Effects of modifiable lifestyle choices and related public health policy in pregnancy
Impact on maternal and offspring outcomes
A population-based linkage study

Thesis by

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Abstract

Alcohol and opioid use during pregnancy are associated with adverse maternal and perinatal outcomes. This thesis examines the impact of public health interventions on alcohol consumption during pregnancy and on perinatal outcomes. Associations between different levels of alcohol consumption and maternal and childhood outcomes are also explored. Finally, the impact of different opioid substitution therapies, Methadone and Buprenorphine, on perinatal outcomes is systematically assessed.

Population-based data from Scotland is used to conduct an interrupted time series analysis of the impact of three public health interventions on alcohol consumption during pregnancy and perinatal outcomes (Chapter 2). To explore different levels of alcohol consumption during pregnancy on perinatal outcomes, women who consumed less than or equal to four units of alcohol per week were compared to women who consumed no alcohol, and women who consumed greater than four units of alcohol per week. Multivariable regression models were used to assess the associations between alcohol consumption and perinatal outcomes (Chapter 3). Finally, a systematic review and meta-analysis was performed to compare methadone and buprenorphine therapies on pregnancy outcomes (Chapter 4 and 5).

In Scotland, approximately one in four women report drinking alcohol in pregnancy. Minimum unit pricing was associated with a reduction in volume of alcohol consumption during pregnancy, and in babies born small for gestational age, neonatal unit admissions, and stillbirths. Alcohol consumption of under four units of alcohol per week was not associated with any increase in adverse perinatal outcomes, but harm was more likely to occur as consumption increased. In a meta-analysis of opioid substitution therapies, Buprenorphine compared with Methadone was associated with improvements in neonatal and maternal outcomes in both RCTs and Cohort Studies.

Alcohol consumption during pregnancy is common, with many women consuming less than four units per week. The implementation of a universal policy to increase the cost of alcohol was associated with a fall in alcohol

consumption among pregnant women and improvement in pregnancy outcomes, and this can be monitored using routinely collected data. Buprenorphine improved perinatal outcomes compared to Methadone.

This body of work uses routinely collected healthcare data to examine the impact of public health measures and treatment strategies to minimise harm from exposure to alcohol and drugs in the pregnant population. A combination of narrative review, systematic review and meta-analysis, time-series analysis, and regression modelling was used to achieve this. The studies included in this thesis highlight the importance of population-based public health measures and evidence-based treatments, demonstrating that such interventions have a positive impact on the pregnant population resulting in improved maternal and childhood outcomes.

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Publications

Kinsella, M., Capel, Y., Nelson, S. M., & Kearns, R. J. (2022). Opioid substitution in pregnancy a narrative review: contemporary evidence for use of methadone and buprenorphine in pregnancy. Journal of Substance Use, 28(6), 919–924.

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Halliday, L., Kinsella, M., Shaw, M., Cheyne, J., Nelson, S.M. and Kearns, R.J. (2022), Comparison of ultra-low, low and high concentration local anaesthetic for labour epidural analgesia: a systematic review and network meta-analysis. Anaesthesia, 77: 910-918.

Presentations

Effects of modifiable lifestyle choices and related public health policy in pregnancy. Impact on maternal and offspring outcomes. A population-based linkage study. An Introduction: August 2020
The University of Glasgow. School of Medicine, Dentistry and Nursing Summerfest Research Day.

Buprenorphine compared with methadone in pregnancy a systematic review and meta-analysis: May 2021.
Post Graduate research day. The University of Glasgow. School of Medicine, Dentistry and Nursing

Effects of modifiable lifestyle choices and related public health policy in pregnancy. Impact on maternal and offspring outcomes. A population-based linkage study. An update: June 2021
The University of Glasgow. College Update.

Analysis of maternal health using Scottish datasets: September 2022
NHS Clyde Annual audit presentations.

Opioid substitution therapies in pregnancy: November 2022
West of Scotland Obstetric Anaesthetists' Association annual meeting.

Opioid substitution in pregnancy. Contemporary evidence for use of methadone and buprenorphine in pregnancy: April 2022
Gynaecological Visiting Society annual meeting: Glasgow.

Opioid substitution in pregnancy a narrative review: contemporary evidence for use of methadone and buprenorphine in pregnancy: May 2022
Felicity Reynolds Oral Presentation (top ten scientific papers): OAA Annual Scientific Meeting. Newport.

Alcohol consumption during pregnancy in Scotland following public health interventions: May 2023
The University of Glasgow, St Mungo's Symposium
First prize – presentation

Alcohol consumption during pregnancy in Scotland following public health interventions: December 2024
Glasgow Anaesthetic Research Club, Glasgow and West of Scotland Anaesthetists' Association

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I would also like to thank my fellow researchers in Glasgow: Dr Halliday and Dr Kyzayeva, who have supported me in finding my feet within academia. I am grateful to Professor Leyland, Professor Pell, and Professor Lawlor for their advice and guidance on developing a career in research. I also appreciate my clinical supervisors Dr Smith, Dr Tong, Dr Sundaram, and Dr Joss, who have been patient while I fleshed out some of my ideas on public health, sometimes during ward rounds, while also supporting my development as a clinical doctor.

I would also like to thank my friends, in particular Leah and Gary. They have been there through the highs and lows of this MD and the pandemic. I always knew they were just a phone call away, and I will be forever grateful for their friendship.

Finally, I would like to thank my family - Gill, Alex, and Lewis - as well as my parents. Gill's patience is off the scale, and the boys have always understood when daddy was "making more graphs" in the office. I look forward to showing them the book I made as a result.

Thank you all.

Author's declaration

The work documented in this thesis was carried out by myself during my employment as a Clinical Research Fellow in the Academic Unit of Anaesthesia, Critical Care and Peri-operative Medicine at The University of Glasgow. In addition to my role at the University of Glasgow, I worked as a Specialist Registrar in Intensive Care Medicine for NHS Education Scotland in Tayside, Lothian, and Greater Glasgow and Clyde. This work was conducted between February 2020 and January 2025. A one-year extension was granted between September 2023 and September 2024 due to ill health.

The Electronic Data Research and Innovation Service (eDRIS) of Public Health Scotland provided the linked routinely collected healthcare data used in Chapters 2 and Chapter 3 of this thesis. Statistical analysis was carried out by myself using their secure analytical platform within the National Safe Haven. Professor Nelson authorised the access to this data.

Dr. Kyzayeva carried out imputation of data and prepared some of the supplemental figures for Chapter 3.

Dr. Halliday and Dr. Capel acted as second reviewers to support the meta-analysis with review of relevant literature outlined in Chapter 5.

