The effect of alcohol consumption on the risk of severe respiratory diseases

A series of systematic reviews and meta-analyses

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Abstract

Introduction: Alcohol is the most commonly used substance in the world and causes approximately 3.3 million deaths every year. Alcohol consumption is a well-recognized risk factor for a range of diseases and injuries. However, there is little knowledge on the relation between alcohol consumption and the occurrence of respiratory diseases.

Objectives: To investigate and quantify the magnitude of the association between alcohol consumption and acute respiratory distress syndrome (ARDS), asthma, chronic obstructive pulmonary disease (COPD), community-acquired pneumonia (CAP), obstructive sleep apnoea (OSA) and tuberculosis (TB).

Methods: Systematic reviews identified comparative observational studies listed on Medline, EMBASE, and Web of Science, published between 1985 and December 2015, with the exception of tuberculosis, for which we performed a separate search from 2005 to 2017. The reference lists of eligible studies were also searched. We imposed no language restrictions. Random effects meta-analysis was used to estimate pooled effect sizes with 95% confidence intervals (CI). Heterogeneity was explored using subgroup analyses. Funnel plots and Egger's asymmetry test were used for the assessment of publication bias.

Results: A total of 145 papers were included in the reviews. Our reviews demonstrated a 83% higher risk of CAP among drinkers (RR= 1.83, 95% CI: 1.30-2.57, I^2= 91%, 17 studies). In addition, the dose-response analysis showed that there is an 8% increase in the risk of CAP for every 10-20 grams higher alcohol intake per day (p for trend=0.136). Also, heavy alcohol consumption was found to significantly increase the odds of ARDS by 89% (OR=1.89; 95% CI, 1.45-2.48, I^2=48%, 13 studies). Furthermore, a sensitivity analysis indicated that this association was primarily due to alcohol abuse (OR=

1.90; 95% CI, 1.40-2.60, I^2=56%, 10 studies). People who consume alcohol are approximately 25% more likely to have OSA compared to people who don't consume alcohol (RR= 1.25, 95%CI 1.13-1.38, I^2=82%, 21 studies). Alcohol consumption increased the risk of TB between 1.9 and 2.8- fold, depending on study design. Moreover, there is a 12% increase in the risk of TB development for a daily alcohol consumption of every 10-20 grams (p for trend=0.559). However, it was not found evidence of an effect of alcohol consumption on the risk of asthma (RR=0.94; 95% CI 0.85-1.04, 12 studies) and COPD (RR=1.11; 95% CI, 0.88-1.40, I^2=94%, I^2 = 75%, 13 studies).

Conclusions: This thesis has established that high alcohol intake is associated with increased risks of several respiratory diseases, and therefore that reducing alcohol intake may have an important role to play in respiratory disease prevention.

Peer- reviewed publications arising from this thesis

1. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of sleep apnoea: a systematic review and meta-analysis. Sleep medicine. 2018 Feb 1;42:38-46.
2. Simou E, Leonardi-Bee J, Britton J. The effect of alcohol consumption on the risk of ARDS: a systematic review and meta-analysis. Chest. July 2018;154(1):58-68.
3. Simou E, Britton J, Leonardi-Bee J. Alcohol and the risk of pneumonia: A systematic review and meta-analysis. 2018 BMJ Open. 2018 Aug 22;8(8).
4. Simou E, Britton J, Leonardi-Bee J. Alcohol consumption and the risk of tuberculosis: a systematic review and Meta-analysis. International Journal of Tuberculosis and Lung Disease. 2018 Nov 1;22(11):1277-1285.

Conference presentations

1. **British Thoracic Society Winter Meeting, London, UK 6–8 December 2017** Poster session: "The effect of alcohol on severe respiratory diseases: A series of systematic reviews and meta-analyses." Simou E, Britton J, Leonardi-Bee J
2. **KBS 2017 - 43rd Annual Alcohol Epidemiology Symposium of the Kettil Bruun Society in Sheffield June 5-9, 2017**
   Oral presentation: “Alcohol consumption and the risk of sleep apnea: a systematic review and meta-analysis". Simou E, Britton J, Leonardi-Bee J
   Oral presentation: “Alcohol consumption and the risk of pneumonia: a systematic review and meta-analysis". Simou E, Britton J, Leonardi-Bee J

Press release arising from this thesis

British Thoracic Society Winter Meeting, December 2017

"High Levels Of Alcohol Consumption Greatly Increases Risk Of Developing Pneumonia And Other Lung Diseases". Simou E
https://www.brit-thoracic.org.uk/pressmedia/2017/high-levels-of-alcohol-consumption-greatly-increases-risk-of-developing-pneumonia-and-other-lung-diseases/

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List of Abbreviations and Acronym

ALI Acute Lung Injury

ARDS Acute Respiratory Distress Syndrome

BMI Body Mass Index

CAP Community-Acquired Pneumonia

CI Confidence Interval

CT Computed tomography

COPD Chronic Obstructive Pulmonary Disease

DALYs Disability-adjusted life-years

FAS Foetal Alcohol Syndrome

FEV1 Forced expiratory volume

FVC Forced vital capacity

GOLD Global Initiative for Chronic Obstructive Lung Disease

GSH Glutathione

HAP Hospital-acquired pneumonia

HR Hazard Ratio

IARC International Agency for Research on Cancer

ICD International Classification of Diseases

ICU Intensive care units

MeSH Medical Subject Headings

MOOSE Meta-analysis of Observational Studies in Epidemiology

NHS National Health Service

NOS Newcastle-Ottawa Scale

OR Odds Ratio

OSA Obstructive Sleep Apnoea

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROSPERO International prospective register of systematic reviews

RR Relative Risk/ Risk Ratio

SIGN Scottish Intercollegiate Guidelines Network

TB Tuberculosis

UK United Kingdom

WHO World Health Organization

1 Chapter 1

Introduction and background

The first chapter provides information about the background and rationale for the thesis. It also presents an overview on alcohol definitions and epidemiology. Other topic areas covered are direct and wider effects of alcohol consumption, alcohol and respiratory diseases, the economic impact of alcohol and the Government's Alcohol strategy in the UK. Finally, the aims and objectives of the thesis are stated.

1.1 Introduction

Across most of the world, alcohol is a fundamental part of people's social lives. In addition to using in celebrations and social occasions, in many societies alcohol is a routine part of many meals. Although less widely used in predominantly Muslim countries, across the rich world and especially in the UK, alcohol drinking is an established part of the lifestyle of many people.
Nevertheless, alcohol is the third largest global risk factor for disease and disability (1). The risks of several common diseases, including cancer, gastrointestinal and liver disease, are increased by alcohol consumption. Other harms associated with alcohol use include dependence, violence, injuries and road accidents (2).

Alcohol is one of the most commonly abused substances worldwide. Alcohol is responsible for a global total of approximately 3.3 million deaths each year (3), including around 9% of deaths in people aged 15 to 29 years, mainly resulting from car accidents, homicides (murders), suicides, and drownings. Furthermore, in the UK each year alcohol is responsible for over a million hospital admissions (2), and in England, the total annual cost on alcohol-related harms is approximately £21bn; of which £3.5bn is a direct cost to the NHS.

In the UK, to minimize the harms associated with alcohol consumption, population-level alcohol policies have been considered which aim to help individuals to change their hazardous drinking behaviors. In March 2012, the Government's Alcohol Strategy was published which considered introducing a minimum unit price for alcohol, controlling the number of licensed premises within residential areas, and banning discounted multi-buy offers (4). However, in July 2013, following a consultation, the government cited that there is currently insufficient evidence to introduce these potentially effective policies (5)**.**

In 2016, the UK Chief Medical Officer published revised guidelines to help people make informed choices about their alcohol consumption (6). The revised guidelines for weekly drinking stated that alcohol was at its safest limit if no more than 14 units were consumed on a weekly basis and that these units should be spread over 3 or more days. The goal of the guidelines was not to eliminate the use of alcohol but to reduce its consumption to a safer level for people's health for a healthier world.

Thus the reduction of alcohol consumption and especially hazardous drinking is a key health priority and because alcohol minimization requires population-level policy measures, it is important that accurate data on the effects of alcohol use on health are readily available to policymakers, policy advocates, and the general public. Furthermore, healthcare decisions for individual patients and for public health policies should be informed by the best available research evidence. However, while the available evidence on alcohol and health is extensive, it is also disparate, and at times conflicting. Therefore, it is particularly important that the evidence base is regularly captured, through systematic review, and synthesized to provide easily understandable and accurate summary estimates of effects.

The toll of regular high alcohol consumption on our hearts and livers is well recognized, but there is much less awareness that alcohol can have a big impact on our lungs. Alcohol consumption is just one factor,

among many, that could potentially increase an individual's risk of developing lung diseases, but it has not been studied extensively in the past. The World Health Organization has recently recognized that alcohol consumption increases the risks of tuberculosis and pneumonia but effects on other respiratory diseases are less well established. Therefore, in order to enlighten, clarify and improve understanding, it was deemed important to study the effects of alcohol on respiratory diseases. Moreover, the exploration of this association can help to inform not just the individuals but also the government about the health risks of alcohol on the respiratory system in order to do informed choices for a better life.

1.2 Literature review

The following sections describe in more detail reviews of the literature relevant to alcohol, including alcohol definition, the epidemiology of alcohol in general, and then the alcohol epidemiology in adults and in young people, the effect of alcohol in pregnancy, the direct effects of alcohol and the alcohol-related death.

1.2.1 Alcohol definitions

Alcohol is a psychoactive substance with dependence-producing properties (3). Alcohol drinking can be categorized using several different definitions, for example: low, moderate, heavy, excessive and binge drinking. However, a big challenge in alcohol research is the variability in the definition of a standard alcohol drink, as different countries define standard drinks and low-risk drinking differently, using grams or units to measure the quantity of consumption.

In the USA, the CDC guidelines define alcohol using grams of ethanol, and more specifically, a standard drink contains 14 grams of pure alcohol (7). Moderate drinking has been defined where up to 1 drink per day consumed by women and up to 2 drinks per day are consumed by men. Any lower amount of alcohol consumption is defined as low

alcohol drinking (8). Heavy drinking is defined as: a weekly consumption of ≥8 and ≥15 drinks for women and men respectively. Binge drinking is a pattern of drinking that brings a person's blood alcohol concentration (BAC) to 0.08 grams percent or above. This happens when women consumed ≥4 drinks per occasion and men consumed 5 or more drinks per occasion. Excessive drinking includes either binge or heavy drinking and also any alcohol consumption by pregnant women or young people aged less than 21(7).

In the UK, units are used to indicate how strong a drink is. Specifically, 1 unit is equal to 8 grams of pure alcohol, and the drink equivalents are 250ml standard 4% beer, 76ml standard 13% wine and 25ml standard 40% spirit (9). According to the Chief Medical Officer's new alcohol guidelines in 2016, it is safest for both men and women not to regularly drink more than 14 units a week in order to keep the health risk from alcohol at a low level. Furthermore, it is stated that it is best to spread the above amount in 3 or more days per week; whereas in the case of pregnancy it is safest not to drink alcohol at all (6). Any alcohol drinking above 14 units is considered as increased or higher risk drinking(10).

The frequency and amount of alcohol consumption can be measured in epidemiology using self-reported measurements. Self-reporting is better for assessing average consumption over a longer time period but one main problem is the fact that the participants tend to under-report the amount that they drink (11).

Moreover, there are other validating methods that assess a range of drinking amounts per occasion; including validated questionnaires such as Alcohol Use Disorders Identification Test (AUDIT), Short Michigan Alcohol Screening Test (SMAST) and CAGE. AUDIT is a screening tool developed by World Health Organization and consists of 10 questions. In the UK, a threshold of 8 or more points is used to identify alcohol-dependent patients with a sensitivity of 84% and specificity of 83%. With a maximum score of 40, low-risk drinking defined between 1-7; hazardous drinking between 8-15; harmful drinking between 16-19 and

a score of ≥20 is an indicator of possible alcohol dependence (12). SMAST is a 13-item questionnaire gathering information about alcohol involvement during the past 12 months. A SMAST score of 1 or 2 is an indicator that there is no problem from alcohol and no action required; whereas a score ≥4 suggests that there is an alcohol problem (13). The CAGE questionnaire is used to detect alcoholism and consists of four simple questions. A total score of ≥ 2 is considered clinically significant (14).

An objective measure for alcohol measurement which is used for binge drinking is blood alcohol content (BAC). BAC is a measure of the amount of alcohol circulating in the bloodstream.

1.2.2 Alcohol epidemiology

Globally, alcohol is one of the most commonly used drugs, and the third leading global risk factor for the burden of disease as measured in disability-adjusted life years; whereas in middle-income countries, alcohol is the most important risk factor (1).

Alcohol intake in the WHO European Region is the highest in the world followed by WHO region of Americas; whereas the Pacific and Africa regions recorded intermediate levels of alcohol drinking (3). Between 1990 and 2014, there was an increase in alcohol drinking levels, partly driven by the high alcohol consumption in the eastern and south-eastern parts of the WHO European region. However, in the central-eastern part, the drinking levels remained stable; whereas a fall was observed in central- western and Mediterranean parts (15).

Worldwide, in 2005 the adult per-capita annual consumption of people aged 15 years and over for alcohol was 6.1 liters and 40.6% of the adult population currently consumed alcohol; whereas 13.6% were former drinkers. (16) In the same year, the sub-Saharan Africa and Eastern Europe regions reported the highest alcohol consumption, with 34.0 liters and 26.4 liters consumed respectively (16). Also, there was a slight increase in the global adult per-capita consumption from 2005 to

2010, as in 2010 the consumption was equal to 6.2 liters for people aged 15 years and older, which equates to 13.5 grams of pure daily alcohol. Furthermore, alcohol consumption accounted for 5.1% of the global burden of disease and injury in 2012. (3) Globally, the most consumed alcoholic beverages are spirits accounted 50.1% of total recorded alcohol, beer which accounts for 34.8% of alcohol consumed and then wine represents the 8% of total alcohol (3).

Between 2001-2002 and 2012-2013 the prevalence of alcohol use increased from 65.4% to 72.7% among the total US population. Similarly, high-risk drinking at the same time periods increased from 9.7% to 12.6% (17).

The Global Burden of Diseases Study showed that alcohol misuse was the largest risk factor for loss of disability-adjusted life-years (DALY) among young people aged 20-24 years between 1990 and 2013. Also, alcohol accounted for 9.0% and 11.6% of DALYs in China and Mexico respectively for young people aged 20–24 years. (18) Alcohol harm was responsible for 3.2% of the total burden of disease and injury in Australia in 2003; whereas two-thirds of the estimated alcohol-attributable harm was due to alcohol abuse, road accidents and suicide (19).

1.2.3 Alcohol consumption in adults

The consumption of alcohol is a well- established part of people's lives across the majority of the Western world. Especially in the UK, alcohol is an acceptable and enjoyable drink for the majority of the adults.

In 2017, 9.6% of Great Britain adults, which equates to 4.9 million people, drank alcohol on five or more days per week during 2017. In the same year, men were more likely to drink alcohol compared to women (61.9% vs 52.4% respectively) (20). Also, data on alcohol consumption from the UK General Lifestyle Survey showed that age is an important

indicator of alcohol drinking, as older adults consumed less alcohol compared to younger adults; however older adults had consumed alcohol more regularly, where it was found that people aged 65 years and over had the highest proportion of everyday drinking (21).

Binge drinking, which is defined as drinking excessive amounts in a short time frame, among adults in Great Britain has only dropped by a small percentage from 18% in 2005 to 15% in 2013 (Figure 1.1). However, the reduction amongst young adults aged 16-24 years has been more pronounced, from 29% in 2005 to 18% in 2013. Additionally, a reduction from 25% to 19% in binge drinking was seen in adults aged 25-44 years (22). Furthermore, in 2016, 7.8 million (26.8%) of the adults in Great Britain binged on their heaviest drinking day, of this 10.3 % were older people aged 65 years and over (23).

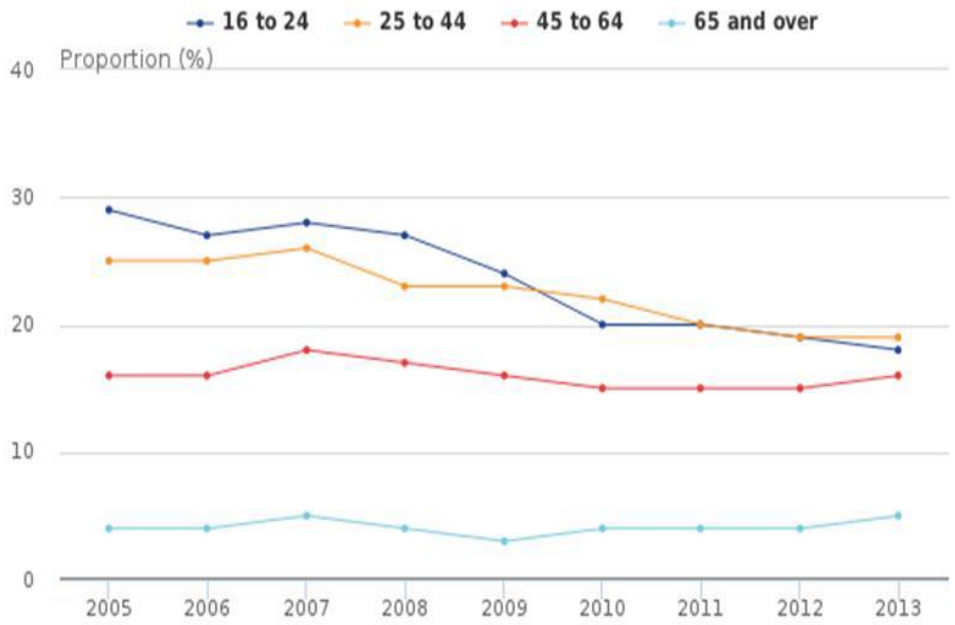


Figure 1. 1 Binge drinking among adults, by age, Great Britain, 2005-2013

Taken from: Office for National Statistics, Adult Drinking Habits in Great Britain, 2013, Source: Opinions and Lifestyle Survey, General Lifestyle Survey, General Household Survey - Office for National Statistics [online] Available from: http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/compendium/opinionsandlifestylesurvey/2015-03-19/adultdrinkinghabitsingreatbritain2013 [Assessed 16 September 2016]

The trend in binge drinking was also increased between 1993 and 2001 among US adults from 1.2 to 1.5 million, with men accounted for 81% of

binge drinking episodes. However, 69% of binge drinking episodes occurred among older adults aged 26 years and over.(24)

1.2.4 Alcohol consumption in young people

Alcohol consumption in young people is important because it is a strong determinant of alcohol use in later life. Young adults aged 18 till 25 years reported high rates of binge drinking which declined by increasing age during 1993 -2001 among US adults (24).

Furthermore, young people who consume alcohol before the age of 15 have a six-fold increase in the risk of alcohol dependence or excessive use in their later life compared to those who start drinking at or above age 21.(25) The Global Burden of Diseases Study found that alcohol use was the leading global risk factor for death for ages 15–24 years between 1990 and 2013.(18)

Alcohol consumption is prevalent among college students and is associated with a broad array of risk behaviors. In 2003, the prevalence of alcohol drinking among US high school students was overall 44.9%; of this 28.8 % were binge drinkers and 16.1% were current drinkers with no binge drinking. Also, a strong dose-response relationship was found between the frequency of binge drinking and other health risk behaviors including riding with a driver who had been drinking, sexually activity, violence, tobacco and drug use. (26)

Furthermore, a longitudinal study assessing the association of exposure to parental supply of alcohol in early adolescence with the risk of alcohol-related problems later on showed that adolescents who were supplied alcohol by their parents had an approximate 2.5 fold higher risk of subsequent binge drinking, alcohol-related harm and symptoms of alcohol use disorder compared to those with no supply. (27)

In 2016, Great Britain estimated that 37.3% of young adults aged 16-24 years reported binge drinking on their heaviest drinking day (23).

Furthermore, in 2017 in Great Britain an estimated 29.2 million adults (or 57%) aged 16 years and over reported that they had drunk alcohol in the previous week. (20)

In England from 1988 to 2013 there was an approximate stable trend, at between 59% and 64%, in the proportion of pupils aged 11-15 years who reported that they have ever drunk alcohol. Specifically, in 2013, 9% of school-aged children reported that they have drunk alcohol during the last week indicating a declining trend since 2003 when 25% of pupils had reported drinking in the last week (28).

1.2.5 Alcohol consumption in pregnancy

Alcohol can have health consequences not only for drinkers but also for individuals associated with the drinkers. Alcohol can have a detrimental effect on preterm birth or low birth weight (29). Also, alcohol consumption during pregnancy is harmful for the foetus; in particular moderate or heavy consumption can lead to Foetal Alcohol Syndrome (FAS). It has been estimated that the global prevalence of alcohol use during pregnancy is 9.8%; with an estimated prevalence of foetal alcohol syndrome of 14.6 per 10. 000 people (30). Also, it is estimated that each year about 119.000 children are born with Foetal Alcohol Syndrome.(30) Children with this serious condition can have restricted growth, facial abnormalities, and dysfunctions of the central nervous system as well as learning and behavioral disorders. The adverse effects of alcohol on the foetus include: severe impact on the brain, and functional abnormalities of heart, kidney, liver, gastrointestinal tract, and the endocrine system. (31)

1.2.6 Mortality

Alcohol consumption can also lead to death. The well- known j-shaped curve, which is controversial, relating alcohol intake to all-cause

mortality showed that non- drinkers and heavy drinkers have higher total mortality rates compared to light or moderate drinkers (32), and this is also the case specifically for cardiovascular mortality (33). A dose-response meta-analysis of 34 prospective studies indicated that low levels of alcohol intake, 1-2 drinks for women and 2-4 drinks for men, was inversely associated with total mortality in both sexes. Furthermore, this meta-analysis confirmed the hazardous effect of excess drinking; however, indicated potential windows of a net beneficial effect of moderate alcohol consumption (34).

Globally, 7.6% of all male deaths and 4% of all female deaths are attributable to alcohol consumption; which equates to approximately 3.3 million deaths each year (or 5.9% of all deaths) as a result of alcohol misuse (3). In the UK during 2016, there were a total of 7327 alcohol-specific deaths, equating to a rate of 11.7 deaths per 100.000 population. This rate indicated an increase compared to the rate in 2001 (10.6 deaths per 100,000 population) (35).

The age-standardised death rate from 1994 till 2013 showed a decline in recent years, but it is still significantly higher compared to 20 years ago (36) The figure below illustrates a stability on the alcohol-related death rates between 2003-2013, and more specifically death rates fell from 15 to 14 per 100.000 population. Contrary to this, between 1994-2003 an upward trend on death rates was observed from 9 to 15 per 100.000 population (Figure 1.2).

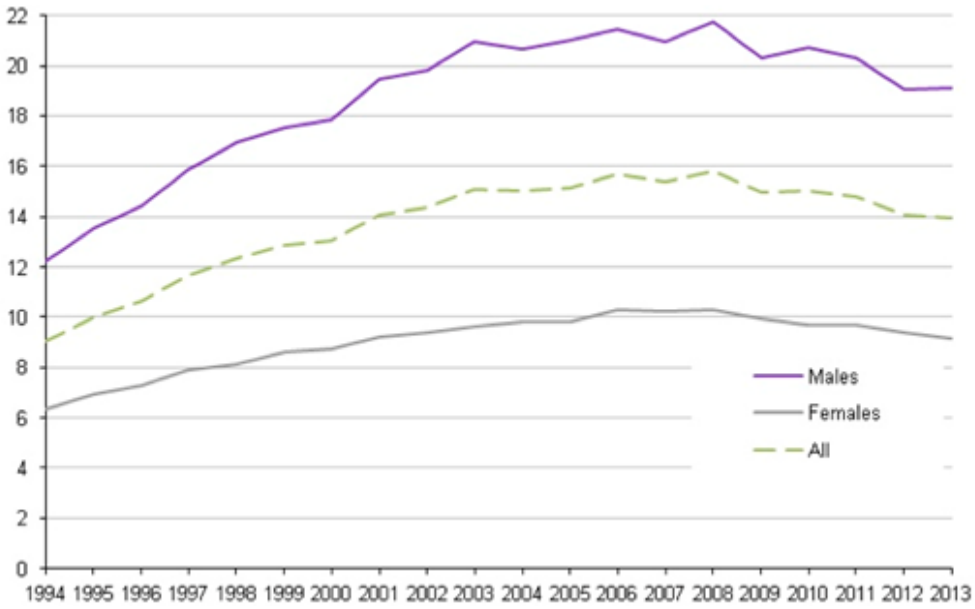


Figure 1. 2 Alcohol-related deaths, United Kingdom, registered in 1994-2013

Age-standardised rates per 100,000 population. Source: Office for National Statistics, National Records of Scotland, Northern Ireland Statistics and Research Agency

1.2.7 Direct effect of alcohol on health

Alcohol is associated with a multitude of severe health consequences and has a detrimental effect on every organ in the human body. The volume, pattern of drinking and quality of alcohol consumed determine the impact of alcohol on chronic or acute health outcomes (3). Alcohol can have detrimental effects in an individual primarily through three intermediate mechanisms: intoxication, dependence, and biological effects. Alcohol intoxication is mainly due to effects on the central nervous system and occurs either in low or moderate consumption levels. Furthermore, alcohol intoxication can have negative consequences in a variety of human functions including physical coordination, perception, cognition, consciousness and behavior. Also, alcohol can further have toxic effects on organs and tissues (3, 37).

Alcohol consumption is also associated with wider detrimental effects such as mental and behavioral disorders, including alcohol dependence. According to the Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10), alcohol

dependence is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated alcohol use. The diagnosis of alcohol dependence should include three or more of the following: a strong desire to consume alcohol, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to alcohol use than to other activities and obligations, increased tolerance, and sometimes a physiological withdrawal state. (38)

The overall prevalence of alcohol dependence in Europe among adults aged 15-64 years estimated to be 3.5 %; whereas it affected an estimated 5.4% and 1.5% for men and women respectively (39). In England, alcohol dependence is higher than across Europe affecting 9.3% of men and 3.6% of women aged between 18 and 64 (40). Furthermore, the prevalence of alcohol dependence among USA adults who excessively drink has been estimated to be 10.2%. Furthermore, the prevalence of alcohol dependence syndrome on binge drinkers is about 10.5% compared to 1.3% on non- binge drinkers (41).

Alcohol is also associated with hospital admissions. Specifically, in England during 2016/17 there were 337 thousand estimated hospital admissions attributable to alcohol consumption. This indicated a 1% lower trend than 2015/16 (339 thousand) but 17% higher trend than 2006/07 hospital admissions (42). However, in USA, 389.000 alcohol-related hospital discharges were recorded in the year 2014 for people aged ≥12 years old indicating a stable rate of all the hospital admissions from 2000 to 2014 (43).

Alcohol consumption has been identified as a detrimental factor for a series of health conditions. According to the International Agency for Research on Cancer (IARC) alcohol is carcinogenic for a series of cancers such as mouth cancer, nasopharynx- pharynx and oropharynx cancers, laryngeal cancer, oesophageal cancer, colon and rectum cancer, liver cancer and female breast cancer (44).

Long-term alcohol misuse also leads to gastrointestinal diseases including liver cirrhosis and pancreatitis (3, 37). Also, other diseases

that are causally associated with alcohol consumption include neuropsychiatric conditions such as alcohol use disorders and epilepsy. Alcohol drinking can also cause intentional or unintentional injuries (3, 45). Other chronic conditions where alcohol is a risk factor are epilepsy, psoriasis and cardiac arrhythmias (37).

1.3 Wider harmful effects of alcohol

Alcohol consumption can also have wider effects. Specifically, alcohol consumption can have an impact on society as a whole and therefore is linked to social consequences such as crime, violence and accidents. In the following sections, the wider effects of alcohol are covered.

1.3.1 Crime, violence and accidents

Alcohol consumption is also associated with many health and social problems, including violence and crime. A meta-analysis assessing the prevalence of alcohol-Involved homicide offending found that 48% of homicide offenders were reportedly under the influence of alcohol at the time of the offense and also that 37% were intoxicated. (46) Specifically, every year in the UK it has been estimated that 44% of violent crimes and 37% of domestic violence incidents are committed under the influence of alcohol (2). Also, alcohol-impaired driving is a major threat to health. Accidents and casualties caused by drink-driving in Great Britain in 2015 accounted for 12% of road deaths and 6% of killed or seriously injured casualties (47).

Specifically, in US the annually estimated episodes of alcohol-impaired driving are 147 million (48). Also**,** in Germany has been estimated that approximately 12% of accidents are due to alcohol consumption and furthermore 95% of these are attributable to a blood alcohol concentration level above 0.05% (49). However, another study has indicated that the risk of a fatal vehicle crash injury is twice as likely when a blood alcohol concentration is only increased to 0.02% (50).

One study in Brazil suggested that legislation lowering the legal blood alcohol content (BAC) level from 0.06 g/L to 0.02 g/L was associated with a significant reduction for both traffic fatality (16% to 7.2%) and traffic injuries (2.3% to 1.8%)(51).

1.4 Cost of the harms of alcohol

The health impact and the societal effects of alcohol misuse and harms have a major economic strain both on the individual and society. In the UK, the average annual cost of alcohol to the society was calculated to be approximately £21 billion; whereas the annual cost for alcohol misuse to the National Health Service was approximately £3.5 billion (52). Alcohol consumption can also lead to crime. In the UK the annual cost from alcohol-related crime has a range of £8bn to £13bn. (53) In UK, alcohol consumption can reduce productivity, to an extent estimated at approximately £7.3bn per year (54). Especially, alcohol dependence is a serious problem with a high economic burden in Europe and estimated annual total direct costs varying from €1 billion to €7.8 billion. (55) The calculated economic cost of excessive alcohol consumption in the US during 2016 was $223.5 billion, of which 72.2% was due to lost productivity, 11.0% to health care costs, 9.4% from criminal justice costs, and 7.5% from other effects (56).

The global burden economic cost due to alcohol consumption accounts for more than 1% of the gross national product in selective high- income and middle –income countries. Moreover, the lost productivity estimated indirect costs attributable to alcohol was the dominant category compared to all alcohol-attributable social costs, with Canada having a total cost of 49% and Thailand a calculated cost of 95%. (45) Similarly, the lost productivity costs in the European Union seem to be the first in the ranking of social costs accounting for half of the total social alcohol economic cost in Europe (57).

1.5 The Government's Alcohol strategy in the UK

As summarized above, there is evidence to suggest that the consumption of alcohol, especially in adults, is harmful to health. Therefore, population-level prevention policies need to be implemented which will minimize the risks of alcohol. The UK government and the administrations of Scotland, Wales and Northern Ireland are responsible for the implementation of alcohol policies. In March 2012, a UK-wide alcohol strategy was developed which aimed to give informed choice to individuals about their hazardous alcohol intake. Specifically, The Government's Alcohol Strategy introduced a minimum unit price for alcohol, to control the number of licensed premises within residential areas, and banned discounted multi-buy offers (4). However, in July 2013, following a consultation, the government concluded that there is currently insufficient evidence to introduce these potentially effective policies and instead put forward an alternative strategy to engage more with the alcohol industry to promote responsible drinking behaviors and prevent crime and disorder (5).

Due to the harmful effects of hazardous alcohol consumption on health and other outcomes, it is imperative that such drinking behaviors are minimized. To enable politicians, policy advocates, and the public to make the most informed decisions, it is important that accurate data on the effects of alcohol use on health are readily available and easily accessible. Nevertheless, one major difficulty is that the available evidence on alcohol and health is becoming extensive but is also disparate, and at times conflicting. Therefore, it is particularly important that the evidence base is regularly captured, through systematic review, and synthesized to provide easily understandable and accurate summary estimates of effects which can be sourced from a single repository that is easily accessible and has content which is easily digestible.

1.6 Alcohol and respiratory diseases

Alcohol has effects on all parts of the body and also associated with many health conditions. As summarized in section 1.2.7 however, the study of alcohol effects to date has been limited primarily to gastrointestinal and liver disease, cancers, and injuries. However alcohol can have wider health effects, and there is growing evidence that alcohol can have adverse effects on the lung, a fact that clinicians, public health advisors, and people often overlooked.

The rationale for these effects includes adverse effects of alcohol, especially in high levels, on the immune system reducing defense against infection and therefore possibly leading to an increased risk of pneumonia and tuberculosis (3). Benjamin Rush first described the association between heavy alcohol consumption and the risk of pneumonia and tuberculosis in 1785 (58), and recent studies reach similar conclusions (59, 60). Alcohol can also influence other diseases such as obstructive sleep apnoea, through sedative and obesity effects. This thesis is focused on the effects of alcohol exposure on the respiratory system.

1.6.1 Tuberculosis

Tuberculosis (TB) is a lung disease caused by infection with the organism *Mycobacterium tuberculosis*. TB is typically spread from person to person through inhalation of infected droplets(61) in some cases leading to lung infection (pulmonary TB) or infection in other sites (extra-pulmonary TB) (62). This infection can remain dormant an asymptomatic (61, 63), but if the immune system becomes compromised (as for example as a result of advancing age), latent TB infection may reactivate leading to the reactivation of tuberculosis. (63)

The inhaled infectious nuclei enter the lung and are deposited in the air sacs of the lungs called alveoli leading to mucus secretion. Then the body’s immune defense is activated resulting in macrophages and T

lymphocytes surrounding the bacteria and trying to control the infection with the formulation of granulomas. However, in case of a weakened immune system such as in an immunocompetent person, a loss of the wall integrity exists and therefore granuloma is unable to contain bacilli leading to the spread of bacillus to other alveoli or organs. (63)

Tuberculosis (TB) is a major global health problem with high morbidity and mortality. In 2016, 10.4 million people fell ill with TB (62). The global incidence of tuberculous in 2016 was 6.3 million new cases (62) whereas in 2013 was approximately 9 million cases (64). The region with the highest incident rate as estimated in 2016 was WHO South-East Asia region (approximately 45%), following by Africa region with 25% of the incident cases, and then by Western Pacific Region (7%) (62) Worldwide, tuberculosis is the ninth leading cause of death, accounting for an estimated annual 1.3 million deaths in HIV-negative people and additional 374.000 deaths in HIV- positive people, in 2016 (62). WHO estimates that the global annual burden of tuberculosis is approximately $12 billion.(65)

The main risk factors for TB include HIV infection, smoking, socio-economic deprivation, undernutrition, diabetes, indoor air pollution and alcohol consumption (66-68).

There is some evidence to support the belief that alcohol is a risk factor for tuberculosis (60, 69). Alcohol misuse is expected to increase in low/ middle-income countries indicated that alcohol may be a crucial factor for the next decades (66). As tuberculosis is a major infectious cause of the global burden of disease, there is still increased interest and available evidence on alcohol and TB, and it is, therefore, important to further assess the impact of alcohol on TB.

1.6.2 Community Acquired Pneumonia

Pneumonia is a lower respiratory tract infection that inflames the air sacs or alveoli in one or both lungs, filling these with fluid or pus. Three main types of pneumonia exist: community-acquired pneumonia (CAP),

hospital-acquired pneumonia (HAP) and healthcare-associated pneumonia. Other types of pneumonia include aspiration and atypical pneumonia (70).

The aspiration of bacteria or contaminating microorganisms can lead to infections in the lower airways. The defense mechanisms of our body include proteins, immunoglobulins, and peptides with antimicrobial activities which all protect the lower airway. Furthermore, the healthy microbiota of the upper airway also plays an important role against the infection. The failure of the defence mechanisms of our body causes inflammatory reactions, blocking the air in the lungs and leading to pneumonia (71).

Community-acquired pneumonia (CAP) is the most common type of pneumonia. In CAP the acute lung infection occurs outside of hospitals or healthcare facilities (72). The most common signs and symptoms of CAP include a cough, dyspnoea, fever, sputum production and chest pain (73, 74).

Globally, Streptococcus pneumoniae is the most common pathogen causing CAP (75). Similarly, in Europe, Streptococcus pneumonia remains the most frequently isolated pathogen which is responsible for approximately 35% of CAP cases, with a range of 11.9% to 68.3%. (76) Other frequent causes of CAP include Haemophilus influenza, Staphylococcus aureus, influenza virus, and other respiratory viruses (72).

In 2014 in the United States, pneumonia (including influenza) was the eighth leading cause of death (77) and according to World Health Organization, in 2015 pneumonia was responsible for 16% of all deaths in children aged under 5 years (78). The Global Burden of Disease Study stated that in 2013, pneumococcal infections caused the highest number of lower respiratory infection deaths in children aged 5 years old. Furthermore, in 2013 it was reported that lower respiratory tract infection is the second most frequent cause of death and years of life lost (79).

Community-acquired pneumonia remains an important cause of morbidity and mortality. Community-acquired pneumonia has an annual incidence in Europe and North America between 5 to 11 cases per 1.000 adults (80). Also, CAP accounts for an annual total of 4 million deaths globally (81). Furthermore, the annual incidence of community-acquired pneumonia requiring hospitalization among US adults is 24.8 cases per 10,000 adults; with the highest incidence especially in oldest people (82). Patients with severe CAP admitted to European intensive care units have a mortality rate of 27% at six months (83). The 30- day death rate for people who are hospitalized because of CAP is between 10% to 12% (72). Worldwide community-acquired pneumonia has a high economic burden; whereas in Europe, CAP is associated with an annual cost estimated at €10.1 billion (76).

The main risk factors for the development of CAP include lifestyle factors such as smoking being underweight, alcohol consumption, poor dental health; immune- comorbid conditions including: history of respiratory disease-COPD, heart failure, cardiovascular disease, chronic liver or renal disease, cancer, diabetes and demetria (74, 84-86). Also, aging of the population is a major risk factor, with specific age group categories being more vulnerable to the disease such as children younger than 5 years and people aged 65 years and over (73, 84). To date, there is some limited evidence that there is an increased risk of CAP with high levels of alcohol consumption (59). However, as CAP is a common disease which can also lead to death it is crucial to integrate the available knowledge in order to have a better understanding of the alcohol effect on pneumonia.

1.6.3 Asthma

Asthma is a chronic lung disease characterized by reversible airflow obstruction and inflammation of the airways (87). Asthma is associated with repeated episodes of wheezing, shortness of breath, chest tightness, and nighttime or early morning coughing (88).

Asthma is a complex disease with a multifactorial aetiology including genetic and environmental factors. When an individual who is predisposed to an irritant or allergen inhales it, the irritant or allergen reaches the epithelium, and IgE antibodies are released thus leading to an allergen-IgE interaction. Mast cells are characterized by the presence of high-affinity receptors (FcεR) for the IgE. Then, the IgE cross-linking on mast cells results in degranulation and release of mediators such as histamine, tryptase, chymase, eicosanoids, free radicals, and performed Th-2–like cytokines. These mediators are responsible for the production of airway narrowing, mucosal oedema and hypersecretion of mucus (89). These effects are termed an 'early phase reaction' that develops within 10 and reaches a maximum between 15-30 min and resolves within 1–3 h (90). Further, the release of a chemical mediator called il5 (interleukin 5) increases the activity from eosinophils which then are responsible for the release of inflammatory cytokines and leukotrienes resulting to the 'late phase reaction' starting after 3–4 h, and may last for 12 h or more' (89, 90).

The main asthma triggers include exposure to indoor/ outdoor allergens, environmental pollutants/irritants, strong odours, occupational exposures, foods, weather, tobacco smoke, exercise, sinusitis/respiratory infections, stress, and medications (91).

Asthma is one of the most common chronic diseases of children and adults in the world (92). It is estimated that ~ 300.000 people suffer from asthma (92). The global asthma prevalence ranging from 1% to 21% in adults and about 20% of children between 6 and 7 years olds experienced episodes of severe wheezing during a year (93).

In the US, there was an increase on asthma prevalence from 7.3% in 2001 to 8.4% in 2010, with a peak between 2008 till 2010. (94) However, the most recent data indicated a fall on asthma prevalence in the US, as asthma affects approximately 7.5% of adults leading to 1.8 million hospitalizations. (95)

In the UK, asthma prevalence is among the highest in the world and specifically has recorded the third highest number of people affected by asthma. (96). It is estimated that in the UK there are on average 5.4 million people with asthma, affecting approximately 1 in every 11 people (97, 98). Also, asthma causes a significant burden to the NHS with 65.000 estimated hospital admissions between 2011-2012 (98). Especially, in England, 4,500,000 people are asthmatics of which 3,600,000 and 932,000 were adults and children respectively (97).

Annual global asthma mortality has been estimated at 250.000 (99). More specifically asthma accounts for about 1 in every 250 deaths worldwide (92). Also, asthma mortality occurred more frequently in low and lower-middle income countries (100). According to WHO estimates, approximately 15 million disability- adjusted life-years are lost per year due to asthma (99). To date, the association between alcohol and asthma is unclear; with some studies reporting that alcohol has a beneficial effect on asthma (101, 102), while others suggested worsening of symptoms (103, 104). However, as asthma is a common lung disease, it is important to explore potentially avoidable causes, and therefore explore the impact of alcohol on asthma.

1.6.4 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease characterized by persistent respiratory symptoms and airflow limitation which is not fully reversible that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (105). Chronic airflow limitation comprises of a number of conditions, the most common are chronic bronchitis and emphysema. Chronic bronchitis is characterized by fibrosis and small airway obstruction whereas emphysema is defined as a condition characterized by enlargement of airspaces and destruction of lung parenchyma with loss of lung

elasticity and closure of small airways (106). In chronic bronchitis, there is inflammation of the airways which leads to mucus secretion, cellular changes (hyperplasia) and alteration of tissue repair. Furthermore, the airway inflammation in COPD is mainly characterized by inflammation of neutrophil and CD8 lymphocytes inflammation (107).

The main symptoms of COPD include dyspnoea, cough, sputum production, wheezing, and chest tightness (108). Spirometry is the tool used for the clinical diagnosis of COPD and a post-bronchodilator FEV1/FVC<0.70 confirms the presence of the COPD disease (108). According to GOLD, COPD can be graded as mild if FEV1≥ 80% predicted, moderate if 50%≤ FEV1≤80%, severe if 30%≤ FEV1≤50%, and very severe if FEV1≤30% (105).

The global prevalence of COPD is difficult to estimate because of differences in methods for establishment of disease prevalence and also due to the underdiagnosis of the disease in low-income countries. According to the Global Burden of Disease Study 2015, the number of COPD cases is estimated to be about 174.483 (109) indicating an increase by 44.2% from 1990 to 2015 (110).

Worldwide COPD is responsible for 3 million deaths (110). Approximately 90% of COPD deaths occur in low and middle-income countries (111). It is also estimated that by 2030 worldwide, COPD will be the third leading factor for mortality and the seventh leading cause for disability (112).

