole magnesium	1030500
5178	Esomeprazole magnesium trihydrate	1030500
5232	Omeprazole magnesium	1030500
5236	Omeprazole magnesium	1030500
5269	Esomeprazole magnesium trihydrate	1030500
5604	Esomeprazole magnesium trihydrate	1030500
6114	Omeprazole	1030500
6490	Esomeprazole magnesium trihydrate	1030500
7255	Omeprazole	1030500
9825	Omeprazole magnesium	1030500
9851	Omeprazole	1030500
9989	Omeprazole	1030500
13015	Omeprazole magnesium	1030500
13282	Omeprazole	1030500
15275	Omeprazole	1030500

18225	Esomeprazole sodium	1030500
22709	Omeprazole sodium	1030500
24360	Omeprazole	1030500
25245	Omeprazole sodium	1030500
25596	Esomeprazole sodium	1030500
26537	Omeprazole	1030500
29422	Omeprazole sodium	1030500
29457	Omeprazole	1030500
29468	Omeprazole	1030500
29835	Omeprazole sodium	1030500
30926	Omeprazole	1030500
31213	Omeprazole	1030500
32914	Omeprazole	1030500
32919	Omeprazole	1030500
32924	Omeprazole	1030500
33022	Omeprazole	1030500
33326	Omeprazole	1030500
33565	Omeprazole	1030500
33873	Omeprazole sodium	1030500
34302	Omeprazole	1030500
34332	Omeprazole	1030500
34411	Omeprazole	1030500
34568	Omeprazole	1030500
34571	Omeprazole	1030500
34577	Omeprazole	1030500
34791	Omeprazole	1030500
34792	Omeprazole	1030500
34812	Omeprazole	1030500
34841	Omeprazole	1030500
34843	Omeprazole	1030500
34967	Omeprazole	1030500
34984	Omeprazole	1030500
35101	Omeprazole	1030500
35257	Omeprazole	1030500
35383	Omeprazole	1030500
35698	Omeprazole	1030500
35699	Omeprazole	1030500
36046	Omeprazole	1030500
36892	Omeprazole	1030500
41454	Esomeprazole magnesium trihydrate	1030500
41501	Esomeprazole magnesium trihydrate	1030500
41992	Omeprazole	1030500
42091	Omeprazole	1030500
42114	Omeprazole	1030500

42533	Omeprazole	1030500
42736	Omeprazole	1030500
42898	Omeprazole	1030500
42900	Omeprazole	1030500
43948	Esomeprazole magnesium dihydrate	1030500
43957	Omeprazole	1030500
43995	Esomeprazole magnesium dihydrate	1030500
44252	Omeprazole	1030500
45173	Omeprazole	1030500
46744	Esomeprazole magnesium dihydrate	1030500
46745	Esomeprazole magnesium dihydrate	1030500
47511	Omeprazole	1030500
49163	Omeprazole	1030500
49433	Omeprazole	1030500
49584	Omeprazole	1030500
50365	Omeprazole	1030500
50372	Omeprazole	1030500
51260	Omeprazole	1030500
51357	Omeprazole	1030500
51548	Esomeprazole magnesium trihydrate	1030500
52379	Omeprazole	1030500
52612	Omeprazole	1030500
52866	Omeprazole	1030500
52971	Omeprazole magnesium	1030500
53337	Omeprazole	1030500
53518	Omeprazole	1030500
53843	Esomeprazole magnesium trihydrate	1030500
54683	Omeprazole magnesium	1030500
55168	Omeprazole magnesium	1030500
55468	Omeprazole	1030500
55700	Omeprazole	1030500
55744	Omeprazole	1030500
55745	Omeprazole	1030500
56235	Omeprazole	1030500
56432	Omeprazole	1030500
56433	Omeprazole	1030500
56479	Omeprazole	1030500
56895	Omeprazole	1030500
57177	Omeprazole	1030500
57311	Esomeprazole magnesium dihydrate	1030500
57528	Omeprazole	1030500
57541	Omeprazole	1030500
57566	Omeprazole magnesium	1030500
57648	Omeprazole	1030500