Definitions

ABV	Alcohol By Volume
adjOR	Adjusted Odd Ratio
adjRR	Adjusted Risk Ratio
AIC	Akaike Information Criterion
ARBD	Alcohol-Related Birth Defect
ARDS	Acute Respiratory distress syndrome
ARIMA	Auto-Regressive Integrated Moving Average
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Central Registry of Controlled Trials
CI	Confidence Interval
CHI	Community Health Index
CMO	Chief Medical Officer
DAG	Direct Acyclic Graph
eDRIS	electronic Data Research and Innovation Service
FAS	Fetal Alcohol Syndrome
FASD	Fetal Alcohol Spectrum Disorder
GDP	Gross Domestic Product
GI	Gastrointestinal
hCG	human Chorionic Gonadotrophin
HED	Heavy Episodic Drinking
HIV	Human Immune Deficiency
HPA	Hypothalamic–Pituitary–Adrenal
ICD	International Classification of Diseases
IQ	Intelligence Quotient
IQR	Inter-Quartile Range
KSI	Killed or Seriously Injured
MBRRACE-UK	Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the United Kingdom
MESAS	Monitoring and Evaluating Scotland's Alcohol Strategy
MD	Doctor of Medicine
mg	milligram
MUP	Minimum Unit Pricing

NAS	Neonatal Abstinence Syndrome
NAD	Nicotinamide Adenine Dinucleotide
ND-PAE	Neurobehavioral Disorders associated with Prenatal Alcohol
NHS	National Health Service
NRS	National Records Scotland
OECD	Organisation for Economic Co-operation and Development
OR	Odds Ratio
pFAS	partial Fetal Alcohol Spectrum
PICO	Population, Intervention, Comparator, and Outcomes
PHS	Public Health Scotland
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR	Risk Ratio
RCT	Randomised Control Trial
SALSUS	Scottish Schools Adolescent Lifestyle and Substance Use Survey
SANRA	Scale of the quality of Assessment of Narrative Review Articles
SBR	Scottish Birth Record
SDG	Sustainable Development Goals
SGA	Small for Gestational Age
SHD	Social Determinants of Health
SIGN	Scottish Intercollegiate Guideline Network
SIMD	Scottish Index of Multiple Deprivation
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SMR	Scotland Morbidity Records
TB	Tuberculosis
UK	United Kingdom
UN	United Nations
UNWTO	United Nations World Tourism Organisation
US	United States
USA	United State of America
vSGA	very Small for Gestational Age
WMD	Weighted Mean Difference
WHO	World Health Organisation

Chapter 1 Alcohol, drugs, and other social determinants of health

1.1 Determinants of health outcomes

The circumstances in which a person is born, grows, lives, and works has a profound impact on their health. The World Health Organisation estimates that 30% - 55% of a person's health outcomes are influenced by these Social Determinants of Health (SDH)[1]. Compared to SDH, medical interventions account for approximately 10 - 15% of health outcomes. SDH contribute to behaviours such as excess alcohol consumption, smoking, and drug use. These behaviours, combined with broader societal difficulties, such as unemployment and housing insecurity, establish societal health inequalities.

Public health interventions can affect health inequalities at all stages of life, but earlier interventions can lead to greater health improvements across the life-course[2]. If changes are adopted in pregnancy, this can have significant benefits for the long-term health of both the mother and the offspring. During pregnancy, women are concerned about their baby's health and are in frequent contact with their healthcare provider, making this a powerful "teachable moment" for promoting positive behavioural change in the years following pregnancy[3].

Adverse health behaviours such as smoking, drug use and alcohol consumption are common and can co-occur during pregnancy leading to significantly poorer health outcomes[4-7]. Improving health outcomes of women who engage in these adverse health behaviours, requires both individualised targeted programs, as well as wider public health policies[8]. Interventions must be well designed as those with the least resources, and consequently often poorer health, have the fewest means to change behaviours or circumstances[3]. This means that without due care, interventions in the health care system designed to reduce inequalities might conversely increase them. Furthermore, all interventions aiming to improve perinatal health must consider that 16% of pregnancies are not planned[9].

Due to difficulties with individualised programs, as well as high unplanned pregnancy rates, public interventions that affect the entire population could have significant beneficial effects on perinatal health. Recent whole-population interventions, such as smoke-free legislation and minimum unit pricing for alcohol, could modify social determinants of health in the pregnant population as well as in the general population. Studies examining smoking policy by Pell et al. in 2008 showed that restrictions on smoking in public places in Scotland led to measurable improvements in hospital admission rates[10]. Following the intervention there was a reduction in admissions with acute coronary syndrome (17% reduction over 20 months, 95% CI: 16%, 18%). The same group extended this work in 2012 and showed improvements in the birth outcomes of preterm deliveries (−11.72%, 95% CI: −15.87%, −7.35%) and babies born small for gestational age (−4.52%, 95% CI −8.28%, −0.60%)[11]. These studies demonstrate the broad impact of this legislation for both the general population, and pregnant women.

The work presented in this MD will explore whether changes in alcohol public policy and newer opioid replacement treatments have impacted maternal and neonatal outcomes. In addition, it will investigate if a whole population dataset can support evidence-based decision making for alcohol consumption guidelines in pregnancy.

1.2 Defining alcohol

Alcohol is the collective term for chemical compounds with a hydroxyl group bound to a saturated carbon atom. Ethanol is ethane (C2H5) with a terminal hydroxyl group (OH) and has the formula C2H5OH. Ethanol is formed by the fermentation of yeast with sugar and water, up to a concentration of 15% and is the only alcohol that humans can safely consume. This thesis will refer to ethanol and alcohol interchangeably, in keeping with clinical medical practice.

The alcohol content of drinks can be expressed in several ways. Alcohol content is most commonly described as Alcohol By Volume (ABV) or using units of alcohol. ABV is the amount (mls) of pure ethanol per 100ml of solution at 20 degrees Celsius and is commonly expressed as a percentage of alcohol, with typical ABV being 5% for beer, 12% for wine and 40% for spirits. A related term to ABV is “alcohol proof” [12]. In the UK, the alcohol proof is 1.8 times the ABV; in the US, proof refers to twice the ABV; in France, proof is the same as the ABV. A “proofed” drink has over 50% ABV, which relates to its ability to ignite when adding gunpowder. Given this term's different definitions and variability, ABV has replaced the Proof system.

The ethanol content of a drink can also be expressed using units of alcohol with one unit of alcohol in the UK relating to 10mls (8 grams) of pure ethanol. What defines a unit of alcohol varies worldwide, with an American unit being 14g of ethanol[13]. In comparison, a Bulgarian unit is 20g, and a Senegalese unit is 1-4g. The World Health Organisation (WHO) defines a standard alcoholic drink as containing 10g of ethanol but acknowledges that each member country defines its “standard unit” differently[14]. Throughout this chapter, individual alcohol consumption is expressed as mls of pure ethanol (ABV) or by UK units (10mls/8grams of ethanol), and for population-level consumption, the volume is expressed as litres of pure ethanol.

1.3 How alcohol consumption is measured

Alcohol intake is difficult to measure accurately with the mainstay of recording alcohol consumption via population-level surveys and alcohol sales data. There is a requirement for a combined approach due to the limitations of surveys and a lack of a long-term validated biomarker to measure an individual's alcohol consumption. Self-reporting measures (surveys) are commonly used. They are, however, limited by low sensitivity and specificity of screening questions, poor recall, underestimation of volume consumed, and variations of questions over location and time[14-18]. To overcome these limitations, alcohol sales figures are also used. Sales figures tend to be accurate due to alcohol regulation and taxation status but do not include details of who is consuming alcohol, alcohol lost to wastage, consumption by tourists, or untaxed alcohol (homebrew or smuggled). Some of these limitations can be overcome using information such as the United Nations World Tourism Organisation data (UNWTO) to extrapolate tourist consumption; however, these corrected estimates have a potential for systematic error and cannot be used for subgroups such as those who are pregnant[19,20].