The main risk factors for COPD include both genetic and environmental factors. Specifically, a deficiency of the serine protease alpha 1 antitrypsin is the most well-known genetic risk factor for the disease.(113) According to environmental risk factors, smoking is the main causative agent of COPD (113, 114); and WHO states that smoking is responsible for 73% of COPD mortality. Also, indoor air pollution from exposure to biomass fuels is another important risk factor for COPD; however the risk of outdoor air pollutants is much smaller for COPD. Other risk factors for COPD include exposure to dust,

chemicals, vapours, and fumes in the workplace. Furthermore, there is an increased risk of COPD according to age, low socioeconomic status and to those with a history of asthma (113). To date the evidence between alcohol and COPD is mixed with some studies reporting that alcohol can increase the risk for COPD (115) or lead to COPD exacerbation (116, 117); while other studies showed a reduced risk (118) or suggested that alcohol has no detrimental effect on COPD mortality (119). Therefore it is important to explore this diverse evidence and further assess the possible impact of alcohol on COPD development.

1.6.5 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) is a disorder characterized by repeated episodes of partial or complete upper airway collapse or obstruction resulting in hypopnoea or apnoea during sleep (120, 121). A diagnosis of OSA is confirmed by demonstration of apnoea's (10-second interruptions of breathing) on overnight polysomnography (122, 123), or of apnoea or hypopnoea resulting in a 3% reduction in oxygen saturation on overnight oximetry (120), occurring 5 or more times per hour (120, 124). The frequency of these events [the apnoea index (AI) or apnoea/hypopnoea index (AHI)] is also used to grade the severity of OSA: AHI ≥5 to <15 episodes being graded as mild, AHI ≥15 to <30 as moderate, and over AHI ≥30 as severe (125, 126).

OSA is considered to be a disorder of the upper airway collapsibility. Specifically, the upper airway which is composed of muscles and soft tissues is responsible for various functions such as speech, swallowing and also provides a passage for air breathing. A narrowing of the upper airway as well as alterations in the soft tissue are both observed in OSA patients compared to normal people, increasing the risk for the airway collapse (127).

OSA patients appear to have a compromised upper airway anatomy and a higher airway dilator muscle activity (genioglossus) (127). In general, the upper airway dilator muscles are highly active during wakefulness and ensure that the airway remains open, but the reduction of muscle activity with the sleep onset results in airway collapsibility. (128).

The main symptoms of obstructive sleep apnoea include snoring, witnessed apnoeas and excessive daytime sleepiness. Other common symptoms of OSA can be non-restorative sleep, tiredness, fatigue, difficulty in maintaining sleep and also headaches especially during morning time (128, 129). The OSA prevalence (apnea-hypopnea index, measured as events/hour>5) has a range of 9% to 38%, with higher estimates in men compared to women. The prevalence of AHI≥ 15 ranged from 6% to 17% (130).

The most well-known risk factor for obstructive sleep apnoea is obesity. It is estimated that OSA is present in the 41% of patients with body mass index greater than 28 (122). Other risk factors for the development of OSA include age and sex; where OSA is more common in people of older age and in male respectively. Cigarette smoking and alcohol consumption have been suggested as possible risk factors for obstructive sleep apnoea (123, 128, 129). More specifically, snorers who also drink alcohol are more vulnerable to obstructive sleep apnoea compared to non-snorers, and this is due to the smaller pharyngeal airway of snorers (131). OSA has also implicated in the aetiology of other medical comorbidities such as cardiovascular diseases (including coronary artery disease, stroke, hypertension), and diabetes mellitus (123). As OSA is a relatively common condition which is associated with health complications it is important to assess the association of alcohol consumption on the risk of OSA.

1.6.6 Acute Respiratory Distress Syndrome

Acute respiratory distress syndrome (ARDS) is a type of acute diffuse alveolar damage with an onset within 7 days after known clinical risk

factors or new/worsening respiratory symptoms. The hallmarks for ARDS are hypoxemia and bilateral opacities using either chest X-ray or computed tomography (CT) scan (132).

The pathology of ARDS includes three overlapping phases: an inflammatory or exudative phase, a proliferative phase and a fibrotic phase (133). The main pathological findings of ARDS include diffuse alveolar damage, capillary injury and alveolar epithelium disruption (134).

The process begins with endothelial and epithelial injury and impaired removal of oedema fluid from the alveolar space leading to an accumulation of protein-rich fluid in the alveoli and consequent diffuse alveolar damage (135). This process also involves the influx of neutrophils and release of pro-inflammatory compounds such as cytokines by inflammatory cells, lung epithelial cells or fibroblasts, in turn initiating or amplifying the inflammatory response in ARDS (134). This exudative phase is followed by the proliferative phase characterized by resolution of pulmonary oedema, the proliferation of type II alveolar cells, fibroblasts and myofibroblasts, and new matrix deposition. The progression of this phase leads to the fibrotic stage (135).

Globally, ARDS is responsible for 10.4% of all the intensive care units (ICU) admissions, and approximately 23% of patients with ARDS need mechanical ventilation (136). ARDS is also associated with high morbidity and mortality (134, 137). Every year ARDS affects approximately 200,000 people and results in approximately 75.000 deaths and 3.6 million hospital bed-days (138). A 2009 systematic review assessing the mortality of ARDS over time demonstrated an overall mortality rate of 44% and 36.2% for observational and RCTs studies respectively and found that these rates were unchanged since 1994 (139).

Risk factors for the development of ARDS and for the closely related diagnosis of Acute Lung Injury (ALI), a term also used before definitions

of ARDS were standardized in 2012 (140), can be classified as direct or indirect according to the mechanism of lung injury (134). The most common clinical disorders include sepsis, pneumonia, aspiration, trauma, pancreatitis, shock, blood transfusions. Other secondary risk factors can be increased age, alcohol consumption possibly via its effects on alveolar barrier function and glutathione homeostasis (141), low serum pH and smoke or toxic gas inhalation (134, 142-144). As ARDS is a very serious condition associated with intensive care treatment and with high death rates it is, therefore, crucial to understand the impact of alcohol on ARDS.

1.7 Aims and objectives of the thesis

The aim of this thesis is to quantify and assess the effect of alcohol consumption on a range of severe respiratory diseases in adults, using a systematic review and meta-analysis methodologies.

The whole thesis has three main tasks. First, a series of systematic reviews and meta-analysis is performed to demonstrate the impact of alcohol on lung diseases. Secondly, by subgroup- analysis and sensitivity analysis, possible determinants of the above impact are analyzed. Thirdly, a dose-response analysis performed in order to assess the risks of the respiratory diseases with respect to specific exposure values when considering alcohol consumption per day.

Briefly, the specific objectives of this thesis were:

1. To quantify the magnitude of association on the risk of:
- Acute Respiratory Distress Syndrome
- Obstructive sleep apnoea
- Community-acquired pneumonia
- Tuberculosis
- Chronic Obstructive Pulmonary Disease
- Asthma

2. To explore whether the association between alcohol and severe respiratory diseases varies by participant and study level characteristics.
3. To determine the dose-response relationship between alcohol consumption and respiratory diseases.

2 Chapter 2

Materials and methods

The systematic reviews and meta-analyses were carried out in adherence with PRISMA (145) and MOOSE (146) guidelines. The protocol was published in the National Institute for Health Research International prospective register of systematic reviews (PROSPERO) under the registration number: 42015029910.

2.1 Modified PICO criteria

A modified version of the PICO criteria was developed in order to assess the eligibility of the identified studies based on the type of study designs, type of populations, type of exposures, and types of outcomes.

2.1.1 Type of populations

The dominant population of interest were all the adults aged 18 years and over.

2.1.2 Type of exposure

The exposure of interest was alcohol. We included all studies which have assessed alcohol consumption defined as ever alcohol drinkers, ex-or former drinkers, non- drinkers. We have also included studies assessing alcohol drinking levels: light, moderate, heavy drinking, alcohol abuse as defined in the included studies.

2.1.3 Type of outcomes

We included all studies which assessed the effect of alcohol on the incidence of respiratory diseases. Diagnosis of disease from death certificates was also eligible for inclusion. The main outcomes of interest were the following:

1. Acute Respiratory Distress Syndrome (ARDS), including acute lung injury (ALI)
2. Obstructive sleep apnoea (OSA)

3. Community acquired Pneumonia (CAP)
4. Tuberculosis (TB)
5. Asthma
6. Chronic Obstructive Pulmonary Disease (COPD), including bronchitis and emphysema

2.1.4 Type of studies

We included existing published systematic reviews and comparative longitudinal or cohort studies which have assessed the effect of alcohol on the outcomes of interest for each health outcome. Where limited longitudinal evidence for particular outcomes was seen, we have also included lower forms of evidence, such as case control and cross-sectional studies.

2.2 Exclusion criteria

Studies comprising of specific populations, for example, participants with HIV, Hepatitis B virus, Hepatitis C Virus were excluded in order to have a generalizable population. Also, studies assessing the effect of alcohol consumption on the risk of hospital- acquired pneumonia were not eligible as exposure to alcohol is unlikely to increase the risk of developing pneumonia in a hospital setting. Studies which referred to other substances or substance abuse disorders were not eligible for inclusion. Also, papers that were reviews/ meta-analyses, clinical trials, editorials, and nonhuman studies were also excluded.

2.3 Search strategy for systematic reviews

Initially, published systematic reviews and meta-analyses assessing the effect of alcohol on the risk of respiratory diseases (ARDS, OSA, CAP, TB, asthma, COPD) on adults were searched. A comprehensive literature search from Medline (via Ovid), EMBASE (via Ovid) and Web of Science from December 1985- December 2015 was conducted. Specific search filters for the identification of systematic reviews were used (147) and also search terms for alcohol and respiratory outcomes were developed from relevant Cochrane Review groups (148). The complete search strategy is provided in the Appendix 1. A further

screening of the references lists of the identified relevant systematic reviews was also screened to identify potentially eligible reviews. The worldwide literature was searched, and no language restriction was applied.

The search strategy was undertaken using the following process:

1. Where the most recent existing review's -end search date was conducted after December 2012, (i.e. <3 years), we did not perform any additional searches.
2. Where the most recent existing review was deemed out of date from having an end search date before December 2012, (i.e. > 3years), and was of good quality, we performed updated searches to identify recent comparative longitudinal, case-control studies or cross-sectional studies.
3. If an existing review was identified but was not deemed to be of sufficient quality (assessed using the AMSTAR quality scale- see section 1.6) and was also deemed out of date, a full search of primary studies was required.
4. Finally, where no existing systematic review was identified, we searched for all comparative longitudinal, cohort, case-control, or cross-sectional studies published between 1985 to December 2015. The start date of 1985 was chosen to enable a comprehensive inclusion of dates whilst enabling the search strategy to be completed in a timely manner.

A 'search diary' was kept giving details for the search strategy, including the names of the databases searched, the search terms used and the search results. The search results, including the titles and the abstracts, were uploaded into Endnote database; along with details for the references.

2.4 Search strategy for observational studies

Comprehensive search strategies were applied to Medline (via Ovid), EMBASE (via Ovid), and Web of Science databases for the period from December 1985 to December 2017. We used search filters (SIGN) for

observational study designs (147) and search terms for both exposure and outcomes developed using relevant Cochrane Review groups (148). When searching, Medical Subject Headings (MeSH) terms were used for Medine and EMBASE; whereas free text words were used for Web of Science. The reference lists of the included studies were also reviewed to identify further potential eligible studies. No language restriction was imposed and where necessary, translations of studies into English were conducted. In case of duplication, the most informative study was used. Two reviewers (E.S, J.L-B) independently screened the titles and abstracts. All relevant studies were obtained, and the full text was screened independently by two reviewers (ES and JL-B). Any disagreements were resolved through discussion or with the help of the third reviewer (JB). The search strategy used for the three databases was presented on Appendix2.

2.5 Data extraction

Two reviewers (ES and JL-B) independently extracted data using a previously piloted form. Variables of interest included: author & year of study, study design, geographic location, reference population, number of people recruited, definitions of exposure (alcohol) and outcome (ARDS, OSA, CAP, TB, COPD, asthma), and adjustment for confounders. Two data extractions forms were created for the extraction of data from systematic reviews and primary studies (see Appendix 8, 9).

2.6 Quality assessment

The assessment of the methodological quality of the identified systematic reviews was conducted independently by two reviewers using the 11 criteria from the Assessment of Multiple Systematic Reviews AMSTAR Scale (Appendix 5) (149). When reviews obtained a score greater than 7 were deemed to be of high quality.

The quality of the primary studies was assessed using the Newcastle-Ottawa Scale. The Newcastle- Ottawa Scale was chosen as it is one of the most widely used validated scales for assessing the methodological quality of comparative observational studies (150), and is also recommended by the Cochrane Collaboration (151). However, the Newcastle- Ottawa Scale has some limitations which need to be mentioned. Firstly, some of the domains may not be relevant for particular review questions and therefore the authors should adapt the items within the scale as required. Additionally, no separate scale exists for cross sectional studies; therefore reviews including such designs need to consider which items from the case control scale would be most relevant. Finally, previous research has shown that the scale can suffer from poor levels of agreement between the two reviewers who independently assess the quality of the studies (150).

In the process of the quality assessment of each article a maximum score of nine stars can be obtained; whereas studies with lower quality obtain fewer stars. In case of a cohort study, the cohort study criteria were used; whereas for case-control studies, the case-control criteria were used. In order to have some consistency in the criteria used across all study designs, we wanted to avoid using a completely different scale, and therefore for a cross-sectional study a modified version of the case-control study criteria was used and in this case, deleting the two questions relating to selection and definition of controls due to their irrelevance for this design, giving a total maximum score of 7- star. All studies, irrespective of their design, were considered to be of high quality if they obtained a score of ≥6 stars. Two reviewers (E. S, J.LB) independently assessed the quality of the included studies. Discrepancies were resolved through discussion and consensus. The quality assessment was not conducted for articles published solely as abstracts due to the lack of information contained within such articles.

2.7 Statistical analysis

Relative measures of effect were estimated as odds ratios (OR), relative risks (RR) or hazard ratios (HR) with 95% confidence intervals. Results were extracted as either adjusted effect measures, crude measures of effect, or using raw data. When available, in preference adjusted estimates were used and specifically were also used risk estimated adjusted for smoking and other socioeconomic factors. Where raw data were extracted from studies, we estimated ORs for case-control studies, whereas for cohort and cross-sectional studies we estimated the RR. Where alcohol exposure was reported either as quantiles or categories, we extracted the effect estimates taking the highest versus the lowest exposure group. We pooled odds ratios and relative risks together since it was assumed that these two measures of effect would be similar due to the outcome measure being uncommon (prevalence < ~10%) (152), however hazard ratios were not pooled with other effect estimates. When there was available data, we included results for men and women separately.

As systematic reviews combine studies that are diverse both clinically and methodologically, and it is likely that the strength of association between alcohol and respiratory outcomes varies by participant and study level characteristics; heterogeneity was anticipated (153). Therefore, the meta- analyses were conducted using random-effects (Der Simonian and Laird) models, using the generic inverse variance method, due to anticipated differences in effect measures as mentioned above and due to the related to the inherent biases within the observational study designs included in the review.

I^2 statistic was used to indicate the percentage of variation between the studies due to heterogeneity (153), with the following thresholds: low (25%-49%), moderate (50%-74%), and high (≥75%) (153). To investigate the sources of heterogeneity in meta-analysis we attempted to identify study-level characteristics that are associated with the variation in study results. Therefore, subgroup analyses were performed to explore reasons for heterogeneity based on factors selected *a priori*

including study design, study quality, geographic location, whether the effect measure was adjusted for potential confounders and the year of publication. We also conducted sensitivity analyses to explore the robustness of our findings, through restricting our analysis to studies which reported the reference groups as those with no alcohol drinking.

Funnel plots were used to visually detect publication bias. However as it can be difficult to determine whether asymmetry exists within a funnel plot, we elected to additionally use statistical tests to formally assess for evidence of publication bias. The test proposed by Peters et al (154) avoids the mathematical association between the log odds ratio and its standard error, and therefore reduces the possibility of false-positive test results that occurs for the Egger's asymmetry test; however in the case of substantial between – study heterogeneity, false- positive results may still occur using the Peters test. Therefore, as substantial heterogeneity was anticipated within these meta-analyses, the Peter's test was not used and we elected to use the Egger's asymmetry test, where data for at least ten studies were available. Stata software version 14 and Review manager software version 5.3 were both used for the statistical analysis. A p-value <0.05 was thought to represent a statistically significance level.

For categorical measures of alcohol drinking, where possible we compared any alcohol consumption with no alcohol consumption (reference group). In cases where the non-alcohol category was not reported in the studies, the lowest exposed category was used as the reference group. Where exposure to alcohol was reported using quantiles or as categories, we took the highest exposure groups compared to the lowest exposed group. Also, in the main analysis, categorical measures of alcohol consumption were further defined as levels of consumption: light, moderate, heavy, binge and alcoholism. Grams of daily alcohol consumption were used as a standard measure, defining: one drink as 0.6 ounces, 14.0 grams, or 1.2 tablespoons of pure alcohol (7). Where possible, we followed the CDC guidelines for the definition of heavy drinking as a weekly consumption of 15, or more

drinks for men, and 8 or more drinks for women; binge drinking as 5, or more drinks during a single occasion for men, or 4 or more for women; and excessive drinking as the presence of either binge or heavy drinking (7). The Dietary Guidelines for Americans defines moderate alcohol drinking defined as the daily consumption of up to one drink for women and two drinks for men (8). Otherwise, we accepted the definitions of alcohol that the included studies used.

2.8 Dose response assessment

A dose-response analysis was performed using a random-effects dose response meta-regression model, assuming a linear dose-response relation and allowed for study level correlations across the categories of quantities of alcohol (155, 156). The decision to fit a linear model was made as it was unlikely that a more complex model assessing a threshold effect could have been fitted due to the small number of studies included in the dose-response analysis and the variability in the definition of alcohol used within in included studies. We acknowledge that the assumption of a linear relationship leads to the limitation that any given change in an independent variable will always produce a corresponding change in the dependent variable, which is unlikely to hold for high levels of alcohol consumption.

Studies included in our analysis were required to have at least three different exposure categories, and the midpoints of categories used to quantify exposure. Grams per day were used as a standard measure for our analysis. If the highest exposure category was open-ended, we took the highest category midpoint to be the lower bound plus 1.2 times the lower boundary (157). When available we included results for men and women separately.

Separate dose-response meta-analyses were conducted for cohort/ longitudinal and case-control/ cross-sectional studies. Dose categories relating to quantities of alcohol were created to equate to 10-20 grams of pure alcohol per day (approximately one drink per day); where

studies reported categories, which contained the same dose ranges we collapsed these into a single dose category through estimating a pooled effect estimates based on a fixed effect meta-analysis model. Where necessary, effect estimates and 95% CI were back-calculated from floated to conventional confidence intervals to enable comparisons to be made to the reference group (non- drinkers or the lowest exposed category (158).

3 Chapter 3

Alcohol consumption and risk of ARDS. A systematic review and meta-analysis

This chapter presents a systematic review and meta-analysis of the impact of alcohol consumption on acute respiratory distress syndrome. The review focused on the identification and analysis of observational studies. An introductory section discussing how alcohol might influence ARDS is included. This chapter also explains the main research methods that were used, the databases searched, the study quality check and the statistical analysis which was used. Furthermore, the result section and the discussion of the main finding of this study were also presented in this research chapter.

At the time of undertaking this review, a search was made in order to identify existing reviews however no previous systematic review of this subject was identified.

3.1 Introduction

Alcohol abuse has been reported to increase the risk of ARDS (159, 160), perhaps because acute alcohol intoxication increases the risk of aspiration and pulmonary infection, while chronic alcohol ingestion disturbs both immunological and non-immunological host defence mechanisms within the airway, resulting in alveolar macrophage immune dysregulation and alveolar epithelial barrier dysfunction (161).

Other possible mechanisms of alcohol effect on ARDS risk are via the depletion of glutathione and the alveolar permeability. More specifically, chronic ethanol exposure decreases pulmonary GSH concentrations, impairs surfactant synthesis and secretion, increases the rate of

apoptosis of type II cells, and alters alveolar capillary permeability (162).

Each year ~ 200.000 people develop ARDS, of whose 50% have a history of alcohol abuse. Even in people who survive ARDS, an increase in the duration of both mechanical ventilation and ICU length of stay is related to alcohol abuse. The mortality of ARDS which is high at >40% is even higher in the people who abuse alcohol and reaches 65% (142). Furthermore at increased risk for the development of ARDS are septic shock critically ill patients with a history of alcohol use (163).

To date however there remains limited and inconsistent evidence on the relation between alcohol consumption and the risk of ARDS. To synthesize this mixed evidence to estimate an overall magnitude of risk, and to explore whether this varies by pre-disposing condition for ARDS, a systematic review and meta-analysis of observational studies of the association between alcohol consumption and ARDS were performed.

3.2 Methods

3.2.1 Study selection

We used the PEOS criteria throughout the review process based on: type of participants, type of exposure, type of outcome, and study design

3.2.2 Type of participants

All studies of adults aged 18 years and over were eligible for inclusion in this review.

3.2.3 Type of exposure

We included all studies which had assessed alcohol consumption, either by self-report or a proxy such as clinical records, defined either as drinking levels (low, moderate, heavy, alcohol abuse, alcoholism) or as frequency (grams/day).

3.2.4 Type of outcome

The outcome of interest was ARDS. We excluded studies limited to specific clinical diagnoses (HIV, Hepatitis B and C virus).

3.2.5 Study design

All the primary comparative observational studies were included (longitudinal/cohort, case-control, cross-sectional).

3.2.6 Search strategy

The initial search for systematic reviews on alcohol and ARDS indicated that no existing systematic review was identified. Therefore, a full search screening of primary studies was performed. Medline (via Ovid), EMBASE (via Ovid), and Web of Science were searched independently by two authors from December 1985 till December 2015. The search terms using every possible combination were the following: Respiratory Distress Syndrome, Adult/ or Adult Respiratory Distress Syndrome/ or Acute Lung Injury/ or Acute Respiratory Distress Syndrome/ or ARDS or ALI.

3.2.7 Data extraction

The data extraction is descripted in Chapter 2 on Section 2.5.

3.2.8 Assessment of study quality

The quality assessment is presented in Section 2.6.

3.2.9 Statistical analysis

The methods for the statistical analysis are presented in Section 2.7. Moreover, studies assessing the effect of definite TRALI (transfusion-related acute lung injury) were analyzed separately and thus not combined in the meta-analysis with other pre-disposing condition resulting in ALI. Also, an additional subgroup analysis was carried out to explain the identified heterogeneity based on pre-disposing condition for ARDS.

3.3 Results

Database searches and reference lists yielded a total of 4392 articles (Figure 2.1). After the removal of 739 duplicates, we identified 3653 articles for titles/abstracts screening, from which we identified 200 articles for full-text review. Of these, 183 were excluded because the study design was a review or a letter (8 studies); or because there was no comparison group (37 studies); insufficient information on exposure and outcome (13 studies); ineligible outcomes such as: sleep apnoea, pneumonia, asthma, COPD, airway obstruction, oxygen desaturation index (68 studies); irrelevant exposure (55 studies); or duplicate data (2 studies). Thus 17 studies met our criteria for inclusion in the review.

3.3.1 Study Characteristics

The characteristics of the 17 included studies in the review are shown in Table 2.1. Twelve studies used a cohort design (163-174); four were case-control studies (175-178), and one a cross-sectional study using survey data (179). A total population of 177,674 people was included. Patients with ARDS had a mean age ranging from 33 to 72.7 years, were more likely to be male ([range: 50% to 85%], 13 studies) and the majority were of white race ([range, 50% to 88%], 8 studies).

All studies were conducted in a hospital setting, with fourteen being conducted in US, two in Europe (167, 171) and one in China (169). Fourteen studies adjusted for confounders (163, 164, 166, 168-177, 179) and seven of these had reported results adjusted for smoking.

Study quality was assessed using the Newcastle-Ottawa Scale for 15 studies (2 studies were published as an abstract only) and of these, 9 (60%) were found to be of high quality. The median risk of bias score was 6, indicating a medium risk of bias (Table 2.2). The main reasons for lower scores in risk of bias were: flawed study design (lack of objective/validated methods for exposure definition), selection bias (representativeness of sample population) and information bias (lack of

provided information description in outcome assessment) or non-adequacy of follow up.

3.3.2 Exposure reporting

Sixteen studies investigated the effects of chronic alcohol exposure, and one the effect of acute exposure assessed by blood alcohol levels (164). Most of the studies reported chronic alcohol exposure assessed alcohol by self- report from a questionnaire (163, 165-170) or interview (174, 179); six used alcohol consumption documented in medical records (171-173, 176-178) and in one study the method of assessment and the definition of alcohol consumption were not defined (175). Measures of alcohol consumption included: drinks/day (170); drinks/week (174, 179); mg/dl alcohol in blood (164), alcoholism (167) and alcohol abuse ascertained either from medical records or questionnaire (163, 165, 166, 168, 169, 171-173, 176-178) . Specifically, alcohol abuse was defined in three of the eleven studies using a validated questionnaire; two defined alcohol abuse using AUDIT test (165, 166) and one using the Short Michigan Alcohol Screening Test (SMAST) (163). All studies analyzed the effects of alcohol exposure as a binary measure, contrasting high with low intake, or a history of abuse with no history of abuse, or any alcohol intake with none.

3.3.3 Outcome reporting

Outcome definitions for ARDS included the American European Consensus Conference Definition (163, 165-170, 172-174, 176-178), death certificates (179), and Berlin definition (164). Two studies did not provide clear information on outcome definition (171, 175).

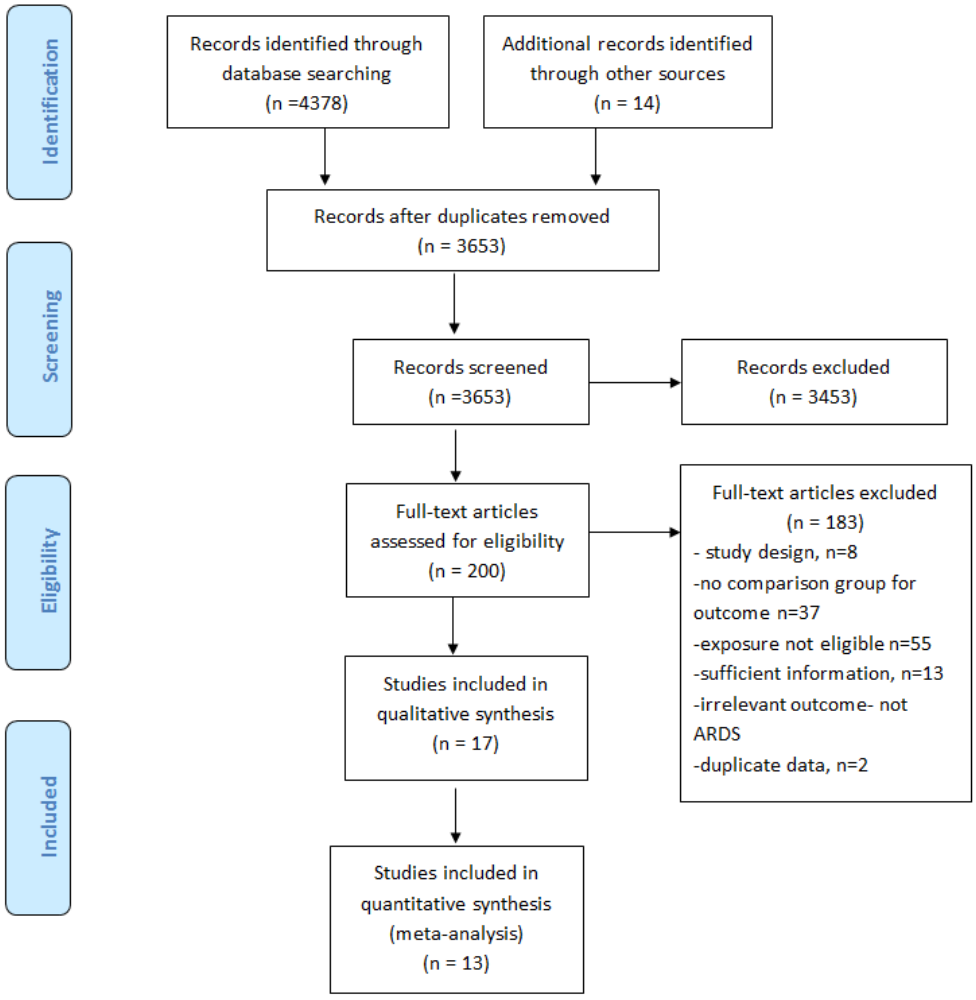


Figure 3. 1 Flow diagram

Table 3. 1 Characteristics of the included studies

Study & Year	Study design	Country	Population/Main predisposing condition	Characteristics of ARDS patients	Number of included people	Alcohol ascertainment	Definition of exposure to alcohol	Definition used to ascertain ARDS	Adjustment
Afshar, 2014(164)	Cohort	USA	Hospital/Trauma	Age: 33years[a] Male: 80.6% White: 57.7%	26,305	Blood alcohol content	>0 mg/dL	Berlin	Adjusted for: age, sex, race, tobacco, diabetes mellitus, immunosuppression medication
Ahmed, 2014(175)	Nested case-control	USA	Hospital	Age: - Male: - White: -	828	-	Any use	-	Matched for: age, sepsis, sex, surgery, ratio of oxygen saturation to fraction of inspired oxygen, and lung injury prediction score
Calfee*2011, (165)	Cohort	USA	Hospital/Trauma	Age: 44 years Male: 81% White: 66%	144	AUDIT Questionnaire	Alcohol abuse	AECC	No adjustment/matching performed
Calfee, 2015 (166)	Cohort	USA	Hospital	Age: 56years Male: 53% White: 88%	426	AUDIT Questionnaire	Alcohol abuse	AECC	Adjusted for: log-NNAL, APACHE II scores, race, diabetes, time elapsed between admission and enrolment
Cardinal-Ferna´ndez, 2013(167)	Cohort	Europe	Hospital/Sepsis	Age: 57years Male: 71.4% White: -	149	Questionnaire	Alcoholism	AECC	No adjustment/matching performed
Gajic*, 2007 (176)	Nested case-control	USA	Hospital (Intensive care)	Age: 61years[a] Male: 50% White: -	74	Medical records	Alcohol abuse	AECC	Matched for: age, sex, and admission diagnosis
Gajic*, 2010(168)	Cohort	USA	Hospital	Age: 57years[a] Male: 65% White:60%	5,584	Questionnaire	Alcohol abuse	AECC	Adjusted for predisposing conditions, high-risk surgery, high-risk trauma, male sex, body mass index, chemotherapy, diabetes, smoking, emergency surgery, tachypnea, hypoalbuminemia, acidosis, Spo_2,Flo_2

Ge, 2014(169)	Cohort	China	Hospital (Intensive care)	Age: - Male: - White: -	343	Questionnaire	Alcohol abuse	AECC	Adjusted for: age, sex, smoking, use of alcohol, history of diabetes, sepsis, septic shock, trauma, pneumonia, aspiration, massive blood transfusion, bacteraemia, pulmonary contusion
Iribarren[b], 2000(170)	Cohort	USA	Hospital	Age:52.8 years Male: 59% White:73%	121,012	Questionnaire	≥3 drinks/day in the previous year	AECC	Adjusted for: age, gender, race, smoking, body mass index, education
Iscimen*, 2008(171)	Cohort	Europe	Hospital/Septic shock	Age: - Male: - White: -	160	Medical records	Alcohol abuse	-	Adjusted for: delayed goal-directed resuscitation, delayed antibiotics, chemotherapy, transfusion, diabetes mellitus.
Kojicic[b], 2012(177)	Case control	USA	Hospital/Pneumonia	Age: 64.5years[a] Male: 50% White: -	596	Medical records	Alcohol abuse	AECC	Matched for: specific pathogen, isolation site, gender and age.
Licker[b], 2009 (172)	Cohort	USA	Hospital	Age: 67years Male: - White: -	869	Medical records	Alcohol abuse >60 grams/day	AECC	Adjusted for: pneumonectomy, ventilator hyper pressure index, fluid infused
Moss, 1996 (173)	Cohort	USA	Hospital/Sepsis, trauma	Age: 45.2years Male: 63% White: 50%	351	Medical records	Alcohol abuse	AECC	Adjusted for: sex, at- risk diagnosis, APACHE II score
Moss, 2003(163)	Cohort	USA	Hospital/Septic shock	Age: 50.1years Male: 68% White:	220	SMAST Questionnaire	Alcohol abuse	AECC	Adjusted for: source of infection, sex, age, chronic hepatic dysfunction, diabetes, severity of illness, nutritional status, and smoking status
TenHoor, 2001 (179)	Cross sectional	USA	Hospital (Decedents)	Age: 72.7years Male: 51% White: 86%	19,003	Interview	≥3drinks/week	Death certificate	Adjusted for: sepsis, cirrhosis, medical or surgical misadventure, injury, non-white, male, age>64 years, current smoking/former smoking
Thakur, 2009(174)	Cohort	USA	Hospital (Intensive care)	Age:55 years Male:85% White: -	1,357	Interview	>14 drinks/week	AECC	Adjusted for: aspiration, chemotherapy, high-risk surgery, pancreatitis, sepsis, shock, smoking,

									cirrhosis and gender
Toy[b], 2012 (178)	Case control	USA	Hospital	Age:54 years Male:49% White:71%	253	Medical records	Alcohol abuse	AECC	No adjustment/matching performed

AECC= American-European Consensus Conference definition; APACHE II =Acute Physiology and Chronic Health Evaluation II; AUDIT =Alcohol Use Disorders Identification Test; FIO2 = fraction of inspired oxygen; logNNAL = log-transformed NNAL [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol] level; SMAST = Short Michigan Alcohol Screening Test; SpO2= oxygen saturation as measured by pulse oximetry.

[a] Median presented.

[b]Outcome definition used within the study is acute lung injury.

Table 3. 2 Critical appraisal of the included studies using Newcastle Ottawa Scale

Study, Year	Stars number			
	Selection †	Comparability ‡	Exposure §	Overall score
Afshar, 2014(164)	3	2	3	8
Ahmed,2014* (175)	-	-	-	-
Calfee, 2011(165)	3	0	2	5
Calfee, 2015(166)	3	1	2	6
Cardinal-Fernandez, 2013(167)	1	0	3	4
Gajic, 2007 (176)	2	1	1	4
Gajic, 2010 (168)	2	2	2	6
Ge , 2014(169)	2	2	3	7
Iribarren, 2000(170)	2	2	2	6
Iscimen, 2008(171)	-	-	-	-
Kojicic, 2012(177)	2	1	1	4
Licker, 2009 (172)	2	1	3	6
Moss 2003(163)	2	2	3	7
Moss, 1996 (173)	1	1	2	4
TenHoor, 2001(179)	2	2	2	6
Thakur, 2009(174)	2	2	2	6
Toy , 2012(178)	2	0	1	3

***Abstract only available-not quality assessment**
† Maximum 4 stars.
‡ Maximum 2 stars.
§ Maximum 3 stars.

3.3.4 Meta-analysis

Thirteen of the studies provided data that could be included in a pooled analysis, which demonstrated that any measure of high exposure to alcohol significantly increased the risk of ARDS by a ratio of 1.89 (95% CI: 1.45, 2.48, I^2=48%, Figure 2.2). No evidence of publication bias was found (funnel plot, Figure 2.3) and Egger's asymmetry test, P = 0.150 (Figure 2.4).

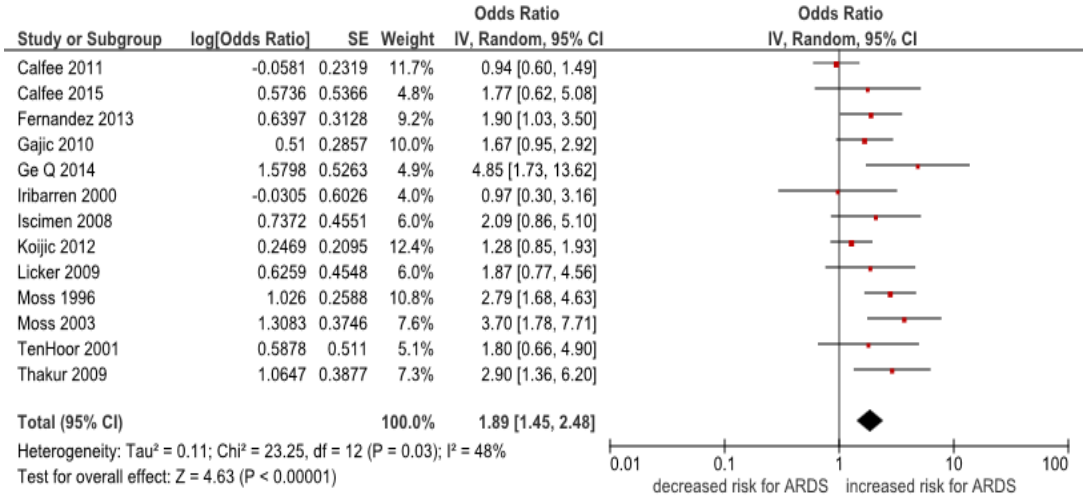


Figure 3. 2 Forest plot of alcohol consumption and the risk of ARDS

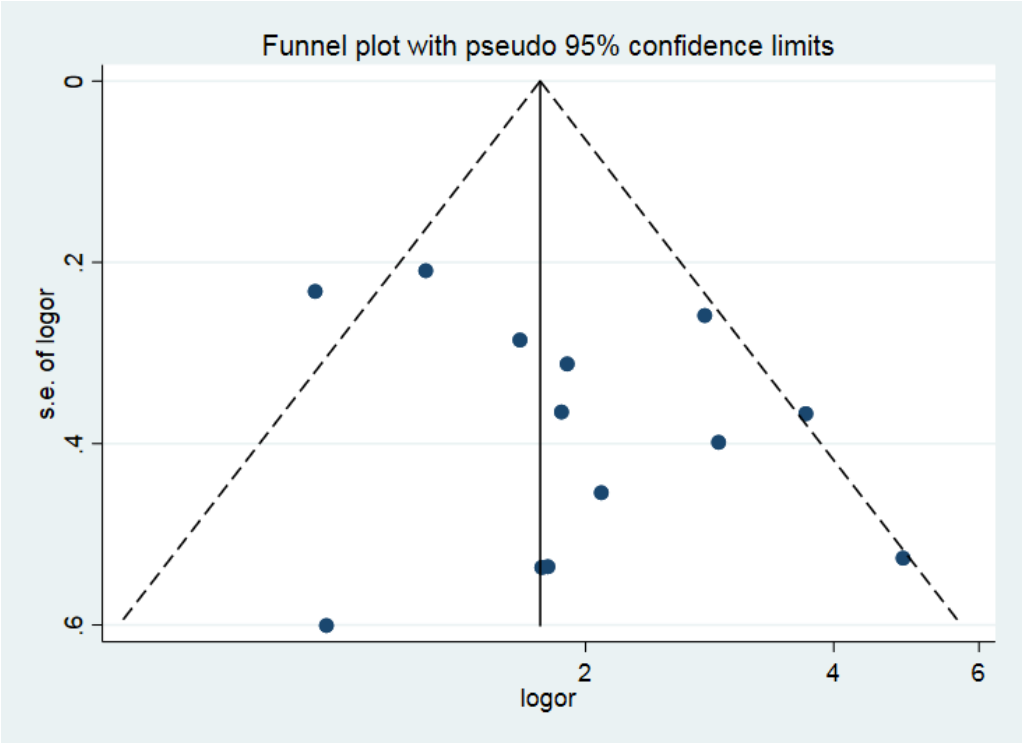


Figure 3. 3 Funnel plot of any high alcohol consumption and the risk of ARDS

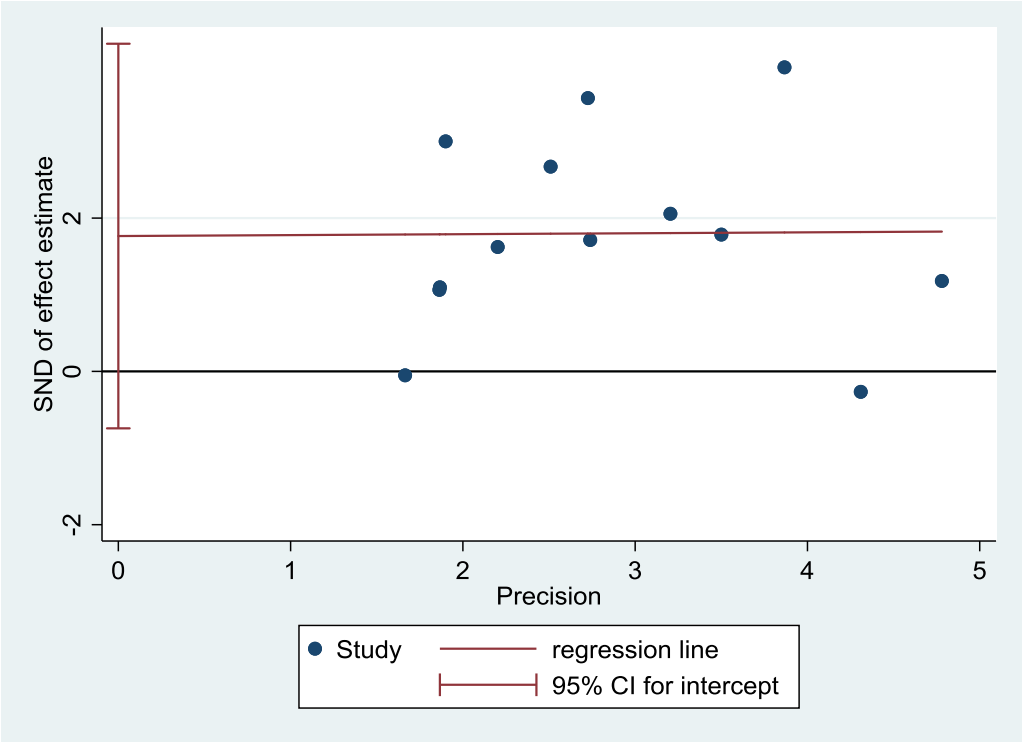


Figure 3. 4 Assessment of publication bias for asthma and alcohol; Egger's asymmetry test

Similar magnitudes of increased risk were seen in sensitivity analyses limited to studies categorizing alcohol intake as alcohol abuse, OR =1.90, (95% CI:1.40, 2.60, I^2=56%, Figure 2.5), and limiting to studies comparing only high alcohol vs low or no alcohol consumption (OR=1.96, 95% CI:1.07, 3.57, I^2=17%, Figure 2.5). However, the only study to use a zero intake as the reference group (170) found no significant effect of consuming of ≥3 drinks per day during the last year (OR=0.97, 95%CI: 0.30-3.16). A further sensitivity analysis excluding one study which compared decendents with a diagnosis of ARDS compared to descendents with other diagnoses (179), had a marginal effect on the magnitude of the association (OR= 1.91, 95% CI: 1.43, 2.54; 12 studies) compared to the unrestricted analysis.