57738	Omeprazole	1030500
58066	Omeprazole	1030500
58216	Omeprazole	1030500
58236	Omeprazole magnesium	1030500
58332	Omeprazole	1030500
58344	Omeprazole	1030500
58946	Omeprazole	1030500
59135	Omeprazole	1030500
59547	Omeprazole	1030500
59725	Omeprazole	1030500
60230	Omeprazole	1030500
60403	Omeprazole	1030500
60409	Omeprazole magnesium	1030500
61029	Omeprazole	1030500
61504	Esomeprazole magnesium trihydrate	1030500
61669	Esomeprazole magnesium dihydrate	1030500
62166	Omeprazole	1030500
63283	Omeprazole	1030500
63324	Omeprazole	1030500
63402	Omeprazole	1030500
63608	Omeprazole	1030500
63691	Omeprazole	1030500
64332	Esomeprazole magnesium trihydrate	1030500
65142	Esomeprazole magnesium dihydrate	1030500
65719	Esomeprazole magnesium trihydrate	1030500
66552	Omeprazole	1030500
66573	Omeprazole	1030500
66643	Omeprazole magnesium	1030500
66903	Omeprazole	1030500
68028	Omeprazole	1030500
69714	Esomeprazole magnesium trihydrate	1030500
69798	Esomeprazole magnesium trihydrate	1030500
69899	Omeprazole	1030500
70170	Omeprazole	1030500
70797	Omeprazole	1030500
70830	Omeprazole	1030500
70964	Esomeprazole magnesium dihydrate	1030500
71065	Omeprazole	1030500
71678	Esomeprazole magnesium dihydrate	1030500
71881	Omeprazole	1030500
71992	Omeprazole	1030500
72435	Omeprazole	1030500

5.8. Covariates: Dipyridamole.

prodcode	Drug-substance	BNF code
689	Dipyridamole	2090000
714	Dipyridamole	2090000
771	Dipyridamole	2090000
1814	Dipyridamole	2090000
2106	Dipyridamole	2090000
3832	Dipyridamole	2090000
5882	Dipyridamole	2090000
21989	Dipyridamole	2090000
25232	Dipyridamole	2090000
25284	Dipyridamole	2090000
30975	Dipyridamole	2090000
30976	Dipyridamole	2090000
31192	Dipyridamole	2090000
34709	Dipyridamole	2090000
35108	Dipyridamole	2090000
43530	Dipyridamole	2090000
46976	Dipyridamole	2090000
51358	Dipyridamole	2090000
59470	Dipyridamole	2090000
60321	Dipyridamole	2090000
60605	Dipyridamole	2090000
62707	Dipyridamole	2090000
64222	Dipyridamole	2090000
64837	Dipyridamole	2090000
64929	Dipyridamole	2090000
66784	Dipyridamole	2090000
66840	Dipyridamole	2090000
67403	Dipyridamole	2090000
67567	Dipyridamole	2090000

5.9. Covariates: Clopidogeral.

product code	drug substance	BNF code
55161	Clopidogrel	2090000
489	Clopidogrel	2090000
40913	Clopidogrel	2090000
52761	Clopidogrel	2090000
42750	Clopidogrel	2090000
836	Clopidogrel	2090000
63450	Clopidogrel	2090000
62978	Clopidogrel	2090000
65909	Clopidogrel	2090000
57036	Clopidogrel	2090000
53751	Clopidogrel	2090000
67037	Clopidogrel	2090000
62855	Clopidogrel	2090000
58347	Clopidogrel	2090000
58448	Clopidogrel	2090000
54700	Clopidogrel	2090000
56807	Clopidogrel	2090000
59904	Clopidogrel hydrogen sulfate	2090000
45905	Clopidogrel hydrogen sulfate	2090000
38349	Clopidogrel hydrogen sulfate	2090000
46891	Clopidogrel hydrogen sulfate	2090000
38998	Clopidogrel hydrogen sulfate	2090000

Appendix 6: Codes for outcomes

6.1. Composite Outcomes: PUB.

med code	read code	description
18027	J120.00	Acute duodenal ulcer
53797	J120z00	Acute duodenal ulcer NOS
53822	J120y00	Acute duodenal ulcer unspecified
73417	J120400	Acute duodenal ulcer with obstruction
44335	J120000	Acute duodenal ulcer without mention of complication
24040	J110.00	Acute gastric ulcer
44324	J110z00	Acute gastric ulcer NOS
24342	J110y00	Acute gastric ulcer unspecified
109546	J110400	Acute gastric ulcer with obstruction
64165	J110000	Acute gastric ulcer without mention of complication
32856	J130.00	Acute peptic ulcer
50048	J130z00	Acute peptic ulcer NOS
67711	J130y00	Acute peptic ulcer unspecified
68661	J130000	Acute peptic ulcer without mention of complication
9853	J121.00	Chronic duodenal ulcer
51406	J121z00	Chronic duodenal ulcer NOS
52138	J121y00	Chronic duodenal ulcer unspecified
44073	J121400	Chronic duodenal ulcer with obstruction
33438	J121000	Chronic duodenal ulcer without mention of complication
18654	J111.00	Chronic gastric ulcer
44309	J111z00	Chronic gastric ulcer NOS
64556	J111y00	Chronic gastric ulcer unspecified
67356	J111400	Chronic gastric ulcer with obstruction
48946	J111000	Chronic gastric ulcer without mention of complication
40997	J131.00	Chronic peptic ulcer
69663	J131z00	Chronic peptic ulcer NOS
70390	J131y00	Chronic peptic ulcer unspecified
52313	J131400	Chronic peptic ulcer with obstruction
99430	J131000	Chronic peptic ulcer without mention of complication
64014	761J100	Closure of gastric ulcer NEC
352	J12.00	Duodenal ulcer - (DU)
22918	J122.00	Duodenal ulcer disease
15175	J12z.00	Duodenal ulcer NOS
1262	J11.00	Gastric ulcer - (GU)
29771	J11z.00	Gastric ulcer NOS
52323	J11z.12	Multiple gastric ulcers
58603	J102400	Oesophageal ulcer due to medicines
670	J13.00	Peptic ulcer - (PU) site unspecified
19928	J13z.00	Peptic ulcer NOS
24021	J102000	Peptic ulcer of oesophagus