In line with the World Health Organisation's practices, the UK monitors individual consumption via representative sampling in addition to population use via alcohol sales data. Until 2017, the UK government regularly surveyed alcohol intake, but following the devolution of Health and Social Care to the Scottish Government, alcohol monitoring was conducted by Public Health Scotland [21]. Current surveys monitoring alcohol consumption in Scotland are the Scottish Health Survey and the Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS). These surveys allow for assessing both patterns and drinking levels over time in representative samples of the Scottish population. The Scottish Government also monitors alcohol sales in Scotland via the taxation system. The Monitoring and Evaluating Scotland's Alcohol Strategy (MESAS) was established to obtain a complete picture of alcohol consumption patterns in Scotland, combining sales data with surveys to provide a comprehensive study of drinking in Scotland[22]. This is the process by which Public Health Scotland monitors the implementation of alcohol policy and trends in alcohol consumption in Scotland. The first phase of MESAS was concluded in 2016, making the following recommendations:

> "Monitoring of alcohol price, affordability, consumption and alcohol-related deaths and hospital admissions should continue. Bringing these together in an annual overview will facilitate early identification and exploration of emerging issues."[23]

This recommendation led to the continued use of MESAS as a tool for the Scottish Government and other organisations to monitor alcohol use over time.

1.4 Alcohol consumption worldwide

Alcohol consumption is typical in modern society and alcoholic drinks are consumed regularly worldwide as part of cultural, religious, and social traditions. Globally, 32 – 43% of the world's population consumed alcohol in the last 12 months; this represents approximately 2.3-3.2 billion individuals[24,25].

The consumption of alcohol is variable in different countries, with greater alcohol consumption seen in countries with higher social developmental indices compared to less economically developed nations. In highly developed countries, 72% of women and 83% of men consume alcohol regularly. In contrast, in countries with low to moderate levels of income, alcohol is consumed by 8.9% of women and 20% of men[24]. Religious beliefs also influence alcohol consumption. In the Eastern Mediterranean region, where there is a high level of adherence to Islamic teaching, only 2.9% of the population consume alcohol whereas in Europe, where Christianity and Atheism predominate, alcohol is consumed by 59.9% of the population. Worldwide, women are less likely to drink alcohol than men, but this difference reduces as a country's development indices increase[25].

There has been a worldwide decline in the number of people who drink alcohol in the last 20 years. In 2000, 47.6% of the world's adult population drank, whereas in 2016, the WHO estimated that 43.0% of people consumed alcohol [25]. This decline was driven by reductions in alcohol use in Europe and America, as more people stopped drinking due to increased recognition of alcohol contributing to poor health[25].

As well as variation in the prevalence of drinking, the volume of alcohol consumption varies over time and region. Worldwide, 6.4 litres of alcohol are consumed per year per adult, equating to 13.9 grams of ethanol per day[25]. When those who do not drink are excluded, the average alcohol per drinker is 32.8 grams of ethanol daily. Of those who consume alcohol, the mean consumption per person has been static over the last 20 years. The static consumption worldwide average is due to an increase in consumption in the Western Pacific and Southeast Asia, with Europeans drinking less[25].

1.5 Alcohol consumption in Scotland

Scotland has a culture of alcohol consumption, in particular drinking to excess and heavy episodic drinking. In 2020, 9.4 litres of alcohol were sold per adult in Scotland, equivalent to 18.0 units per week per adult[22]. Using self-reported alcohol consumption, intake was 15.5 units per week for men and 8.8 units per week for women with the majority (73%) of alcohol sold in Scotland for consumption off-premises (off-sales), such as supermarkets or local shops. Alcohol sales in Scotland are composed of 31% wine, 31% spirits, 27% beer, and 6% cider[22].

In the last two decades, there has been a trend toward lower total alcohol consumption in Scotland. During the 2000s, there was a peak in alcohol consumption, followed by a gradual reduction in alcohol sales and consumption. The decline in alcohol sold in Scotland is believed to be related to an increase in non-drinkers, with an increase from 11% to 17% of the adult population between 2003 and 2019. The reduction in drinkers has led to less alcohol being sold in Scotland in 2020 than in 2005. In 2020, 9.4 litres of alcohol were sold per adult per year in Scotland, falling from an average of 10.3 litres sold between 2005 and 2010. During 2020, Scotland reported the lowest per-adult alcohol sales since records began in 1994[22].

The levels of alcohol consumed and associated trends are variable between gender and age. Women historically drink less alcohol than men, but this difference has narrowed recently. In 2019, 8.8 units per week were consumed by female drinkers, down from 10.6 units per week in 2003. This reduction of 1.8 units per week per drinker compared to 5.3 units per week for men between 2003 and 2016 (21.8 units to 15.5 units) [22]. Age is strongly associated with the likelihood of drinking over time and there is an ongoing trend of declining alcohol consumption in young people[26]. In 1990, 50% of 12-year-old children had drunk alcohol, compared to 35% in 2018. There has also been a trend for younger adults (16-24 years old) not to consume alcohol, while older adults (45- 55 years and above) are more likely to be drinkers, see Figure 1-1.

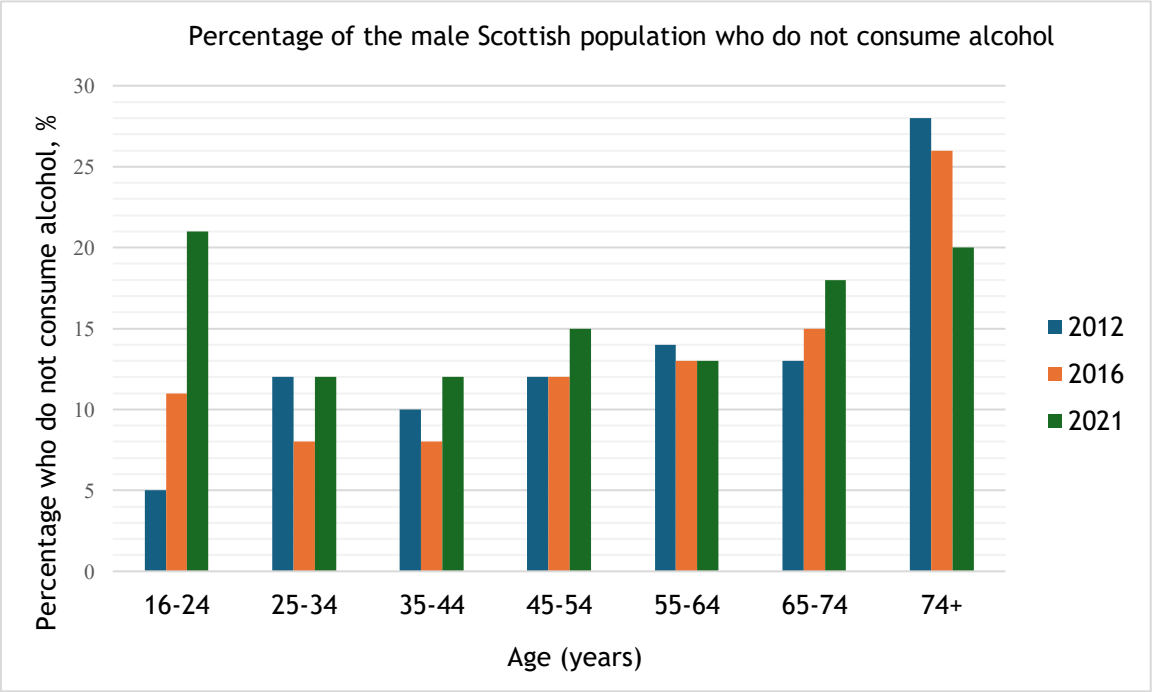


Figure 1-1: Proportion of the Scottish population (male) who did not consume alcohol by age in 2012, 2016 and 2021.