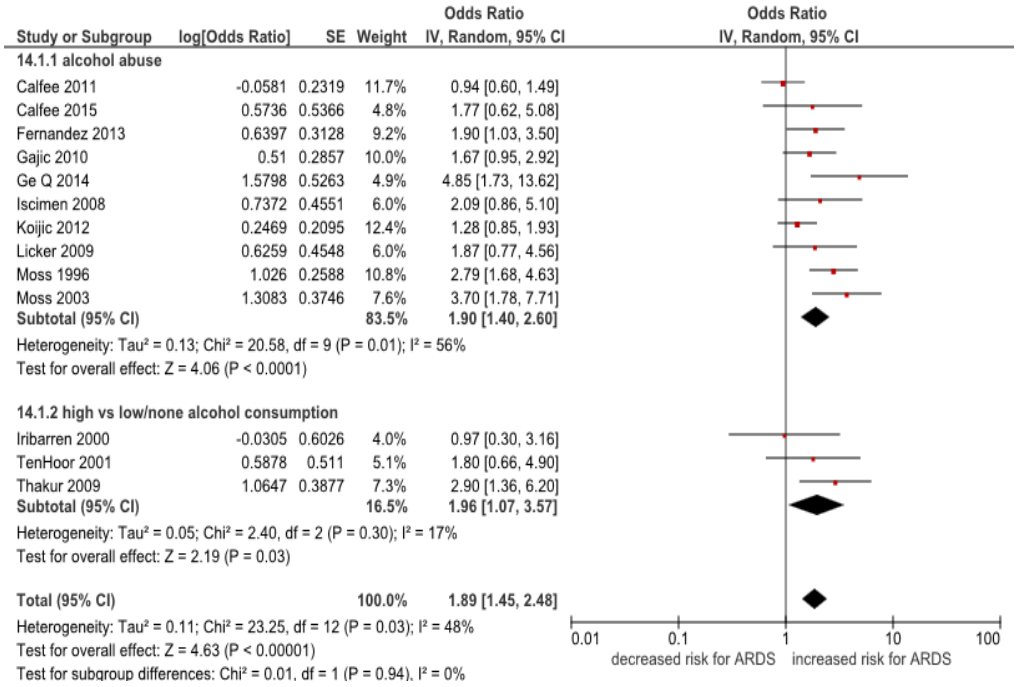


Figure 3. 5 Forest plot of alcohol consumption and the risk of ARDS; subgroup analysis based on alcohol abuse vs high alcohol consumption

3.3.5 Subgroup analyses

Subgroup analysis found that the predisposing condition (trauma, sepsis/septic shock, pneumonia) for ARDS explained heterogeneity between the studies (p-value for subgroup differences = 0.003); where an increased risk of ARDS associated with alcohol consumption was

only apparent in patients with sepsis/septic shock (OR= 2.76, 95% CI: 1.80- 4.24, 4 studies; Figure 2.6).

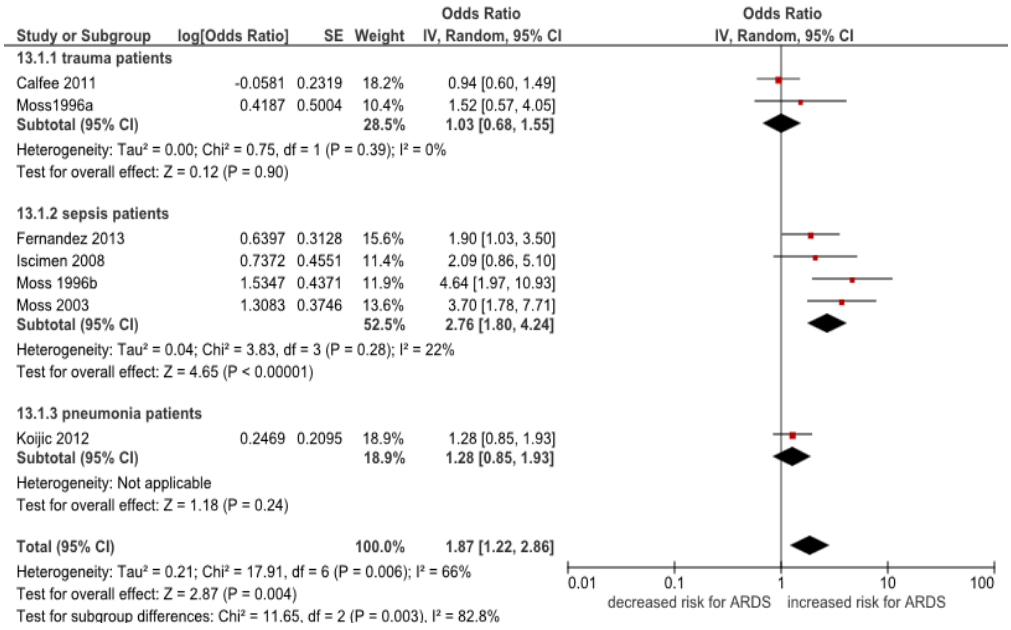


Figure 3. 6 Forest plot of alcohol consumption and the risk of ARDS; subgroup analysis in patients with trauma, sepsis and pneumonia

Further analyses to explore reasons of heterogeneity in the meta-analysis showed no statistically significant interaction by study design (case-control, longitudinal/cohort, cross-sectional; p=0.22), study quality (high vs low; p=0.21), country of study (USA, Europe, China; p=0.19), effect estimate (adjusted vs unadjusted analysis; p= 0.21), and year of publication (1995-2005 versus 2006 -2015; p= 0.20). Results presented in Table 2.3

Table 3. 3 Exploration of heterogeneity for alcohol consumption and the risk of ARDS

Factor	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	1.89 [1.45, 2.48]	48%	-
Study design			0.22
Case control	1.28 [0.85, 1.93]	-	
Cohort	2.02 [1.48, 2.77]	51%	
Cross sectional	1.80 [0.66, 4.90]	-	

Methodological quality			0.21
High quality (>6)	2.23 [1.62, 3.07]	12%	
Low quality (<6)	1.56 [0.98, 2.49]	72%	
Geographic location			0.19
USA	1.78 [1.30, 2.43]	53%	
Asia	4.85 [1.73, 13.62]	-	
Europe	1.96 [1.18, 3.24]	0%	
Effect estimate			0.21
Adjusted analysis	2.08 [1.59, 2.72]	32%	
Unadjusted analysis	1.30 [0.66, 2.56]	69%	
Publication year			0.20
Publication year: 1995-2005	2.44 [1.54, 3.86]	28%	
Publication year: 2006-2015	1.71 [1.27, 2.30]	42%	
Predisposing condition			0.003
Trauma	1.03 [0.68, 1.55]	0%	
Sepsis patients	2.76 [1.80, 4.24]	22%	
Pneumonia patients	1.28 [0.85, 1.93]	-	

Two studies were identified which assessed the effects of alcohol on the risk of transfusion-related ALI (176, 178). These studies both found that alcohol increased the risk of TRALI [results – p value=0.006 (37% vs 18%), OR=3.0 and 95% CI: 1.07- 8.7]. A meta-analysis of these two studies could not be performed as the first study (176) did not provide sufficient information to allow OR to be estimated due to the study using individual matching to identify the controls. Two further studies could not include in the meta-analysis. The first of these compared risks of ARDS in those with alcohol detected in blood compared with those with no detectable alcohol (164); as the effects of acute alcohol intoxication are very different from chronic alcohol exposure, this study was not included in the meta-analysis. This study found that the presence of

alcohol in blood was associated with an increased risk of ARDS (OR=1.50). The second study was only published in abstract form (175), which did not provide sufficient information to allow ORs to be estimated due to the study using individual matching. Briefly, this study showed that ARDS cases were more likely to consume alcohol (17% vs 10%) compared to controls.

3.4 Discussion

This review reports the first meta-analysis of observational studies of the association between alcohol consumption and the risk of ARDS among adults. We found evidence of a 1.89-fold increase in the odds of ARDS in persons with high alcohol consumption, which in subgroup analyses appeared to be attributable to the effect of exposure defined as alcohol abuse and also in those with sepsis or septic shock as the pre-disposing condition for ARDS.

Our review is based on a comprehensive search of the worldwide literature held in key medical databases and using search terms from recognized sources, complemented by searches of reference lists from identified publications. We imposed no language restriction in our searches. It is therefore likely that our results are representative and generalizable. The absence of publication bias further validates our findings.

Being based largely on observational studies raises the possibility of bias which may be introduced in our analysis. However, misclassification bias due to the inclusion of former/ lower drinkers in the reference group is likely, if anything, to have reduced the magnitudes of estimated effects. However, the subgroup analyses were conducted in an attempt to explore reasons for heterogeneity, and we found that there were no significant differences according to study quality, study design, effect estimate, continent or year of publication.

A previous narrative review has drawn attention to the potential importance of chronic alcohol abuse in the aetiology of ARDS (162),

finding an increased incidence of ARDS in alcohol abusers. Also, a narrative review published in 2009, which only included four studies on alcohol and ARDS, concluded that alcohol abuse is a risk factor for the development of ARDS (142). Our findings extend the conclusions of this work, identifying a summary effect estimate and that the increased risk applies predominantly to ARDS arising from sepsis.

The mechanism or mechanisms by which alcohol consumption might increases the risk of ARDS, particularly among patients with sepsis, are not fully understood. However, effects on membrane permeability (180, 181), glutathione depletion (182-184), toll-like receptor up-regulation (185), expression of transforming growth factor beta-1 (186, 187) and impairment of macrophage function are all potential explanations (188).

Our review thus provides comprehensive evidence that high alcohol consumption increases the risk of ARDS.

4 Chapter 4

Alcohol consumption and risk of sleep apnoea. A systematic review and meta-analysis

In this study, a systematic review and meta-analysis was undertaken, which focused on the identification of observational studies assessing the effect of alcohol consumption on the risk of obstructive sleep apnoea. This chapter starts with an introduction of the influence of alcohol on OSA. Also, the methodology, the quality assessment, the statistical analysis and an overview of the results from the systematic review and from meta-analysis were also presented. Furthermore, the main conclusions drawn from this study were also discussed. At the time the present review was undertaken no previous systematic review was identified through searching the databases. Therefore, this review will help in quantifying and assessing the impact of alcohol on OSA.

4.1 Introduction

OSA is thought to be more common among people who consume alcohol, possibly because alcohol increases upper airway collapsibility (123, 189, 190) and also because alcohol intake can contribute to a higher body mass index. Alcohol drinking can impair normal breathing by reducing the motor output to the upper airway, leading to airway obstruction. Alcohol use can further result in the relaxation or hypotonia of the oropharyngeal muscles, leading to obstructive sleep apnoea (189, 191). Alcohol can diminishes the arousal responses to upper airway occlusion, worsening the hypoxia degree at sleep in patients with OSA (192). Heavy drinkers are at high risk for OSA but also moderate alcohol ingestion can increase the frequency of obstructive apnoea's and hypopneas episodes (193, 194). Specifically, moderate alcohol doses increase the upper airway resistance in normal subjects (195). Even after the consumption of only one drink, the risk of snoring and OSA is elevated in normal sleepers (194).

Especially alcohol ingestion before bedtime can increase the risk of obstructive sleep apnoea (196). This can happen because alcohol before bed increases the upper airway resistance resulting in sleep apneas in asymptomatic snorers with a more pronounced effect at the first 2 hours after the alcohol consumption (190, 196, 197). High alcohol consumption before bedtime (3 oz) in patients with OSA causes an exacerbation in both the frequency and severity of hypoxic events and further shortens the time between sleep onset till the most severe event (196). Even modest alcohol consumption can have aggravating effects on nocturnal breathing in patients suffered from obstructive sleep apnoea (194).

However, evidence on the effect of alcohol consumption on the risk of OSA remains discrepant, with some studies reporting an increased risk in those who consume alcohol (124, 198, 199), and others finding a decreased risk (200, 201). To clarify and quantify the association between alcohol consumption and the risk of OSA a systematic review and meta-analysis of comparative epidemiological studies including data on alcohol consumption affects and OSA in adults was carried out.

4.2 Methods

4.2.1 Search strategy

No existing systematic reviews were identified on alcohol and sleep apnoea. Therefore, a full search screening of primary studies was required. For this reason, we performed a systematic review and meta-analysis including all the comparative observational studies published between 1985 to December 2015.

4.2.2 Inclusion criteria and search strategy

We included all longitudinal, cohort, case-control and cross-sectional studies assessing the association between alcohol consumption and sleep apnoea in adults aged 18 years and over identified from comprehensive searches of Medline (accessed via Ovid), EMBASE

(accessed via Ovid) and Web of Science databases between December 1985 and December 2015. The search terms using every possible combination were the following: Sleep Apnea Syndromes or hypopnea or OSA or SHS and Alcohol Drinking. The full search term strategy is presented in Appendix 1.

4.2.3 Measures of outcome and exposure

Where objective measures of OSA severity were available, these were assessed using the Respiratory Distress Index (RDI) or Apnoea-Hypopnea Index (AHI), where a higher score indicated increased severity. Where possible, an AHI≥5 or RDI≥5 was used to define the presence of OSA, and a score <5 to define the absence of OSA. Subjective measures of OSA (self-report) were also used.

The methodology for categorical measures of alcohol drinking is presented in Section 2.5. Continuous measures of alcohol consumption were standardized, into units per week using recognized definitions: 1 drink being defined as 0.6 ounces, 14.0 grams or 1.2 tablespoons of pure alcohol (7) or using the UK guidelines we defined 1 drink as 8 grams of ethanol (9). Also, for continuous data, we standardized alcohol to grams of ethanol per week. Where alcohol intake was expressed in daily terms, we multiplied these by 7 to obtain a per-week figure.

4.2.4 Data extraction

The data extraction is descripted in Chapter 2 on Section 2.5.

4.2.5 Quality assessment

The quality assessment is presented in Section 2.6.

4.2.6 Statistical analysis

The methodology used for the statistical analysis is presented in Section 2.7. Continuous effect measures were estimated as mean differences (MD) with 95% CI. Where more than two categories of

exposure to alcohol were presented within a study, we combined the categories using a standard formula to estimate pooled means and the pooled standard errors (148).

Additional subgroup analyses were performed according to ascertainment of alcohol levels (excessive vs low/moderate) and OSA (objective versus subjective). Furthermore, to assess whether the association between alcohol and OSA was independent of Body Mass Index (BMI), we performed a sensitivity analysis restricted to studies which provided BMI-adjusted measures of effect. We also performed sensitivity analyses restricted to studies which provided smoking-adjusted measures of effect.

4.3 Results

4.3.1 Overview of included studies

From an initial of 4378 studies identified from the literature searches, 14 further studies were added after the search of the reference list of the primary studies. After the duplicate removal, 3653 articles had potentially eligible titles and abstracts. Of these, 178 had potentially eligible full texts. After the full-text screening and the exclusion of non-eligible papers, 31 studies met our criteria for inclusion in the systematic review (Figure 3.1). A total population of 3.742.940 people was included. Patients with OSA had a mean age of 51.8 years.

Twenty of the included studies used a cross sectional design (198, 199, 201-218) , nine were case control studies (124, 200, 219-225) and two were cohort studies (226, 227). Eleven studies were conducted in Asia (Korea (5 studies), India (2) Israel (1) Taiwan (1), Japan (1), Pakistan (1)) (124, 199, 203, 204, 207-209, 217-219, 221); ten in US (201, 202, 206, 213-216, 223, 226, 227), four in Australia (212, 222, 224, 225); five in Europe (Denmark, United Kingdom, Ireland, Norway, German) (198, 200, 205, 211, 220) and one in Africa (210).

Most studies assessed alcohol consumption by self-report using a standardized questionnaire; one study measured alcohol dependence used International Classification of Diseases (ICD-9) codes (201). Fifteen studies reported the quantity of alcohol as a continuous measure (number of drinks, units of alcohol or grams of ethanol consumed) and 11 studies used categories (124, 199, 201, 206, 208, 211, 213, 215-217, 219) including; current drinking (124, 213, 216); alcohol abuse (219); alcohol dependence (201), harmful alcohol (209),excessive (211),binge drinking (215), habitual drinking (199, 217) and regular drinking (210). The remaining five studies did not provide additional information about how alcohol was quantified (204, 207, 208, 221, 225). Ten of the 31 included studies reported alcohol consumption as a binary exposure, comparing any intake with no intake (124, 203, 204, 206-208, 213, 218, 221, 226). The results are presented in Table 3.1.

Twenty-three studies ascertained sleep apnoea using polysomnography either measuring its presence and severity using the Apnoea-Hypopnea Index (AHI) (124, 199, 200, 204-208, 211, 214, 216-220, 222-227) or the Respiratory distress index (RDI) (198, 212). Seven studies relied on self-report (202, 203, 209, 210, 213, 215, 221) and in the remaining study, sleep apnoea was ascertained using ICD codes (201).

The methodological quality using the Newcastle-Ottawa Assessment Scale (Table 3.2) showed that quality of the included studies ranged from 2 to 7, with only one study deemed to be of high quality (overall score ≥6) (226). Lower quality scores were primarily due to lack of adjustment for confounding factors, using selective populations or a self-report assessment of alcohol exposure. Thirteen studies reported effect estimates adjusted for confounders (124, 201-204, 209-211, 213, 215, 219, 222, 226); with six adjusted for smoking (124, 203, 204, 209, 214, 226).

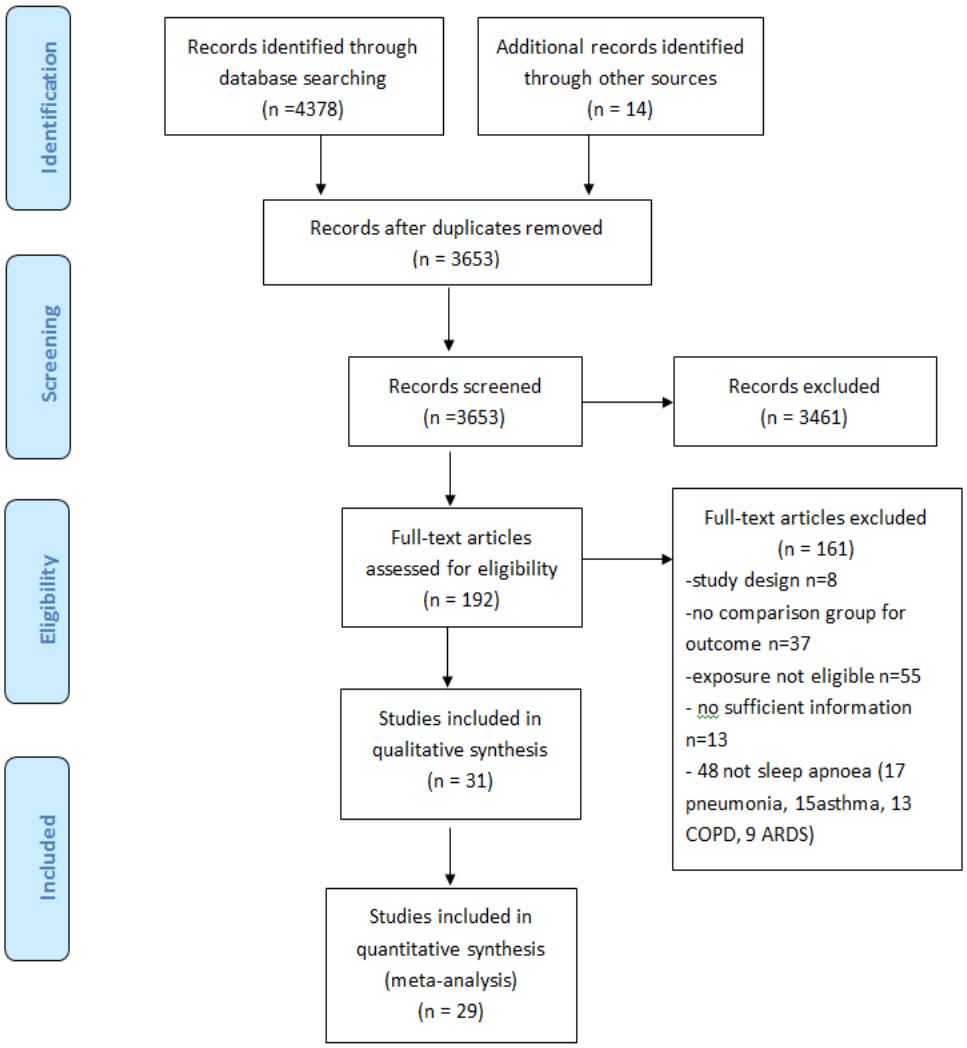


Figure 4. 1 Flow chart of studies

Table 4. 1 Characteristics of the included studies

Study& Year	Study design	Included people	Geographical location	Population	Alcohol ascertainment	Alcohol definition	Sleep apnoea ascertainment	Sleep apnoea definition	Adjustment
Baik, 2014 (124)	Case-control	470	Asia/Korea	General population	Self-report	Current drinker's vs no drinkers	polysomnography	AHI>=15 vs AHI<5	NRG1 genotype, age, sex, BMI, neck circumference
Coughlin, 2004 (200)	Case-control	104	Europe/United Kingdom	People recruited from clinic and general public	Self-report	Units/week 0-4 units vs 4-50 units	polysomnography	AHI>=15 vs AHI<5	-
Enright, 2001 (202)	Cross sectional	1922	North America/US	Elderly population	Self-report	>=25 drinks/week	Self-report questionnaire	-	Chronic bronchitis, clinic care, marital status
Fredheim, 2011 (205)	Cross-sectional	137	Europe/Norway	Population recruited from Obesity/Centre	Self-report	Units/week	Polysomnography	AHI>=5 vs AHI<5	-
Gilat, 2014 (219)	Case-control	5588	Asia/Israel	General population	Self-report	Alcohol abuse	polysomnography	-	Matched for: age and sex
Heiskel, 2002 (220)	Case-control	549	Europe/ German	Hospital sleep laboratory population	Self-report	7glasses/week vs 8 to>21glasses/ week	Polysomnography	-	-
Hussain,	Cross-		Asia/Pakist	General	Self-report	Alcohol yes vs	Self-report		sex, age, BMI,

2009 (203)	sectional	2497	an	population		no		-	collar size, shift work, nasal blockage, current smoker, family history of snoring
Hwang, 2010 (207)	Cross-sectional	224	Asia/Taiwan	hospital volunteer helpers	Self-report	Alcohol yes vs alcohol no	Polysomnography	AHI>=5 vs AHI<5	-
Jennum, 1994 (198)	Cross sectional	1426	Europe/Denmark	General population	Self-report	Beverage: 10grams/day of ethanol	Respiratory distress index	RDI>=5 vs RDI<5	-
K.Kang, 2013 (221)	Case-control	1305	Asia/Korea	General population	Self-report	Alcohol yes vs alcohol no	Self-report (Berlin questionnaire)	(high risk vs low risk of OSA)	-
K.Kang, 2014 (209)	Cross-sectional	7955	Asia/Korea	General population	Self-report	Harmful yes vs no harmful alcohol	Self-report Berlin questionnaire	high risk of OSA	sex, age, educational level, occupation, shift work, smoking status, exercise, musculoskeletal diseases, diabetes, hypertension
Kang, 2014 (208)	Cross-sectional	383	Asia/Korea	sleep clinic patients	Self-report	Alcohol yes vs alcohol no	Polysomnography	AHI>=5 vs AHI<5	-
Kim, 2006 (204)	Cross-sectional	472	Asia/Korea	General population (40-69 years)	Self-report	Alcohol yes vs no	Polysomnography	AHI>=5 vs AHI<5	Age, sex, smoking, BMI, hypertension

Marshall, 2008 (212)	Cross-sectional	380	Oceania/Australia	General population	Self-report	Grams/week	Respiratory distress index	RDI>=5 vs RDI<5	-
McArdle, 2006 (222)	Case-control	42	Oceania/Australia	Sleep clinic of a hospital	Self-report	Grams/week	polysomnography	AHI>=15 vs AHI<5	waist circumference, age
Mc Cague, 2014 (211)	Cross-sectional	926	Europe/Ireland	hospital	Self-report	Excessive vs no excessive drinking	polysomnography	AHI>30 vs AHI<5	Adjusted (not known the variables)
Ngahan,2010 (210)	Cross-sectional	411	Africa/Africa	General population	Self-report	Regular drinking	Self-report (Berlin questionnaire)	(high risk vs low risk of OSA)	waist circumference, snoring
Nieto, 2000 (206)	Cross-sectional	6132	North America/US	Middle-aged and elderly population	Self-report	Alcohol no vs >7drinks/week	Polysomnography	AHI>=5 vs AHI<5	-
Yue, 2014 (213)	Cross-sectional	39461	North America/US	General population	Self-report	Current alcohol use (within the past 12 months) vs never	Self-report questionnaire	-	gender, age, race, marital status, income, education, asthma, diabetes, hypertension
Peppard, 2000 (214)	Cross-sectional	893	North America/US	General population	Self-report	Drinks/week	polysomnography	AHI>=5 vs AHI<5	-
Peppard, 2006 (226)	Cohort	1420	North America/US	General population	Self-report	Drinks/day 0 drinks vs 3 drinks	polysomnography	AHI>=5 vs AHI<5	age, BMI, neck and waist circumference, current cigarette smoking antidepressant,

									antihypertensive, cholesterol-lowering medication
Popovici, 2013 (215)	Cross sectional	14.089	North America/US	General population	Self-report	Binge drinking	Self-report	-	Age, race/ethnicity, years of schooling, current employment and marital status, number of persons in the household, labor market income in the past year, and being born outside the U.S, smoking, diabetes, hypertension, depression, panic disorder, psychological or emotional abuse
Shamsuzzaman,2014 (223)	Case-Control	54	North America/US	sleep laboratory patients	Self-report	Drinks/week	polysomnography	AHI>=5 vs AHI<5	-
Sharafkhaneh, 2005 (201)	Cross sectional	3.647.328	North America/US	General population	ICD 9 codes	Alcohol dependence	ICD 9 codes	-	age, sex, and ethnicity
Sharma, 2006 (199)	Cross sectional	2.150	Asia/India	General population	Self-report	Habitual drinking (>100gr/day)	Polysomnography	AHI>=5 vs AHI<5	-

						yes vs no habitual			
Simpson, 2015 (224)	Case-control	4271	Oceania/Australia	Cases form sleep study/Controls from population	Self-report	Grams/week	polysomnography	AHI>=15 vs AHI<15	-
Udwadi, 2003 (217)	Cross-sectional	250	Asia/India	General population	Self-report	Habitual vs no habitual drinking	Polysomnography	AHI>=5 vs AHI<5	-
Wetter, 2004 (227)	Cohort	811	North America/US	General population	Self-report	Drinks/week	Polysomnography	AHI>=5 vs AHI<5	-
Worsnop 1998 (225)	Case control	25	Oceania/Australia	General population	Self-report	-	polysomnography	AHI	-
Yaggi, 2005 (216)	Cross sectional	1022	North America/US	Middle-aged population from sleep centre	Self-report	Current vs no current alcohol	polysomnography	AHI>=5 vs AHI<5	-
Zenda, 2014 (218)	Cross sectional	243	Asia/Japan	General population	Self-report	Alcohol yes (150grams/week) vs alcohol no	Polysomnography	AHI>=5 vs AHI<5	-

***quality assessment not performed for studies only published in abstract form**

Table 4. 2 Critical appraisal of included studies using Newcastle Ottawa scale

Study, Year	Stars number		
	Selection †	Comparability ‡	Exposure §
Baik, 2014 (124)	3	1	1
Coughlin, 2004 (200)	2	0	1
Enright, 2001 (202)	2	1	2
Fredheim, 2011 (205)	1	0	2
Gilat, 2014 (219)	3	1	1
Heiskel, 2002 (220)	2	0	2
Hussain, 2009 (203)	1	1	2
Hwang, 2010 (207)	1	0	1
Jennum, 1994 (198)	2	0	2
K.Kang, 2013 (221)	3	0	2
K.Kang, 2014 (209)	1	2	2
Kang, 2014 (208)	1	0	2
Kim, 2006 (204)	1	2	1
Marshall, 2008 (212)	2	0	1
McArdle, 2006 (222)	3	1	1
Mc Cague, 2014* (211)	-	-	-
Ngahane,2010 (210)	-	-	-
Nieto, 2000 (206)	2	0	2
Pan, 2014 (213)	1	1	2
Peppard, 2000 (214)	2	0	3
Peppard, 2006 (226)	2	2	2
Popovici, 2013 (215)	1	0	1
Shamsuzzaman,2014 (223)	3	0	1
Sharafkhaneh, 2005 (201)	2	1	2
Sharma, 2006 (199)	2	0	2
Simpson, 2015 (224)	2	0	0
Udwadi, 2003 (217)	1	0	2
Wetter, 2004 (227)	2	0	1
Worsnop 1998 (225)	3	0	1
Yaggi, 2005 (216)	1	0	2
Zenda, 2014 (218)	2	0	1

***Abstract only available-not quality assessment**

† Maximum 4 stars.

‡ Maximum 2 stars.

§ Maximum 3 stars.

4.3.2 Meta-analysis findings

A pooled analysis of the 21 studies from which relative risks could be estimated found the overall risk of OSA to be increased by 25% in people who consumed alcohol at all, or in higher amounts, than those who consumed no, or lower amounts of alcohol, respectively (pooled RR 1.25, 95% CI 1.13 to 1.38, I^2=82%; Figure 3.2). Evidence of publication bias was detected in the meta-analysis of 21 studies (Egger's test, p =0.001, Figure 3.3). A stratified analysis based on the effect measure used found very similar results for studies reporting ORs (1.26, 95% CI 1.04 to 1.53, I^2=79, 14 studies) and those reported risk ratios (1.27, 95% CI 1.08 to 1.49, I^2=86%, 7 studies).

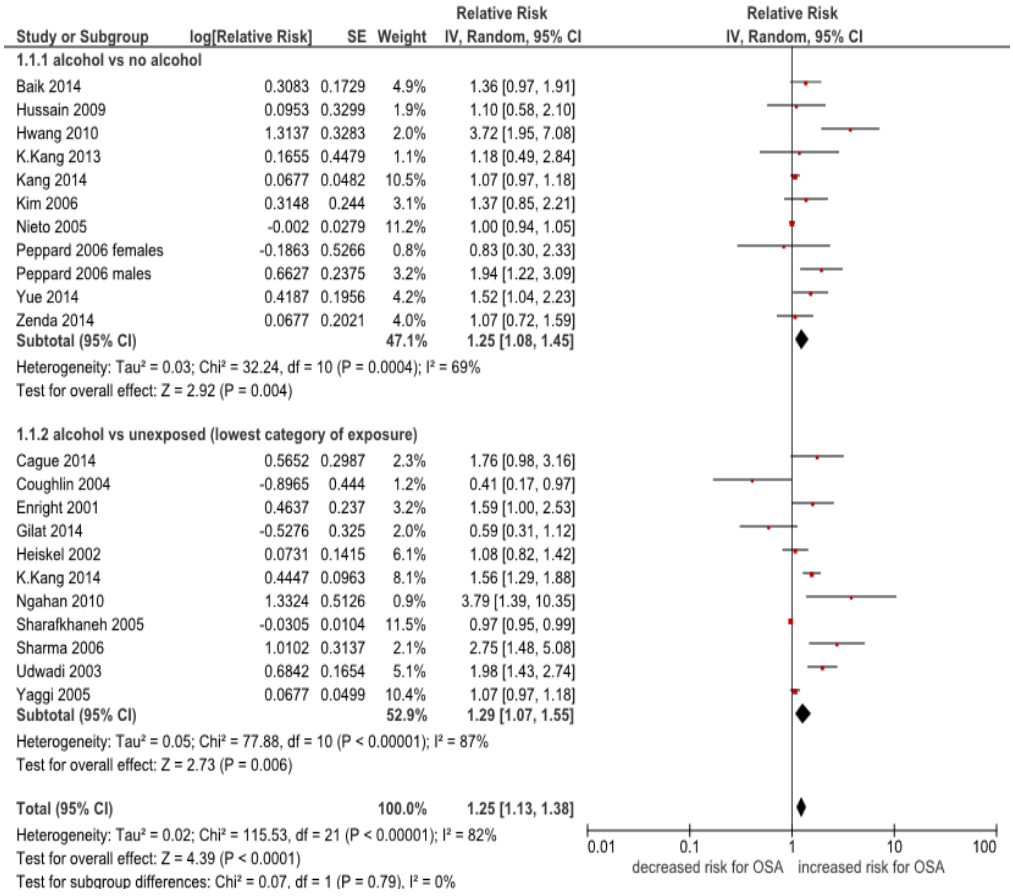


Figure 4. 2 Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of OSA

*A pooled analysis of 22 comparisons from 21 studies; one study reported estimates separately for men and women [13]

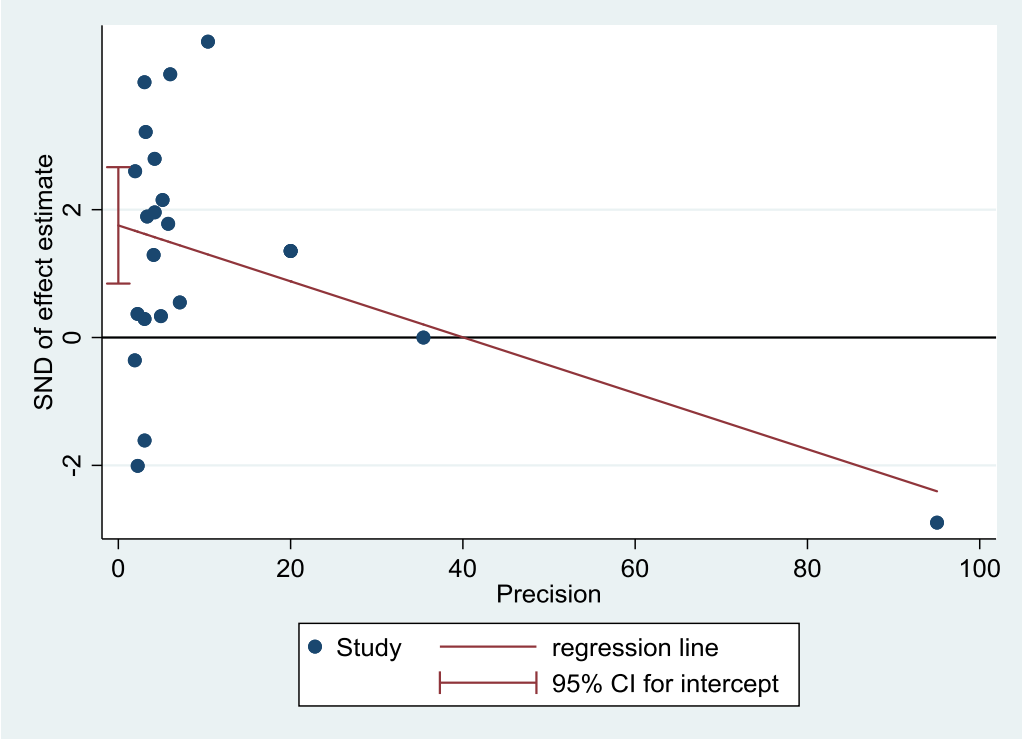


Figure 4. 3 Egger's plot for the assessment of publication bias

A further eight studies presented average levels of consumption of alcohol in people with and without OSA (198, 205, 212, 214, 222-224, 227). A meta-analysis of these studies found that people with OSA consumed, on average, approximately 2 units alcohol per week more than people without OSA (pooled mean difference 1.93, 95% CI -2.62 to 6.49, I^2=66%, Figure 3.4); however, the effect was not significant (p=0.41). Data from the remaining two studies (215, 225) were reported in insufficient detail for inclusion in either of the above meta-analyses: one of these studies found a 9% increased risk of OSA in those who consumed alcohol compared to those with no alcohol consumption (215) while the other reported no significant association (p=0.82) (225).

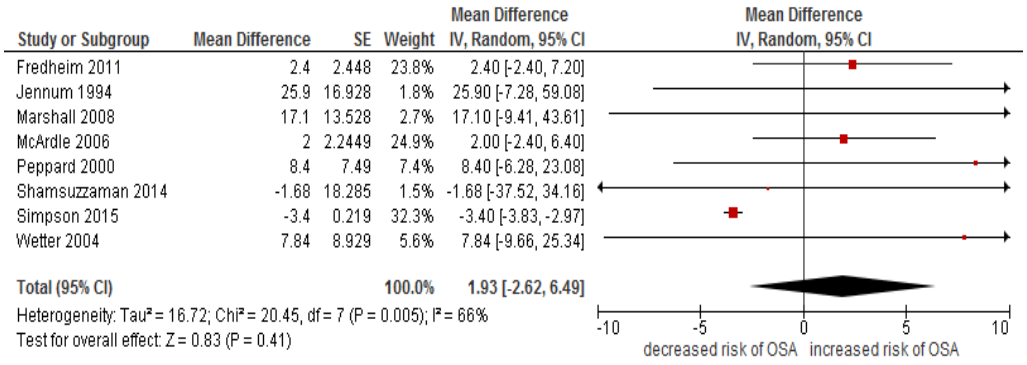


Figure 4. 4 Forest plot of the association between levels of alcohol consumption in people with and without OSA

Among the 21 studies included in the pooled analysis of relative risks a sensitivity analysis showed that relative to people who did not consume any alcohol, those who consumed alcohol had 25% higher risk in OSA (pooled RR 1.25, 95%CI 1.08 to 1.45, I^2=69%, 10 studies). However, in studies comparing any alcohol intake to low intake the risk of OSA was increased by 29% (pooled RR 1.29, 95%CI 1.07 to 1.55, I^2=87%, 11 studies) (Figure 3.2). A further sensitivity analysis restricted to the four studies which provided BMI-adjusted estimates (124, 203, 204, 226) found similar results to the main analysis, with a 41% increased risk of OSA in people who consume alcohol at all or in higher amounts (pooled RR 1.41, 95% CI 1.13 to 1.75, I^2=0%, 4 studies). However, studies which provided smoking-adjusted estimates (124, 203, 204, 226) found a marginally larger magnitude of effect compared to the main analysis (pooled RR 1.56, 95% CI 1.38 to 1.76, I^2=0%, 4 studies).

4.3.3 Subgroup analyses

Subgroup analyses of the 21 studies found that methodological quality (high versus low; p =0.69), study design (cross-sectional, case-control, longitudinal/cohort; p=0.25), adjustment for confounders (p=0.40), level of alcohol consumption (excessive vs moderate/low; p=0.65) and ascertainment of sleep apnoea (subjective vs objective; p=0.26) did not explain high level of heterogeneity. However, regarding the year of study publication, more recent studies which published from 2006-2015

showed higher risk of sleep apnea (45% increased risk) compared to studies published from 1995-2005 (7% risk) (Figure 3.5). Moreover, the geographic location of the study was found to explain heterogeneity between the studies, with a quantitative interaction seen between High and Low/Middle Income Countries (p-value for subgroup differences = 0.01, Figure 4) relating to a larger effect size in Low/Middle Income Countries (pooled RR 1.47, 95% CI: 1.17-1.85) compared to High Income Countries (pooled RR 1.07, 95% CI: 0.98-1.17) (Figure 3.6). The full information for the exploration of heterogeneity is given in Table 3.3.

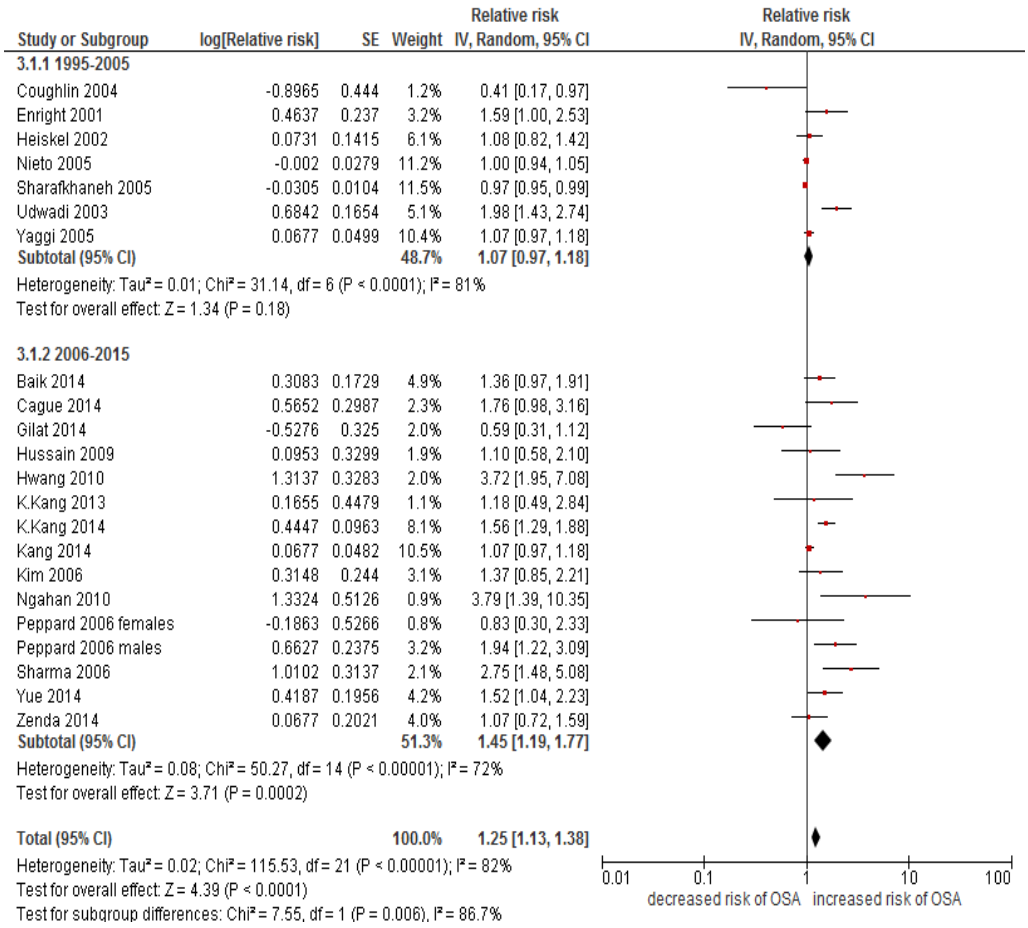


Figure 4.5 Forest plot of alcohol consumption and the risk of OSA; subgroup analysis based on publication year

Table 4. 3 Exploration of heterogeneity between alcohol consumption and risk of OSA

Factor	Number of studies	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	21	1.25 (1.13-1.38)	82%	-
Study design				
Cross-sectional	15	1.27 (1.15, 1.42)	85%	0.25
Case control	5	0.93 (0.65 – 1.34)	60%	
Cohort	1	1.45 (0.65 – 3.19)	54%	
Methodological quality				0.69
Higher quality	1	1.45(0.65-3.19)	54%	
Lower quality	20	1.23(1.11-1.36)	82%	
Ascertainment of sleep apnoea				0.26
Objective	14	1.16 (1.06-1.28)	81%	
Subjective	7	1.39 (1.03-1.88)	85%	
Level of alcohol consumption				0.65
Excessive	8	1.33(1.03-1.73)	85%	
Low/moderate	13	1.24(1.09-1.43)	77%	
Alcohol ascertainment				0.75
Alcohol vs no alcohol	9	1.25(1.08-1.45)	69%	
Alcohol vs unexposed (lowest category of exposure)	12	1.30 (1.09-1.55)	86%	
Geographic location				0.01
High income countries	9	1.07(0.98-1.17)	70%	
Low/middle income	12	1.47(1.17-1.85)	79%	

countries				
Effect estimate				0.40
Adjusted for confounders	10	1.36(1.08-1.70)	82%	
Unadjusted for confounders	11	1.21(1.04-1.40)	81%	
Publication year				0.006
19955-2005	7	1.07 [0.97, 1.18]	81%	
2006-2015	14	1.45 [1.19, 1.77]	72%	

There were insufficient data to combine study results in an exposure-response analysis, but one study estimated that for every drink consumed per day there was a 25% increased odds of at least mild sleep-disordered breathing in men (p for trend=0.006) (226). In contrast, in women, there was no significant exposure-response relation (p for trend=0.73).