3101	J11.12	Pyloric ulcer
29317	J124.00	Recurrent duodenal ulcer
2489	J102.00	Ulcer of oesophagus
42150	J102z00	Ulcer of oesophagus NOS
2785	J080000	Ulcerative stomatitis
53669	J12y.00	Unspecified duodenal ulcer
65737	J12yz00	Unspecified duodenal ulcer NOS
71904	J12y400	Unspecified duodenal ulcer with obstruction
71150	J12y000	Unspecified duodenal ulcer without mention of complication
53081	J11y.00	Unspecified gastric ulcer
44284	J11yz00	Unspecified gastric ulcer NOS
73697	J11y400	Unspecified gastric ulcer with obstruction
73338	J11y000	Unspecified gastric ulcer without mention of complication
50497	J13y.00	Unspecified peptic ulcer
60249	J13yz00	Unspecified peptic ulcer NOS
99670	J13y400	Unspecified peptic ulcer with obstruction
67082	J13y000	Unspecified peptic ulcer without mention of complication
4636	J68zz00	Gastrointestinal tract haemorrhage NOS
4354	J68z200	Upper gastrointestinal haemorrhage
15517	J68z000	Gastric haemorrhage NOS
44637	J130100	Acute peptic ulcer with haemorrhage
53126	J131100	Chronic peptic ulcer with haemorrhage
70456	J13y100	Unspecified peptic ulcer with haemorrhage
2814	J12y100	Unspecified duodenal ulcer with haemorrhage
18001	J120100	Acute duodenal ulcer with haemorrhage
18625	J121111	Bleeding chronic duodenal ulcer
48951	J121100	Chronic duodenal ulcer with haemorrhage
11124	J110111	Bleeding acute gastric ulcer
30054	J110100	Acute gastric ulcer with haemorrhage
36583	J111111	Bleeding chronic gastric ulcer
57958	J11y100	Unspecified gastric ulcer with haemorrhage
63582	J111100	Chronic gastric ulcer with haemorrhage
2712	J680.11	Vomiting of blood
44489	1994	Vomiting blood - fresh
44691	1995	Vomiting blood - coffee ground
1188	J680.00	Haematemesis
105959	J179.00	Perforation of stomach
5521	J130200	Acute peptic ulcer with perforation
37620	J131200	Chronic peptic ulcer with perforation
64111	J13y200	Unspecified peptic ulcer with perforation
657	J12y200	Unspecified duodenal ulcer with perforation
18324	J120200	Acute duodenal ulcer with perforation
23087	J121211	Perforated chronic duodenal ulcer
11104	J111211	Perforated chronic gastric ulcer

14671	J110200	Acute gastric ulcer with perforation
36461	J11y200	Unspecified gastric ulcer with perforation
53336	J111200	Chronic gastric ulcer with perforation
45304	J130300	Acute peptic ulcer with haemorrhage and perforation
96622	J13y300	Unspecified peptic ulcer with haemorrhage and perforation
28366	J12yy00	Unspec duodenal ulcer; unspec haemorrhage and/or perforation
37643	J121200	Chronic duodenal ulcer with perforation
48730	J120300	Acute duodenal ulcer with haemorrhage and perforation
71881	J121300	Chronic duodenal ulcer with haemorrhage and perforation
93436	J12y300	Unspecified duodenal ulcer with haemorrhage and perforation
71403	J110300	Acute gastric ulcer with haemorrhage and perforation
71897	J111300	Chronic gastric ulcer with haemorrhage and perforation
94397	J11yy00	Unspec gastric ulcer; unspec haemorrhage and/or perforation
74496	5329	ulcer duodenum
74539	5329PT	ulcer peptic duodenum
74848	5320	ULCER DUODENUM PERFORATED
75354	5319TM	ULCER STOMACH
75550	5319PP	ULCER PREPYLORIC
75673	5339	ulcer peptic
76394	5339DB	duodenal ulcer bleeding
77740	5329BD	ULCER DUODENAL RECURRANCE
79977	5310	ULCER GASTRIC PERFORATED
82405	5330	ulcer peptic perforated
83017	5319PT	ULCER PEPTIC STOMACH
83963	5310PT	ULCER PEPTIC STOMACH PERFORATED
88070	5320PT	ULCER PEPTIC DUODENUM PERFORATED
88195	5310TM	ULCER STOMACH PERFORATED
6333	J11.11	Prepyloric ulcer