Adapted from Scottish Health survey report [21]

A small proportion of Scotland's population consumes a large percentage of the sold alcohol. In 2019, 10% of adults drank 48% of all self-reported alcohol in Scotland [22]. People living in the least deprived / highest Scottish Index of Multiple Deprivation (SIMD) regions consistently reported alcohol consumption above levels recommended by guidelines, but when they did so, the mean consumption was lower than seen in people from the lowest SIMD regions. The mean alcohol consumption for those who consume more than the recommended weekly units (14 units per week) was 27.7 units per week in people from areas of lowest deprivation and 42.8 units per week for those in the highest level of deprivation.

During the COVID-19 pandemic, individual behaviours and data collection were variable and generally of low-quality [27]. The self-reported alcohol consumption collection methodology was adapted in line with government pandemic public health measures, thus making a direct comparison with the

prior year more difficult. Data on alcohol consumption during the lockdown period (2020-2023) should therefore be interpreted with caution.

1.6 Alcohol consumption worldwide in pregnant women

Alcohol consumption in pregnancy is poorly recorded worldwide. A systematic search was used to estimate alcohol consumption per country, with worldwide figures of 9.8% (95% CI: 8.9 – 11.1) and varying between 0% (Saudi Arabia) and 60% (Ireland) following analysis of 328 studies[28]. This analysis is the only comprehensive epidemiological estimation of global maternal alcohol consumption published.

Worldwide there is a lack of routine screening in pregnancy, with considerable variation between countries[29]. In Australia, only 45% of health care professionals enquire about maternal alcohol use, while in Norway, 97% do so[30,31]. The lack of routine enquiry and documentation of alcohol consumption in pregnancy leads to best estimates being derived from samples and surveys. The Centres for Disease Control (CDC) in the USA estimate that 13.5% of those who are pregnant drink alcohol[32]. In Europe, the Multinational Medication Use in Pregnancy Study conducted an online survey of 7,905 pregnant or recently pregnant women and found that 16% per cent of women reported drinking alcohol during pregnancy[33]. This study found significant variations between the European countries, e.g. Norway (4.1%) and the UK (28.5%). Outside North America and Europe, smaller studies have estimated a similar percentage of alcohol consumption in pregnancy[34-36].

1.7 Alcohol consumption in pregnant women in Scotland

The first regular monitoring of alcohol consumption during pregnancy occurred with the quinquennial UK Infant Feeding Survey. The feeding survey reported in 1995 that 66% of UK women reported drinking alcohol during pregnancy, with the majority (71%) consuming less than one unit per month[37]. From 1995, this figure declined, with 61% of women drinking during pregnancy in 2000 before falling to 54% in 2005, and 41% in 2010[38]. The results of the Infant Feeding Survey are consistent with a pooled estimate from cohort studies by Popova et al. which estimated 41.3% (95% CI: 32.9, 49.9) of pregnant women in the United Kingdom consumed alcohol[28]. This broad estimate reflects wide time period of data collection (1982-2010) as well as the diversity in the study protocols from the 20 studies used to generate the estimate.

Scotland, as a stand-alone region, started to record alcohol consumption in pregnancy in 2010. During the UK Feeding Survey 2010, a regional breakdown reported that 35% of women in Scotland reported alcohol consumption, which was lower than the English average of 41%[38]. Following the devolution of health care in Scotland, the Scottish Maternal and Infant Nutritional Survey reported alcohol intake in pregnancy. In 2017, this survey reported that 88% of women did not drink when they became aware of pregnancy and that 23% had stopped drinking before becoming pregnant[39]. The survey did not report how many women drank before becoming aware they were pregnant. 12% of women reported continued alcohol consumption, with only 0.1% (of the total survey respondents) reporting weekly consumption. Due to differences in collection methodology, the UK and Scottish surveys cannot be directly compared to evaluate progression over time.

In addition to the Infant Feeding surveys, there has been one large research project looking at maternal alcohol use. The Growing Up in Scotland cohort is a longitudinal study including 14,000 children born in Scotland between 2004 and 2011[40]. The survey was conducted ten months after birth and asked mothers about the consumption of alcohol in terms of frequency and units per week. In this survey, most women (80%) reported not drinking during pregnancy. Of those who drank, 96% reported 1-2 units per day, 3% reported 3-4 units per day, and 1% reported 5+ units per day. Throughout the survey, there was a trend

for reduced alcohol intake in terms of complete abstinence and volume consumed in those who continued to drink.

The Scottish Government commissioned the Scotland Morbidity Records System (SMR), a national data recording system for patients' medical records, to overcome the lack of routinely collected healthcare data. The SMR02 record records maternity care, and since April 2013, during a pregnancy booking appointment, a midwife will record a woman's self-reported alcohol consumption "in an average week". The level consumed is recorded at between "0" and "97" units per week with any level above 97 coded as 98 units, and unknown coded as 99. This recording of alcohol is contemporaneous and continuous and covers the entire Scottish population. As Scottish health care is free at the point of access via the NHS, almost all pregnancies in Scotland will be recorded in SMR02. It is not legally required to complete SMR02, but Public Health Scotland estimates 98% completeness[41]. The SMR system includes approximately five million persons, or 50,000 births per year, and can be linked with other datasets produced by the Scottish NHS and partner organisations. The key strength of the SMR system is that it can be linked to other data. There are two benefits of linkage: comprehensive healthcare data and understanding multigenerational health. Comprehensive healthcare data is achieved by linking several SMR data sets together with other datasets on admission to hospitals, prescriptions, and birth and death records. Also, National Records Scotland (NRS) datasets can be linked, as these datasets are legally required to be completed to allow quality control monitoring. A second benefit of SMR is that the linkage between health records over generations allows maternal and offspring health monitoring on topics such as maternal alcohol consumption.

Public Health Scotland governs the SMR system and the national datasets on behalf of the Scottish Government and the Convention of Scottish Local Authorities. The cornerstone of Public Health's digital intelligence is the Community Health Index (CHI), which contains a record of all patients who have received NHS care in Scotland under a unique and personal 10-digit number. Work on developing CHI and linkage of data falls to the electronic Data Research and Innovation Service (eDRIS), an agency established to support data research and understand health using Scotland's comprehensive datasets.

1.8 Alcohol and social deprivation

Deprivation is a critical mediator in alcohol-related harm, and residents of Scotland's postcodes with the highest indicators of deprivation are six times more likely to be admitted to hospital with alcohol-related conditions than those residing in postcodes with the lowest levels of deprivation [42]. The same level of alcohol consumed by individuals in areas of lower socioeconomic status areas has a more significant negative impact on health; this is termed the "Alcohol Harm Paradox"[43]. This is most likely due to other comorbidities and patterns of drinking, with higher volumes of alcohol being drunk in more deprived communities and more frequent drinking occurring in less deprived communities[19,44]. People living in the most deprived communities have double the level of disease burden as those in the least deprived areas[45].