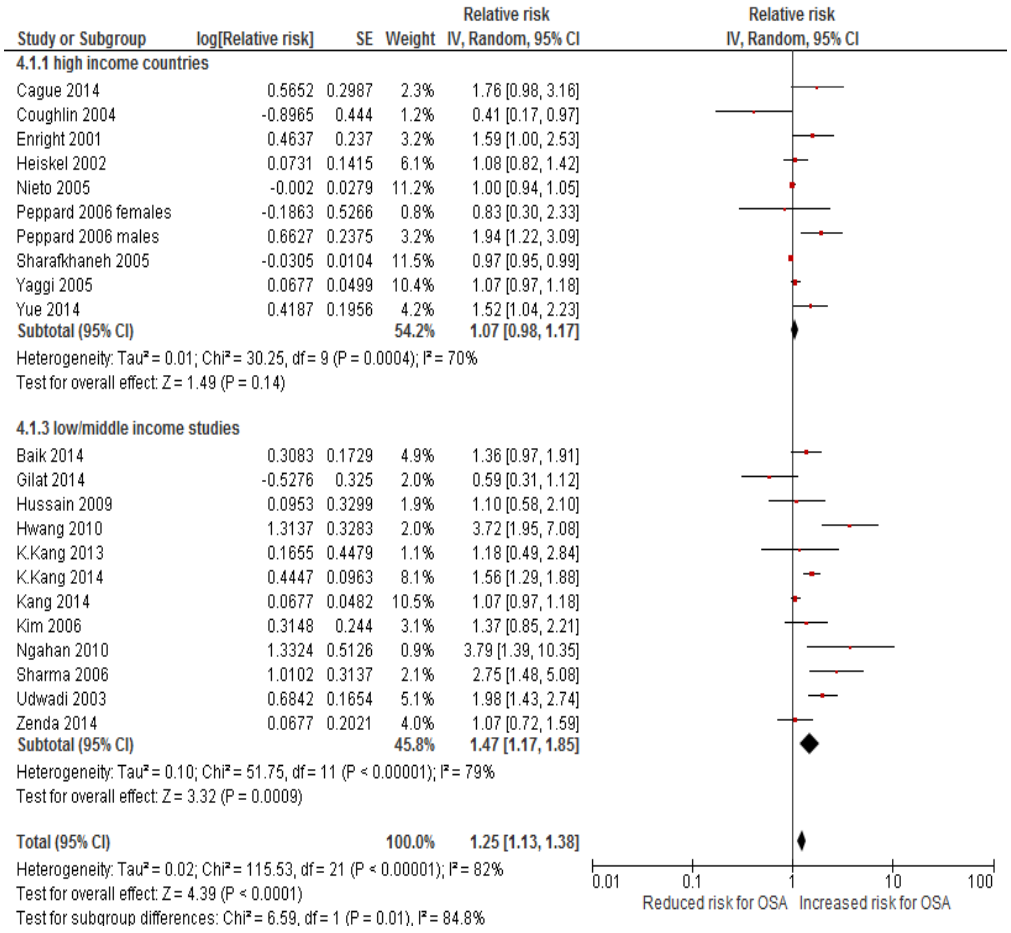


Figure 4. 6 Forest plot of alcohol consumption and the risk of OSA; subgroup analysis based on high vs low/middle income countries

4.4 Discussion

Alcohol consumption is associated with a range of important health consequences, and a history of alcohol consumption is common among people with OSA. It is plausible that alcohol increases the risk of OSA because alcohol consumption reduces genioglossal muscle tone, predisposing to upper airway collapse (228) and generally increasing upper airway resistance (229). High alcohol intakes also contribute to dietary energy intake, and hence in some cases a high body mass index, which is itself a risk factor for OSA (123). However, the extensive scientific literature of studies of the association between OSA and alcohol intake provides mixed evidence on the qualitative and quantitative nature of this association, making systematic review and meta-analysis likely to be particularly helpful in this context.

This review combines all available worldwide literature assessing the association between alcohol consumption and the risk of OSA, and demonstrates that people who consume alcohol, either in relation to no exposure or in those with relatively high intakes compared to those with low intakes, are approximately 25% more likely to have OSA.

Inevitably, our review findings are limited by publication bias and the low methodologic quality of the included studies, but they at least provide a comprehensive and systematic overview and synthesis of the available worldwide evidence. Another limitation of our study is the fact that only 13 of the 31 included studies adjusted for confounders; however, no appreciable difference was seen between studies which did and did not adjust for confounders. Our analysis also highlighted a high level of heterogeneity between study findings, which subgroup analysis indicated was related to economic development, with the association between alcohol and OSA appearing to be stronger in countries of low or middle income. The explanation for this finding is not clear but confounding by obesity or other lifestyle factors is a potential factor since alcohol consumption is more likely to be limited to the most affluent in low- and middle-income settings. Although we expected the

association between alcohol and OSA to be confounded by obesity, our restricted analysis of studies presenting BMI-adjusted estimates confirmed an independent effect of alcohol which was in fact slightly stronger than the unadjusted estimate, indicating that obesity is not the main mechanism responsible for the higher risk of OSA among those who consume alcohol.

A previous narrative review published in 2005 also found that sleep-disordered breathing was likely to be more common in relation to alcohol consumption, with heavy drinkers being at particularly high risk of OSA (194). However, that study also highlighted that whilst 2 or 3 drinks before bedtime can promote sleep, this effect is not sustained after a few days of regular consumption. With more sustained regular alcohol intake, and with alcohol intake earlier in the day, alcohol consumption can be associated with insomnia (194). It therefore appears likely that the timing and regularity of alcohol consumption are both important to the effect of alcohol on OSA since airway muscle relaxation and reduced sensitivity to apnoea are both likely to be greatest when alcohol levels are rising, as for example after bedtime consumption (196, 197). Our data do not enable us to estimate the nature of the exposure-response relation for either alcohol at bedtime, or alcohol in general (data being limited to single study (226)), on the occurrence or severity of OSA, but these questions could in principle be resolved by randomized trials. We also searched for randomized controlled trials on alcohol and sleep apnoea but found none. Therefore, there is a need for the conduction of future clinical trials in order to address this important question.

Our findings thus provide confirmation that alcohol consumption may cause or exacerbate OSA, adding further evidence that reducing alcohol intake is of potential therapeutic and preventive value in this condition. However, the wider literature suggests that this may especially be the case with alcohol consumed shortly before bedtime. Whilst our findings do not confirm or refute the causality of this

association, health care professionals might consider advising against bedtime alcohol among people with, or at risk of, OSA.

5 Chapter 5

Alcohol consumption and risk of community-acquired pneumonia. A systematic review and meta-analysis

This chapter presents a systematic review and meta-analysis of observational studies assessing the effect of alcohol on community-acquired pneumonia. Also, in this chapter, a dose-response analysis between alcohol and CAP will be presented. This chapter starts with a discussion of the possible mechanisms alcohol influence CAP. Then the methodology is presented. Also, the result section is presented covering all the study characteristics of the included studies, the procedure of the study selection, the quality assessment scores and also the results of the meta-analysis. Also, the discussion section follows which includes a summary of the main findings, a presentation of the strengths and limitations and a comparison of the findings with other studies.

5.1 Introduction

Alcohol consumption is a potential risk factor for pneumonia. Alcohol can increase the host susceptibility to infectious diseases and especially to bacterial pneumonia (230). There are several possible mechanisms to explain the observation that alcohol consumption increases the risk of pneumonia, including the sedative properties of alcohol which can reduce oropharyngeal tone, leading to an increased risk of aspiration of microbes (230). Also, the acute and chronic ethanol abuse can cause damage in cellular components of innate and the adaptive immune response (230). Specifically, high levels of alcohol intake can modify alveolar macrophage function, hence diminishing pulmonary defence against infection (231, 232). Moreover, high alcohol consumption is often associated with malnutrition (233) as it interacts with nutrient metabolism and utilization (234), resulting in the impairment of immunity and increases CAP risk.

To date, however, evidence on the association between alcohol consumption and CAP is limited. A systematic review and meta-analysis published in 2010, using evidence published before August 2009, found a 6% increase in the risk of pneumonia per standard drink of 12 g of pure alcohol per day, but the number of studies reviewed (five) was small (59). However, there is an increase in the interest on this topic and also several studies have been published in the past nine years. For this reason, a systematic review and meta-analysis, to quantify the association between alcohol consumption and risk of CAP was carried out.

5.2 Methods

5.2.1 Inclusion criteria

All studies assessed the effect of alcohol on CAP were included, and where possible, we also analyzed the association between alcohol consumption and the occurrence of pneumonia due to specific organisms (for example, *Streptococcus pneumonia*).

5.2.2 Exposure ascertainment

Alcohol consumption defined either by self-report (interview or questionnaire) or using medical records. Also, alcohol use corresponded to drinking levels (low, moderate, heavy, and alcoholism) or to frequency measures (grams/units/drinks per day/week).

5.2.3 Outcome ascertainment

Community-acquired pneumonia diagnosis based: on a clinical diagnosis (chest x-ray, blood test), physician diagnosis and medical records including ICD codes or self-report.

5.2.4 Search strategy

The search strategy is presented in Chapter 2. The Medline search filters were the following: [exp Alcohol-Related Disorders/ OR Alcohol Drinking/ OR (alcohol adj3 (drink$ OR intoxicat$ OR use$ OR abus$ OR misus$ OR risk$ OR consum$ OR withdraw$ OR detox$ OR treat$ OR therap$ OR excess$ OR reduc$ OR cessation OR intervention$)).tw. OR (drink$ adj3 (excess OR heavy OR heavily OR harm OR harmful OR hazard$ OR binge OR problem$)).tw. OR alcoholic$.tw.] AND [exp Respiratory Tract Infections/ OR (acute respiratory infection*.tw.) OR (lower respiratory infection*.tw.) OR (lower respiratory tract infection*.tw.) OR exp Pneumonia/ OR (pneumon* OR bronchopneumon* OR pleuropneumon*).tw. OR exp Bronchitis/ OR (bronchit* OR bronchiolit*).tw]. The full search strategy is presented in Appendix 2.

5.2.5 Data extraction

The data extractions are presented in Chapter 2.

5.2.6 Quality assessment

The quality assessment of the primary studies is presented in Chapter 2.

5.2.7 Statistical analysis

The statistical analysis is presented in Chapter 2.

Further subgroup analyses were performed according to CAP diagnosis (clinical diagnosis vs death records) and measure of effect estimated (ORs vs RRs). Sensitivity analyses restricted to studies provided smoking- adjusted estimates and age- adjusted estimates were also conducted.

5.2.8 Dose-response assessment

The methodology used to assess the doses response relationship is presented in Chapter 2, on Section 2.8.

5.3 Results

The searches identified a total of 4589 studies published between December 1985 and December 2017, of which 17 were eligible for inclusion in the systematic review (Figure 4.1). The characteristics of the 17 included studies are presented in Table 4.1. A total population of 287,184 people was included in our review. Seven studies used a cohort design (235-241), nine used a case-control design (242-250) and one used a cross-sectional design(251). Eight studies were conducted in America (236, 240, 241, 246, 248-251); five in Europe (238, 242, 244, 245, 247), two in Asia (235, 237) and two in Australia (239, 243). Three studies reported separate estimates of the association between alcohol and CAP for men and women (236, 242, 245), and 12 studies reported effect estimates adjusted for confounders (235-237, 240, 242, 244, 245, 247-251).

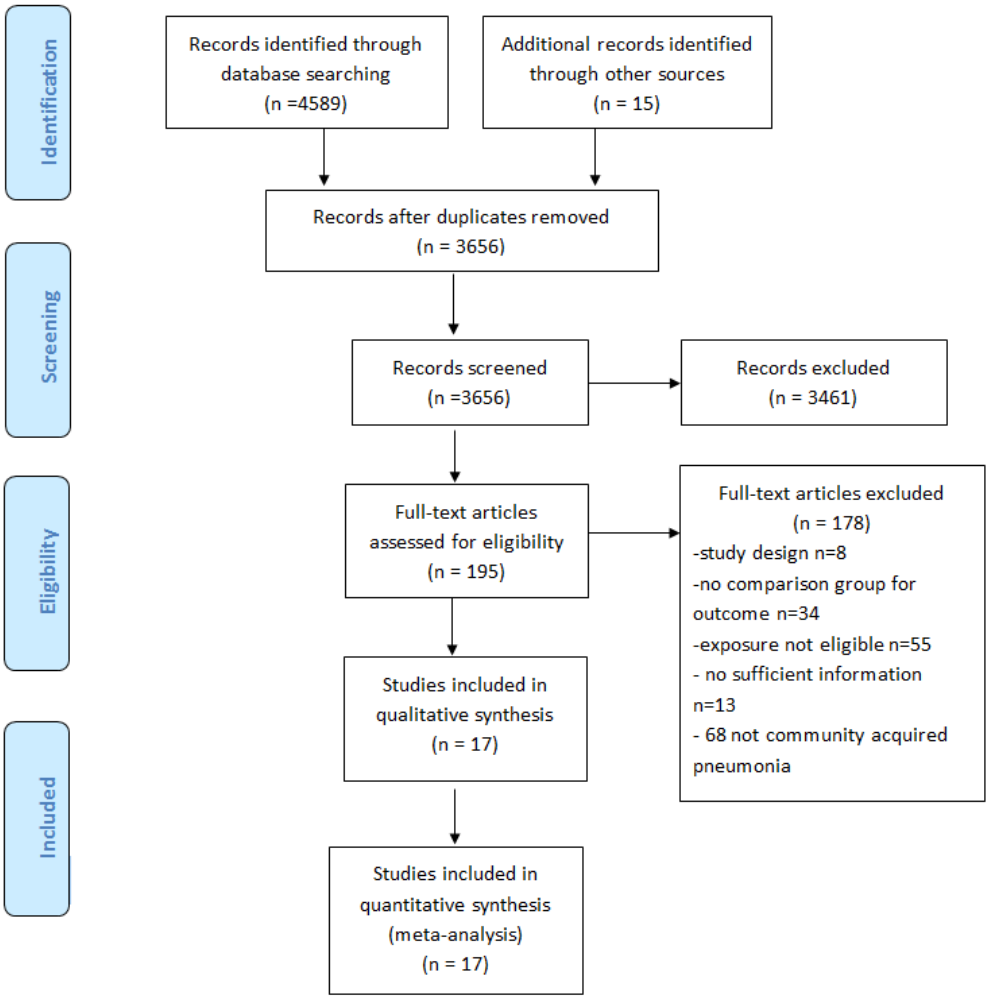


Figure 5. 1 Flow diagram

The majority of studies assessed alcohol consumption by self-report, based either on a standardized questionnaire or on an interview while five studies used reported intake data from medical records (238, 241, 246, 248, 249). The reference group for nine studies comprised people who never consumed alcohol (235-237, 239, 243, 245, 247, 249, 250); whereas the reference group for the remaining eight studies comprised people who consumed the lowest quantity of alcohol(238, 240-242, 244, 246, 248, 251).

Seven studies ascertained CAP using a clinical diagnosis; and five of these used chest x-ray radiography (243-245, 247, 250). A further seven studies ascertained CAP using ICD codes (235, 237, 239, 241,

242, 248) and medical records (248) and two studies used self-report interview (240, 251). The remaining study ascertained CAP via physician diagnosis using medical records (236).

The methodological quality of the case-control, cohort, and cross-sectional studies ranged from five to eight, with a median score of six. Ten studies were deemed to be of high quality (≥6 score) (235, 236, 238-240, 242, 244, 247-249); whereas lower scores tended to arise from failure to adjust for confounders, or using self-reported methods to ascertain alcohol consumption. The results of the quality assessment are presented in detail in Table 4.2.

Table 5. 1 Characteristics of the included studies

Study & Year	Study design	Geographical location	Alcohol ascertainment	Alcohol definition	CAP ascertainment	Confounders adjusted	Effect estimate
Almirall 1999 (247)	Case-control	Europe/Spain	Self-report/ questionnaire	Quartiles of alcohol intake >35.3 versus 0 (grams/day)	Clinically suspected and chest radiography	Age, sex, municipality	Odds ratio
Almirall 2008 (245)	Case control	Europe/Spain	Self-report /questionnaire	Quartiles of alcohol intake(grams/day) Men: >80 versus 0 Women: >40 versus 0	Clinically suspected and chest radiography	Age, sex, primary care practice	Odds ratio
Baik 2001 (236)	Cohort	America/US	Self-report/questionnaire	Men: >30 versus never Women: >30 versus never (Grams/day)	Physician diagnosis/Medical records	Age, smoking status, BMI, quintile of metabolic equivalent	Relative risk
Breitling 2016 (240)	Cohort	America/US	Self-report/questionnaire	Quartiles of alcohol intake Men: >20 versus ≤ 20 Women: >10 versus 0 (grams/day)	Self-report questionnaire	Age, sex, smoking, BMI, diabetes mellitus, stroke, congestive heart failure, cancer	Relative risk
Clough 2003 (243)	Case control	Australia	Self-report/interview	Alcohol yes versus alcohol no	Clinically suspected/ X-ray findings	-*	Odds ratio
Fernandez-Sola 1995 (244)	Case control	Europe/Spain	Self-report/ Interview & questionnaire	High intake (men: >100g, women:>80g) versus lower intake (grams/day 2 years before submission)	Clinically suspected/ Chest X-ray	Liver cirrhosis, smoking, COPD, diabetes, heart failure, malnutrition	Odds ratio
Innoue 2007 (237)	Cohort	Asia/Japan	Self-report/questionnaire	Current versus never drinking	Mortality ICD codes	Age and history of diabetes mellitus	Hazard ratio
Jackson 2009 (248)	Case-control	America/US	Medical records	Current alcoholism vs no alcoholism	ICD9 codes	Age, sex, pneumonia-free person-time	Odds ratio
Koivula 1994(238)	Cohort	Europe/Finland	Medical records	Alcoholism vs no alcoholism	Medical records	Age, sex, chronic conditions	Relative risk
Lipsky 1986	Case-control	America/US	Medical records	Heavy versus moderate (drinks/day)	Clinically suspected	-*	Relative risk

(246)							
Loeb 2009 (250)	Case-control	America/US	Self-report /questionnaire	Alcohol yes (previous 12 months) versus alcohol no(grams/month)	Clinically suspected and chest radiography	Multivitamins, smoking, history of gas and fumes exposure	Odds ratio
Phung 2013(239)	Cohort	Australia	Self-report/questionnaire	Alcohol yes versus alcohol no	Hospital records - ICD codes	-*	Hazard ratio
Quraishi 2013(251)	Cross sectional	America/US	Self-report/interview	alcohol consumption (≤30 versus >30 drinks per month)	Self-report interview	-*	Relative risk
Shen 2013 (235)	Cohort	Asia/China	Self-report/interview	Excessive versus never drinkers (units/week)	Mortality ICD codes	Age, Sex, education, housing, monthly expenditure, smoking, BMI, exercise, health status	Hazard ratio
Watt 2007 (249)	Case control	America/US	Medical records	Alcoholism/ alcohol use versus no use of alcohol	Clinically suspected Pneumococcal isolation in patient from sterile body fluid	Smoking, BMI, electricity/ indoor plumbing in home, living with unvaccinated child, unemployed, wood/coal, smoke	Odds ratio
Yende 2013 (241)	Cohort	America/US	Medical records	Alcohol abuse vs no alcohol abuse	ICD-9 codes	-*	Relative risk
Zaridze 2009 (242)	Case control	Europe/Russia	Self-report interview	≥3bottles (per week) versus <=0·5 bottles of vodka	ICD codes Death records	Age, city, and smoking	Relative risk

*** Crude analysis reported**

Table 5. 2 Quality assessment using Newcastle Ottawa scale

Study, Year	Stars number			
	Selection †	Comparability ‡	Exposure §	Overall
Almirall 1999 (247)	4	1	1	6/9
Almirall 2008 (245)	3	1	1	5/9
Baik 2001 (236)	4	2	2	8/9
Breitling 2016 (240)	3	2	2	5/9
Clough 2003 (243)	4	0	1	5/9
Fernandez-Sola 1995 (244)	3	2	1	6/9
Innoue 2007 (237)	3	1	1	5/9
Jackson 2009 (248)	4	1	1	6/9
Koivula 1994(238)	4	1	3	8/9
Lipsky 1986 (246)	3	0	2	5/9
Loeb 2009 (250)	2	2	1	5/9
Phung 2013(239)	3	0	3	6/9
Quraishi 2013(251)	1	0	1	2/6
Shen 2013 (235)	3	2	3	8/9
Watt 2007 (249)	4	2	1	7/9
Yende 2013 (241)	4	0	2	6/9
Zaridze 2009 (242)	3	2	1	6/9

5.3.1 Meta-analysis findings

Fourteen of the 17 included studies provided data from which pooled relative risks could be estimated, and a pooled analysis of these studies found the risk of CAP to be significantly increased in people who consumed alcohol at all, or in higher amounts, relative to those who consumed no, or lower amounts of alcohol respectively (pooled RR= 1.83, 95% CI 1.30 to 2.57, I^2= 91%, Figure 4.2).

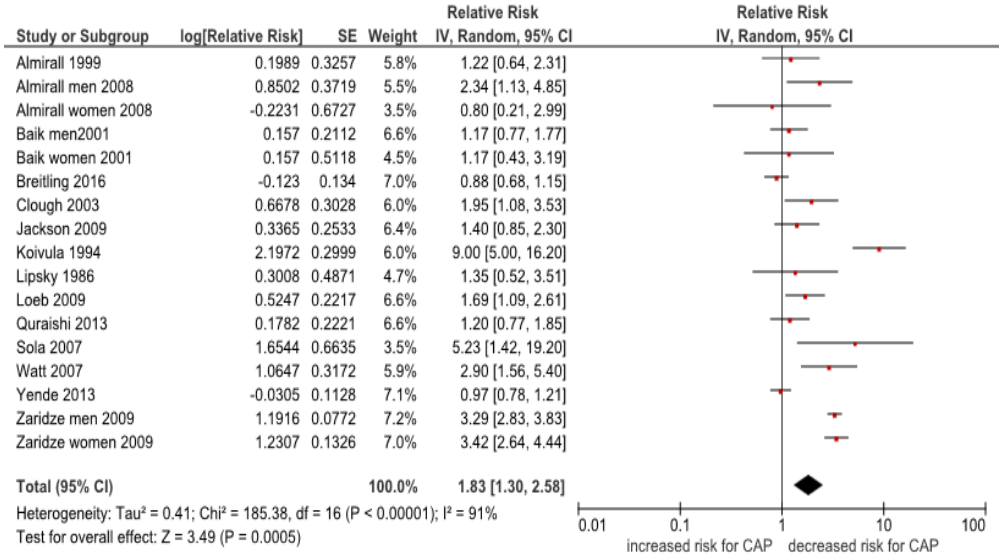


Figure 5. 2 Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of CAP

There was no evidence of publication bias detected visually via a funnel plot (Figure 4.3), and statistically via Egger's asymmetry test (p= 0.596, Figure 4.4).

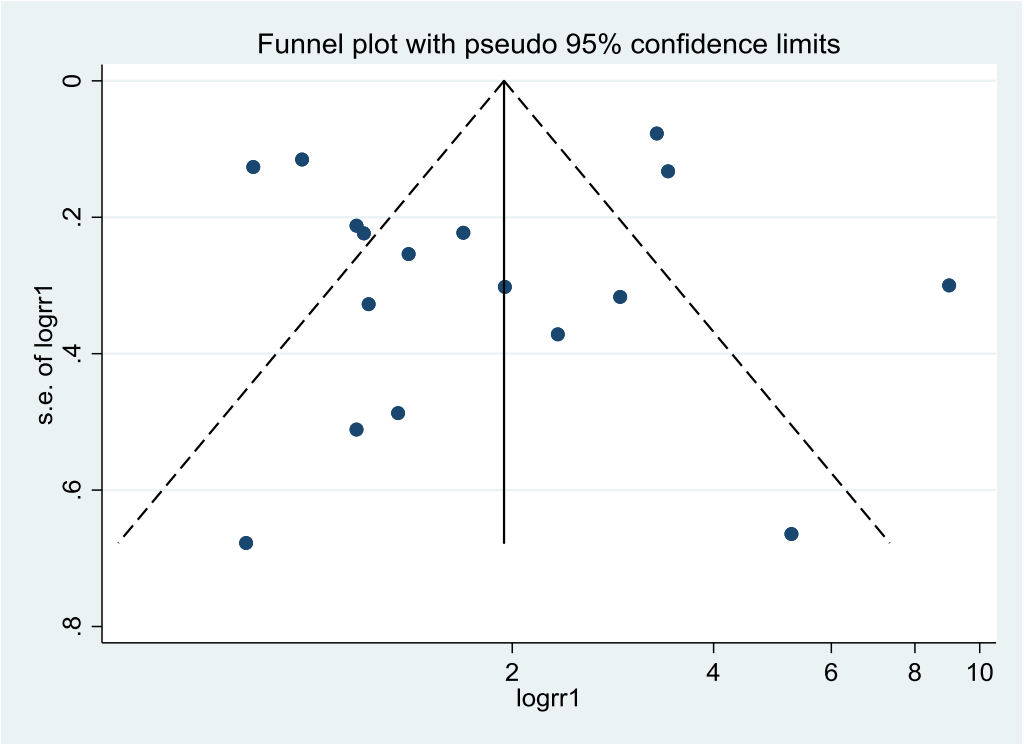


Figure 5. 3 Funnel plot of alcohol vs no alcohol or lowest exposure to alcohol for studies presented the results as RRs

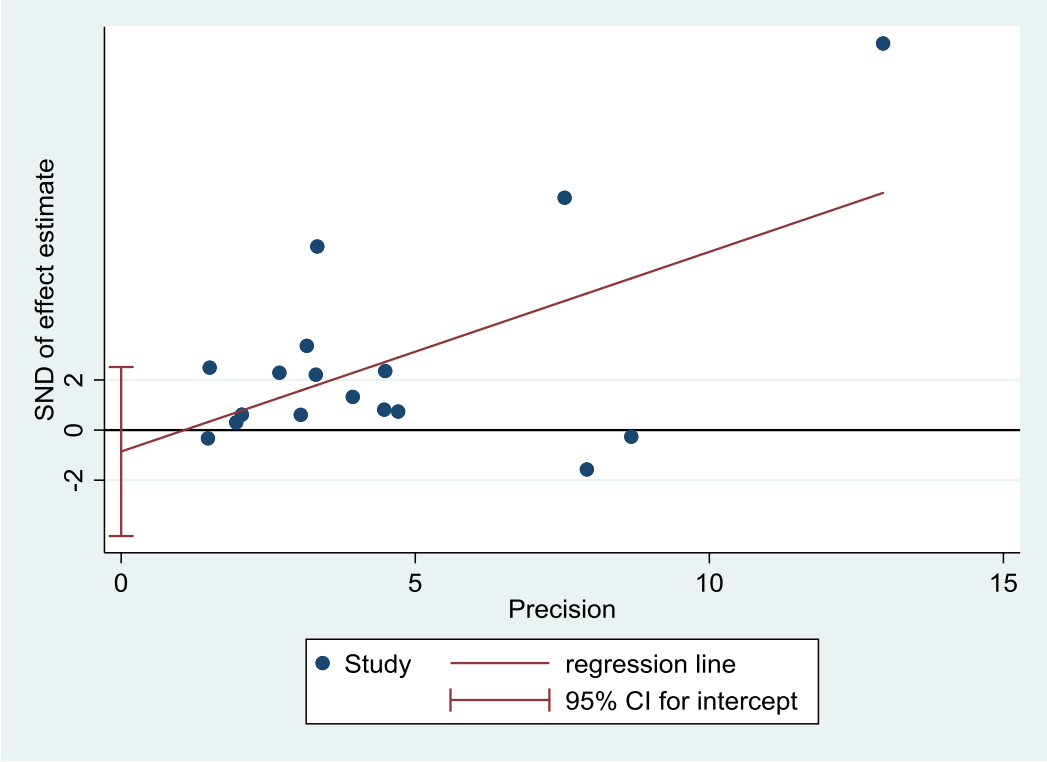


Figure 5. 4 Egger's plot for the assessment of publication bias

Subgroup analyses exploring the reason for heterogeneity in the meta-analysis of these 14 studies are presented in Table 4.3. Heterogeneity was not explained by study design (case-control, longitudinal/cohort, cross-sectional; p for subgroup differences=0.07), methodological quality (high versus low; p=0.09) or gender (male versus female; p=0.74). However, significant differences were found according to adjustment for confounders (adjusted versus unadjusted; p=0.03), continent of study (America, Europe, Australia; p=0.0003), and ascertainment of CAP (clinical diagnosis vs death records; p=0.002). Furthermore, no difference was found for studies presented OR estimates compared to studies presented RR estimates (p for subgroup differences=1.00).

Additionally, no significant differences were found by the definition of the reference group for alcohol consumption (p=0.39; Figure 4.5). However, high heterogeneity (I^2=95%) was detected within the second subgrouping which used the lowest category of exposure as the reference group, where the following definitions were used: no alcoholism (238, 248),no alcohol abuse (241), moderate drinking (246), ≤30 drinks/month(251), ≤ 0.5 bottles of vodka(242); <100gr/day for men and <80 gr/day for women (244), and <20 gr/day and <10 gr/day for men and women respectively (240); however, the gradient of exposure did not seem to be related to the magnitude of effect.

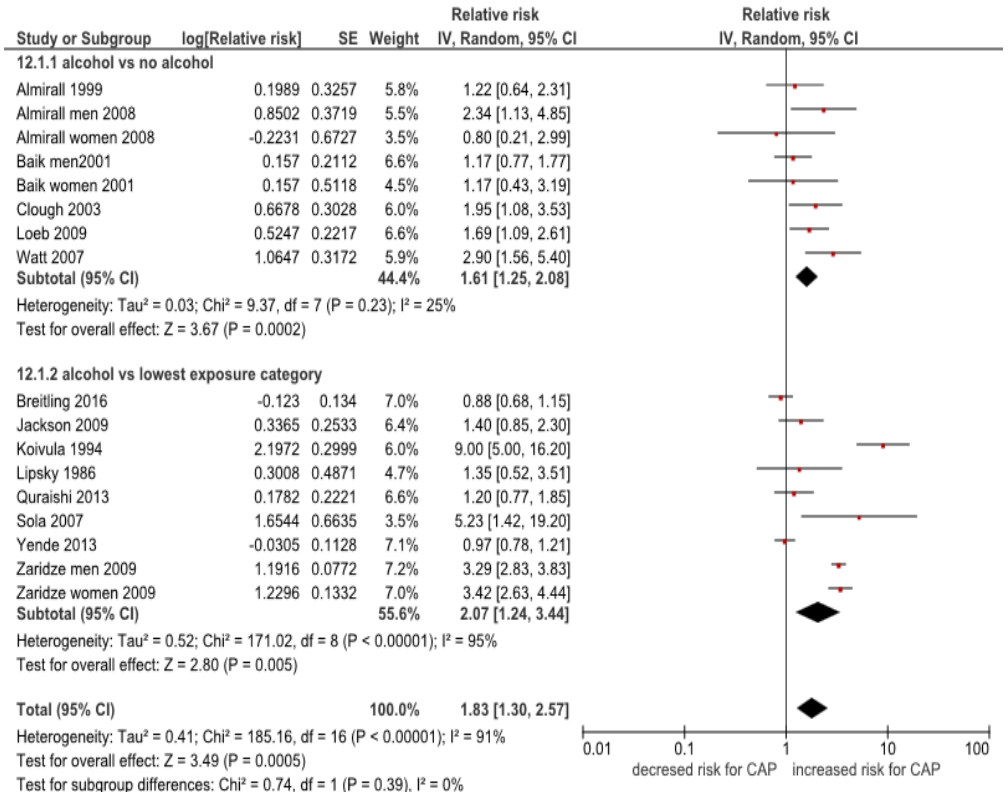


Figure 5. 5 Forest plot of the association between alcohol consumption and the risk of CAP according to reference group for alcohol consumption (lowest exposed category vs no alcohol consumption)

Table 5. 3 Exploration of heterogeneity for alcohol and CAP risk

Factor	Number of studies	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	14	1.83 [1.30, 2.58]	91%	-
Study design				0.07
Case control	9	2.16 [1.64, 2.85]	71%	
Cohort	4	1.56 [0.84, 2.91]	92%	
Cross sectional	1	1.20 [0.77, 1.85]	-	
Methodological quality				0.09
High quality (>6)	8	2.20 [1.40, 3.47]	93%	
Low quality (<6)	6	1.36 [0.99, 1.87]	57%	
Alcohol consumption				0.39
Alcohol vs no alcohol	6	1.61 [1.25, 2.08]	25%	
Alcohol vs lowest category of exposure	6	2.07 [1.24, 3.44]	95%	
CAP ascertainment				0.002
Clinical diagnosis	11	1.81[1.25, 2.61]	81%	
Death records	1	3.33 [2·92, 3.79]	0%	
Geographic location				0.0003
America	8	1.25 [1.00, 1.56]	56%	
Europe	5	3.03 [2.08, 4.43]	77%	
Australia	1	1.95 [1.08, 3.53]	-	
Effect estimate				0.03
Adjusted for confounders	10	2.05 [1.39, 3.01]	91%	
Unadjusted for confounders	4	1.20 [0.89, 1.62]	41%	
Measure of effect estimate				1.00
ORs	7	1.81 [1.38, 2.36]	25%	
RRs	7	1.81 [1.10, 2.99]	95%	
Sex				0.74
Men	3	2.10 [1.00, 4.41]	91%	
Women	3	1.71 [0.64, 4.57]	0%	

A sensitivity analysis restricted to the six studies which provided smoking-adjusted estimates found a larger magnitude of effect compared to the main analysis (pooled RR= 2.01, 95% CI 1.25 to 3.23, I^2=93%, 6 studies, Figure 4.6). Similarly, the studies provided age-adjusted effect estimated found a risk of 1.90 (pooled RR= 1.90, 95% CI 1.20 to 3.02, I^2=93%, 7 studies, Figure 4.7).

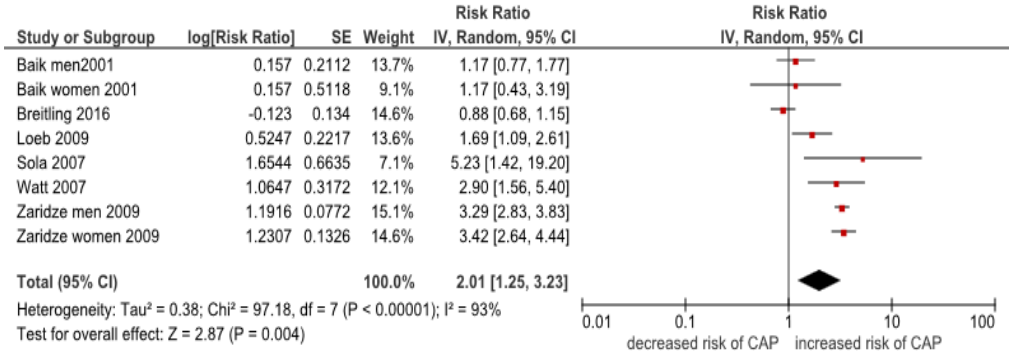


Figure 5. 6 Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of CAP on studies provided smoking adjusted effect estimates

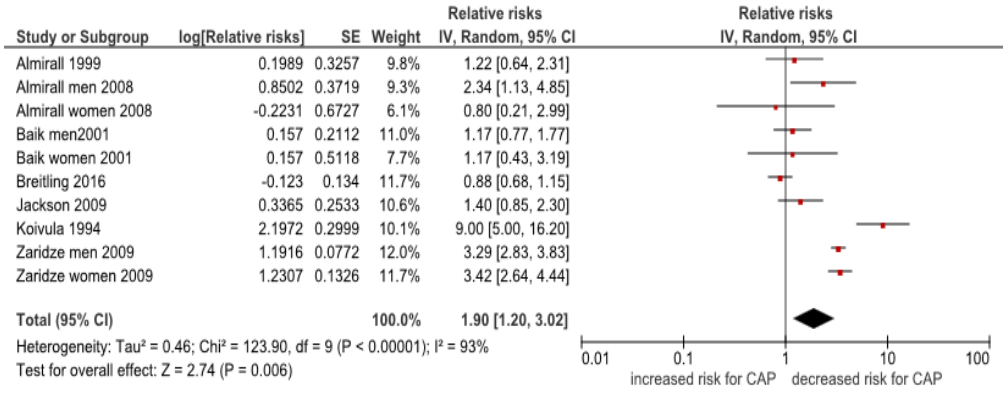


Figure 5. 7 Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of CAP on studies provided age-adjusted effect estimates

The remaining three studies presented effect estimates as hazard ratios (235, 237, 239), and a pooled analysis of these studies estimated a hazard ratio for CAP in relation to alcohol consumption of 0.90 (pooled HR= 0.90, 95%CI: 0.79 to 1.03, I^2=0, 3 studies, Figure 4.8).

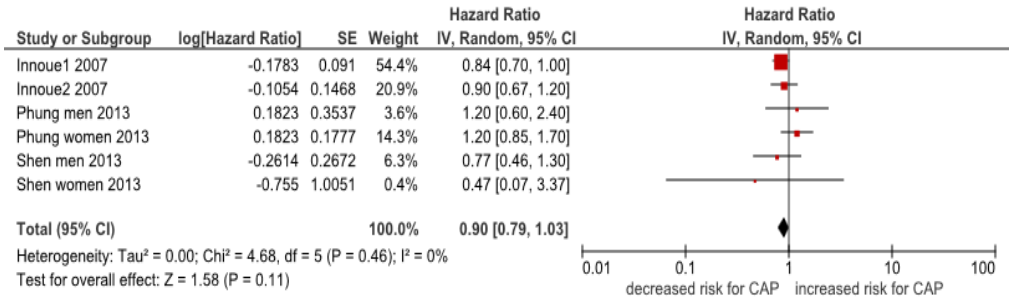


Figure 5. 8 Forest plot of the association between alcohol consumption and the risk of CAP on studies presented HRs estimates

Two studies assessing the effect of alcohol on pneumococcal disease-specific strains of pneumonia were identified (246, 249). A pooled analysis of these studies found that there was more than a doubling of risk of *Streptococcus pneumoniae* CAP in people who consumed alcohol (RR= 2.16, 95% CI 1.05 to 4·48, I^2=42%).

5.3.2 Biological gradient meta-analysis

Five of the included studies provided data enabling a dose-response meta-analysis (236, 242, 243, 245, 247); of which: one used a cohort design (data reported separately for men and women) and four were case-control studies. A pooled analysis of the dose-response data from the cohort study found no significant gradient in the quantity of alcohol associated with the risk of CAP (p for trend=0.136). In contrast, the pooled analysis of the dose-response data from the four case-control studies indicated that there was a significant gradient in the quantity of alcohol associated with an 8% increase in the risk of CAP for every 10-20 grams of pure alcohol consumed per day (equivalent to 1 drinks/day) (pooled RR= 1.08, 95% CI 1.06 to 1.09; p<0.0001; Figure 4.9).

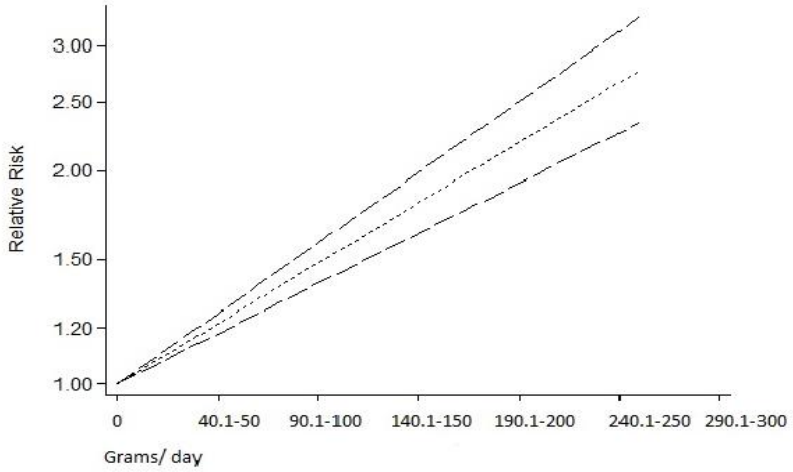


Figure 5. 9 Linear dose–response meta-analysis for the association between alcohol intake categories (g/day) and the risk of CAP

5.4 Discussion

Alcohol consumption is a recognized and avoidable risk factor for a range of diseases and injuries, including neuropsychiatric conditions, gastrointestinal and cardiovascular disease, cancer, suicide and violence (252). To date however the association between alcohol consumption and pneumonia risk has attracted relatively little attention.