6.2. Uncomplicated ulcers.

medcode	read code	Description
352	J12.00	Duodenal ulcer - (DU)
1262	J11.00	Gastric ulcer - (GU)
1295	J14.15	Stomal ulcer
3101	J11.12	Pyloric ulcer
6333	J11.11	prepyloric ulcer
9853	J121.00	Chronic duodenal ulcer
15175	J12z.00	Duodenal ulcer NOS
15821	J13.11	Stress ulcer NOS
18027	J120.00	Acute duodenal ulcer
18654	J111.00	Chronic gastric ulcer
19928	J13z.00	Peptic ulcer NOS
22918	J122.00	Duodenal ulcer disease
24021	J102000	Peptic ulcer of oesophagus
24040	J110.00	Acute gastric ulcer
29317	J124.00	Recurrent duodenal ulcer
29771	J11z.00	Gastric ulcer NOS
32856	J130.00	Acute peptic ulcer
40997	J131.00	Chronic peptic ulcer
44309	J111z00	Chronic gastric ulcer NOS
44324	J110z00	Acute gastric ulcer NOS
44335	J120000	Acute duodenal ulcer without mention of complication
50048	J130z00	Acute peptic ulcer NOS
51406	J121z00	Chronic duodenal ulcer NOS
53081	J11y.00	Unspecified gastric ulcer
53669	J12y.00	Unspecified duodenal ulcer
53797	J120z00	Acute duodenal ulcer NOS
64165	J110000	Acute gastric ulcer without mention of complication
64913	J14.12	Gastrocolic ulcer
68661	J130000	Acute peptic ulcer without mention of complication
69663	J131z00	Chronic peptic ulcer NOS
4354	J68z200	Upper gastrointestinal haemorrhage
670	J13.00	Peptic ulcer - (PU) site unspecified
24342	J110y00	Acute gastric ulcer unspecified
44284	J11yz00	Unspecified gastric ulcer NOS
50497	J13y.00	Unspecified peptic ulcer
52138	J121y00	Chronic duodenal ulcer unspecified
53822	J120y00	Acute duodenal ulcer unspecified
60249	J13yz00	Unspecified peptic ulcer NOS
64556	J111y00	Chronic gastric ulcer unspecified
65737	J12yz00	Unspecified duodenal ulcer NOS
67082	J13y000	Unspecified peptic ulcer without mention of complication
67711	J130y00	Acute peptic ulcer unspecified

70390	J131y00	Chronic peptic ulcer unspecified
73338	J11y000	Unspecified gastric ulcer without mention of complication
74496	5329	ulcer duodenum
74539	5329PT	ulcer peptic duodenum
75354	5319TM	ULCER STOMACH
75550	5319PP	ULCER PREPYLORIC
75673	5339	ulcer peptic
82043	5349MR	ULCER MARGINAL
83017	5319PT	ULCER PEPTIC STOMACH
85989	J126.00	
89023	J113.00	
58603	J102400	Oesophageal ulcer due to medicines
89234	J125.00	Anti-platelet induced duodenal ulcer
63001	J112.00	Anti-platelet induced gastric ulcer
89227	J112z00	Anti-platelet induced gastric ulcer NOS
33438	J121000	
48946	J111000	
99430	J131000	
52323	J11z.12	Multiple gastric ulcers
71150	J12y000	
4636	J68zz00	Gastrointestinal tract haemorrhage NOS
15517	J68z000	Gastric haemorrhage NOS
2489	J102.00	Ulcer of oesophagus
42150	J102z00	Ulcer of oesophagus NOS

6.3. Lower gastrointestinal bleeding.

med code	read code	Description
60346	J14y100	Unspecified gastrojejunal ulcer with haemorrhage
96628	J140100	Acute gastrojejunal ulcer with haemorrhage
106330	J140300	Acute gastrojejunal ulcer with haemorrhage and perforation
110244	J141300	Chronic gastrojejunal ulcer with haemorrhage and perforation
621	J573011	Rectal bleeding
2044	J510900	Bleeding diverticulosis
3872	J573.11	Bleeding PR
6554	J573012	PRB - Rectal bleeding
6574	J573000	Rectal haemorrhage
32446	J573100	Anal haemorrhage