The pattern in which alcohol is consumed has an impact on the harm caused with heavy episodic drinking (HED or "binge drinking") associated with an increase in alcohol-related harm. Consuming more than five drinks in one episode increases harm in both the short and long term, even when controlling for other determinants of health[46]. HED is associated with deprivation, drinking early in life, male sex, family history of alcohol excess, drug use, and poor health (mental and physical). This increase in risk means that both quantity and pattern of use are essential factors in estimating a person's potential harm associated with alcohol.

Alcohol is associated with significant healthcare usage as well as economic effects. In a recent Organisation in Economic Co-operation and Development (OECD) report, the direct cost of health care to treat those who drink over 1-1.5 drinks per day is $138 billion per year (4.2 % of health care spending), with a cost to wider society of greater unemployment (0.33%), and reduction in productivity (0.24%)[47]. In Scotland, there are 38,370 admissions per year related to alcohol, costing the NHS £267.8 million per year[42]. The cost of reduced Gross Domestic Product (GDP) related to alcohol worldwide is $1.6 trillion (US dollars) per year[47], and in Scotland, the cost of lost GDP is £3.6 billion per year[48]. The costs to GDP must be balanced with the cost benefits of alcohol production, especially in Scotland. It has been estimated that Scottish

Distilleries and Brewers contribute 3% to the Scottish Economy or £3.9 billion per year[49].

In addition to the economic impact of alcohol use, there are numerous other effects on society. Intoxication increases the risk of harm relating to trauma, violence, and road traffic collisions. Alcohol-related violence leads to 90,000 deaths worldwide per year, with alcohol consumption involved in approximately 50% of violence relayed injuries presenting to accident and emergency departments [50]. In the UK, in 2019, 2,050 people were killed or seriously injured (KSI) by a driver over the drink-drive limit, representing 6% of all KSI events that were reported[51]. As with many aspects of alcohol intake and alcohol-related harm, drunk drivers are more likely to be male, compared with drivers involved in all road accidents (78% compared to 69% respectively).

Alcohol has direct and indirect effects on a person and society. The conceptual model for how alcohol consumption causes harm is presented in Figure 1-2, using the DAGitty package in R[52].

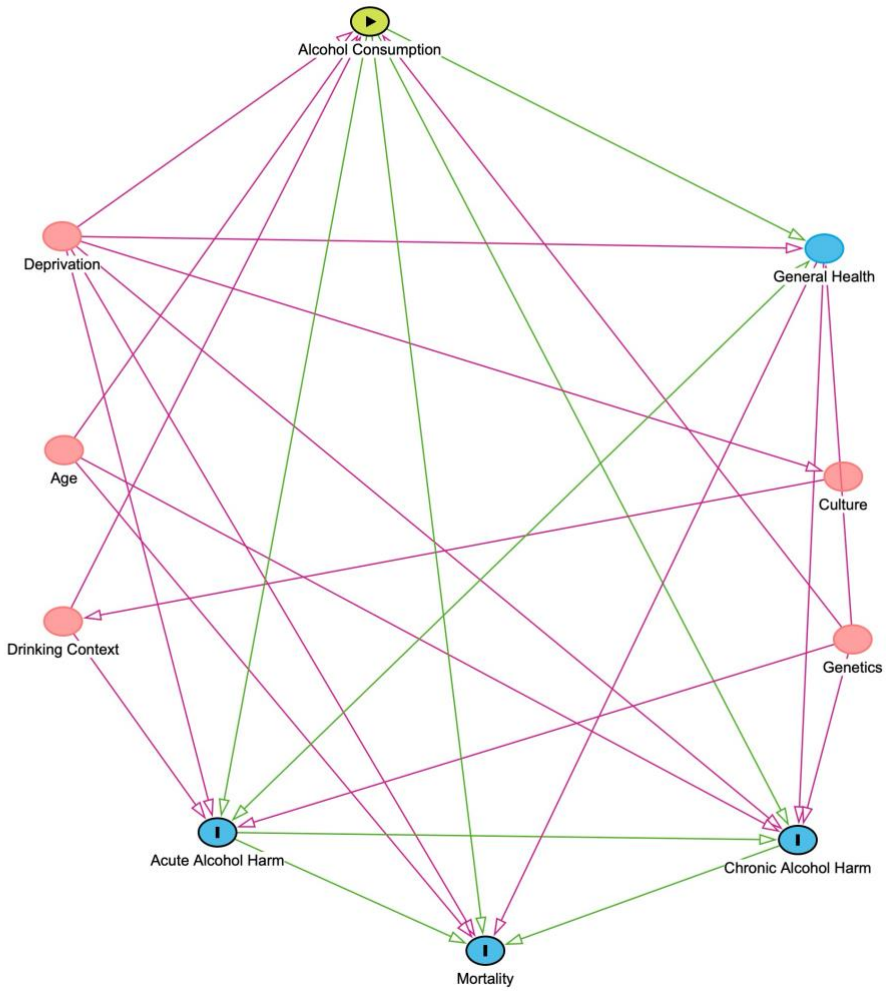


Figure 1-2: Conceptual direct acyclic graph model of alcohol consumption and health outcomes. Graphic produced by MK.

Alcohol consumption, as outlined above, can cause acute and chronic harm in addition to mortality. When considering acute harm, there is a direct relationship between consumption and harm but there is also cofounding due to deprivation, age and the context in which alcohol is consumed. A person's genetics may act as a mediator of acute harm, and the culture in which they live, a proxy confounder for alcohol-related harm.

1.9 Effects of alcohol on the body

Alcohol is contained in many drinks and foods produced as part of normal metabolic processes and affects all body systems. Ethanol is most frequently consumed orally, but pulmonary, intravenous, topical, and rectal administration have also been described[53]. Following oral intake, the stomach absorbs 10% alcohol and 90% in the small intestine. As ethanol is lipid and water-soluble, the intestinal lining readily absorbs it. Ethanol distribution depends on vascular supply, with rapid equilibrium occurring in the brain, kidneys, and liver. Alcohol is poorly absorbed by fat and is not bound to any proteins in the plasma.

The presence of carbohydrates and drugs delay the rate of alcohol absorption in the stomach. Drugs that increase alcohol absorption include cimetidine, antihistamines, phenothiazines, and metoclopramide[54]. Ethanol itself delays gastric emptying at concentrations greater than 20-30% ABV, whereas higher alcohol concentrations increase the speed of absorption as there is an increased concentration gradient. Finally, carbonation increases the rate of absorption, gastric emptying, and stomach distension[55].