5.4.1 Summary of the findings

This meta-analysis of studies published over the past 30 years- demonstrates a clear and statistically significant relation between alcohol consumption and the risk of community-acquired pneumonia. The effect was strong, with a 1.8-fold increase in risk among those who consumed alcohol at all, or in higher amounts, relative to those who consumed no, or lower amounts of alcohol respectively and significantly related to the level of intake, with no evidence of publication bias. The dose-response analysis indicated that consuming drinks that contain 10-20 grams of alcohol per day was linked to an 8% increased risk of acquiring community-acquired pneumonia. Furthermore, the findings of

the subgroup analysis indicated significant differences in the risk of pneumonia according to the continent of the study; with Europe having the highest rate (threefold) for CAP risk.

5.4.2 Strengths and limitations

This study represents a comprehensive review of the global literature with no language restriction, making this analysis the most complete to date, and our findings likely to be generalizable. There was significant heterogeneity between the studies in our analysis, but our subgroup analyses indicate that this arose primarily from the continent in which the study was carried out (America, Europe, Australia); adjustment for confounders; and the ascertainment of CAP (death vs clinical diagnosis). Misclassification bias arising from the inclusion of non-drinkers in the lowest category of alcohol intake in some studies can be another possible limitation in our review but will result in a more conservative estimate of effect. A dose-response relationship was identified. However, the included studies did not report dose-response relations separately for men and women, so we are unable to carry out a comparative analysis. Furthermore, confounding as a result of the existence of other factors that were not usually adjusted for in the included studies (e.g. socioeconomic status, malnutrition) could not be explored.

5.4.3 Comparison with other studies

Our findings extend those of an earlier review and meta-analysis, carried out in 2010 (59). Another review focused on risk factors for invasive pneumococcal diseases indicated an elevated risk for invasive pneumococcal disease due to alcohol consumption in six of the four studies included in the meta-analysis model (253). Likewise, another recent meta-analysis indicated an elevated risk for invasive pneumococcal disease due to alcohol consumption in six of the four studies included in the meta-analysis model (254). Similarly, our separate meta-analysis focused on pneumococcal infections including

two of these studies, due to our eligibility criteria, showed an elevated risk for pneumococcal acquisition.

A previous systematic review and meta-analysis found that people with a daily alcohol consumption of either 24, 60, and 120 grams have a 12 %, 33% and 76 % increased risk of CAP respectively (59). Our dose-response analysis generated a slightly less strong effect, of an 8% increase in risk per 10-20 grams of (pure) alcohol consumed per day.

A general systematic review published by Almirall et al in 2017 (86) focused on risk factors of community-acquired pneumonia, but provided only a narrative summary of findings and stating that no definite conclusion could be drawn. In contrast, our review found evidence of a doubling in the risk of CAP in people who consumed alcohol. Furthermore, our demonstration of a significant exposure-response association increases the likelihood, given the strength of the observed association and its consistency across a range of subgroups, that the observed association is causal. Further evidence of causality arises from studies demonstrating that alcohol consumption impairs alveolar macrophages and increases carriage of pneumonia pathogens (231, 232, 255).

5.4.4 Clinical implications

The findings from the present review highlight the need to address high alcohol consumption as a means to prevent community-acquired pneumonia. Clinicians managing patients with pneumonia could for example counsel reducing alcohol intake as a means to prevent further episodes, and those addressing high alcohol consumption in more general terms could add an increased risk of pneumonia as a further reason to reduce intake.

Our findings also have implications for public health: in Europe for example, the estimated annual costs of CAP are approximately €10.1

billion (76), might be reduced substantially by more pro-active clinical and public health measures to reduce alcohol consumption.

5.5 Conclusion

Our findings thus provide clear evidence that alcohol increases the risk of pneumonia. Informing people who drink alcohol of this risk, especially those who consume high levels of alcohol, both in clinical contacts and through public health policy, may, therefore, help to prevent this disease.

6 Chapter 6

Alcohol consumption and risk for tuberculosis. A systematic review and meta-analysis

In this chapter a meta-analysis and a systematic review of the observational studies which assessed the relation of alcohol on the risk of tuberculosis was presented. This chapter includes the following parts: an introduction of the effect of alcohol on tuberculosis, the methodology and statistical analysis which were used, the results of both systematic review and meta-analysis and a discussion of the main findings of the study.

6.1 Introduction

Alcohol consumption is also a potential risk factor for TB, because alcohol can impair the immune system (256, 257) and increase susceptibility to both primary infection and reactivation of disease (258). Also, alcohol can have indirect influences on the immune system, as it affects the nutrition leading to a suppression of the immune response (259). Moreover, alcohol is also associated with a higher risk of malnutrition and liver disease both of which impair immunity and lead to a higher risk of TB (260).

Another possible explanation of the association between alcohol consumption and TB is that alcohol thrives in specific populations that easily facilitate the spread of tuberculosis such as homelessness, imprisonment, and illicit drug users, all of which also increase the risk of tuberculosis (261, 262).

Globally, in 2015, alcohol use was responsible for 11.4% of tuberculosis deaths in HIV- negative people. Furthermore, in the same year, alcohol alongside with diabetes and smoking were the three main leading factors which were accounted for approximately a quarter of tuberculosis deaths and DALYs (263).

A systematic review published almost 10 years ago identified that alcohol is associated with TB (60), and was updated in a new systematic review and meta-analysis published in 2017 (69). However, both of these reviews limited their searches to two databases, and may thus have missed important studies, while the most recent review(69) included studies only up to June 2016, since when several relevant studies have been published. Another review assessed the effects of alcohol on the risk of active TB, but used only self-reported symptoms of productive cough and haemoptysis to ascertain disease status (264).

We have therefore performed a comprehensive systematic review and meta-analysis to provide a more valid estimate of the magnitude and exposure-response characteristics of the association between alcohol intake and tuberculosis risk.

6.2 Methods

The review included studies which met the following inclusion criteria: (1) comparative observational study designs (cohort/ longitudinal, case-control, cross-sectional); (2) adults aged 18+ years; (3) alcohol consumption reported as an exposure; (4) comparative/reference group of either no alcohol consumption or the lowest exposed category; and (5) tuberculosis reported as an outcome. We excluded studies related to latent tuberculosis, multidrug-resistant TB, TB prevention, treatment compliance, and hospital-acquired TB.

6.2.1 Search strategy

The search strategy is presented in Chapter 2. The Medline search filters for TB were the following: exp Tuberculosis or TB or Phthisic or (Pulmonary adj3 phthisis).mp or (Mycobacterium adj3 tuberculosis).mp or (Tuberculosis adj3 pulmonary).mp or Pleural tuberculosis.mp or Latent tuberculosis.mp. The full database search strategies are provided at Appendix 2.

6.2.2 Data extraction

The full methods for the data extraction are presented in Chapter 2.

6.2.3 Exposure definition

Our exposure of interest was alcohol consumption. Alcohol consumption defined either by self-report (interview or questionnaire) or using medical records. Also, alcohol use corresponded to drinking levels (low, moderate, heavy, and alcoholism) or to frequency measures (grams/units/drinks per day/week).

6.2.4 Case definition

The case definition for a diagnosis of active TB defined by: self- report using questionnaire & interview, bacteriologically confirmed (positive culture or smear) TB, or initiation of TB therapy based on a doctor's assessment of clinical data.

6.2.5 Quality assessment

The quality assessment of the studies is presented in Chapter 2.

6.2.6 Statistical analysis

The statistical analysis is presented in Chapter 2.
We also conducted sensitivity analyses to explore the robustness of our findings, through restricting our analysis to studies which assessed the effects of alcoholism or alcohol abuse, studies that recruited from HIV populations and studies that adjusted for smoking as a confounder.

6.2.7 A dose-response analysis

The methodology for the dose response analysis is presented in Chapter 2.

6.3 Results

The electronic searches yielded a total of 1739 articles, and a further 14 were identified from reference list searches. After removal of 400 duplicates, 1353 articles were screened for title/ abstract eligibility and 121 found to justify full-text screening.

Of these, 72 were excluded due to the ineligibility of the outcome or the exposure (n=12) or the exposure (n=2); or insufficient data on alcohol consumption (n=4); no comparison group for the outcome (n=52); or outcome information was incorporated with other diseases (n=2). Thus, 49 studies met our inclusion criteria and were included in the review (Figure 5.1).

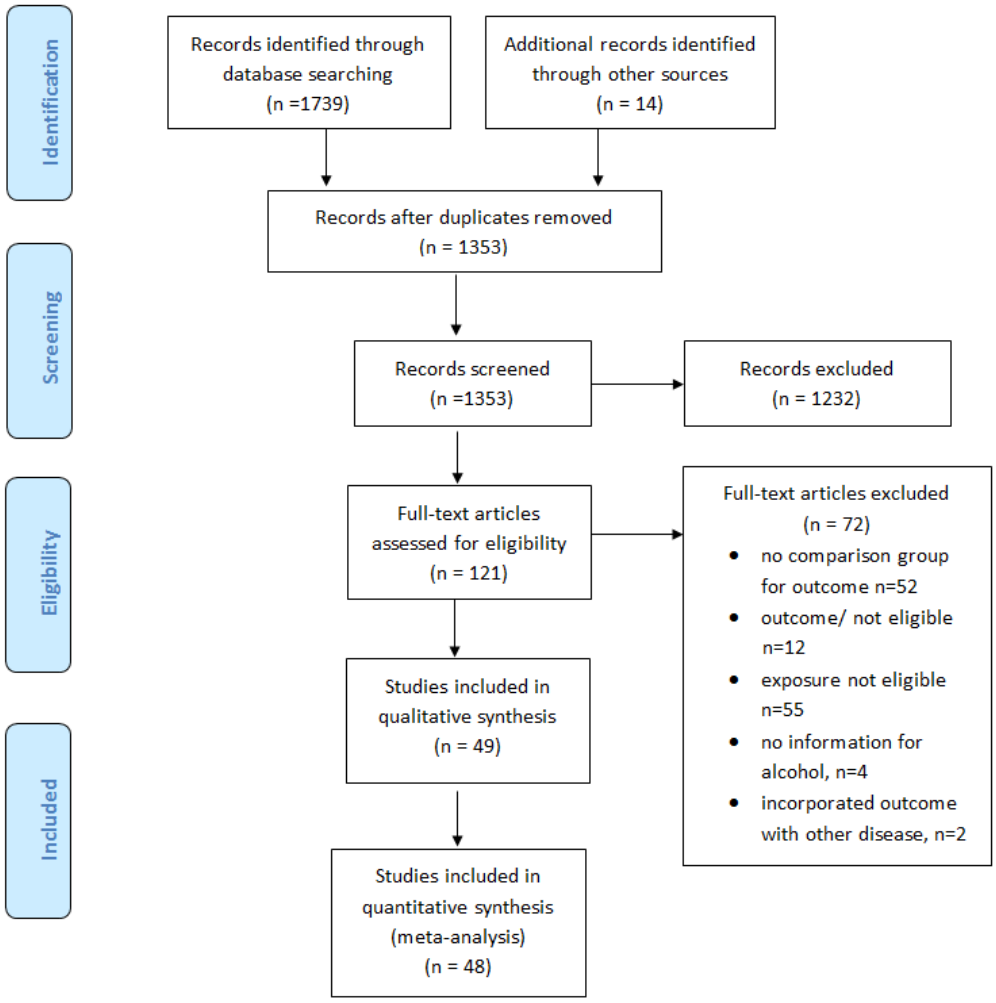


Figure 6. 1 Flow diagram

6.3.1 Overview of the studies

The study characteristics of the included studies in this review are presented in Table 5.1. The studies included a total of 560.598 participants, and the mean ages of people with TB within the sixteen studies reported this was ranged from 33.6 to 59.1 years.

Twenty-eight studies were conducted in Asia; 10 in Africa; 7 in America and 4 in Europe. Thirty-three were case-control studies; ten were cross-sectional and six were cohort studies. Forty-four of the studies reported ORs or RRs (265-308); 4 reported HRs (309-312) and one did not

provide sufficient information (313).Thirty-four studies provided adjusted effect estimates and thirteen of these had also adjusted for smoking (265, 269-271, 275, 277, 283, 285, 290, 293, 296, 305, 312).

The majority of studies (45 studies) assessed alcohol use through self-report via a questionnaire or an interview. Of the rest, two studies assessed alcohol using the AUDIT (Alcohol Use Disorders Identification Test), one study used ICD codes (274), and one used medical records (275).

The reference group for 27 studies comprised people who never consumed alcohol, while in three studies the comparison was between consumption defined as abuse or non-abuse (274, 276, 294), and five studies compared alcoholism to no alcoholism (273, 277, 288, 303, 310). The reference group for the remaining fourteen studies comprised people who consumed the lowest quantity of alcohol.

For the diagnosis of TB, the majority of studies used bacteriological confirmation with sputum smear and/ or culture and chest x-ray characteristics. Others used ICD codes (274, 293, 311, 312); medical records (287); questionnaire (268); record linkage (308), clinic database data (276); Revised National Tuberculosis Control Programme definition (290). In three studies the method of TB ascertainment was not provided (271, 289, 304).

The quality assessment scores indicated that 24 studies were of high quality. However, 23 studies found to have a low-quality score, with the main reason for this was either the lack of adjustment for confounders; the information bias as a result of the lack of provided information description in the outcome or exposure assessment; or due to a low response rate. No quality assessment was conducted for two studies for which only an abstract was available. In total, the quality assessment indicated a median score of 6 with a range of: 2-8 (Table 5.2).

Table 6. 1 Characteristics of included studies

Study& Year	Study design	Geographical location	Population	Characteristics of people with TB	Number of included subjects	Alcohol ascertainment	Alcohol definition	Tuberculosis ascertainment	Adjustment/ matching
Alemu, 2015 (265)	Case-control	Africa	HIV population	Male: 46% Mean age: -	446	Questionnaire interview	Alcohol consumption Yes vs no	Sputum microscopy, X-ray, histopathology, culture or molecular	Adjusted for: HAART, CPT, IPT, smoking, khat, TB family patient
Bhat, 2017(305)	Case-control	India/Asia	District population	Male: 79% Mean age: -	1602	Questionnaire	Alcohol consumption Yes vs no	Sputum smear and culture examinations	Adjusted for: age, sex, occupation, BMI, family income, history of asthma, chewing tobacco, smoking tobacco, blood sugar
Bhana, 2017(304)	Cross-sectional	Africa	Hospital population	Male: 24.8% Mean age:46.8	1332	AUDIT Questionnaire	Alcohol consumption Yes vs no	-	No adjustment/ matching performed
Boccia, 2011 (294)	Case-control	Africa	General population	Male:53.9% Mean age:36	370	Questionnaire/ interview	Alcohol abuse >3 drinks per occasion	Sputum sample culture positive	Adjusted for sex, age group, area of residence, household socioeconomic position
Bym, 2014 (291)	Case-control	Indonesia/Asia	General population	-	152	Self-report	Alcohol consumption yes vs no	Sputum positive test	Matched for: sex, age and ethnic
Chelleng 2014 (266)	Case-control	Asia	Occupational population	-	873	Questionnaire	Alcohol consumption yes vs no	sputum smear and culture positive	Adjusted for: age and sex, BMI, income, literacy
Chen, 2015 (267)	Case-control	China/Asia	General population	Male: 74.4% Mean age: -	1156	Self-report Questionnaire	Alcohol drinking (yes vs no)	Bacteriological results	Matched for: gender and age

Cois, 2013 (268)	Cross-sectional	South Africa/ Africa	Research database data	-	8115	CAGE Questionnaire	Problem drinking vs moderate/ abstainers	Questionnaire Has a doctor or nurse or health worker at a clinic or hospital told you that you have or have had TB	Matched for: gender and age
Coker 2006 (295)	Case-control	Russia/ Europe	General population	-	668	Questionnaire	Heavy drinking at least once/month in past year	Culture positive	Adjusted for: age, sex, diabetes
Davis, 2016 (269)	Case-control	Kazakhstan/Asia	General population	Male:55% Mean age:35.4	1600	Questionnaire	Ever drank alcohol vs never alcohol	Culture methods	Adjusted for: age, sex, ethnicity, education level, incarceration, marital status, smoking, drug use, HIV, diabetes
de Lima, 2016 (296)	Case-control	Brazil/ South America	Outpatient population	Male:61.4% Mean age:36	622	Questionnaire	Alcohol yes (Women: >=120 ml & Men: >= 150 ml At the same time within the last 30 days) vs no	Sputum smear and culture positive	Adjusted for: sex, smoking
Fox, 2015 (270)	Case-control	Canada/North America	HIV population	-	65	Self-report Questionnaire/ Interview	Recent alcohol use	Culture positive	Adjusted for: age stratum, sex, living with a person with smear-positive tuberculosis, visiting a gathering house, room occupancy, and low vegetable intake, smoking, cannabis use
Gajalakshmi, 2009 (271)	Case-control	India/Asia	Rural general population	-	2912	Interview	Ever vs never drinkers	-	Adjusted for: age, education, smoking

Gambhir, 2010 (297)	Case-control	Asia	Hospital population	Male:78.9% Mean age: 43.2	287	Questionnaire	Regular alcohol use >= 200 ml of 40%–60% alcohol for four days or more in a week for the last five years or more.	Sputum smear positive	Matched for: age and sex
Gninafon, 2010 (272)	Case-control	Africa	General population	Male: 69.5% Mean age: 35.2	600	Questionnaire	Daily alcohol use yes vs no	Smear-positive	Matched: age and sex
Gyawali, 2012 (273)	Cross-sectional	Asia	General population	Male:40.9% Mean age: -	986	Self-report Questionnaire	Alcoholic (yes vs no)	Sputum smear	No adjustment/ matching performed
Hill 2006 (298)	Case-control	Africa	Outpatient population	Male: 65% Mean age: 33.6	300	Questionnaire	current/past vs never consumers	Sputum smear and culture positive	Matched for: age and sex
Hochberg, 2017(306)	Case control	India/Asia	General population	Male: 75.1% Mean age: 45	409	AUDIT questionnaire	Alcohol consumption Yes vs no	Smear positive	No adjustment/ matching performed
Hong, 2017(307)	Case-control	Korea/ Asia	Two research databases data	Male: 61.2% Male: 58.1%	2459	Self-report Questionnaire	Current vs non-drinkers	sputum smear and culture positive	No adjustment/ matching performed
Hsu, 2014 (274)	Case-control	Taiwan/Asia	Research database data	Male:65.4% Mean age:57.7	71951	ICD 9 codes	Alcohol abuse	ICD 9 codes	Matched for: age, sex, year/month of index visit
Inghammar, 2011 (309)	Cohort	Sweden/Europe	General population	-	28.907	Questionnaire	Problematic drinking yes vs no	Confirmed bacteriology or diagnosed by a clinician	No adjustment/ matching performed
Jung, 2015 (275)	Cohort	Asia	Gastric cancer population	Male: 87.5% Mean age: -	1776	Medical records	Alcohol history yes vs no	Culture	Adjusted for: sex, age, BMI, smoking, previous TB infection, surgery gastrectomy
Kan, 2011 (300)	Case-control	Asia	Outpatient population	Male:72.8% Median age:63	624	Questionnaire	Daily alcohol use Frequency	Sputum smear positive	Matched for: age, sex

							& amount of alcoholic beverages		
Kibret, 2013 (301)	Case-control	Africa	HIV population	Male:56.6% Mean age:36.7	613	Questionnaire/ interview	alcohol drinking yes vs no	Sputum smear positive	No adjustment/ matching performed
Kim, 2005 (276)	Case-control	USA /North America	Clinic database data	Male: - Mean age: 37.7	919	Questionnaire	Alcohol abuser	TB database clinic data	Adjusted for: ethnicity, married, homeless, drug user, HIV positive, type of crime, length of stay in jail
Kolappan, 2007 (277)	Cross-sectional	India/Asia	General population	-	93.945	Self-report Questionnaire	Alcoholism vs non-alcoholism	Sputum smear/ culture examination	Adjusted for: age, sex, smoking
Kolappan, 2009(278)	Case-control	India/Asia	Rural and urban units	Male:87% Mean age: -	1530	Self-report Questionnaire/ interview	Alcohol user vs non-drinkers Ever had consumed alcoholic liquor before interview	Sputum smear or culture examination	Adjusted for: age and sex, biomass fuel
Ladefoged, 2011 (279)	Case-control	Greenland/ North America	Hospital population	Male: 58% Median age:37	730	Questionnaire	Alcohol often (at least once/week) vs seldom (less than once a week)	X-ray/positive histology/culture positive	Adjusted for: age, sex, ethnicity, town, immunosuppressive treatment, occupation
Lakshmi, 2010 (313)	Case-control	Asia	General population	-	378	Questionnaire	Alcohol intake yes vs no	Sputum smear positive	Matched for: age and residence area
Lienhardt, 2005 (280)	Case-control	West Africa/ Africa	General population	Male: 69% Mean age: -	2325	Questionnaire	Alcohol intake Current/past vs never	Smear-positive	Matched for: age
Lin, 2015 (281)	Cross-sectional	Taiwan/Asia	Hospital and public health centre population	-	2.979	Self-report Questionnaire	Alcohol consumption (yes vs no)	Sputum culture	No adjustment/ matching performed
Marak, 2015 (282)	Cross-sectional	India/Asia	Outpatient patients	Male:63.6% Mean age: -	210	Self-report Questionnaire	Current alcohol consumer ≥1 drink in the year preceding the survey vs never	Confirmed bacteriology or diagnosed by a clinician	No adjustment/ matching performed

Mendoza, 2010 (310)	Cohort	Canada/North America	Clinic database data	Male:57% Mean age: -	33.146	Questionnaire	Alcoholism yes vs no	Sputum smear and culture positive	Adjusted for: immunosuppressive condition, age, LBTI treatment, Closeness of contact, drug use, ethnicity, socioeconomic status, sex, country with high tuberculosis prevalence
Murrison, 2016 (283)	Case-control	Africa	HIV hospital and outpatient populations	Male: - Median age: 38	279	Questionnaire	Drinks/week ≥15 drinks vs 0 drinks	Sputum smear microscopy or sputum culture	Adjusted for: smoking, age, education, employment status, household income, CD4, History of previous TB, Duration of HIV
Nielsen, 2010 (284)	Case-control	Greenland/ North America	Hospital population	-	754	Questionnaire	Frequent (every day or 1-6 times/week) vs (non-frequent <1/ week)	Culture/x-ray	Matched for: sex, age and district, 25(OH)D and ethnicity
Pednekar, 2012 (312)	Cohort	India/Asia	General population	-	35.102	Questionnaire	Drinkers vs never drinkers	ICD codes	Adjusted for age, education, and tobacco use.
Pokhrel 2010 (302)	Case-control	Asia	Hospital population	Male: - Mean age: 35	375	Questionnaire	Alcohol consumption yes vs no	Chest x-ray and positive active sputum smear	Matched for: age
Prasad, 2009 (303)	Case-control	Asia	Hospital population		444	Questionnaire/ interview	Alcoholism yes vs no	Sputum smear-positive +interview	Matched for: age, sex
Rao, 2011 (286)	Cross-sectional	India/Asia	General population	-	9.538	Questionnaire	Alcohol consumption (yes vs no)	Sputum samples smear microscopy and solid media culture methods	No adjustment/ matching performed
Rao, 2014 (285)	Cross-sectional	India/Asia	General population	-	95.071	Questionnaire	Alcohol/day Heavy alcohol (>500 ml/day for	Sputum smear specimen	Adjusted for: sex, age, smoking, social class

							>20 years) Vs Non-alcohol consumers		
Rodriguez, 2015 (287)	Cross-sectional	Africa	HIV population	Male:33% Mean age:38.2	300	Questionnaire/ Interview	Heavy/moderate drinker vs light/non-drinker	Medical records	Adjusted for: age, marital status, outdoor environment
Sacchi, 2012 (288)	Case-control	Brazil/ South America	Indigenous general population	Male:57.1% Mean age: -	189	Questionnaire/ interview	Alcoholism yes vs no	X-ray, thorax CT (computed tomography) and/or positive sputum smear or culture.	Matched for: age, geographic location
Savicevic, 2013 (299)	Case-control	Europe	General population	-	600	Questionnaire	Current vs never consumer Daily alcohol last 12 months Vs Less than once a week, last 12 months	Culture positive pulmonary TB	Matched for: age, sex, country of residence
Schluger, 2013 (289)	Case-control	Asia	General population	Male:50% Mean age: -	173	Self-report Questionnaire	Regular alcohol users	-	No adjustment/ matching performed
Shetty, 2006 (290)	Case-control	India/Asia	Outpatient population	-	378	Questionnaire	Alcohol use Current (at least 6 months) vs never	Revised National Tuberculosis Control Programme (RNTCP) case definition	Adjusted for: age, sex, marital status, religion, household income, persons per room, cooking fuel, smoking
Soh, 2017(308)	Cohort	Asia	Research database data	Male:73.5% Mean age:59.1	57471	Questionnaire	Alcohol consumption Yes vs no	Record linkage	No adjustment/ matching performed
Verma, 2012 (292)	Cross-sectional	Asia	HIV population	-	184	Self-report Questionnaire/ interview	Alcohol habit yes vs no	Culture /smear	No adjustment/ matching performed
Yen, 2017 (311)	Cohort	Asia	General population	Male:41.9% Mean age:43.2	46.196	Self-report Questionnaire	Heavy alcohol consumption: intoxication at least once/week	ICD 9 codes	Adjusted for: age, sex, marital status, educational level

						interview	vs never drinking		
Zaridze, 2009 (293)	Case-control	Russia/Europe	General population	-	48.557	Questionnaire	Weekly intake (≥3 bottles of vodka vs <0.5 bottles of vodka)	ICD codes	Adjusted for: age, city, and smoking

Table 6. 2 Critical appraisal of included studies using Newcastle Ottawa scale

Study, year	Stars number		
	Selection†	**Comparability‡**	**Exposure§**
Alemu, 2015 (265)	3	2	2
Bhat, 2017(305)	3	2	2
Bhana, 2017(304)	0	0	2
Boccia, 2011 (294)	4	1	1
Bym, 2014* (291)	-	-	-
Chelleng 2014 (266)	3	1	1
Chen, 2015 (267)	3	1	1
Cois, 2013 (268)	1	1	3
Coker 2006 (295)	4	1	1
Davis, 2016 (269)	4	2	2
de Lima, 2016 (296)	3	2	1
Fox, 2015 (270)	3	2	1
Gajalakshmi, 2009 (271)	3	2	2
Gambhir, 2010 (297)	3	1	2
Gninafon, 2010(272)	4	2	1
Gyawali, 2012 (273)	2	0	1
Hill 2006 (298)	3	1	2
Hochberg, 2017(306)	2	0	3
Hong, 2017(307)	4	0	1
Hsu, 2014 (274)	3	0	1
Inghammar 2011 (309)	2	0	2
Jung, 2015 (275)	2	2	2
Kan, 2011 (300)	4	1	1
Kibret KT, 2013 (301)	3	0	2
Kim, 2005 (276)	3	2	1
Kolappan, 2007(277)	2	2	1
Kolappan, 2009(278)	4	1	2
Ladefoged, 2011 (279)	3	1	3
Lakshmi, 2010 (313)	2	1	2
Lienhardt, 2005 (280)	4	0	1
Lin, 2015 (281)	1	0	1
Marak, 2015 (282)	1	0	2
Mendoza, 2010 (310)	2	1	3
Murrison, 2016(283)	2	2	1
Nielsen, 2010 (284)	3	1	1
Pednekar, 2012 (312)	2	2	3
Pokhrel 2010 (302)	2	1	2
Prasad, 2009 (303)	3	1	1
Rao, *2010 (286)*	1	0	1
Rao, 2014 (285)	2	2	2
Rodriguez, 2015 (287)	2	1	1
Sacchi, 2012 (288)	3	1	2
Savicevic, 2013 (299)	4	1	2
Schluger, 2013* (289)	-	-	-
Shetty, 2006 (290)	2	2	1
Soh, 2017(308)	3	0	3
Verma, 2012 (292)	2	0	1
Yen, 2017 (311)	2	2	3

Zaridze, 2009 (293)	4	2	2

***Abstract only available-not quality assessment**
† Maximum 4 stars
‡ Maximum 2 stars
§ Maximum 3 stars

6.3.2 Meta-analysis findings

Forty-eight of the forty-nine studies were included in the meta-analysis. One study could not be included in the meta-analysis, as data were reported in insufficient detail (313); briefly in this study both the TB cases and controls were non- consumers of alcohol. Forty-four of the 48 included studies provided data from which pooled odds ratios could be estimated. A meta-analysis of these studies showed a 90% increase in the odds of TB among people who consumed alcohol at all, or in higher amounts, than in those who consumed no, or lower amounts of alcohol respectively (pooled OR= 1.90, 95% CI 1.63 to 2.23, I^2= 82%, Figure 5.2).

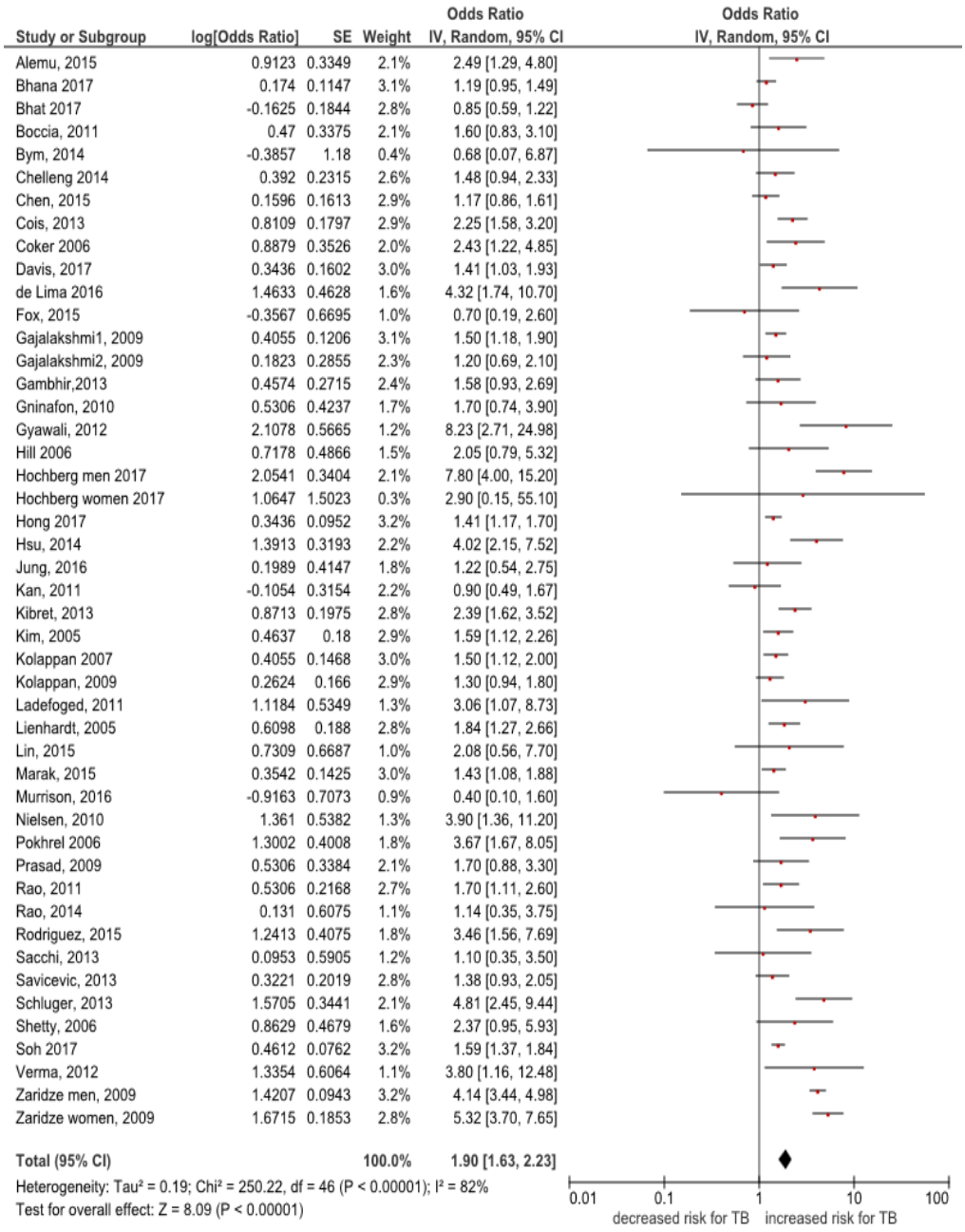


Figure 6. 2 Forest plot of the association between any alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of TB

No evidence of publication bias was detected either visually via a funnel plot (Figure 5.3) or statistically via Egger's asymmetry test (P = 0.54, Figure 5.4).

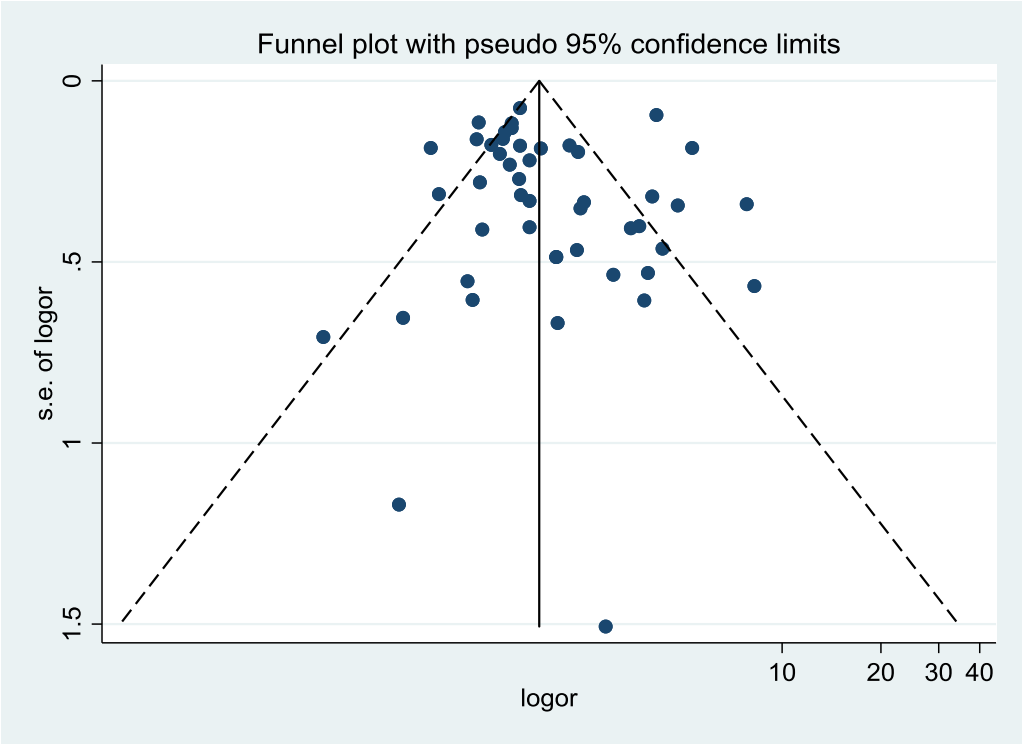


Figure 6. 3 Funnel plot of alcohol consumption and the risk of TB

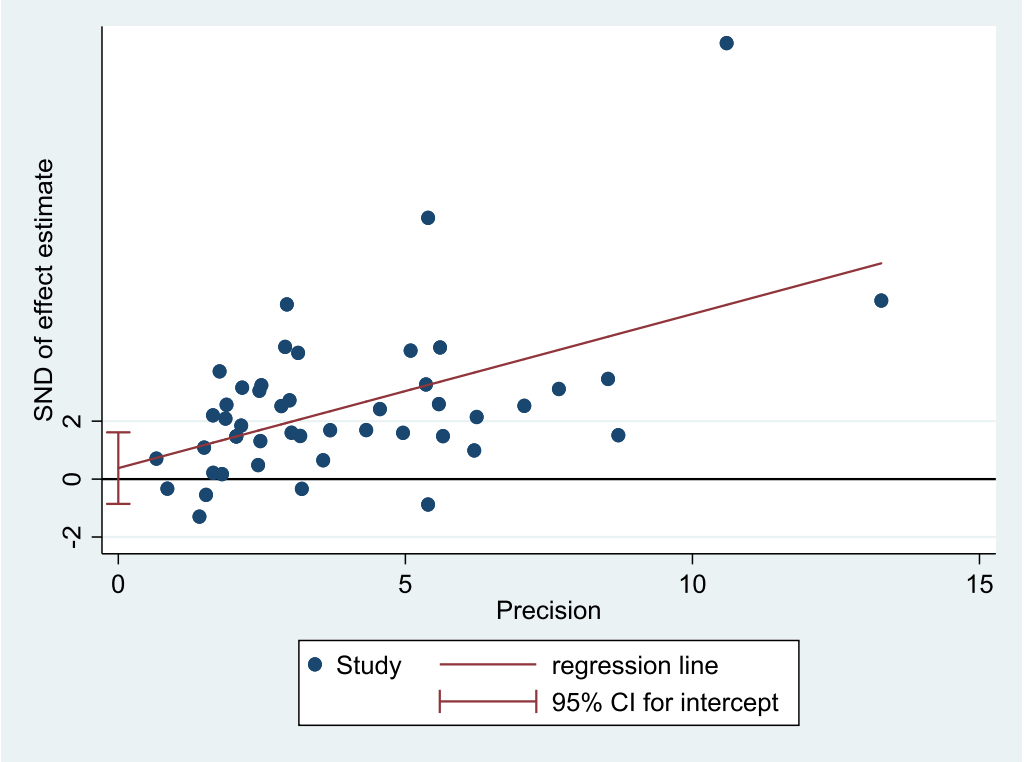


Figure 6. 4 Assessment of publication bias for TB and alcohol; Egger's asymmetry test

Subgroup analyses exploring the possible reasons for the identified heterogeneity in the meta-analysis are presented (Table 5.3) However, the high level of heterogeneity was not explained by study design (case-control, longitudinal/cohort; p for subgroup differences=0.24), methodological quality (high versus low; p=0.31), adjustment for confounders (adjusted versus unadjusted; p=0.32), country of study (America, Asia, Europe, Australia; p=0.25) or year of publication (2005-2010 versus 2011 -2018; p= 0.28).

Table 6. 3 Exploration of heterogeneity for the association of alcohol consumption and risk of TB

Factor	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	1.90 [1.63-2.23]	81%	-
Study design			0.24
Case control	1.94 [1.58, 2.38]	84%	
Cohort	1.57 [1.36, 1.82]	0%	
Cross sectional	1.82 [1.41, 2.36]	65%	
Methodological quality			0.31
High quality (>6)	1.71 [1.34, 2.18]	86%	
Low quality (<6)	2.02 [1.65, 2.46]	73%	
Geographic location			0.25
America	2.05 [1.24, 3.41]	49%	
Asia	1.68[1.44,1.96]	68%	
Europe	3.00 [1.69, 5.32]	90%	
Africa	1.85 [1.41, 2.42]	62%	
Effect estimate			0.32
Adjusted analysis	1.80 [1.48, 2.20]	82%	
Unadjusted analysis	2.12 [1.64, 2.75]	80%	
Publication year			0.28
Publication year: 2005-2010	2.13 [1.57, 2.87]	87%	
Publication year: 2011-2018	1.76 [1.50, 2.08]	71%	

Sensitivity analyses were conducted restricting the meta-analysis to studies with *a priori* defined criteria. Studies which reported the reference group as no drinking produced a pooled effect estimate lower

than the unrestricted meta-analysis, with an OR of 1.60 (95%CI: 1.39-1.84, I^2=63%, 25 studies, Figure 5.5) (265-267, 269, 271, 275, 278, 280-283, 285, 286, 290-292, 296, 298, 301, 302, 304-308). Analysis limited to studies categorizing alcohol intake as alcohol abuse/alcoholism found a similar magnitude of increased risk compared to the unrestricted meta-analysis (pooled OR=1.81, 95%CI: 1.28-2.57, I^2=66%, 8 studies) (273, 274, 276, 277, 288, 294, 300, 303). Restricting the meta-analysis to TB patients with HIV co-infection showed similar results to the main meta-analysis (OR=2.02, 95%CI: 1.22-3.36, I^2= 55%, 6 studies) (265, 270, 283, 287, 292, 301). Also restricting the meta-analysis to studies reporting smoking-adjusted estimates showed that alcohol consumption was also associated with increased risk for TB (pooled OR=1.73, 95%CI: 1.18-2.53, I^2= 91%, 12 studies) (265, 269-271, 275, 277, 283, 285, 290, 293, 296, 305).

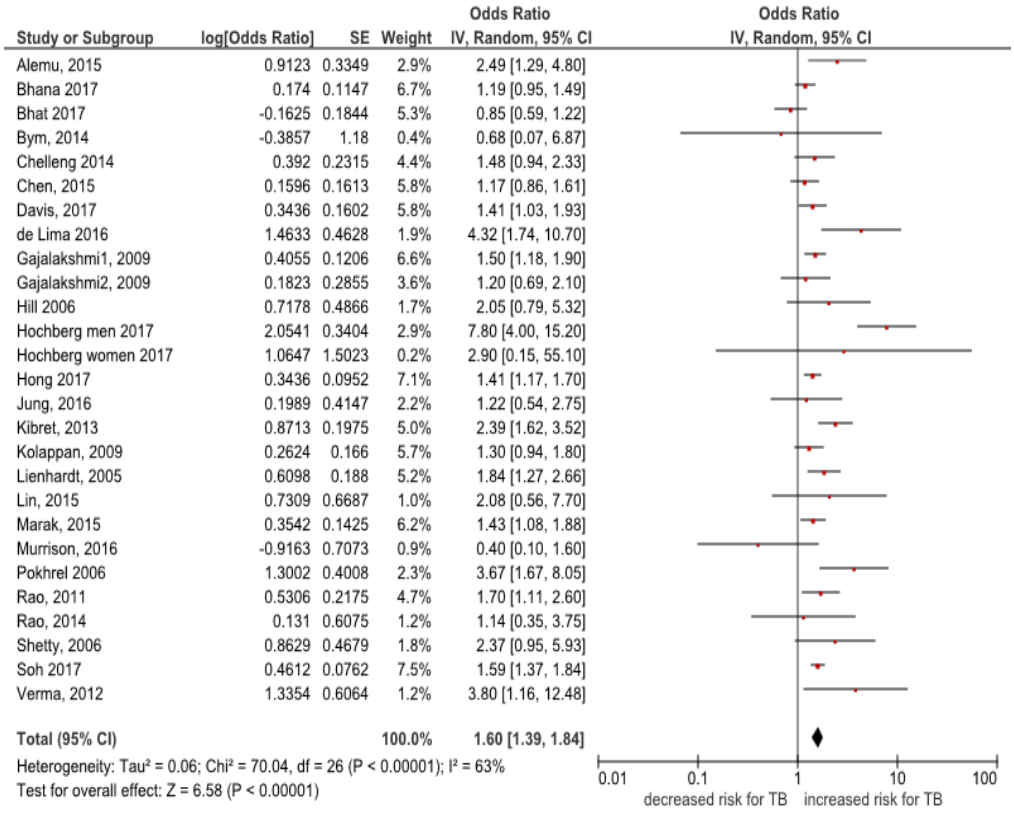


Figure 6. 5 Forest plot of the association between any alcohol versus no alcohol consumption and the risk of TB

Four of the 48 included studies presented effect estimates as hazard ratios (309-312). A separate pooled analysis of these studies found a higher hazard ratio of 2.81 for TB in relation to alcohol consumption (95% CI: 2.12-3.74, I^2= 9%, Figure 5.6).

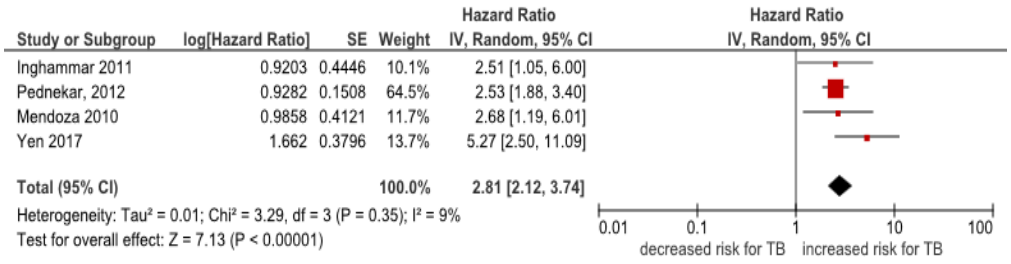


Figure 6. 6 Forest plot of the association between alcohol consumption versus non-alcohol/lower alcohol consumption and the risk of TB (data presented as hazard ratios)

6.3.3 Dose response effect

Three of the included studies provided data which enabled a dose-response effect meta-analysis (283, 285, 293). The pooled dose-response analysis identified a significant increase in TB risk in relation to the quantity of alcohol consumed, by 12% for every additional 10-20 grams daily intake (pooled RR= 1.12, 95% CI 1.10 to 1.13; p<0.0001; Figure 5.7).

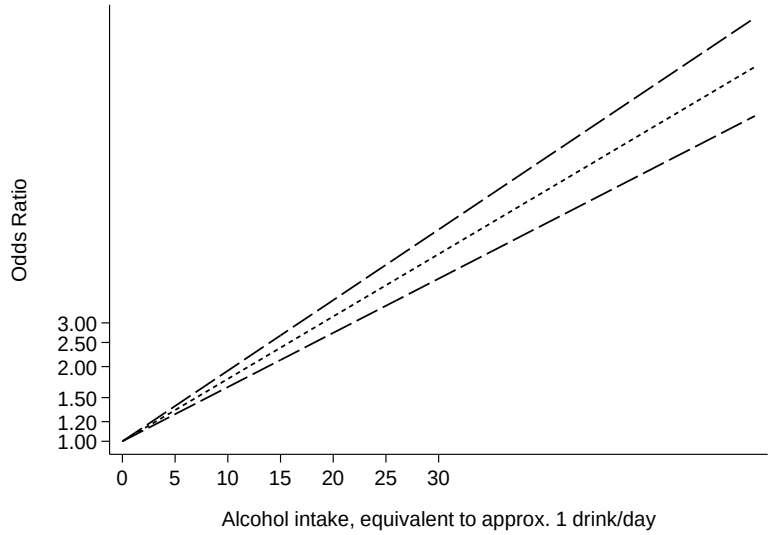


Figure 6. 7 Linear dose response meta-analysis for the association between categories of alcohol intake (grams/day) and the risk of TB

6.4 Discussion

6.4.1 Summary of the findings

In this systematic review and meta-analysis, we provide contemporary estimates of the effect of alcohol consumption on the risk of TB among adults. Our pooled analysis demonstrates a 90% higher odds of TB risk in relation to alcohol consumption, and that the magnitude of this effect appears robust to differences in alcohol reference group definition and to be consistent in subgroup analyses. The effect is also exposure-related.

6.4.2 Strengths and limitations

Our study constitutes a comprehensive review using specific search strategy and with no language restriction. A large number of studies were identified and included in our meta-analysis. Also, our results are likely to be generalizable, as our review includes global evidence of many different countries. There was also no evidence of publication

bias. However, we found a high level of between-study heterogeneity. Almost all of the studies ascertained alcohol intake by self-report methods, raising the possibility of reporting bias, but the potential for misclassification arising from inclusion of non-drinkers in the lowest exposure category in some studies does not seem to have influenced our findings, since the estimated effect of alcohol was similar; if slightly lower, in those studies involving a zero- intake reference group. Residual confounding or recall bias arising from retrospective designs may also have influenced our results.

6.4.3 Comparison with other studies

A meta-analysis by Lönnroth et al (60), published ten years ago, showed that there is a three-fold increased risk only in people with an average daily alcohol consumption of more than 40 grams or have an alcohol use disorder. This estimate is higher than that arising from our dose-response analysis, which indicated that a daily alcohol consumption of 40-50 grams would lead to a 48% increased risk for TB. A possible explanation for this difference is the inclusion of alcohol use disorder in the analysis of Lönnroth study (60).

Recently a meta-analysis of alcohol effects on TB incidence published in 2017 by Imitiaz et al (69), which was an update of the previous published systematic review of Lönnroth (60)estimated a 35% increase in risk among those who consume alcohol relative to those who do not, and the risk was marginally greater (RR=1.50) when drinkers were also included in the reference category. They also performed a dose-response analysis indicating an increasing risk of TB with increasing amounts of alcohol consumed, but when they performed categorical dose-response meta-analyses non-significant results were found for the ≤ 24 and >24 to ≤ 60 alcohol categories. In contrast to the previous systematic review by Imitiaz (69), our more comprehensive searches and meta-analysis found that drinkers are 1.60 times more likely to have TB compared to non-drinkers. Similarly, higher odds of TB (OR=1.90) were also found when in our analysis people who consumed

low alcohol were included in the reference group. We further found that consuming drinks that contain 10-20 grams of alcohol every day was linked to a 12% increased risk of TB, but we did not perform a categorical dose-response meta-analysis as Imitiaz et al did (69). However, the Imitiaz study was restricted to searches of only two databases which, as acknowledged by the authors, will miss eligible studies, therefore making their findings misleading. This concern is borne out by our finding of 33 eligible studies that were missed from the Imitiaz et al review, (69) making our estimates more likely to be valid.

Another meta-analysis in 14 high Tuberculosis burden countries assessed the effect of alcohol, diabetes, low body mass index on the risk of self-reported symptoms of active tuberculosis was conducted in 2014 by Patra et al (264). They found that ever drinking was associated with a 26% increased risk of TB symptoms in men and with a 50% increased risk in women when adjusted for age and education. However, adjustment for further confounders showed a non-significant association. However, Patra study (264) relied on self-reported productive cough and haemoptysis to ascertain active TB, which while a pragmatic approach is likely to be less valid than the clinical diagnoses used in our meta-analysis.

6.5 Conclusions

In conclusion, our review confirms that alcohol drinking is associated with an increased risk of tuberculosis. Also, in the dose-response analysis, the increase in tuberculosis risk associated with every 10-20 grams of linear increment in daily alcohol intake. Therefore, our findings suggest that measures that reduce alcohol consumption are likely to lead to a reduced risk of TB in the general population.

7 Chapter 7

Alcohol consumption and risk for asthma. A systematic review and meta-analysis

In this chapter, a systematic review and meta-analysis of the observational studies were conducted to determine if the consumption of alcohol would be a risk factor for the development of asthma. This chapter also includes introduction, methods, results and discussion sections.

7.1 Introduction

Alcohol may have either beneficial or adverse effects on asthma. Alcohol can cause bronchodilation by relaxing airway muscle tone (87, 314), and reduce upper airway sensitivity and hence responses to asthma triggers, resulting in a potential reduction in asthma attacks (87). Furthermore, alcohol consumption over time may depress the immune system leading in a diminished capacity to produce antibodies against foreign antigens (87).

However other studies have reported that alcohol may be a potential risk factor for asthma. Alcohol drinking can lead to symptoms of bronchoconstriction or flushing. Sulphite additives in alcoholic beverages such as wines and beers can also be a trigger for asthma (315). Sensitivity to salicylates may also be a trigger for wine-induced asthmatic responses (316). Furthermore, acetaldehyde is a well- known primary metabolite of ethanol and may be responsible for causing bronchoconstriction in people with asthma, in particular in Asian populations due to genetically reduced capacity to metabolize alcohol (314). Acetaldehyde can also cause hypersensitivity reactions through the release of histamine and other chemicals from mast cells (87, 317).

To date, however, there is little published and inconsistent evidence on the effect of alcohol on the risk of asthma. To synthesize this sparse

and mixed evidence to investigate and quantify an overall magnitude of risk, and further to explore whether this varies by participants or study characteristics, we conducted a systematic review and meta-analysis of observational studies to assess the relation between alcohol and asthma.

7.2 Methods

7.2.1 Identification of existing systematic reviews

Initially, published systematic reviews and meta-analyses assessing the effect of alcohol on the risk of asthma on adults were searched. No existing systematic reviews assessing the association between alcohol and the risk of asthma were identified from the searches; therefore, we performed a systematic review using the following methods.

7.2.2 Methods for conducting the systematic review

The methodology for the systematic review is presented in Chapter 2.

7.2.3 Data sources and Search strategy

The search strategy is presented in Chapter 2. Specifically, the Web of Science search filters for alcohol and asthma were the following: (alcohol* OR alcoholic beverage OR alcohol consumption OR alcohol drinking OR alcohol use OR alcohol intake OR alcoholism OR alcohol abuse OR ethanol* OR ethanol concentration) and (Asthma OR wheeze). All the search filters used for the three databases are presented in the Appendix 2.

7.2.4 Data extraction

The data extractions are presented in Chapter 2.

7.2.5 Quality assessment

The quality assessment of the primary studies is presented in Chapter 2.

7.2.6 Data analysis

The statistical analysis is presented in Chapter 2. Additional subgroup analyses were performed according to of alcohol levels (excessive vs low/moderate) and asthma ascertainment (objective versus subjective). Also, sensitivity analyses restricted to studies which provided smoking or BMI adjusted estimates were conducted.

7.3 Results

7.3.1 Search results

The comprehensive search identified 4378 articles with an additional 14 articles from the screening of the reference lists. After the exclusion of the duplicates, 3653 articles remained for inspection. After the screening of the titles and the abstracts, an additional 3461 clearly irrelevant articles were excluded, leaving 192 papers for full- text evaluation. A second assessment based on the reading of full- text was performed and 176 articles were excluded. The main reasons for exclusion were: ineligible study design; ineligible exposure; the study didn't provide sufficient information for either exposure or outcome; the outcome was not asthma, or all the study population had asthma. Thus, 16 papers were included in the review and 12 provided sufficient information to be included in the meta-analysis. The PRISMA flowchart shows the process of identification and study selection (Figure 6.1).

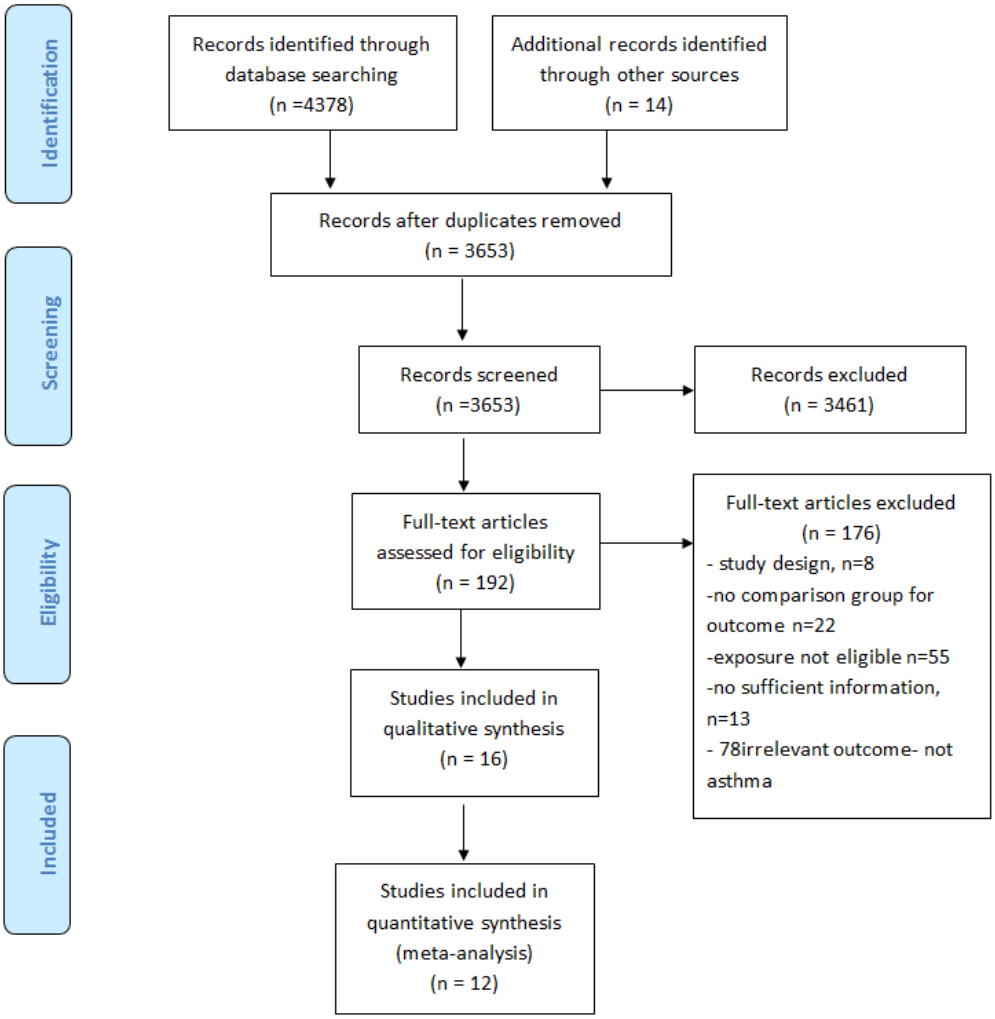


Figure 7. 1 Flow chart of studies

7.3.2 Characteristics of the included studies

The characteristics of the 16 included studies, which included a total population of 845,675 people, are shown in Table 6.1. Seven studies reported the mean age of the asthma group, which ranged from 21.7 to 53.8 years (104, 118, 318-322). Also, asthma patients were more likely to be female (range, 51.2% to 80.1%, 7 studies). Four studies reported the percentage of white non-Hispanic in the study samples and it varied from 54.8% to 77.8% (104, 319, 323, 324).

Twelve studies were cross-sectional (101-104, 118, 318-321, 323, 325, 326); two were cohort (327, 328) and two were case-control studies

(322, 324). Ten studies were published between 2010 and 2015. The majority of studies were from the USA (101, 102, 104, 118, 318, 319, 323, 324, 328). Four studies were conducted in Europe (321, 322, 325, 326); two studies in Asia (103, 320) and one study was conducted in Australia (327). Six studies adjusted for confounders (101, 103, 321-323, 328); with four of these also adjusted for smoking (103, 322, 323, 328).

The study quality of the 16 included studies using the Newcastle-Ottawa Scale identified two high-quality studies (322, 328) (12.5%) (Table 6.2). The study quality assessment score of the studies included ranged from 1 to 7, with a mean score of 3. The main reasons for lower scores were: self-report of alcohol and asthma reporting of crude (unadjusted) measures of effect.

7.3.3 Exposure reporting

Twelve studies assessed alcohol drinking by self-report using a questionnaire (101, 102, 118, 318-321, 324-328). In four studies the method of alcohol ascertainment was not mentioned. The definition of alcohol consumption included drinks per month, drinks last year (n=1), drinks last month, drinks per day, risky drinking and heavy drinking. Fourteen studies reported alcohol as a binary exposure and one study reported alcohol as a continuous measure.

7.3.4 Outcome Reporting

Asthma diagnoses were ascertained by self-report (n=12) from a questionnaire (103, 318, 321, 322, 325-327); interview (101, 320) or a physician diagnosis (319, 323, 324). Also, asthma definition ascertained by: the International Classification of Diseases (ICD-9) codes (328); physician diagnosis (102, 118) and medical records (104).

Table 7. 1 Characteristic of included studies

Author & Year	Study design	Geographical location	Population	Cases characteristics	Number of included people	Alcohol ascertainment	Alcohol definition	Asthma ascertainment	Adjustment
Agrawal, 2012 (103)	Cross-sectional	Asia (India)	People aged 20–49 years from 109.041 households	-	156,316	-	Alcohol use Never vs ever	Self-report questionnaire	Adjusted for: sex, age, marital /employment status, education, environmental factors, geographic location, wealth index, religion, smoking, BMI, dietary intakes of milk or milk products, house type, castle/ tribes, foods (eggs, fish, vegetables, beans, chicken or meat)
Aly, 2011 (104)	Cross-sectional	USA	Women in a Medical Center (hospital)	Mean age:29.3 54.8% white non- Hispanic 45.2% black non- Hispanic	17.073	-	Alcohol use yes vs no	Medical records	-
Dowdell, 2011 (318)	Cross-sectional	USA	Adolescents and young adults, aged 18 to 26 years participated in the Wave III survey. Data from database	Mean age: 21.7 51.2% female 77% white 16% black	4.874	Self-report questionnaire	Number of dinks the last year	Self-report questionnaire	-

Ford, 2004 (319)	Cross-sectional	USA	Participants aged >=20 years US population sample	Mean age:44.8 40.9% men 59.1% female 77.8% non-Hispanic, white	16.541	Self-report questionnaire	Drinks/ month	Self-report Physician diagnosis	-
Graat, 2007 (326)	Cross-sectional	Europe (Netherlands)	Noninstitutionalized Population aged>60 years in an area of Netherlands	Total Average age: 73,3 years 50% male	652	Self-report questionnaire	Alcohol yes vs no Glasses/ day Abstainers (0< glasses/day<1), light, occasional, Moderate/ heavy drinkers (>3glass/day: men, >2 glass/day: women)	Self-report Questionnaire	-
Lee, 2013 (320)	Cross-sectional	Asia (Korea)	Only women aged 20-49 years	Mean age: 36.3	5031	Self-report questionnaire	Heavy alcohol: >5 drinks per occasion or >=1 drink/day	Self-report interview	-
Lieberoth, 2012(321)	Cross-sectional	Europe (Denmark)	Population-based sample of twins aged 12-41 years at baseline	Mean age: 27.4 44.9% male 55.1% female	19349	Self-report questionnaire	Heavy drinkers: ≥4 units/day vs <1 units/month	Self-report questionnaire	Adjusted for age, gender, BMI, physical activity, and years of education
Lucke, 2007 (327)	cohort	Australia	Women permanent residents and citizens from Australian national health insurance	-	40.000	Self-report questionnaire	Risky drinker vs non-drinkers	Self-report questionnaire	-

			database.						
Miguel Diez,2012 (325)	Cross sectional	Europe (Spain)	Nationwide representative sample of the civilian, non-institutionalized population	61.5% female	21,230	Self-report questionnaire	Alcoholic drinks during last two weeks Yes vs no	Self-report question naire	-
Niami, 2005 (101)	Cross-sectional	USA	Population-based of US adults	-	235,730	Self-report questionnaire	Moderate Men: ≤2 drinks/day, women: ≤1 drink/day vs nondrinking (no alcohol during the past 30 days)	Self-report interview	Adjusted for age and gender
Oraka, 2010 (323)	Cross-sectional	USA	Adults aged 18 years or older Sample households US civilian population	63.6% female 75% non-Hispanic white 12.9% non-Hispanic black	186.738	-	Alcohol use Current vs never	Self-report Physician diagnosis	Adjusted for: age, sex, race/ethnicity, education, family income, marital status, employment status, body mass index, smoking, other chronic conditions.
Shaheen, 2008 (322)	Case-control	Europe (UK)	Adults aged 16–50, registered with 40 general practices in Greenwich, South London	Mean age: 34.1 61.8% female 12.7% non-white	3438	-	Red wine ≥5 glasses /day vs <1 glass/week Tea >6 per day vs	Self-report Question naire	Adjusted for: age, sex, body mass index, social class, housing tenure, employment status, whether a single parent, smoking, passive smoke

							never tea		exposure at home, and total energy intake
Song, 2010 (118)	Cross-sectional	USA	Population-based middle-aged and older US women	Mean age:53.8	38570	Self-report questionnaire	Alcohol intake rarely/never 1–3 drinks/ month, 1–6 drinks/week, and _1 drink/day)	Physician diagnosis	-
Tran, 2011 (328)	cohort	USA	People voluntarily underwent a health examination offered by a northern California prepaid health plan	55% whites, 27% blacks, 11% Asians, and 4% Hispanics	126.019	Self-report questionnaire	Alcohol intake ≥3 drinks per day vs never	Hospital diagnosis using ICD codes	Age, sex, ethnicity, body mass index, education, smoking, and alcohol intake.
Trojan, 2014 (102)	Cross-sectional	USA	Population completed a fee-for-service preventive medical examination at the Cooper Clinic in Dallas, Texas	94.1% white 66.2% male 47% Aged>50 years	12,944	Self-report questionnaire	Drinker vs non-drinker	Physician diagnosis	**-**
Young, 2001 (324)	Case-control	USA	active and retired service members of the US Air Force	80.1% female 72.3% white, non-Hispanic 4.9% white Hispanic 6.7%Asian 6.7% black Hispanic	1130	Self-report questionnaire	At least 1 drink last month vs none drink in last month	Self-report Physician diagnosis	-

Table 7. 2 Critical appraisal of included studies using Newcastle Ottawa scale

Study, Year	Stars number		
	Selection†	Comparability‡	Exposure§
Agrawal, 2012 (103)	1	2	2
Aly, 2011(104)	1	0	2
Diez, 2012(325)	1	0	2
Dowdell, 2011(318)	1	0	1
Ford, 2004(319)	1	0	1
Graat, 2007(326)	0	0	1
Lee, 2013(320)	1	0	1
Lieberoth(321)	1	2	1
Lucke, 2007(327)	3	0	2
Niami, 2005(101)	1	1	1
Oraka, 2010(323)	1	2	2
Shaheen, 2008 (322)	3	2	1
Song, 2010(118)	0	0	2
Tran, 2011(328)	2	2	3
Trojan, 2014(102)	1	0	2
Young, 2001(324)	3	0	1

7.3.5 Meta-analysis

A meta-analysis of the twelve studies which provided sufficient data (101-103, 118, 320-327), found no association between alcohol consumption and the risk of asthma (pooled relative risk [RR] [95% confidence interval, CI]: 0.94 [0.85-1.04]) (Figure 6.2). Considerable heterogeneity was detected across studies (I^2 = 75%). There was no evidence of publication bias in the funnel plot (Figure 6.3), or in Egger's statistical asymmetry test (Egger's test P = 0.288, Figure 6.4).

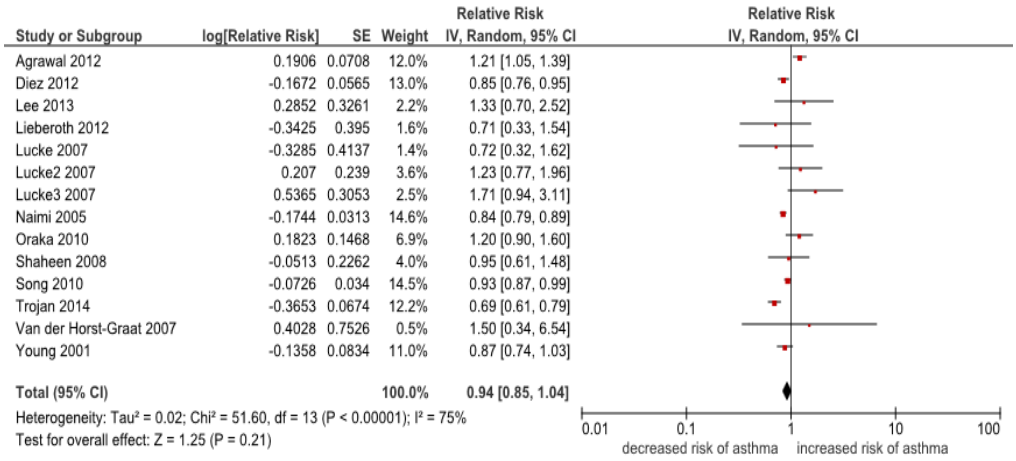


Figure 7. 2 Forest plot from meta-analyses assessing the effect of alcohol consumption on the risk of asthma

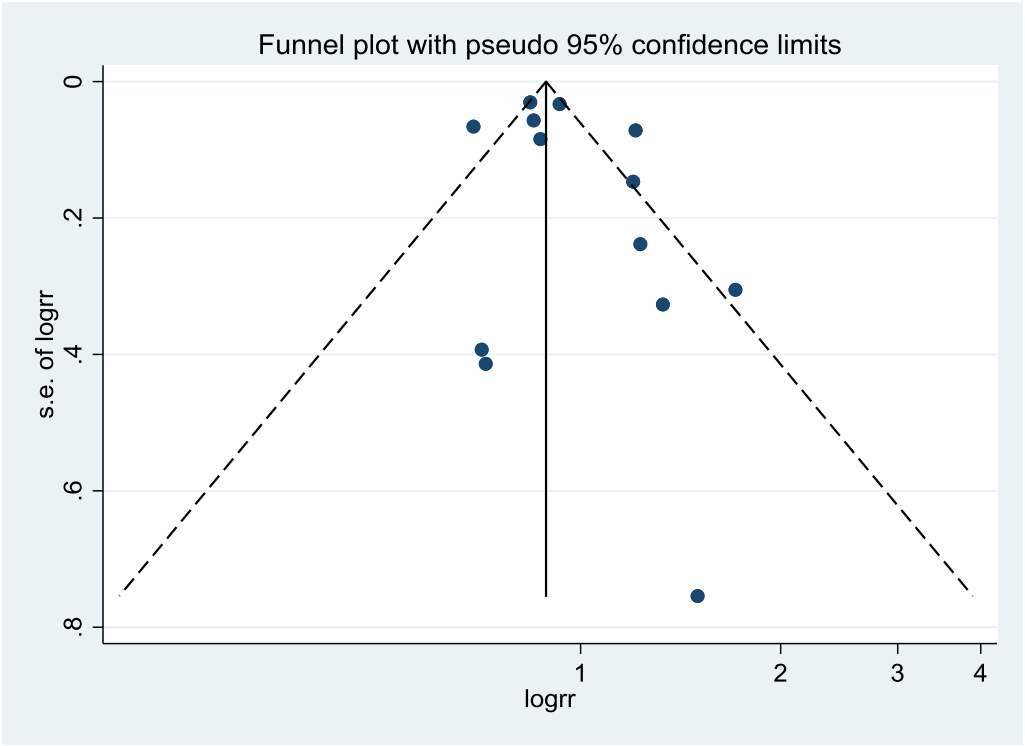


Figure 7. 3 Funnel plot of alcohol consumption and the risk of asthma

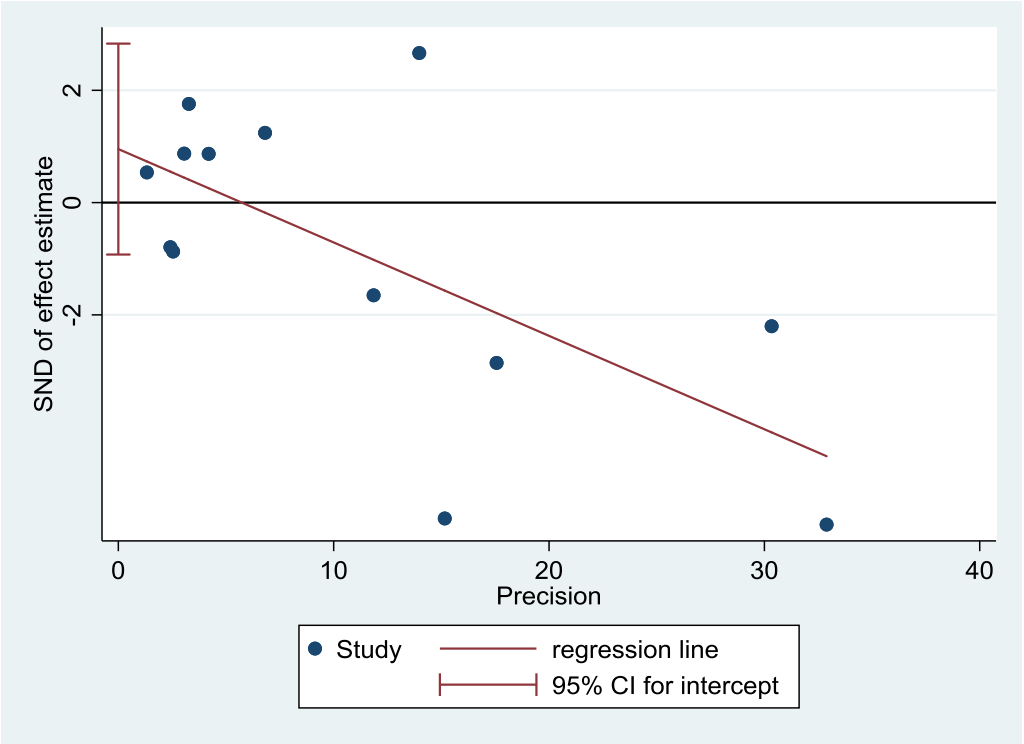


Figure 7. 4 Assessment of publication bias for asthma and alcohol; Egger's asymmetry test

7.3.6 Subgroup analyses

Subgroup analysis showed that there was some evidence of a difference according to year of publication (p=0.05); where the pooled effect size for the more recently published studies (2006-2015) was significantly smaller than those published between 1985 and 2005 (recent studies: RR=0.98, 95% CI; 0. 58-1.13; older studies: RR=0.84, 95% CI; 0.80-0.89, Figure 6.5).

Furthermore, heterogeneity between studies was explained by the continent in which the study was conducted (Asia, America, Europe, Australia, p=0.0001) (Figure 6.6); where the largest magnitude of effect was seen in the pooled analysis of two studies conducted in Asia (RR=1.22, 95% CI: 1.06-1.39); compared to the smallest magnitude of effect seen in the four studies conducted in Europe (RR=0.85, 95% CI: 0.77, 0.95).

Further subgroup analyses exploring reasons for heterogeneity in the meta-analysis (Table 6.3) found no statistically significant difference in the magnitude of effect by reference group of alcohol (no alcohol vs lowest category of exposure, P=0.32), methodological quality (high vs low, P = 0.95), adjustment of confounders (adjusted vs unadjusted analysis, P=0.39), study design (cross-sectional, case-control, cohort studies; P= 0.34), or asthma ascertainment (subjective vs objective, P=0.20).

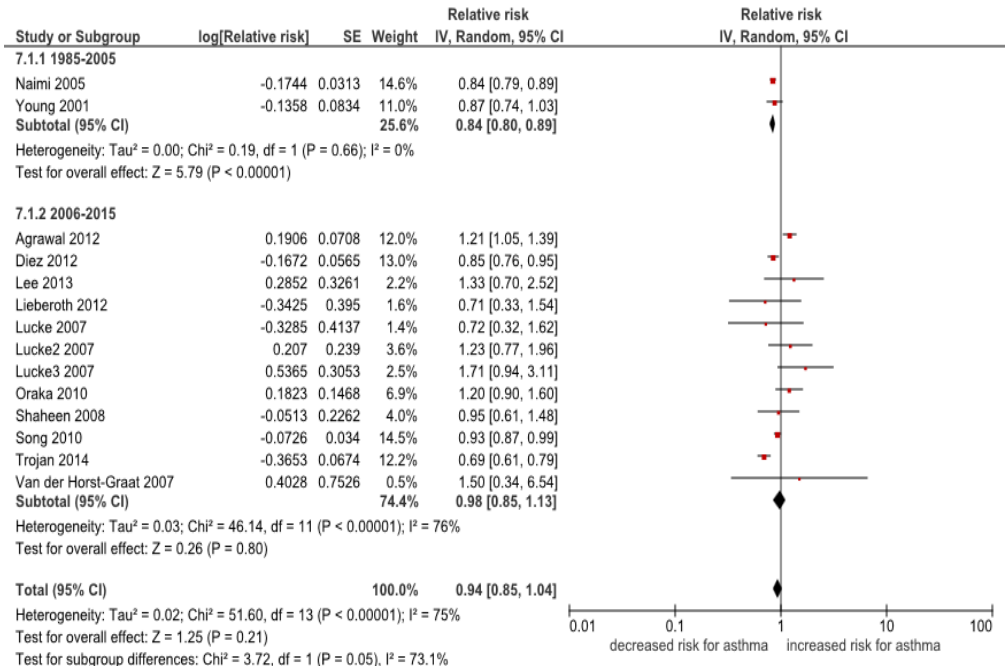


Figure 7. 5 Subgroup analysis assessing the effect of alcohol consumption on the risk of asthma according to publication year

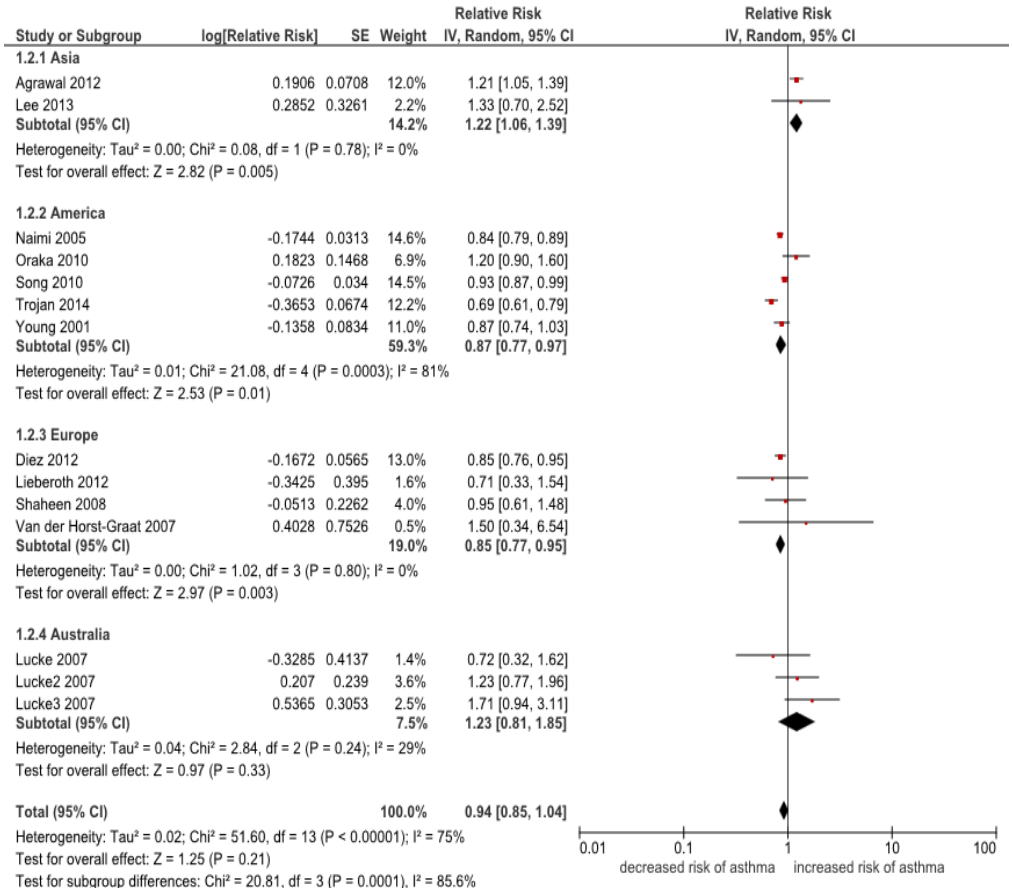


Figure 7. 6 Subgroup analysis assessing the effect of alcohol consumption on the risk of asthma according to geographic location

Table 7. 3 Exploration of heterogeneity between alcohol consumption and risk of asthma

Factor	Number of studies	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	12	0.94 [0.85, 1.04]	75%	
Study design				0.34
Cross-sectional	9	0.92 [0.82, 1.04]	82%	
Case control	2	0.88 [0.76, 1.03]	0%	
Cohort	1	1.23 [0.81, 1.85]	-	
Methodological quality				0.95
Higher quality	1	0.95 [0.61, 1.48]	-	
Lower quality	11	0.94 [0.84, 1.04]	77%	
Ascertainment of asthma				0.20
Objective	2	0.81 [0.61, 1.08]	93%	
Subjective	10	0.99 [0.87, 1.13]	70%	
Alcohol ascertainment				0.32
Alcohol vs no alcohol		0.99 [0.82, 1.19]	82%	
Alcohol vs lowest category of exposure		0.89 [0.81, 0.98]	56%	
Geographic location				0.0001
Asia	2	1.22 [1.06, 1.39]	0%	
America	5	0.87 [0.77, 0.97]	81%	
Europe	4	0.85 [0.77, 0.95]	0%	
Australia	1	1.23 [0.81, 1.85]	29%	
Effect estimate				0.39
Adjusted for confounders	5	1.01 [0.79, 1.28]	0%	
Unadjusted for confounders	7	0.89 [0.79, 1.01]	67%	
Publication year				0.05
1985-2005	2	0.84 [0.80, 0.89]	0%	
2006-2015	10	0.89[0.85,1.04]	76%	

7.3.7 Sensitivity analyses

A sensitivity analysis restricting to the seven studies which used non-drinkers as the reference group (102, 103, 323-327) found similar results to the main meta-analysis, where no significant association was seen (pooled RR= 0.99, 95%CI: 0.82, 1.19, I^2 = 82%, Figure 6.7).

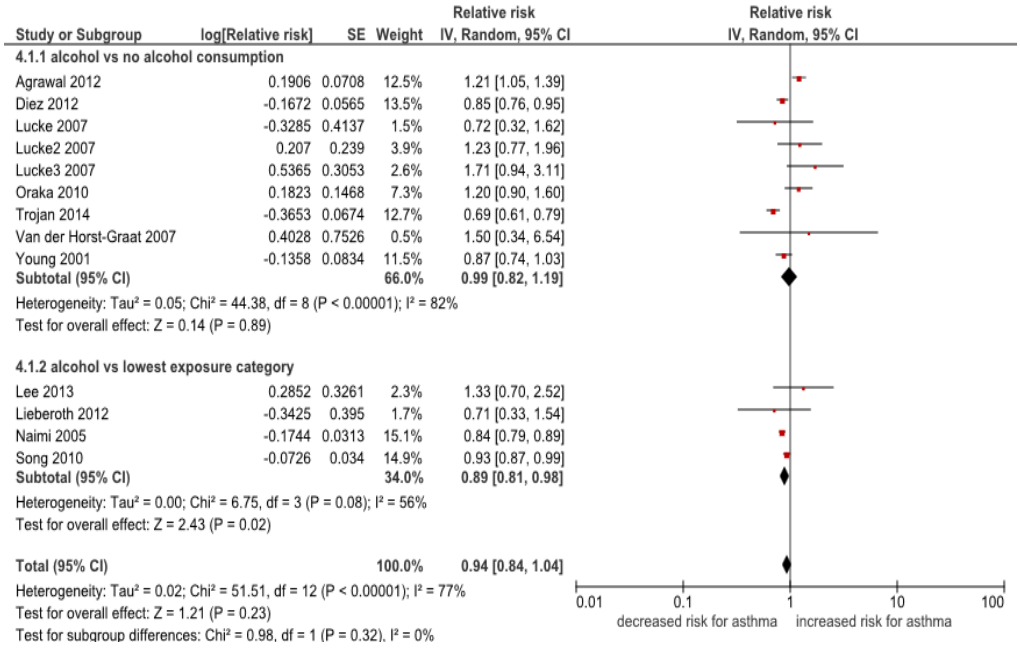


Figure 7. 7 Subgroup analysis assessing the effect of alcohol consumption on the risk of asthma according to reference group of alcohol

However, further sensitivity analyses restricted to studies which provided estimates adjusted for either smoking or body mass index (BMI) showed both significant pooled estimates (smoking-adjusted: pooled RR= 1.19, 95% CI: 1.05-1.34, I^2=0 (103, 322, 323): BMI-adjusted: pooled RR=1.17, 95%CI: 1.04-1.32, I^2=0) (103, 321-323).

One study included in the main meta-analysis provided further information on specific alcohol preference; where wine consumption does not seem to have an effect on the risk of asthma compared to people who preferred to consume beer (adjusted OR= 0.87, 95% CI: 0.51-1.46) (321).

7.3.8 Not included studies in the meta-analysis

Four of the 16 eligible studies could not be included in the meta-analysis: one study found that people who consumed ≥ 3 drinks per day had a similar risk of being hospitalized for asthma compared to those who were lifelong non-drinkers (adjusted HR=1.1, 95% CI: 0.8-1.5) (328). Another study found that alcohol consumption during pregnancy increased the risk of maternal asthma over 3-fold (RR=3.24, 95% CI: 1.65-6.34) (104). A further two studies found no significant difference in the number of alcoholic drinks consumed by people with and without asthma [mean difference of 0.22 drinks; p-value not reported (318); mean difference -0.5 drinks; p value=0.64 (319)]. The above two studies could not be pooled in a meta-analysis due to the lack of reporting of standard errors.

7.4 Discussion

7.4.1 Summary of the findings

Alcohol is a well-known risk factor for a range of diseases; however, until now there is much less awareness of the effect of alcohol on asthma. Consequently, alcohol consumption was examined as a risk factor for the development of asthma through meta-analyses of observational studies published over the last 30 years. The review showed that there is no effect of alcohol consumption on asthma. Similarly, a sensitivity analysis on drinkers compared to non- drinkers showed that alcohol has no impact on the risk of asthma (RR=0.99), further validating our initial findings. We also stratified our pooled results by reference group of alcohol, adjustment analysis, study design, and quality, and way of asthma ascertainment and no significant difference between studies were found, indicating a robustness of our findings. Subgroup analyses based on geographic location showed increased risks in Asia and Australia, but not in the other countries, where reduced risks were seen, which potentially reflect a slightly higher risk of asthma

arising from genetic differences in alcohol metabolism (329); it is possible that this explanation also accounts for the finding that alcohol can trigger bronchospasm in Japanese people with asthma (330). However, overall these findings suggest that alcohol intake is not a clinically significant risk factor for asthma.

7.4.2 Strengths and limitations

This study represents an extensive review gathering the available worldwide evidence, using comprehensive search strategies and with no language restriction. Also, the lack of evidence of publication bias further validates our results.