The liver, stomach, pancreas, and brain metabolise most (90%) of ingested alcohol with other excretions of ethanol in urine, sweat, and respiration. The three pathways in the liver to metabolise alcohol are fixed oxidative, inducible microsomal, and fatty acid oxidation. Oxidation by the alcohol dehydrogenase pathway is responsible for most alcohol metabolism, where alcohol is converted to acetic acid in a two-step process. Ethanol is converted to acetaldehyde by alcohol dehydrogenases in the cytosol with the end products of this first step acetaldehyde and nicotinamide adenine dinucleotide (NAD^+). NAD^+ is reduced to form $NADH^+$ H^+ in a reversible process, metabolised for energy and buffering. Acetaldehyde is converted to acetic acid via aldehyde dehydrogenases in the mitochondria and acetic acid is converted to acetyl Co-A, which enters the citric acid cycle. During high levels of alcohol intake, cytochrome P450 (CYP2E1) is activated and can lead to increased metabolism of ethanol to acetaldehyde in the smooth endoplasmic reticulum. In addition, ethanol can be converted to fatty acids in the liver and pancreas as an alternative means of metabolism. A minor pathway in the liver, but the main pathway in the brain, is the conversion

of ethanol to acetaldehyde via peroxisome that reduces hydrogen peroxide to water and oxygen using catalase (See Figure 1-3). Metabolism of alcohol is a saturable process and occurs via Michaelis-Menten kinetics. At low levels, alcohol metabolism increases as the concentration rises before becoming saturated and then does not increase any further [53].

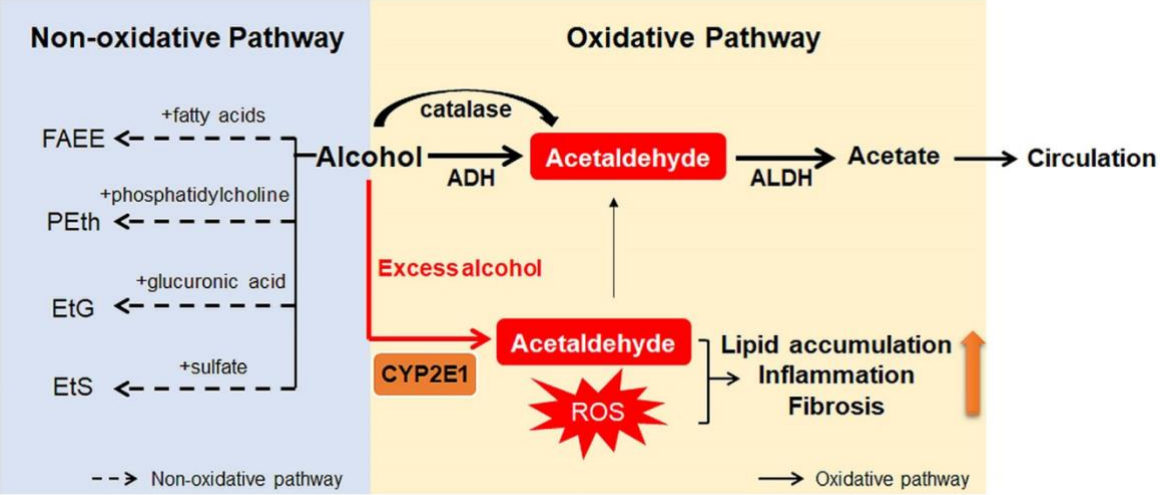


Figure 1-3: Scheme for alcohol metabolism in the liver.
Reprinted under CC BY 4.0 [53].

The intermediate compound, acetaldehyde, is responsible for the majority of the effects of alcohol intake. Accumulation of acetaldehyde can lead to sympathetic nervous system activation mediated via dopamine and serotonin with stimulation of the hypothalamus and greater levels of sympathomimetics amines and pituitary-adrenal hormones. This activation affects flushing, tachycardia, hypertension, and increased diuresis.

The effects of alcohol are influenced by genetics and biological sex. Accumulation of acetaldehyde can result in unpleasant sympathetic system activation, thus acting to discourage alcohol in populations who carry these variants. Single nucleotide polymorphism in the alcohol dehydrogenase and aldehyde dehydrogenase genes affect a person's ability to metabolise alcohol[56]. The variants alcohol dehydrogenase 1B*2 are more common in Asian and African societies and are associated with reduced alcohol dependence rates[56]. Conversely, variations in aldehyde dehydrogenase lead to reduced side effects, and variants 1A1*2 and 1A1*3 are associated with a higher degree of alcoholism[56]. Women typically have higher levels of alcohol in circulation due to reduced levels of alcohol dehydrogenase in the stomach, lower first-pass

metabolism in the liver, lower total body water content, and differences in drinking patterns. Women will absorb more alcohol than a comparable-sized man due to reduced levels of alcohol dehydrogenase in the stomach, and the same volume of alcohol will have a more significant effect on women than men due to the lower volume of distribution (higher body fat percentage). Women tend to have reduced alcohol-related harm compared to men due to lower drinking volumes and frequencies. However, these differences in harm have reduced over time, potentially due to increasing opportunities, the decline of traditional gender roles, and women starting families at a later age [57]. The other differences between sex responses due to alcohol occur due to stress and gonadal hormones as well as several neurotransmitters (dopamine, GABA, N-acetyl aspartate) mediated alcohol effects on the central nervous system [58-60].

1.9.1 Alcohol and disease

Alcohol is associated with over 60 diseases with harm related to both consumption volume and pattern of use[61]. The World Health Organisation estimates that worldwide, alcohol consumption leads to 3 million deaths per year (5.3% of worldwide deaths) [25], with this excess mortality leading to a 0.9-year lower life expectancy in OECD member states[47]. The disability associated with alcohol is believed to be 132.7 million disability-adjusted life years (DALYs) per year, accounting for 5.1% of total DALYs[47].

Alcohol-related morbidity and mortality can occur in a range of bodily systems, and can be categorised into direct toxicity (e.g. cellular damage to the pancreas, liver, brain, and heart), intoxication, and dependency [61]. Figure 1-4 outlines the main medical conditions related to alcohol excess.

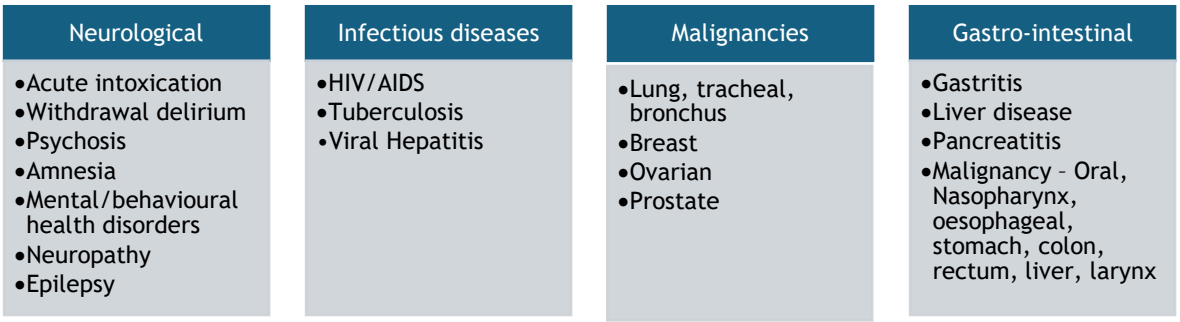


Figure 1-4: Diseases that are directly and indirectly related to alcohol.
Graphic produced by MK [61]

Alcohol has also been linked to the development of malignancy. Worldwide, every year, 741,300 malignancies are caused by alcohol, equating to around 4.1% of malignancies overall[62]. Alcohol causes malignancy in the oral cavity, pharynx, larynx, oesophagus, colon, rectum, liver, and female breast tissue[63]. Causal mechanisms for malignancy include ethanol or acetaldehyde altering DNA, proteins, and lipids as well as alterations in hormones (oestrogen and androgens) and distribution of oxidation by blocking antioxidants, such as vitamin A, vitamin E, B vitamins, zinc, iron, folic acid, and thiamine[50]. The risk of malignancy is related to the dose of alcohol and pattern of drinking but not to the type of alcoholic drink[61]. As the volume of alcohol increases, the risk of malignancy typically increases, but this is not consistent across all malignancies

or regions of the world[64]. The effects on malignancy from binge drinking are not purely due to higher volumes of alcohol consumed, but the specific pattern and harms of this behaviour[65].