The high level of identified heterogeneity is a limitation of the systematic review. However, the performance of the exploratory analysis using subgroup analyses indicated that this could be partially explained by differences in study-level characteristics (geographic location and publication year). Another limitation of this review is the low methodological quality of the included studies, as only two studies found to be of high quality. Furthermore, only six of the 16 studies provided adjusted effect estimates, therefore increasing the potential for confounding in our effect estimate. Also, the measurements of alcohol consumption from self-reported questionnaires were susceptible to recall.

7.4.3 Comparison with other studies

A narrative review assessing the relationship of asthma and substance abuse concluded that pure ethanol can be effective and act as a bronchodilator for asthma by possibly relaxing the airway smooth muscle tone, although the mechanisms are not fully understood (331). Another study further supports the evidence that alcohol may also act as a bronchodilator (332).

Another narrative review of clinical and experimental studies showed contradictory evidence on the effect of alcohol on asthma. The review concluded that the evidence is mixed, with some studies reporting a protective effect of alcohol on asthma; whereas other showed that alcohol can be an aggravating factor for asthma. However, this review also suggests that additives in alcoholic drinks and not pure alcohol may be responsible for the bronchoconstriction caused (87). Moreover, allergic sensitivities to beer, spirits, and liquors components have also been studied. Specifically, allergy to grains and yeast have both suggested as a reason to beer sensitivity. Furthermore, liquors such as sherry and whisky are capable to cause allergic reactions due to specific non-alcohol components that these liquors include (333). Also, a further study proposed that sensitivity to the sulphite additives and salicylates which can be found in wines may play a role in asthmatic episodes (316). Although not directly comparable, we did not focus on the clarification of specific components of the alcoholic drinks that are responsible for asthma triggers. However the meta-analysis indicated that pure alcohol consumption is not associated with increased risk of asthma; rather, any effect is likely to be due to either to differences in metabolism or to the presence of other (non- alcohol) components in alcoholic beverages (333).

Our restricted analysis of studies presenting smoking-adjusted effect estimates showed an increased risk of asthma indicating that there is confounding by smoking in the association between alcohol and asthma. Similarly, our sensitivity analysis on BMI-adjusted estimates showed an elevated risk for the development of asthma, indicated that BMI is also a confounder to the association between alcohol and asthma. Therefore, future studies should adjust for smoking and BMI. The above findings were also consistent with other studies. Specifically, a meta-analysis on BMI and incident asthma in adults showed that both overweight and obesity were associated with a 51% increased odds of incident of asthma (334). Moreover, a dose-response relationship was also observed indicating that increasing BMI is associated with

increasing odds of incident of asthma. Another systematic review and meta-analysis quantifying the association on obesity and asthma which provided separate results according to gender found that overweight men were 20 times more likely to have asthma and obese men have a 43% increased risk for asthma. Similarly, the corresponding risk of overweight and obese women were 1.25 and 1.78 respectively (335). Also, another review assessing the effects of smoking on respiratory health indicated that smokers were 1.61 times more likely to develop asthma (336).

7.5 Conclusions

In conclusion, this systematic review suggests that alcohol consumption has no clinically relevant impact on the risk of asthma. Furthermore, the review suggests that there is confounding by BMI and smoking in the association between alcohol and COPD.

8 Chapter 8

Alcohol consumption and risk for COPD. A systematic review and meta-analysis

The present chapter presents a systematic review and meta-analysis aimed to systematically evaluate the available evidence from observational studies regarding the effect of alcohol drinking on the development of chronic obstructive pulmonary disease (COPD). This systematic review will provide a detailed summary of the research methods that were used, a result section including the characteristics of the studies, quality assessment, and estimates from the meta-analysis. Then a discussion section summarizing the findings of the present review, the advantages and drawbacks as well as a discussion of what the review has contributed (confirming/rebutting) to the existing evidence base have also presented.

8.1 Introduction

Alcohol consumption is potentially linked to the occurrence of COPD via several mechanisms. One possible underlying mechanism is through mucociliary dysfunction since alcohol can impair the innate immune response via altering the airway mucociliary clearance (337). Alcohol ingestion may also impair immunity via effects on macrophage phagocytosis, on alveolar epithelial barrier integrity and glutathione levels (116), potentially leading to COPD exacerbation. Also, alcohol consumption can interfere with some COPD medications (steroids and antibiotics), aggravating the risk for COPD development (116).

Smoking is also the most important risk factor for COPD risk, and there is evidence that smoking is an important potential confounder of any link between COPD and alcohol consumption. Specifically in one study they found that the association of alcohol with COPD death varied with smoking status, as occasional and moderate drinking but not high

drinking were associated with lower risk for COPD death among ex-smokers (235); whereas another study suspect that residual confounding by smoking may play a role in the explanation of their findings, as tobacco confounding may partly obscure the positive effect of alcohol on COPD but also may over-estimate the negative effect of heavy drinking on COPD (119). Also, a further study supports the hypothesis that confounding by smoking exists, as it was found that alcohol didn't have an effect on COPD exacerbation risk independent of smoking (116). However, primary studies may suffer from methodological weaknesses, where attempts to overcome confounding by smoking may have been inadequately performed.

However, to date, it is not clear whether alcohol consumption is a risk factor for the development of COPD. Some studies suggested that alcohol consumption can be a risk factor for COPD (115, 338, 339); however other studies showed that alcohol has a beneficial effect for COPD (118, 340). Also, a narrative review on alcohol and airway functions published on 2008, confirms the diversity of the results of studies on COPD and alcohol stating that it is challenging to draw a specific conclusion for this association (314). Therefore, a systematic review and meta-analysis were performed in order to summarize the mixed and inconsistent evidence and identify the impact of alcohol on COPD.

8.2 Methods

8.2.1 Identification of existing systematic reviews

At the first stage previously published systematic reviews and meta-analyses ascertaining the effect of alcohol consumption on the risk of Chronic Obstructive Pulmonary Disease (COPD) were searched. Detailed information for the systematic review search strategy is provided on Appendix 1. The searches did not identify any systematic reviews or meta-analyses estimating the effect of alcohol drinking on

the risk of COPD; hence a systematic review was conducted using the following methods.

8.2.2 Methods for conducting the systematic review

The methodology for the systematic review is presented in Chapter 2.

8.2.3 Search Strategy

The full search strategy is presented in Chapter 2. Specifically the following key words were used in every possible combination: (Chronic Obstructive Lung Disease or Chronic Bronchitis or Lung Emphysema) and (alcohol or alcoholism). The full search strategy for the three databases is presented in Appendix 2.

8.2.4 Data extraction

The data extractions are presented in Chapter 2.

8.2.5 Quality assessment

The quality assessment of the primary studies is presented in Chapter 2.

8.2.6 Data Analysis and Statistical Methods

The statistical analysis is presented in Chapter 2. Further subgroup analyses were conducted according to COPD definition (objective vs subjective). Two additional sensitivity analyses were performed. The first sensitivity analysis was conducted excluding a study which reported outlier results compared to the other studies included in the meta-analysis. In order to assess the role of smoking on the relation between alcohol and the risk of COPD, a further sensitivity analysis was performed in studies which provided smoking-adjusted effect estimates.

8.3 Results

8.3.1 Search results

The initial comprehensive search retrieved 4378 articles. A further of 14 articles were also included after the reference list search. The removal of duplicates left 3653 articles for inclusion. After the screening of the titles/ abstracts, a total of 192 studies remained for full-text screening. An additional 177 irrelevant articles were excluded due to: ineligible study design, all the study population had COPD, ineligible exposure and lack of information for both alcohol and COPD. Thus, 15 articles were included in this systematic review and 13 of them were also eligible for inclusion in the meta-analysis (Figure 7.1).

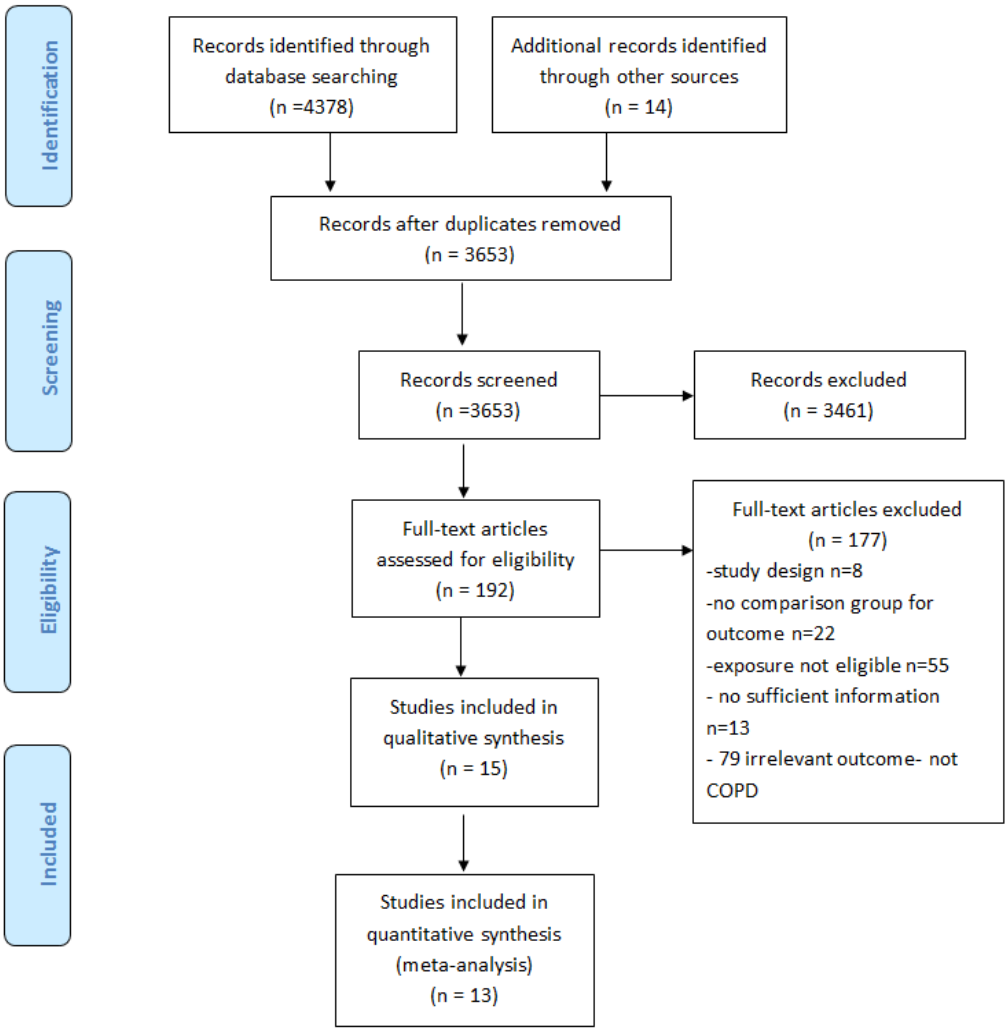


Figure 8. 1 Flow chart of studies

8.3.2 Characteristics of the included studies

The included studies were published between 1991 and 2013 and a total population of 539,250 participants from three different continents (Table 7.1). Specifically, six studies were conducted in Europe (119, 325, 326, 339-341), five were conducted in USA (115, 118, 328, 338, 342) and four were conducted in Asia (235, 343-345). The majority of the studies (12 of 15) were population-based (115, 118, 119, 235, 325, 326, 339, 340, 342-345), one was a hospital-based study(341), one was a lab-based study (338) and the last one was conducted in a health maintenance organization (328). Only four studies provided information about the participant's characteristics (115, 118, 325, 341). Briefly, the patients' age ranged from 53.8 to 63 (115, 118, 341); whereas two studies provided information on gender which showed that COPD patients were more likely to be female than male (range, 54.5% to 61.5%) (115, 325).

Nine studies were cross-sectional (115, 118, 325, 326, 338, 340-342), four were cohort (119, 235, 328, 343) and the remaining two were case-control studies (339, 344). Ten of the 15 papers provided adjusted effect estimates, all of these 10 papers adjusted for smoking (119, 235, 328, 338, 339, 341-345). Nine studies included the non-drinkers in the reference group (115, 119, 235, 326, 328, 341, 342, 344, 345); whereas the other six provided information for the lowest exposed alcohol category.

8.3.3 Exposure reporting

Alcohol consumption was assessed by self-report using a questionnaire in 13 of the 15 studies (115, 118, 119, 325, 326, 328, 339-345). The remaining two studies assessed the consumption of alcohol by interview (235, 338). The studies defined alcohol as: drinks past year, grams/week/day, drinks/day/week/month, glasses/day, bottle/week, units /week. In one study the definition of alcohol was not provided (115).

8.3.4 Outcome Reporting

Seven studies ascertained COPD using ICD codes from death records (119, 235, 339, 343-345) or from a hospital clinical diagnosis (328). Four studies ascertained COPD by self-report using a questionnaire (325, 326, 340, 341) and a further study used a self-report physician diagnosis for the assessment of COPD (115). Two studies used a physician diagnosis for the assessment of COPD (118, 342). One study ascertained COPD using a clinical diagnosis which also reported the definition used to ascertain COPD using the American Thoracic Society definition (338).

8.3.5 Quality assessment

The quality assessment score ranged from 2 to 7 stars (Table 7.2), with seven of the fifteen studies (46.6%) having a score of ≥ 6 stars indicating a medium risk of bias (119, 235, 328, 339, 343-345). The remaining studies had a lower score due to subjective reporting of COPD or due to reporting of crude (unadjusted) measures of effect.

Table 8. 1 Characteristics of included studies

Author & Year	Study design	Geographical location	Population	Characteristics of people with COPD	Number of included people	Alcohol ascertainment	Alcohol definition	COPD ascertainment	Adjustment
Calvert, 1991(338)	Cross-sectional	USA	Lab-based	-	541	Interview	Current (drinking during past year) vs former/non-drinkers	American thoracic society definition	Adjusted for: smoking, occupational dust, serum TCDD*
Diez,2012 (325)	Cross sectional	Europe (Spain)	Population-based households	61.5% female	21,230 people	Self-report questionnaire	Alcoholic drinks during last two weeks Yes vs no	Self-report questionnaire	-
Finkelstein, 2009(115)	Cross-sectional	USA	Population-based aged 40 years and older	Mean age: 60.3 45.5% male	18.342	Self-report questionnaire	Alcohol yes vs no	Self- report Physician diagnosis (subject reporting)	-
Graat, 2007(326)	Cross sectional	Europe (Netherlands)	Noninstitutionalized Population aged>60 years	Total Average age: 73,3 years 50% male	652 participants	Self-report questionnaire	Alcohol yes vs no Glasses/ day Abstainers (0< glasses/day<1), light, occasional, Moderate/ heavy drinkers (>3glass/day: men,>2 glass/day: women)	Self-report Questionnaire	-
Reilly, 2008(343)	Cohort	Asia (China)	Population-based (data base)	-	158,666	Self-report Questionnaire	Alcohol yes vs no ≥ 12 times during last year	Death records by ICD codes	Adjusted for: age, smoking, hypertension, no high school education, physical inactivity,

									underweight, northern or rural China
Schooling, 2009(344)	Case-control	Asia (China)	Population-based decedents aged ≥60 years	-	10484	Self-report questionnaire	High alcohol consumption (at least weekly, and >13.7 g (women) or >27.4 g (men) of ethanol/occasion) vs never drinking	Death records by ICD codes	Adjusted for: age, sex, education, physical activity, physical activity in longest held occupation and smoking
Shen, 2013 (235)	Cohort	Asia (China)	Population-based Elderly aged >65 years	-	62824	Interview	Excessive (>21 units/week for men) and >14 units/week for women vs never	Death records by ICD codes	Adjusted for age group, sex, education, housing type, monthly expenditure, smoking status, BMI, exercise, health status, smoking
Sisson, 2005(342)	Cross-sectional	USA	Population-based	Total: 46.6% male	15,294	Self-report questionnaire	>90 drinks/ month vs never drinker	Physician diagnosis	Adjusted for: age, sex, smoking, race/ethnicity, low education, BMI, diabetes, CHF
Song, 2010(118)	Cross-sectional	USA	Population-based middle-aged and older women	Mean age:53.8	38570 women	Self-report questionnaire	Alcohol intake rarely/never 1–3 drinks/ month, 1–6 drinks/week, and <1 drink/day)	physician diagnosis	-
Suadicani, 2001(341)	Cross-sectional	Europe (Denmark)	Hospital-based	Mean age: 63 years Only men	3331 men	Self-report questionnaire	Heavy use (> 35 drinks/ week) vs abstainers	Self- report questionnaire	Adjusted for: smoking, inhalation, retirement,

									systolic blood pressure, height, NS- phenotype
Tabak1, 2001(119)	Cohort	Europe (Finland, Italy, Netherlands)	Population-based middle-aged men	-	2953 men	Self- report questionnaire	High (>9 drinks/day) vs non-drinkers	Death records by ICD codes	Adjusted for: age, body mass index, pack-years of smoking, energy intake
Tabak2, 2001(340)	Cross sectional	Europe (Netherlands)	Population based Aged 20-59 years	-	13651	Self- report questionnaire	Moderate/ heavy (>30 grams/day) vs none/occasional (≤ 10 grams/day)	Self-report questionnaire	-
Tran, 2011(328)	Cohort	USA	People voluntarily underwent a health examination at health maintenance organization	Total 55% whites, 27% blacks, 11% Asians, and 4% Hispanics	126.019	Self-report questionnaire	Alcohol intake ≥3 drinks per day vs non-drinkers	Hospital diagnosis using ICD codes	Adjusted for: age, sex, ethnicity, body mass index, education, and smoking.
Yuan, 1997[a](345)	Cohort	Asia (China)	Population-based middle-aged men 45-64 years	-	18.136 men	Self-report questionnaire	≥29 drinks/week vs non-drinkers	Death records by ICD codes	Adjusted for age, level of education, and cigarette smoking
Zarizde, 2009(339)	Case-control	Europe/Russia Self-report	Population-based Aged 15–74 years	-	48.557	Self-report Questionnaire	Weekly intake (≥ 3 bottles of vodka vs < 0.5 bottles of vodka)	Death records by ICD codes	Adjusted for: age, city and smoking

*****TCDD: 2,3,7,8-tetrachlorodibenzo-pdioxin

[a] Data presented for chronic bronchitis and emphysema

[b] Data presented for chronic bronchitis

Table 8. 2 Critical appraisal of included studies using Newcastle Ottawa scale

Study, Year	Stars number		
	Selection†	Comparability‡	Exposure§
Calvert, 1991(338)	1	2	1
Diez, 2012(325)	1	0	2
Finkelstein, 2009(115)	1	0	1
Graat, 2007(326)	0	0	2
Reilly, 2008(343)	2	2	3
Schooling, 2009(344)	3	2	1
Shen, 2013(235)	2	2	3
Sisson, 2005(342)	2	2	1
Song, 2010(118)	0	0	2
Suadicani, 2001(341)	0	2	2
Tabak1, 2000(119)	2	2	2
Tabak2, 2000(340)	1	0	2
Tran 2011(328)	1	2	3
Yuan, 1997(345)	1	2	3
Zarizde, 2009(339)	4	2	1

8.3.6 Meta-analysis

Thirteen of the fifteen studies were included in the meta-analyses. Ten of the 13 studies provided data from which pooled Relative Risks could be estimated. A meta-analysis of these studies found no evidence of an effect of alcohol consumption on the risk of COPD (pooled relative risk [RR], 95% CI: 0.88-1.40, Figure 7.2). High heterogeneity was also

identified among the included studies (I^2=94%).

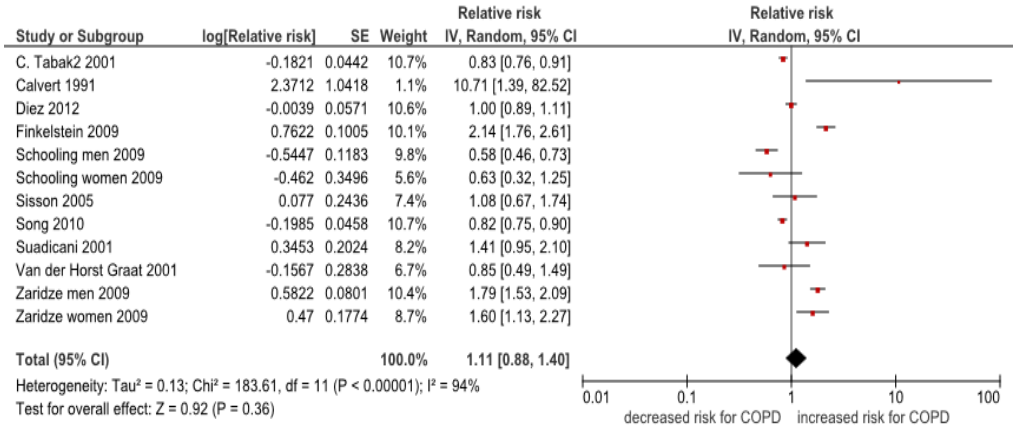


Figure 8. 2 Forest plot of the association between alcohol consumption and the risk of COPD

Similarly, a separate meta-analysis on three studies providing a measure of risk as hazard ratios found that alcohol drinking has no impact on the risk of COPD (pooled HR= 1.06, 95% CI: 0.75-1.49, I^2= 73%, Figure 7.3) (119, 235, 343). However, all of these studies reported the risk of death from COPD.

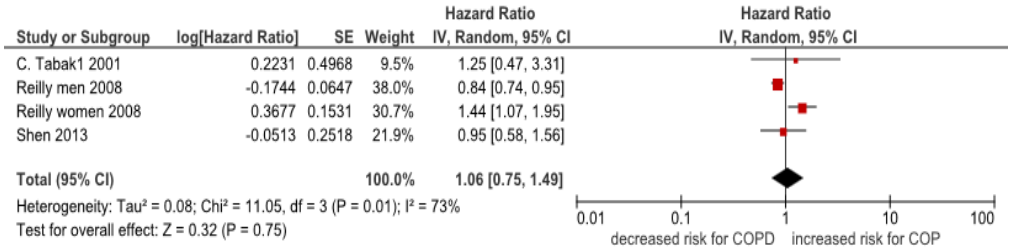


Figure 8. 3 Forest plot of the association between alcohol consumption and the risk of COPD on studies presented HRs estimates

Two further studies could not be included in the meta-analysis (328, 345). The first study assessed the effect of alcohol consumption on the risk of COPD hospitalization. This study showed that people who consumed ≥ 3 drinks per day had a similar risk of hospitalization for COPD as to those who were lifelong non-drinkers (adjusted HR=1.0, 95% CI: 0.8-1.3) (328).

The second study did not provide adequate information to calculate an effect estimate; therefore, the results of this study are presented in a descriptively way. This study showed that people who consumed ≥ 29 drinks per week had a similar risk of death from COPD and emphysema compared to those who were non-drinkers (345).

8.3.7 Publication bias

The visual assessment of the funnel plot from studies presented a pooled relative risk, showed that there is some asymmetry (Figure 7.4); however, no evidence of publication bias was detected from the Egger's asymmetry plot (Figure 7.5) (P=0.301). Publication bias could not be assessed in studies reporting Hazard Ratios due to an insufficient number of studies (n=3 studies).

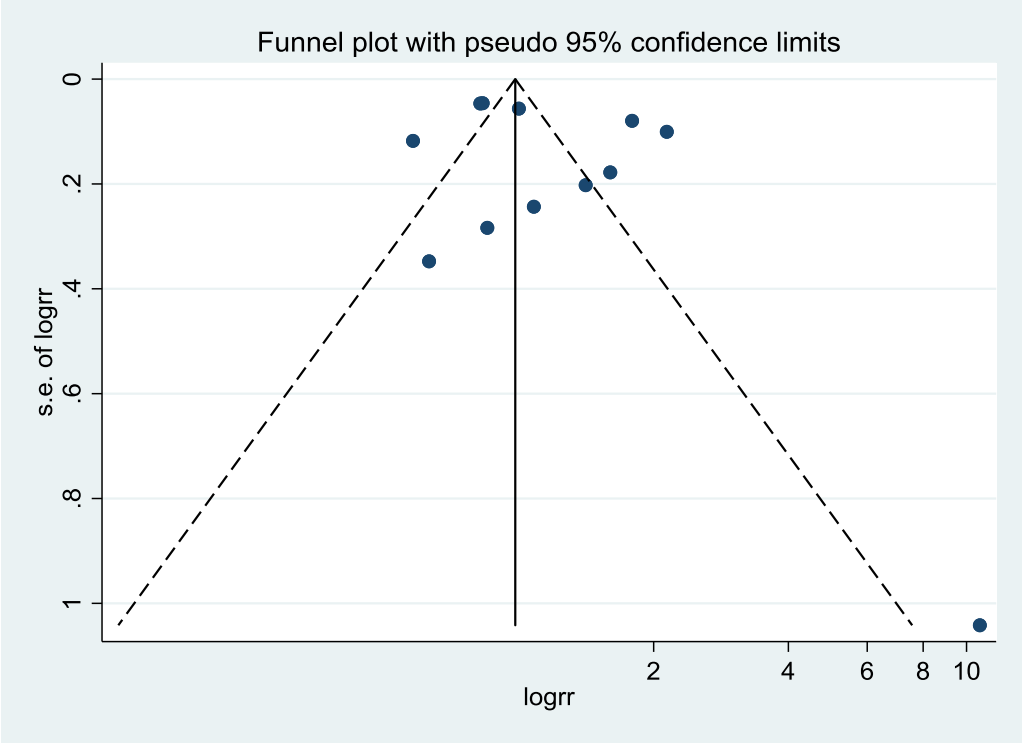


Figure 8. 4 Funnel plot of alcohol consumption and the risk of COPD

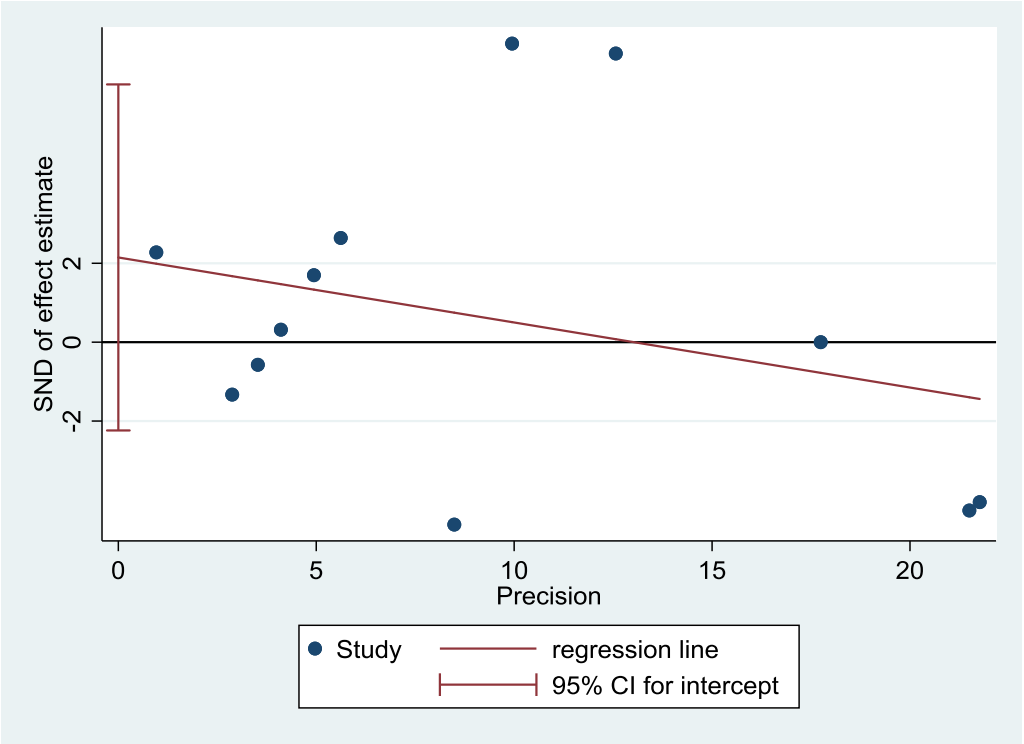


Figure 8. 5 Assessment of publication bias for COPD and alcohol; Egger's asymmetry test

8.3.8 Subgroup analyses

Due to the high level of identified heterogeneity in the studies reporting relative risks, subgroup analyses were performed in order to explore possible reasons for the heterogeneity. The results of the subgroup analyses were summarized in Table 7.3. Subgroup analyses identified significant differences according to geographic location (Asia; Europe; USA; p=0.0001); where the pooled effect size for the studies conducted in the USA was the highest (RR=1.50, 95% CI: 0.74- 3.03) (115, 118, 338, 342), and the lowest risk for alcohol and COPD was identified in one study conducted in Asia (RR= 0.58, 95% CI: 0.47, 0.73), which reported a protective effect.

Further subgroup analyses were also conducted; however, none of these explained the high levels of heterogeneity (study design, p=0.07, study methodological quality [high vs low quality], p= 0.81, adjustment of confounders [adjusted vs unadjusted analysis], p=0.62). Furthermore,

no statistically significant difference in the magnitude of effect was found by COPD ascertainment (objective vs subjective, p= 0.77), publication year (1985 - 2005 vs 2006 -2015, p= 0.87), and reference group of alcohol (non-drinkers vs lowest exposed category, p=0.69, Figure 7.6).

Table 8. 3 Exploration of heterogeneity between alcohol consumption and risk of COPD

Factor	Number of studies	Pooled RR (95% CI)	I^2	P value for subgroup differences
Overall result	10	1.11 [0.88-1.40]	94%	
Study design				0.07
Cross-sectional	7	1.22 [0.88, 1.67]	93%	
Case control	2	1.03 [0.53, 2.02]	96%	
Cohort	1	0.83 [0.76, 0.91]		
Methodological quality				0.81
Higher quality	2	1.03 [0.53, 2.02]	96%	
Lower quality	8	1.13 [0.89, 1.43]	93%	
Ascertainment of COPD				0.77
Objective	5	1.09 [0.72, 1.64]	94%	
Subjective	5	1.18 [0.84, 1.65]	95%	
Alcohol ascertainment				0.69
Alcohol vs no alcohol	5	1.02 [0.58, 1.79]	93%	
Alcohol vs lowest category of exposure	5	1.16 [0.89, 1.51]	955	
Geographic location				0.0001
America	4	1.50 [0.74, 3.03]	96%	
Europe	5	1.20 [0.89, 1.60]	94%	
Asia	1	0.58 [0.47, 0.73]	0%	
Effect estimate				0.62
Adjusted for confounders	5	1.21 [0.75, 1.94]	92%	
Unadjusted for confounders	5	1.05 [0.80, 1.38]	95%	
Publication				0.87

year				
1985-2005	5	1.07 [0.76, 1.52]	70%	
2006-2015	5	1.12 [0.80, 1.56]	96%	

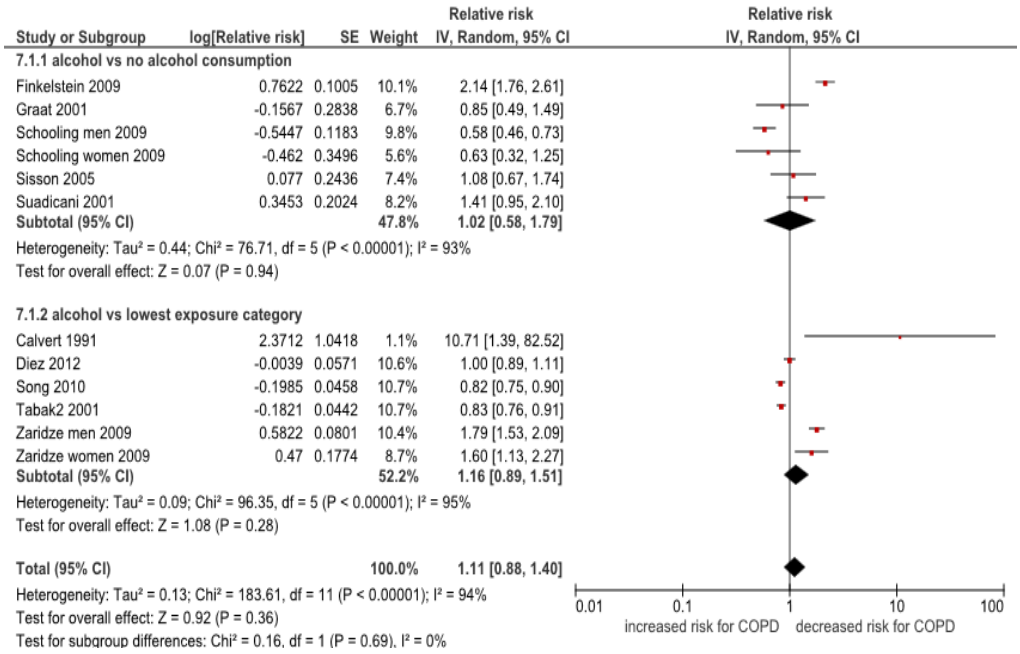


Figure 8. 6 Subgroup analysis assessing the effect of alcohol consumption on the risk of COPD according to ascertainment of alcohol

8.3.9 Sensitivity analyses

A sensitivity analysis restricting to the five studies which used non-drinkers as the reference group found the magnitude of effect was similar to the main meta-analysis which included all studies reporting risk ratios (pooled RR= 1.02, 95% CI: 0.58-1.79, I^2=93%) (115, 326, 341, 342, 344). A further sensitivity analysis was conducted excluding the study which had outlier results; this study recruited a highly selective population of workers who were exposed to tetrachlorodibenzo-p-diocin (TCDD- substance) (338). The sensitivity analysis found a similar magnitude of effect compared to the main meta-analysis which included all studies reporting relative risks (pooled RR=1.09, 95% CI: 0.86-1.37, I^2=94%). A further sensitivity analysis restricting to studies which provided smoking-adjusted estimates found

a similar magnitude of effect compared to the main meta-analysis (pooled RR= 1.21, 95% CI: 0.75- 1.94, I^2=92%, 5 studies) (338, 339, 341, 342, 344).

A further separate analysis was performed in studies reporting high alcohol consumption (326, 339-342, 344). The findings of this analysis showed that even high alcohol levels are not a risk factor for COPD development (pooled RR= 1.03, 95% CI: 0.74- 1.45, I^2=93%, 6 studies).

8.4 Discussion

8.4.1 Summary of the findings

Alcohol consumption was examined as a risk factor for COPD through meta-analyses of observational studies (case-control, cohort and cross-sectional) published in the last 30 years. Separate meta-analyses comparing the highest with the lowest or non-exposed alcohol intake category using a random effect model were conducted. Our findings indicate that alcohol consumption is not associated with COPD risk. These findings were consistent in the meta-analysis of studies provided RRs estimates and in studies provided Hazard ratio estimates from COPD mortality, but also in the sensitivity analysis comparing drinkers to non-drinkers. Furthermore, even high alcohol intake was not shown to have an effect on COPD. To assess the role of smoking as a confounder in the association of alcohol and COPD, a further analysis restricted on studies provided smoking-adjusted effect estimates found no evidence of increased risks of COPD in those who consume alcohol.

Subgroup analyses found significant differences between alcohol and COPD in relation to the study continent. More specifically, the highest COPD risk was observed in US studies and the lowest risk in a study conducted in Asia. Although it is not fully clear this difference in ethnic groups, it can be partially explained due to ethnic differences in access to care, normal spirometry or susceptibility to COPD. Furthermore, the

research found that black and Asian COPD patients were significantly less likely to be current smokers compared to white people indicating that smoking patterns may play an important role (346).

In the other subgroup analyses, no significant differences were identified on the relationship on alcohol and COPD according to study design, methodological quality, year of publication, adjustment or not for confounders, the definition of alcohol and COPD.

8.4.2 Strengths and limitations

There are some notable strengths of this study that deserve to be mentioned. The study represents a comprehensive review searching all the available worldwide literature using specific search terms for the outcome, exposure and the study design. No language restriction was imposed making our results more likely to be generalizable.

Also, separate in-depth meta-analyses were conducted in studies with relative risk estimates and in studies with hazard ratio estimates. The consistent result from both of the aforementioned analyses provides some validation to our results. Additionally, we attempted to explore reasons for heterogeneity between the study estimates through conducting a series of subgroup analyses.

Furthermore, the subgroup analyses indicated that the findings of this review were robust to differences in definitions of alcohol consumption, COPD, study design, study quality, year of publication and adjusted effect estimates as indicated in the subgroup analyses.

However, the review has also some limitations. Firstly, no clinical information for alcohol was captured and self-report questionnaires were used to assess alcohol consumption. Therefore, the self-reporting is subject to recall, where people with COPD may report their consumption of alcohol differentially to those who do not have COPD. Furthermore, the different definitions of alcohol in the included studies

resulted in high levels of heterogeneity which was primarily arisen according to subgroup analyses results on the study continent.

8.4.3 Comparison with other studies

A narrative review published in 2007 focused on alcohol's effect on airways functions stated that it is a challenge to draw firm conclusion on the role of alcohol on COPD (314). However, the narrative review suggests some themes that emerge, such as that heavy alcohol consumption is likely to worsen the smoking-related COPD risk. Furthermore, it is proposed that moderate alcohol consumption may reduce the risk for COPD death. The review also suggests that specific caution should be given to separate the effect of smoking in the analysis of alcohol and COPD. However, the finding of our systematic review and meta-analysis are not comparable with the above review; as we found that heavy alcohol consumption does not appear to be related to COPD risk. Also, the meta-analysis on hazard ratios estimates indicated no effect of alcohol on COPD mortality.

Our results are consistent with another two studies on alcohol intake and COPD exacerbations. More specifically, the first study evaluated the relationship between alcohol consumption and the risk of acute exacerbation of COPD. This study found no significant association on self-reported baseline alcohol intake and the risk of subsequent COPD exacerbations (117). Also, a second study conducted on a veteran population quantifying alcohol by AUDIT, CAGE or binge drinking was not associated with an increased risk of COPD exacerbation independent of tobacco use. Briefly, the initial age-adjusted effect estimates proposed an increased risk in patients with audit scores≥6, CAGE scores ≥2, however, when tobacco was included in the multivariate model the risk disappeared. These findings suggest that the initially observed association may not be due to the direct effect of alcohol on COPD but rather is due to the confounding by smoking which is mainly associated with alcohol consumption (116).

A separate analysis was performed in our review in studies that had provided smoking-adjusted effect estimates as smoking is the main risk factor for COPD; however, no significant association was identified in order to support the hypothesis of a synergistic effect of alcohol and smoking on the risk of COPD.

A systematic review and meta-analysis assessing the global and regional COPD burden across world regions of studies based on spirometry data found that the highest COPD prevalence was in America ranged from 13,3% to 15,2% in 1990 and 2010 respectively; whereas the lowest prevalence estimated in South East Asia (347). In accordance to this review, we found the lowest risk of COPD in one Asian study; whereas the studies conducted in USA, reported the highest risk. The Asian study was of high quality, adjusting for confounders; however, the outcome assessment was death from COPD whereas the others are mostly occurrence of COPD. However, when comparing the result from this study to the meta-analysis result from other studies which used death from COPD as the outcome, we do not see a similar protective effect of alcohol on the risk of COPD mortality.

8.5 Conclusion

This review did not support the hypothesis that alcohol consumption, even in high levels, has an effect on Chronic Obstructive Pulmonary Disease. A significantly decreased risk was only identified in Asian study.

9 Chapter 9

General discussion

9.1 Overview

Alcohol is one of the most widely consumed products in the world. Moderate alcohol consumption has some benefits, as it can improve mood and social integration, and may also protect, at low levels of intake, against cardiovascular disease and diabetes mellitus (252). However, drinking alcohol to excess can have negative effects, increasing the risk of health problems, accidents, injuries, crime and episodes of violence (252).

Alcohol consumption is a well-established risk factor for a range of diseases and disorders, with cancers (348) and gastrointestinal diseases (349, 350) being perhaps the most widely researched. However, the spectrum of health effects of alcohol could be substantially greater than this, but in some disease areas, very little research has been carried out. This is particularly true of respiratory disease. Alcohol may have an impact on the respiratory system by weakening the immune system, leaving people more susceptible to infection with bacteria, mycobacteria or viruses; by contributing to weight gain and hence to obesity-related diseases such as sleep apnoea, and perhaps also, through effects on inflammation, influence the risk of asthma and COPD. The research described in this thesis explores some of these potential associations and finds increased risks of clinical relevance in relation to several lung diseases. In some cases, these increased risks occurred at low levels of alcohol intake. The main associations described are now discussed, in turn.

9.1.1 Findings on alcohol and ARDS

ARDS is a rare disease with a crude incidence of 78.9 per 100,000 person-years (138). However, this disease is important as it is a life-threatening condition with high mortality which varies across countries. In UK, ICU and hospital mortality rates from ARDS are 41.9% and 53.5% respectively (351). ARDS is a common and important complication of critical illness; globally representing over 10% of total ICU admissions and 23% of all patients requiring mechanical ventilation, thus have a high potential to utilize significant healthcare resources (136). ARDS is also an important condition due to the fact that it is very expensive to treat. Estimates have shown that the cost for ICU care accounted for 13.4% of hospital costs. In USA, estimates have shown that the average total hospital costs for ARDS were $128,860, with the majority of this cost born in the ICU ($97,810)(352).

In this thesis chronic alcohol abuse was found to be a significant, independent risk factor for the development of acute respiratory distress syndrome (ARDS) among critically ill patients, where alcohol abusers had an approximate 1.9 -fold increase in the odds of developing ARDS. This finding suggests that screening for alcohol use, in acutely ill patients admitted to hospital using tools such as AUDIT or SMAST(12, 13), may help to predict the risk of ARDS. The review also found that the increased risk applied predominantly to ARDS arising from sepsis, with sepsis patients who also consume alcohol being nearly three times more likely to have ARDS. However, the more targeted the approach is, then the cheaper this would be. Therefore, knowing that sepsis is the main risk factor for ARDS risk, the main focus should be on screening for alcohol use in those acutely ill patients who are admitted to hospital with sepsis.

9.1.2 Findings on alcohol and OSA

Obstructive sleep apnoea (OSA) is the most common medical disorder that causes excessive daytime sleepiness and is considered a major

public health issue with significant impact on health care expenditure. OSA prevalence ranges from 9% to 38% in different studies, but is particularly common, with prevalence exceeding 30%, in people who are obese (130). Therefore, the prevalence of sleep apnoea is increasing in line with trends of increased obesity. Moreover, the increase in OSA prevalence can also be due to changes in measurement techniques and definitions for classifying respiratory events. However, even the increase in OSA knowledge there is still a large number of undiagnosed and untreated patients, as a result leading to a higher risk of other health complications. These consequences result in a significant economic burden (353).

In this thesis alcohol consumption was found to be an important risk factor for the development of OSA, as it significantly increased disease risk by 25%. Moreover, the association was independent of BMI. Furthermore, the review indicated that people in low/ middle -income countries who consume alcohol appear to have a higher risk of sleep apnoea than people consuming alcohol in high-income countries. This finding may be related to misclassification bias where there is an under-diagnosis of OSA due to lack of evaluation or tests to assess it. The included studies of this review were published from 1985 to 2015; however, during this period it is likely to have been changed in the ascertainment of OSA, which can possibly explain the fact that the most recent studies published from 2006-2015 showed that consuming alcohol was associated with a higher risk of sleep apnea in the subgroup analysis due to better ascertainment and reduction in misclassification bias.

More evidence from a separate review of randomized trials assessing the impact of alcohol on breathing parameters during sleep further supports the findings from this systematic review. Specifically, it was found that alcohol is a significantly increased risk factor for OSA; further suggesting that alcohol consumption prior to falling asleep results in significant increase in Apnea–Hypopnea Index (AHI) (354). Therefore, consuming alcohol just before retiring to bed (nightcap), should be

avoided in order to reduce the risk of OSA. Moreover, the understanding of the impact of alcohol on the risk of OSA may lower the health-related costs from the care of this disease.

9.1.3 Findings on alcohol and CAP

Pneumonia is a common lower respiratory tract infection, for which treatment with simple antibiotics usually results in complete and uneventful recovery, which sometimes causes death. Pneumonia is also a costly infection as it is associated with high rates of hospitalization and length of hospital stay. According to NICE, each year in UK between 0.5% and 1% of adults will have community-acquired pneumonia (CAP). Moreover, 5-12% of adults with lower respiratory tract infection who visit GP are diagnosed with pneumonia, of whom, 22-42% will be admitted to hospital and between 5-14% will die; whereas 1 to 10% will need intensive care unit treatment (355). Furthermore, the economic burden of CAP in Europe is high and it is approximately 10.1 billion per year; of which €5.7 billion, €0.5 billion and €0.2 billion are the costs associated with patient care, outpatient care, and drugs respectively. Also, the indirect costs of lost working days are estimated to be €3.6 billion (76).

This thesis indicated that alcohol consumption is an important risk factor for CAP as it increases the risk of CAP by 83% among people who consume alcohol at all or in higher amounts relative to those who consumed no or lower amounts of alcohol. Furthermore, a dose-response relation was present indicating an 8% increased risk of CAP for every 10-20 grams of daily alcohol consumption. Alcohol can make people more susceptible to lung infections including bacterial pneumonia, further increasing the risk of mortality and morbidity and contributed to the pneumonia burden of disease (258). Therefore, knowing the current situation of the substantial impact that alcohol has on the development of community-acquired pneumonia, specific measures should be taken to reduce the consumption of alcohol in

order to further reduce the hospitalization and related costs of treatment as well as the mortality of CAP.

9.1.4 Findings on alcohol and tuberculosis

Tuberculosis (TB) is a common worldwide disease and is also a major infectious cause of the global burden of disease. Although TB is treatable with antibiotics it can potentially be fatal if left untreated and furthermore demands high costs for treatment. More specifically, TB is responsible for 1.8% of all disability-adjusted years lost and for 2.2% of all deaths (356). Alcohol consumption is a major contributor to the global TB burden of disease as it has estimated to cause 22 incident cases and 2.35 deaths per 100.000 people with TB in 2014 (69).

In this thesis, alcohol was found to be an important risk factor for TB with an approximately two-fold increase in TB risk. An exposure-response analysis showed that for every 10-20 grams daily alcohol intake, there was a 12% increase in the risk of TB. Also, persons with compromised immune systems, such as people living with HIV, have a higher risk of having TB. Considering the substantial effect of alcohol on TB, this indicates that more action to target the harmful use of alcohol for the prevention and treatment of TB are needed. Moreover, England has high rates of drinking and also has the highest TB rates in UK and further in Western Europe; therefore, social protection measures and patient support should be implemented for the management of TB and alcohol comorbidity. The knowledge of the high impact of alcohol consumption on TB can further support the implementation of WHO health target to end the TB epidemic and eliminate the death and incidence rates from TB.

9.1.5 Findings on alcohol and asthma

Asthma is a common chronic lung condition, especially in children, causing wheezing and breathing difficulties. Asthma is usually treated with bronchodilator and steroid inhalers. Asthma causes 1% of all

disability-adjusted life years lost and 0.7% of all deaths (356) and approximately £1.1 billion per year in UK health service. Therefore, identification of possible risk factors for this disease is important.

This thesis found that alcohol consumption has no significant effect on the risk of asthma. However, smoking and BMI seemed to be important confounders, where evidence from our sensitivity analyses restricted to studies which adjusted for both BMI and smoking indicated an increased risk of asthma. Therefore, smoking and BMI moderate the effect of alcohol on the risk of asthma. More evidence arising from a recent meta-analysis which found that the combined effect of BMI, smoking, drinking alcohol and solid fuel use were associated with double or triple risk for asthma development (357). Furthermore, Asians appeared to have a high incidence of bronchoconstriction after drinking alcohol, which leads to higher risk for asthma development, and this fact was also apparent in our analysis where a higher risk was only found in Asian people compared to American and European populations.

9.1.6 Findings on alcohol and Chronic Obstructive Pulmonary Disease

Worldwide, chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality, with high health-care costs. Specifically, COPD contributes to approximately 3% of all disability-adjusted life years lost and to 5.36% of all deaths (356). Therefore, COPD is a serious disease which is more common in later life, with smoking being one of the most important risk factors.

This thesis found no significant evidence that alcohol intake had an impact on the risk of COPD. We further found that restricting our analyses to studies which had an adjustment for smoking did not alter these findings, which implies that alcohol is not a risk factor for COPD regardless of smoking status. However, further analysis suggested that differences in COPD risk exist according to ethnicity; where Asian

people who consumed alcohol had a significantly lower risk in COPD compared to European and American people. This finding may be due to ethnic differences in the susceptibility to COPD or in the way that cigarettes were smoked; or due to chance as a result of only one study being identified in an Asian population.

Overall, the thesis highlights that individuals who consume alcohol are particularly susceptible to respiratory diseases and specifically they are more likely to develop acute respiratory distress syndrome (ARDS), pneumonia, tuberculosis (TB), and obstructive sleep apnoea (OSA). Alcohol seems to have an effect on infectious diseases as it weakens or impairs the immune responses by damaging immune cells and therefore leaving people susceptible to pulmonary infections. However, for OSA given the study design, the low quality of the included studies, the risk of bias (mainly due to potential confounding, but also some concern for measurement bias), the considerable heterogeneity, and the concern for publication bias, it seems that the strength of the evidence is “very low”, limiting the degree of confidence in the results. On the contrary, for ARDS, most of the evidence came from cohort studies, limiting the possibility of selection bias and also providing a temporal framework to assess causality and therefore providing strong scientific evidence. ARDS was ascertained using an objective measurement and moreover, low levels of heterogeneity and no publication bias were identified. The magnitude of effect was also large and the majority of studies adjusted for potential confounders, permitting a greater confidence in the findings.

Similarly, for TB and CAP the main reasons to downgrade the evidence quality were the high level of heterogeneity and risk of bias, mainly due to selection bias and lack of adjustment for confounders. However, a large magnitude of effect, a dose response effect, the objective ascertainment of CAP and TB, the non-evidence of publication bias and the fact that the majority of the studies adjusted for confounders; are all reasons to upgrade the assessment of evidence quality.

On the contrary, the thesis suggests that alcohol consumption does not have an effect on asthma. However, in the majority of relevant studies asthma was assessed subjectively, thus downgrading the evidence quality. Also, of the sixteen studies, twelve were cross sectional; only six adjusted for confounders and only two were of high quality. Moreover, even if publication bias was not present; high levels of heterogeneity were identified and an exposure-response analysis could not be carried out due to lack of data. Also, the risk of bias due to confounding is a significant concern in the types of observational study designs in the review. Furthermore, the presence of confounding by BMI and smoking may draw into question about the validity of the overall estimate.

Alcohol consumption was also not found to be an independent risk factor for COPD, however in this review a high level of heterogeneity was identified and many studies were cross sectional which does not help to determine cause and effect. Therefore, the findings from this review should be interpreted with caution.

9.2 Implication of study findings

Overall, alcohol appears to affect the respiratory system; and the findings of the thesis highlight a higher degree of confidence especially for ARDS, tuberculosis and pneumonia. Healthcare decisions for individual patients and for public health policies should be informed by the best available research evidence. The objective of systematic reviews and meta-analyses is to identify, assess, summarize and quantify all the available evidence from the primary studies. Therefore, systematic reviews provide the best source of evidence and play a vital role in decision making in evidence-based practice. Therefore, the results arising from this thesis can have implications on knowledge, clinicians, public health, and policy.

The higher risk of OSA in people who consumed alcohol can be used to recommend advising against alcohol in people with, or at high risk of, OSA. Also, timing and regularity of alcohol consumption are likely to be important to its effect on OSA. Furthermore, the fact that the association appeared stronger in countries of low and middle income indicates that effective public health interventions are crucial especially in these countries. As TB and CAP are both still major global health problems, the findings of an increased risk due to alcohol consumption makes the development of effective policy measures, especially in vulnerable populations, and treatment interventions, are imperative for the prevention of these diseases. Furthermore, although ARDS is a rare condition, it has a high mortality so identifying and intervening to reduce alcohol intake is likely to reduce the incidence of this condition. Also, specific attention should be given to the most vulnerable groups (sepsis patients) to eliminate the aggravating factor of alcohol in the development of ARDS.

9.2.1 Knowledge

The findings from the present review can be used to improve the knowledge and furthermore:

- Help in clarification and better understanding of the risk of alcohol on severe respiratory diseases.
- Present accurate and transparent information in order to help people to make informed choices about their own drinking for a better life quality.
- Support individual behaviour change.

9.2.2 Clinicians

The findings of these reviews can support clinicians when faced up with questions of how to treat patients with lung diseases and thus

counseling patients to reduce alcohol consumption and hence reduce the risk of serious respiratory illness. Therefore clinicians, doctors and nurses in specialist and general practice setting should be informed about these increased risks of severe respiratory disease resulting from alcohol in order to make the best effort for both the early recognition /screening and brief interventions of alcohol in patients with respiratory diseases. Moreover, healthcare professionals should be regularly trained in order to ensure the accessibility of effective treatment and rehabilitation for harmful or dependent alcohol drinkers.

In general, this research will help to improve patient care by providing clinicians and patients with reliable information on the effects of alcohol consumption on the risks of common respiratory diseases.

9.2.3 Public Health impact

Alcohol misuse is a very important public health problem in all around the world. Systematic reviews can lead as supporting evidence on delivering alcohol brief interventions on primary care settings. The implementation of early interventions can have a high public health impact on the reduction of alcohol consumption in people; and especially on those who drink in a harmful way before they become alcohol dependent and making their treatment very difficult. Therefore, society should be responsible for the provision of treatment services for alcohol dependents in the base of health protection/ improvement.

Alcohol production, distribution, and marketing are becoming increasingly globalized. Furthermore, nowadays cheap alcohol is readily available. Therefore, the implementation of price controls through taxation on alcohol products can be an effective public health measure aiming to reduce affordability and availability of alcohol. Also, restriction of alcohol consumption, setting minimum drinking age legislation, can further help to control the availability of alcohol in people.

Furthermore, more proactive public health measures aiming to reduce the harmful use of alcohol consumption can further reduce:

- hospital admissions and alcohol-related deaths
- the annual cost of respiratory diseases
- the economic burden- annual costs from alcohol
- the wider harms of alcohol including alcohol-related medical problems, road accidents, crime and violence episodes or loss of productivity

9.2.4 Policy

An alcohol policy should consist of a set of principles and strategies in order to be effective and applicable both in national and international level. These systematic reviews and meta-analyses highlight that alcohol intake is linked to increased risks of several severe respiratory diseases (acute respiratory distress syndrome, obstructive sleep apnoea, community-acquired pneumonia and tuberculosis) in adults. Reducing alcohol consumption is highly likely to reduce the risk of these diseases. Therefore, it is important that accurate data from systematic reviews to be readily available to policymakers. Thus, this evidence can be used to inform policy and can be taken into account for the implementation of policy interventions to address chronic respiratory diseases.

Furthermore, the results of these reviews could help to inform UK government strategy for alcohol consumption in terms of building the evidence base about the risk of alcohol on respiratory system in order to help to promote good practice and guidance using this evidence. In general, the evidence of these reviews can help in the development of global and national alcohol policies aiming to reduce the harmful alcohol use.

Therefore, the main policy components should include:

- Strengthening of countries policies to reduce alcohol use and its health consequences
- Implementation of targeted measures to reduce both affordability and availability of alcohol

- Implementation of higher taxes aiming to reduce affordability
- Implementation of highly targeted measures for heavy drinkers
- Introduction of a minimum unit price aiming to further reduce the harmful use of alcohol
- Restrictive rules of alcohol advertising

This thesis reveals the existence and the magnitude of a problem arising from the consumption of alcohol in many respiratory diseases. Therefore, the findings from this scientific research can have an impact on public policy and also play a key role in the policy decision. Policy makers should be aware on the health effects of alcohol on respiratory system in order to make the best effort to develop health policies to address the problem. This can be achieved by building the evidence and strengthening government's policies on alcohol reduction. Moreover, the implementation of specific and targeted price policy measures, such as taxation of alcoholic beverages based on their alcohol content can be an effective measure affecting consumers demand and thus aiming to control heavy drinkers and alcohol abusers who experiencing the greatest amount of harm in the community. Also, policies that reduce the affordability are very effective; and therefore the government should support the implementation of pricing measures, including a minimum unit alcohol pricing, which can substantially reduce the alcohol harm and increase government's revenue. To sum up, alcohol taxation and pricing policies are cost- effective measures to eliminate the consequences of alcohol consumption.

Moreover, findings from the thesis emphasize the necessity of interventions to prevent heavy alcohol consumption, for example by clinicians dealing with patients with respiratory diseases, through appropriate history-taking and delivery of alcohol interventions. Furthermore, the development of alcohol treatment programs for those who seek treatment can further improve lung health.

9.3 Strengths and limitations

The main strengths of the systematic reviews and meta-analyses are that comprehensive and systematic search strategies were used. Briefly, the comprehensive search strategies included using MeSH terms and combinations of keywords for both exposures and outcomes. Also, specific search filters for the observational studies were used (147). Furthermore, three databases were searched (Medine, EMBASE, and Web of Science) and the available worldwide evidence was searched without any language restriction making the results more likely to be generalizable. In addition, the reference lists of the included studies were further searched in order to include potential eligible studies. Another important strength of the study is the quality assessment of the included studies which performed in each of the systematic reviews. The screening of titles and abstracts as well as of the full texts was performed in duplicate by two reviewers aiming to eliminate the possibility of selection bias. In the same way, doubling in the data extraction forms was followed. Also, the series of systematic reviews and meta-analyses were conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (145) and the Meta-analysis Of Observational Studies in Epidemiology (146) and the protocol of the study was published in PROSPERO under the registration number CRD42015029910.

Taking into account the fact that the definition of alcohol consumption varies between the different studies, it is noteworthy the effort we made to define the degree of exposure to alcohol following the CDC guidelines and the Dietary Guidelines for Americans. Due to anticipated heterogeneity between studies, we performed various explorations of heterogeneity using subgroup analyses and sensitivity analyses. Also, separate analyses were performed included the studies which have adjusted for important confounders such as age, smoking, BMI, HIV to assess whether the effect was maintained after adjustment. Furthermore, we assessed for the evidence of publication bias visually through the Begg's funnel plot and formally using the Egger statistical

test, with only one of the meta-analyses finding potential evidence of publication bias. Where possible, a dose-response analysis was also implemented strengthening further our results.

However, there are also some notable limitations. An attempt was made to include all the available published evidence; however grey literature and conference proceedings were not included in the review. Therefore, it is likely that a small number of potentially eligible unpublished studies may have been missed. As our reviews featured diverse populations, it is not surprising that high levels of heterogeneity were identified in five (TB: I^2=82%, OSA: I^2=82%, CAP: I^2=91%, COPD: I^2 = 94%, asthma: I^2=91%) of the six reviews. Several other sources of heterogeneity were explored using subgroup and sensitivity analyses however it is likely that we were not able to explain all of the variation identified in the meta-analyses.

Also, the included studies used different exposure measurements and cut-off values. To provide some consistency across studies, where possible, we used defined consumption of alcohol based on the CDC guidelines and the Dietary Guidelines for Americans, however in several papers there was insufficient information presented, therefore we accepted the paper's definition of high and low alcohol consumption. Thus, this created a serious challenge for these reviews in terms of categorizing the exposure to alcohol into low, middle and high groups; thus, there is the potential for misclassification to exist.

The self-reporting of alcohol consumption in the majority of the studies included in the reviews could lead to recall bias, where people with the severe respiratory diseases may remember their exposure to alcohol differently to people without the disease. The results are likely to have some residual confounding due to lack of adjustment, therefore confounding for other existence factors that were not usually adjusted for in the included studies could not be explored. Also, the inclusion of cross-sectional studies in our review has limited our results as cross-

sectional studies can't assess a temporal relationship between exposure and outcome.

9.4 Recommendations for future work

The thesis has highlighted the need of the implementation of further cohort studies in the future, which assess the effect of alcohol on the risk of severe respiratory diseases. An important advantage of the cohort studies is the fact that exposure is identified before the outcome, can lead to a temporal framework in order to assess causality and therefore can provide stronger scientific evidence compared to other comparative observational designed studies. Due to anticipated confounding in the observational studies, there is a need for future studies to perform adjusted analyses which take into account important prognostic factors that may have influenced the association of alcohol and lung diseases.

Also, future studies should be designed using validated assessment methods for alcohol consumption such as AUDIT questionnaires (12), instead of using a self-report measurement for alcohol, which can be subject to issues related to recall. Moreover, further research needs to focus on the causal architecture that underlies the disease instead of solely the identification of the risk factors. Therefore, the application of Bradford Hill criteria for the determination of causal inference should be implemented in future studies.

9.5 Overall conclusion of the study

This thesis has evaluated the effect of alcohol consumption by systematically reviewing the available worldwide literature on the risk of the development of severe respiratory diseases. Furthermore, the thesis highlights that alcohol intake is linked with an increased risk of tuberculosis, community-acquired pneumonia, obstructive sleep apnea, and acute respiratory distress syndrome and thus suggesting that reducing alcohol intake may play an important role in severe respiratory disease prevention. However, the strength of the relation appeared to differ according to specific characteristics.

Appendices

Appendix 1. Search Strategy for systematic reviews

Medline (Ovid) search terms
1. Meta-Analysis as Topic/
2. meta analy$.tw.
3. metaanaly$.tw
4. Meta-Analysis/
5. (systematic adj (review$1 or overview$1)).tw
6. Exp Review Literature as Topic/
7. or/1-6
8. cohrane.ab
9. embase.ab
10. (psychlit or psyclit).ab
11. (psychinfo or psycinfo).ab
12. (cinahl or cinhal).ab
13. science citation index.ab
14. bids.ab
15. cancerlit.ab
16. or/8-15
17. reference list$.ab
18. bibliograph$.ab
19. hand-search$.ab
20. relevant journals.ab
21. manual search$.ab
22. or17/21
23. selection criteria.ab
24. data extraction.ab
25. 23 or 24
26. Review/
27. 25 and 26
28. Comment/
29. Letter/

30. Editorial/
31. animal/
32. human/
33. 31 not(31 and 32)
34. or/28-30,33
35. 7 or 16 or 22 or 27
36. 35 not 34
37. exp Alcohol-Related Disorders/
38. Alcohol Drinking/
39. (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw.
40. (drink$ adj3 (excess or heavy or heavily or harm or harmful or hazard$ or binge or problem$)).tw.
41. alcoholic$.tw.
42. 37 or38 or 39 or 40 or 41
43. exp Respiratory Tract Infections/
44. acute respiratory infection*.tw.
45. lower respiratory infection*.tw.
46. lower respiratory tract infection*.tw.
47. exp Pneumonia/
48. (pneumon* or bronchopneumon* or pleuropneumon*).tw.
49. exp Bronchitis/
50. (bronchit* or bronchiolit*).tw
51. or/43-50
52. exp Respiratory Distress Syndrome, Adult/ or Adult Respiratory Distress Syndrome/ or Acute Lung Injury/ or Acute Respiratory Distress Syndrome/ or ARDS.mp. or ALI.mp.
53. exp tidal volume/ or exp respiration, artificial/ or tidal volume.mp. or (protective adj3 ventilat*).mp. or (pressure* adj3 limited*).mp. or LPVS.mp.
54. 52 or53
55. exp Tuberculosis/
56. TB/
57. Phthisic
58. (Pulmonary adj3 phthisis).mp.

59. (Mycobacterium adj3 tuberculosis).mp.
60. (Tuberculosis adj3 pulmonary).mp.
61. Pleural tuberculosis.mp.
62. Latent tuberculosis.mp.
63. or/55-62
64. exp Sleep Apnea Syndromes/
65. (sleep$ adj3 (apnea$ or apnoea$)).mp
66. (hypopnea$ or hypopnoea$).mp
67. OSA.mp
68. SHS.mp
69. OSAHS.mp
70. or/64-69
71. Lung Diseases, Obstructive/
72. exp Pulmonary Disease, Chronic Obstructive/
73. emphysema$.mp.
74. (chronic$ adj3 bronchiti$).mp.
75. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
76. COPD.mp.
77. COAD.mp.
78. COBD.mp.
79. AECB.mp.
80. or/71-79
81. exp Asthma/
82. asthma$.mp
83. (antiasthma$ or anti-asthma$).mp
84. Respiratory Sounds/
85. wheez$.mp
86. Bronchial Spasm/
87. bronchospas$.mp.
88. (bronch$ adj3 spasm$).mp
89. bronchoconstrict$.mp
90. exp Bronchoconstriction/
91. (bronch$ adj3 constrict$).mp
92. Bronchial Hyperreactivity/

93. Respiratory Hypersensitivity/
94. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp
95. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp
96. or/81-95
97. 51 or 54 or 63 or 70 or 80 or 96
98. 36 and 42 and 97
Embase search terms
1. exp Meta Analysis/
2. ((meta adj analy$) or metaanalys$).tw
3. (systematic adj (review$1 or overview$1)).tw
4. or/1-3
5. cancerlit.ab
6. cohrane.ab
7. embase.ab
8. (psychlit or psyclit).ab
9. (psychinfo or psycinfo).ab
10. (cinahl or cinhal).ab
11. science citation index.ab
12. bids.ab
13. or/5-12
14. reference lists$.ab
15. bibliograph$.ab
16. hand-search$.ab
17. manual search$.ab
18. relevant journals.ab
19. or 14-18
20. data extraction.ab
21. selection criteria.ab
22. 20 or 21
23. review.pt
24. 22 and 23
25. letter.pt
26. editorial.pt

27. animal/
28. human/
29. 27 not (27 and 28)
30. or/25-26,29
31. 4 or 13 or 19 or 24
32. 31 not 30
33. substance-related disorders/
34. ((drug or substance) adj (Addict$ or abus$ or dependen$)).mp
35. (intoxicat$ or abstinen$ or withdrawal$).mp.
36. (excessive$ adj use$).mp.
37. (use$ adj disorder$).mp.
38. (drinking adj behavi$3).mp.
39. drinking behavior.mp.
40. alcohol$.mp.
41. alcoholism/
42. (alcohol adj abuse).mp
43. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42
44. *PNEUMONIA/
45. bacterial pneumonia/ or infectious pneumonia/
46. Mycoplasma pneumonia/
47. COMMUNITY ACQUIRED PNEUMONIA/
48. mycoplasma pneumon*.tw.
49. (community-acquired pneumon* or community acquired pneumon*).tw.
50. 44 or 45 or 46 or 47 or 48 or 49
51. respiratory distress syndrome, adult/
52. ((acute adj lung adj injur:) or (shock adj lung) or ards).tw.
53. ((acute or adult) and (respiratory adj distress)).tw.
54. or/52-53
55. Tuberculosis/
56. TB/
57. Phthisic
58. (Pulmonary adj3 phthisis).mp.
59. (Mycobacterium adj3 tuberculosis).mp.
60. (Tuberculosis adj3 pulmonary).mp.
61. Pleural tuberculosis.mp.

62. Latent tuberculosis.mp.
63. or/55-62
64. Sleep Apnea Syndrome/
65. (sleep$ adj3 (apnea$ or apnoea$)).mp.
66. (hypopnea$ or hypopnoea$).mp.
67. OSA.mp.
68. SHS.mp.
69. OSAHS.mp.
70. or/64-69
71. Chronic Obstructive Lung Disease/
72. Obstructive Airway Disease/
73. Chronic Bronchitis/
74. Lung Emphysema/
75. emphysema$.tw.
76. (chronic$ adj3 bronchiti$).tw.
77. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
78. COPD.tw.
79. COAD.tw.
80. COBD.tw.
81. AECB.tw.
82. or/71-81
83. exp Asthma/
84. asthma$.mp.
85. (antiasthma$ or anti-asthma$).mp.
86. Abnormal Respiratory Sound/
87. Wheezing/
88. wheez$.mp.
89. Bronchospasm/
90. bronchospas$.mp.
91. (bronch$ adj3 spasm$).mp.
92. bronchoconstrict$.mp.
93. Bronchus Hyperreactivity/
94. Respiratory Tract Allergy/
95. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or

hyperreactiv$ or allerg$ or insufficiency)).mp.
96. House Dust Allergy/
97. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp
98. or/ 83-97
99. 50 or 54 or 63 or 70 or 82 or 98
100. 32 and 43 and 99
Web of science search terms
(alcohol* OR alcoholic beverage OR alcohol consumption OR alcohol drinking OR alcohol use OR alcohol intake OR alcoholism OR alcohol abuse OR ethanol* OR ethanol concentration) AND (Pneumonia OR pneumon* OR bronchopneumon* OR bronchitis OR respiratory distress syndrome OR Acute respiratory distress syndrome OR Adult respiratory distress syndrome OR Asthma OR wheeze OR Chronic obstructive pulmonary disease OR chronic obstructive airway disease OR obstructive lung disease OR emphysema OR Tuberculosis OR TB OR phthisis OR Sleep apnea* OR sleep apnoea* OR Obstructive sleep apnea* OR Obstructive sleep apnoea*) AND (Systematic Review OR review* OR meta-analysis*)

Appendix 2. Search Strategy for observational studies

Medline (Ovid) search terms
1. Epidemiologic studies/
2. Exp case control studies/
3. Exp cohort studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. Cohort analy$.tw.
7. (Follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. Longitudinal.tw.
10. Retrospective.tw.
11. Cross sectional.tw.
12. Cross-sectional studies/
13. Or/1-12
14. exp Alcohol-Related Disorders/
15. Alcohol Drinking/
16. (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw.
17. (drink$ adj3 (excess or heavy or heavily or harm or harmful or hazard$ or binge or problem$)).tw.
18. alcoholic$.tw.
19. 14 or 15 or 16 or 17 or 18
20. exp Respiratory Tract Infections/
21. acute respiratory infection*.tw.
22. lower respiratory infection*.tw.
23. lower respiratory tract infection*.tw.
24. exp Pneumonia/
25. (pneumon* or bronchopneumon* or pleuropneumon*).tw.
26. exp Bronchitis/
27. (bronchit* or bronchiolit*).tw.
28. 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29. Respiratory Distress Syndrome, Adult/ or Adult Respiratory Distress Syndrome/ or Acute Lung Injury/ or Acute Respiratory Distress Syndrome/ or ARDS.mp. or ALI.mp.
30. exp tidal volume/ or exp respiration, artificial/ or tidal volume.mp. or (protective adj3 ventilat*).mp. or (pressure* adj3 limited*).mp. or LPVS.mp.
31. 29 or 30
32. exp Sleep Apnea Syndromes/
33. (sleep$ adj3 (apnea$ or apnoea$)).mp.
34. (hypopnea$ or hypopnoea$).mp.
35. OSA.mp.
36. SHS.mp.
37. OSAHS.mp.
38. 32 or 33 or 34 or 35 or 36 or 37
39. Lung Diseases, Obstructive/
40. exp Pulmonary Disease, Chronic Obstructive/
41. emphysema$.mp.
42. (chronic$ adj3 bronchiti$).mp.
43. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
44. COPD.mp.
45. COAD.mp.
46. COBD.mp.
47. AECB.mp.
48. 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. exp Asthma/
50. asthma$.mp.
51. antiasthma$.mp.
52. Respiratory Sounds/
53. wheez$.mp.
54. Bronchial Spasm/
55. bronchospas$.mp.
56. (bronch$ adj3 spasm$).mp.
57. bronchoconstrict$.mp.
58. exp Bronchoconstriction/
59. (bronch$ adj3 constrict$).mp.

60. Bronchial Hyperreactivity/
61. Respiratory Hypersensitivity/
62. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
63. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
64. 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63
65. 28 or 31 or 38 or 48 or 64
66. 13 and 19 and 65
Embase (Ovid) search terms
1. Clinical study/
2. Case control study
3. Family study/
4. Longitudinal study/
5. Retrospective study/
6. Prospective study/
7. Randomized controlled trials/
8. 6 not 7
9. Cohort analysis/
10. (Cohort adj (study or studies)).mp.
11. (Case control adj (study or studies)).tw.
12. (follow up adj (study or studies)).tw.
13. (observational adj (study or studies)).tw.
14. (epidemiologic$ adj (study or studies)).tw
15. (cross sectional adj (study or studies)).tw.
16. Or/1-5,8-15
17. substance-related disorders/
18. ((drug or substance) adj (Addict$ or abus$ or dependen$)).mp
19. (intoxicat$ or abstinen$ or withdrawal$).mp.
20. (excessive$ adj use$).mp.
21. (use$ adj disorder$).mp.
22. (drinking adj behavi$3).mp.
23. drinking behavior.mp.
24. alcohol$.mp.
25. alcoholism/

26. (alcohol adj abuse).mp
27. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. *PNEUMONIA/
29. bacterial pneumonia/ or infectious pneumonia/
30. Mycoplasma pneumonia/
31. COMMUNITY ACQUIRED PNEUMONIA/
32. mycoplasma pneumon*.tw.
33. (community-acquired pneumon* or community acquired pneumon*).tw.
34. 28 or 29 or 30 or 31 or 32 or 33
35. respiratory distress syndrome, adult/
36. ((acute adj lung adj injur:) or (shock adj lung) or ards).tw.
37. ((acute or adult) and (respiratory adj distress)).tw.
38. or/35-37
39. Sleep Apnea Syndrome/
40. (sleep$ adj3 (apnea$ or apnoea$)).mp.
41. (hypopnea$ or hypopnoea$).mp.
42. OSA.mp.
43. SHS.mp.
44. or/39-44
45. OSAHS.mp.
46. Chronic Obstructive Lung Disease/
47. Obstructive Airway Disease/
48. Chronic Bronchitis/
49. Lung Emphysema/
50. emphysema$.tw.
51. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).tw.
52. (chronic$ adj3 bronchiti$).tw.
53. COPD.tw.
54. COAD.tw.
55. COBD.tw.
56. AECB.tw.
57. or/46-56
58. exp Asthma/
59. asthma$.mp.

60. Abnormal Respiratory Sound/
61. Wheezing/
62. Bronchospasm/
63. wheez$.mp.
64. bronchospas$.mp.
65. (bronch$ adj3 spasm$).mp.
66. bronchoconstrict$.mp.
67. Respiratory Tract Allergy/
68. Bronchus Hyperreactivity/
69. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)). mp.
70. House Dust Allergy/
71. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp
72. or/ 58-71
73. 34 or 38 or 44 or 57 or 72
74. 16 and 27 and 73
Web of science search terms
(alcohol* OR alcoholic beverage OR alcohol consumption OR alcohol drinking OR alcohol use OR alcohol intake OR alcoholism OR alcohol abuse OR ethanol* OR ethanol concentration) AND (Pneumonia OR pneumon* OR bronchopneumon* OR bronchitis OR respiratory distress syndrome OR Acute respiratory distress syndrome OR Adult respiratory distress syndrome OR Asthma OR wheeze OR Chronic obstructive pulmonary disease OR chronic obstructive airway disease OR obstructive lung disease OR emphysema OR Sleep apnea* OR sleep apnoea* OR Obstructive sleep apnea* OR Obstructive sleep apnoea*) AND (longitudinal * OR case control* OR Cohort* OR case-control OR observational)

Appendix 3. Search Strategy for TB

Medline via Ovid search terms
1. Epidemiologic studies/
2. Exp case control studies/
3. Exp cohort studies/
4. Case control.tw.
5. (cohort adj (study or studies)).tw.
6. Cohort analy$.tw.
7. (Follow up adj (study or studies)).tw.
8. (observational adj (study or studies)).tw.
9. Longitudinal.tw.
10. Retrospective.tw.
11. Cross sectional.tw.
12. Cross-sectional studies/
13. Or/1-12
14. exp Alcohol-Related Disorders/
15. Alcohol Drinking/
16. (alcohol adj3 (drink$ or intoxicat$ or use$ or abus$ or misus$ or risk$ or consum$ or withdraw$ or detox$ or treat$ or therap$ or excess$ or reduc$ or cessation or intervention$)).tw.
17. (drink$ adj3 (excess or heavy or heavily or harm or harmful or hazard$ or binge or problem$)).tw.
18. alcoholic$.tw.
19. 14 or 15 or 16 or 17 or 18
20. exp Tuberculosis/
21. TB/
22. Phthisic.mp.
23. (Pulmonary adj3 phthisis).mp.
24. (Mycobacterium adj3 tuberculosis).mp.
25. (Tuberculosis adj3 pulmonary).mp.
26. Pleural tuberculosis.mp.
27. Latent tuberculosis.mp.
28. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

29. 13 and 19 and 28
30. limit 29 to yr="2005 -Current"
Embase via Ovid search terms
1. Clinical study/
2. Case control study
3. Family study/
4. Longitudinal study/
5. Retrospective study/
6. Prospective study/
7. Randomized controlled trials/
8. 6 not 7
9. Cohort analysis/
10. (Cohort adj (study or studies)).mp.
11. (Case control adj (study or studies)).tw.
12. (follow up adj (study or studies)).tw.
13. (observational adj (study or studies)).tw.
14. (epidemiologic$ adj (study or studies)).tw.
15. (cross sectional adj (study or studies)).tw.
16. Or/1-5,8-15
17. Tuberculosis/
18. TB/
19. Phthisic
20. (Pulmonary adj3 phthisis).mp.
21. (Mycobacterium adj3 tuberculosis).mp.
22. (Tuberculosis adj3 pulmonary).mp.
23. Pleural tuberculosis.mp.
24. Latent tuberculosis.mp.
25. or/17-24
26. substance-related disorders/
27. ((drug or substance) adj (Addict$ or abus$ or dependen$)).mp
28. (intoxicat$ or abstinen$ or withdrawal$).mp.
29. (excessive$ adj use$).mp.
30. (use$ adj disorder$).mp.
31. (drinking adj behavi$3).mp.
32. drinking behavior.mp.

33. alcohol$.mp.
34. alcoholism/
35. (alcohol adj abuse).mp
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 16 and 25 and 36
38. limit 37 to yr="2005 -Current"
Web of Science search terms
(alcohol* OR alcoholic beverage OR alcohol consumption OR alcohol drinking OR alcohol use OR alcohol intake OR alcoholism OR alcohol abuse OR ethanol* OR ethanol concentration) AND (Tuberculosis OR TB OR phthisis OR active Tuberculosis OR latent Tuberculosis OR mycobacterium) AND (longitudinal * OR case control* OR Cohort* OR case-control OR cross sectional OR cross-sectional OR observational)

Appendix 4. Screening criteria for titles and abstracts

PICO Table for titles and abstracts screening		
Criterion	**Guidance notes**	**Decision**
1.Year	Include studies published during or after 1985. Exclude studies published before 1985 Emphasis to be given on the most recent studies (up to date).	
2.Study Design	To include: systematic reviews (meta-analysis/reviews/reviews of reviews) and all longitudinal observational studies (prospective and retrospective cohort and longitudinal studies)	
3.Type of participants	To include studies looking at the adults populations. Exclude: Studies on special populations (e.g patients HBV/HCV infected)	
4.Health Outcomes	The study should look at the following diagnosed health outcomes: Alcohol consumption and respiratory diseases related to: • Pneumonia or bronchitis • Acute-Adult respiratory distress syndrome (ARDS) • Asthma or wheeze • Chronic obstructive pulmonary disease (COPD) or emphysema • Tuberculosis or phthisis • Sleep apnoea or apnoea	

5.Exposure	Does the study look at one of the following exposures: Alcohol, alcoholism, specific alcohol drinks, alcohol risk factors (dietary factors, lifestyle factors: temperament, childhood behaviour problems, family history alcoholism, depression, loneliness, anxiety, low self-esteem, high stress, peers, advertising) More specifically, does the study include a measure of alcohol consumption? For the alcohol to include all drinking levels: light, moderate and heavy drinking, according to drinks/day or gr of ethanol/day. Alternative, for the drinking levels will be defined: 1 unit as 8 g or 10ml of ethanol, and light as ‹ 2 units per day; moderate as 2-3 units per day; heavy as ≥ 4 units per day, in accordance with standard recommended alcohol allowance guidance (UK).	

Appendix 5. Quality assessment checklist for systematic reviews

AMSTAR Checklist for systematic reviews
Questions
1. Was an 'a priori' design provided?
2. Was there duplicate study selection and data extraction?
3. Was a comprehensive literature search performed?
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?
5. Was a list of studies (included and excluded) provided?
6. Were the characteristics of the included studies provided?
7. Was the scientific quality of the included studies assessed and documented?
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?
9. Were the methods used to combine the findings of studies appropriate?
10. Was the likelihood of publication bias assessed?
11. Was the conflict of interest included?

Appendix 6. Quality assessment checklist for primary studies

Newcastle-Ottawa quality assessment scale for case control studies

Selection

1) Is the case definition adequate?
a) yes, with independent validation *****
b) yes, eg record linkage or based on self-reports
c) no description

2) Representativeness of the cases
a) consecutive or obviously representative series of cases *****
b) potential for selection biases or not stated

3) Selection of Controls
a) community controls *****
b) hospital controls
c) no description

4) Definition of Controls
a) no history of disease (endpoint) *****
b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) *****
b) study controls for any additional factor *****

Exposure

1) Ascertainment of exposure
a) secure record (eg surgical records) *****

b) structured interview where blind to case/control status *****

c) interview not blinded to case/control status

d) written self-report or medical record only

e) no description

2) Same method of ascertainment for cases and controls

a) yes *****

b) no

3) Non-Response rate

a) same rate for both groups *****

b) non-respondents described

c) rate different and no designation

In the case of a cross sectional study the modification was that we deleted the questions about the selection and the definition of controls limited the high score in 7. For this circumstance a good quality study should have a score of: >=5.

Newcastle-Ottawa quality assessment scale for cohort studies

Selection

1) Representativeness of the exposed cohort

a) truly representative of the average _____ (describe) in the community *****

b) somewhat representative of the average _____ in the community *****

c) selected group of users eg nurses, volunteers

d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) drawn from the same community as the exposed cohort *****

b) drawn from a different source

c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) secure record (eg surgical records) *****

b) structured interview *****

c) written self-report

d) no description

4) Demonstration that outcome of interest was not present at start of study

a) yes *****

b) no

Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) study controls for _____ (select the most important factor) *****

b) study controls for any additional factor *****

Outcome

1) Assessment of outcome

a) independent blind assessment *****

b) record linkage *****

c) self report

d) no description

2) Was follow-up long enough for outcomes to occur

a) yes (select an adequate follow up period for outcome of interest) *****

b) no

3) Adequacy of follow up of cohorts

a) follow up rate >=70% *

b) follow up rate < 70%

c) no statement

Appendix 7. Data extraction forms for systematic reviews

Reviewer name: **Study Author and Year:**

REVIEW DETAILS	
Article name	
Aim of the review	
Review Design	
Definition of Alcohol	
Alcohol ascertainment/ subgroups (e.g. *drinking levels: light, moderate and heavy drinking, number of drinks per day or gr of ethanol/day, number of drinks per year, age since started alcohol consumption, specific alcohol drinks, alcoholism, gender)*	
Definition of health condition	Method of diagnosis: Exposure ☐ Outcome ☐ Both ☐
REVIEW SEARCH PARAMETERS	
Databases searched	
Other search methods undertaken (e.g. websites, reference checking)	
Years searched	
Study type inclusion criteria	

Study type exclusion criteria	
Number of studies included	
Method of synthesis (meta-analaysis, meta regression)	
REVIEW POPULATION & SETTING	
Included population demographics	
Other demographics reported (e.g. ethnicity, place of residence, occupation, education, socioeconomic)	
Excluded population demographics	
European studies included	
Settings of included studies (e.g. developed/non-developed, public/private health care, urban/rural)	
Translations included?	
OUTCOMES	
Primary Outcomes (including analysis)	
Secondary Outcomes	
Follow up period	
Method of analysis (e.g how studies were combined and analysed)	
RESULTS	
From Primary Outcome	

From secondary Outcome	
LIMITATIONS	
Identified by author	
Identified by review team	
Evidence gaps and/or recommendations for future research	
SOURCE OF FUNDING	
(e.g. Government (NHS), voluntary/charity, pharmaceutical company)	

Appendix 8. Data extraction forms for primary studies

Reviewer name: **Study Author and Year:**

DESCRIPTION OF STUDY	
Study Design	Cohort ☐ Prospective ☐ Retrospective ☐ Nested Case control ☐
Name of Cohort Data collection years	Start date (year): End date (year): Years of follow-up data:
Definition of Alcohol (Any record of the number of drinks per day or gr of ethanol per day, number of drinks consumed annually, record of drinking levels: light, moderate and heavy drinking age since started alcohol consumption, specific alcohol drinks, alcoholism)	
Definition of health condition	Method of diagnosis: Exposure Outcome Both
Setting (e.g. developed/non-developed, public/private health care, urban/rural)	
Country- European?	
Selection of controls (for nested case control	

studies only)	
PARTICIPANTS	
Inclusion criteria	
Exclusion criteria	
Number entering into study (may not be recorded)	
Final number of participants evaluated	
DEMOGRAPHICS OF STUDY POPULATION	
Age (mean, SD, range)	
Gender (n, % male)	
Other demographics reported (e.g. ethnicity, place of residence, occupation, education, socioeconomic)	
RESULTS	
Outcome	Adjusted measure of effect with 95% CI (in preference) Crude measure of effect with 95% CI Raw numbers P value
1.first outcome	Exposure: Comparator: Result:
2. second outcome	Exposure: Comparator: Result:

SOURCE OF FUNDING	
(e.g. Government (NHS), voluntary/charity, pharmaceutical company)	
LIMITATIONS	
Identified by author	
Identified by review team	
Evidence gaps and/or recommendations for future research	

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