The metabolism of alcohol causes liver damage due to direct effects from acetaldehyde, altered metabolic pathways, and reactive oxygen species. Aldehyde is reactive and covalently binds to proteins, lipids, and nucleic acids, disturbing their functions. In addition to this direct damage, the increased generation of NADH as alcohol is metabolised leads to more fatty acid formation and fatty liver development. Finally, the inducement of the CYP2E1 pathways leads to more oxygen-free radicals and, thus, cellular damage. The consequences of this increased fatty acid, oxidative stress, tissue hypoxia and dysregulation of the immune response lead to liver steatosis, fibrosis, cirrhosis, hepatocellular carcinoma, and hepatitis[66,67].

Alcohol also affects cardiac, respiratory, and neurological function. Cardiac conditions related to alcohol exposure include atrial fibrillation, ischemic heart disease, congestive heart failure, strokes, hypertensive disease, and cardiomyopathy[68]. Ethanol and alcohol dehydrogenase are cardiotoxic in themselves, but there is a synergistic role with other micronutrient deficiencies. Respiratory diseases associated with alcohol include community-acquired pneumonia, tuberculosis (TB), and Acute Respiratory Disease Syndrome (ARDS). Community-acquired pneumonia occurs more often in those with alcohol use disorder due to impairments in protective airway reflexes, impairments to the immune system, and malnutrition[69]. TB infection is associated with alcohol due to suppression of humeral and cell-mediated immunity, alteration in drug metabolism, and impacts on treatment compliance[70]. The risk of developing and dying from ARDS is exacerbated by a combination of oxidative stress and glutathione depletion[71]. Neurological conditions caused by alcohol intake include acute intoxication, alcohol dependence and withdrawal, seizures, memory impairment, neuropathy, ataxia, and depression[72,73]. The alteration in neurotransmitter pathways, in combination with the toxic effects of alcohol and micronutrient deficiencies, play a causal role.

Alcohol-related dependence is related to a balance between positive reinforcement and avoidance of negative consequences. Alcohol withdrawal occurs when there is sudden removal of the central nervous system suppression

associated with alcohol and is characterised by tachycardia, sweating, tremors, seizures, and hallucinations. Alcohol is associated with many other social determinants of health, in particular deprivation, and commonly co-occurs with mental health disorders[74]. The World Health Organisation estimates a sevenfold increase in the risk of suicide after consumption of alcohol[25].

1.10 The harmful effects of alcohol in pregnancy

Alcohol causes harm in all stages of childbirth, both to the mother and offspring. Before pregnancy, alcohol intake is related to increased rates of sexually transmitted diseases, assault, rape, unplanned teen pregnancies, and interpersonal and domestic violence[75,76]. During pregnancy, alcohol is associated with delayed recognition of pregnancy, miscarriage, premature delivery, intrauterine growth retardation, low birth weight and stillbirth. Following birth, there is a risk of sudden infant death syndrome and fetal alcohol spectrum disorder (FASD)[50,77]. The harmful effects are interlinked with other poor outcome indicators, such as teenage pregnancy. Teenage pregnancy itself is associated with preterm delivery, reduced antenatal education, reduced birthweight of offspring and engagement with maternity services, all of which can be caused by or lead to changes in alcohol consumption[78]. An outline of potential mechanisms of alcohol-related harm is presented in Figure 1-5.

A pregnant woman consuming ethanol affects the fetus due to transfer via the placenta and accumulation in the amniotic fluid. Ethanol can be detected in amniotic fluid within 15-45 minutes of an alcohol infusion and reaches equilibrium in the maternal circulation within 2 hours[79,80]. The elimination of alcohol by the fetus is around 50% slower than that of the mother[81] and fetal alcohol exposure is further increased by swallowing of amniotic fluid in utero[82]. The direct effects of alcohol on pregnancy have been categorised into mechanisms of altered placental structure, changes in placental function and umbilical cord blood flow, altered placental hormonal signalling, and teratogenicity[83].

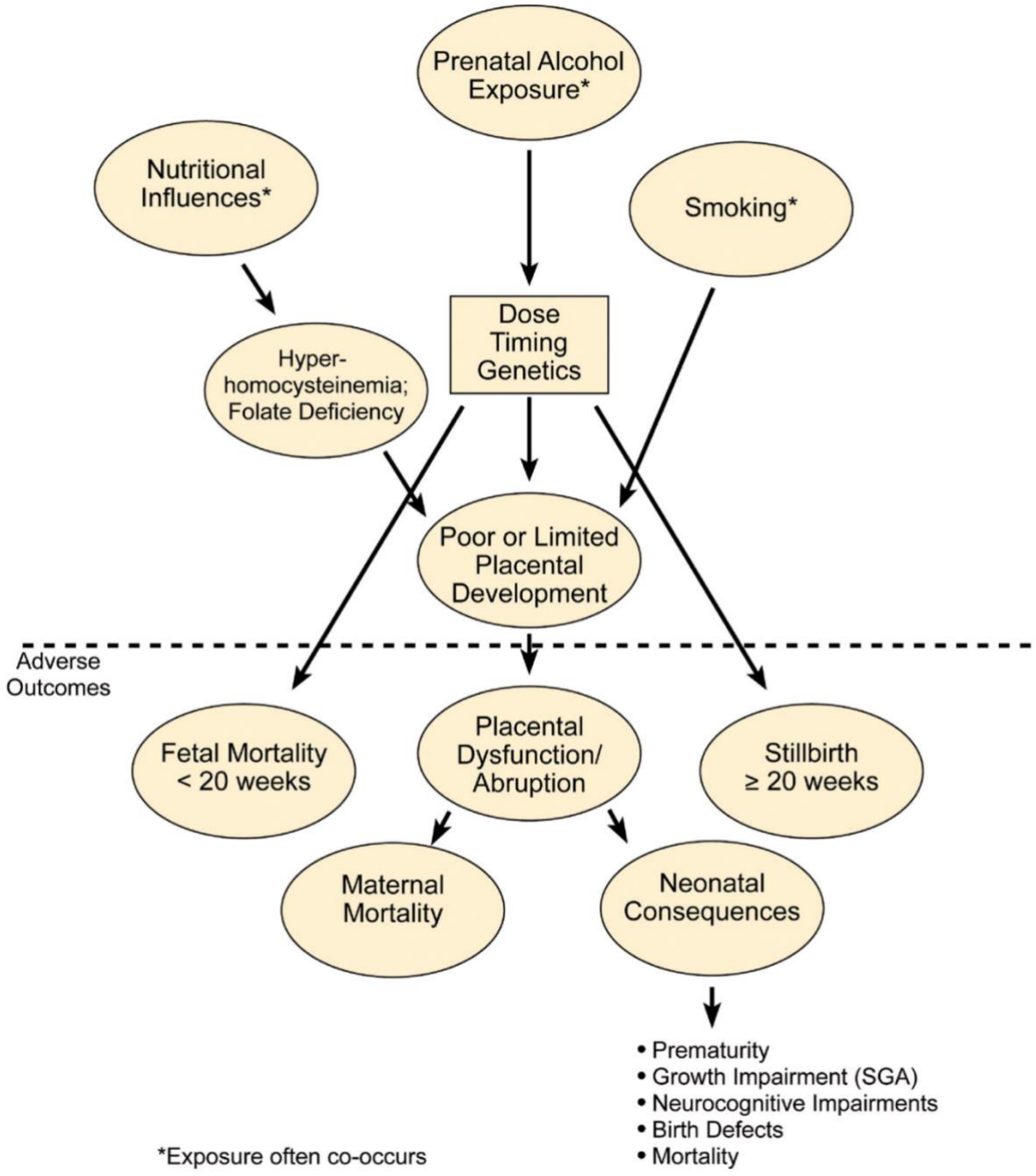


Figure 1-5: Mechanisms of alcohol-related harm.
Reprinted with permission from Burd et al. [83]

1.10.1.1 Placental structural dysfunction

Alcohol consumption has been found to lead to reductions in placental weight due to remodelling and structural and vascular pathology. Women who drink during pregnancy have lower placental weight than non-drinkers[84]. The reduction in weight of the placenta is believed to be related to how the placenta handles maternal alcohol. There is limited alcohol dehydrogenase in the placenta, so alcohol is either passed into the fetal circulation or is handled by non-oxidative pathways, forming fatty acid ethyl esters. Whilst these do not pass into fetal circulation, they can cause damage to placental tissues.

1.10.1.2 Functional changes in placental and umbilical cord

Alcohol affects vascular tone via direct vasoconstriction and intravascular coagulation. In animal and bench studies, ethanol leads to vasoconstriction of placental blood vessels. The placental vasoconstriction is mediated by reduced L-arginine, increased thromboxane levels, and impairments in omega-3 polyunsaturated fatty acids[83-86]. The net effects are increased vasoconstriction, which leads to decreased oxygen transport, fetal acidosis, and higher oxidative stress for the fetus. Changes in vascular tone have been observed in a wide range of blood alcohol concentrations[87]. Other compounds mediate these effects, and nicotine mediates vasoconstriction of placental blood vessels[83]. Vascular effects and hormonal changes lead to increased thrombosis in placental vessels in animal studies, thus potentially impeding blood flow. Due to the harms associated with tissue sampling during human pregnancy, there is little direct evidence of intra-gestational changes. Still, the risk of fetoplacental disruption at the time of delivery is higher in those who consume alcohol than those who do not[88].

1.10.1.3 Hormonal disruption

Multiple everyday hormonal actions are disrupted by maternal ethanol use. Alcohol impairs gonadotrophin-releasing hormone binding its receptor, increasing the risk of miscarriage[89]. 11-beta-hydroxysteroid dehydrogenase type II disruption leads to elevated cortisol levels following ethanol exposure, which is associated with increased hypertension in adulthood[83]. Alterations in the

metabolism of human chorionic gonadotrophin (hCG), progesterone, and growth factors also contribute to altered health outcomes following fetal alcohol exposure[83]. Alcohol's harmful effect on normal cytokine signalling leads to impairments in the development of the fetal immune system[90]. Placentae of offspring who have fetal alcohol spectrum disorder have been found to contain low maternal serum α-fetoprotein, low human placental lactogen, low pregnancy-specific β1-glycoprotein and higher levels of oestrogens[83].

1.10.1.4 Teratogenicity

Alcohol is a teratogen. Alcohol intake during pregnancy affects all organs, but especially the central nervous system. The intake of alcohol during pregnancy results in oxidative stress leading to angiogenesis, neurogenesis, impairments in the endocrine system, altered gene expression, alteration in amino acid expression and increased prostaglandin synthesis[91]. The results of the altered gene expression reduce overall brain volume and reduction in grey/white matter in the cerebrum and cerebellum. In addition to the neurodevelopmental effects of alcohol, there is the potential disruption to the hypothalamic–pituitary–adrenal (HPA) axis with increased tone in the HPA axis leading to potential dysregulation of stressors and events in later life. There is also potential for disruptions to the development of other organ systems, such as the liver, renal system, heart, GI tract and immune system[82].

1.10.1.5 Timing of alcohol intake during pregnancy

The timing of alcohol consumption in relation to pregnancy is associated with variable teratogenic effects. Animal models have been used to study the effects of alcohol exposure during development. In an animal study in 2013 by Kleiber et al., mice were subjected to variable levels of ethanol during gestation and early development to approximate human gestation[92]. This study found that during the equivalent of the first trimester, there was an increase in appropriate cell apoptosis and disruption in genes associated with spatial learning and processing of stress in adulthood. In the second trimester equivalent, there were disruptions in genes associated with developing the inhibitor neurons (GABAergic), serotonin receptors and hypothalamic-pituitary axis. Disruption of these pathways is linked to behavioural issues and reduced ability to process stress in later life. Finally, when ethanol exposure occurred in the equivalent to

the 3rd trimester, disruption in steroid secretions, folic acid metabolism, and circadian rhythm occurred.

Alcohol consumption in pregnancy is closely associated with other behavioural factors, such as smoking. This results in an adverse and synergistic relationship with adverse outcomes such as being small for gestational age and sudden infant death syndrome[7,93].

1.10.2 Risk of birth outcomes associated with alcohol intake in pregnancy.

Associations of alcohol intake in pregnancy and birth outcomes have been rigorously studied. This section will overview the risk and potential pathophysiology of stillbirths, spontaneous abortions, prematurity, low birth weight, and fetal alcohol spectrum disorder (FASD).

1.10.2.1 Stillbirth

Alcohol intake in pregnancy, in particular high-volume intake, is associated with an increase in stillbirths. A cohort analysis of 655,979 singleton births in the USA found a 40% increase in stillbirths in women who drank alcohol during pregnancy compared to non-drinkers[94]. A smaller study (24,768 births) reported an adjusted risk ratio of stillbirth of 2.96 (95% CI: 1.37, 6.41) [95]. This study observed a dose-dependent increase in stillbirth, with the rate of stillbirth increasing from 1.37 per 1,000 births for women consuming less than one drink per week to 8.83 per 1,000 births for women consuming five drinks per week or more.

1.10.2.2 Spontaneous abortions

The use of alcohol in early pregnancy has been linked to miscarriage. In a meta-analysis of 24 cohort and case-control studies (231,808 pregnancies), the odds of miscarriage were higher in drinkers compared to non-drinking counterparts (OR 1.19, 95% CI: 1.12, 1.28) [96]. Every additional drink consumed increased the chance of a spontaneous abortion (OR 1.06, 95% CI: 1.01, 1.10). A limitation of this meta-analysis was that only three studies included adjusted outcomes, and there was a lack of data on spontaneous abortions, as many occur before a pregnancy is recorded or before enrolment in a study can occur.

Other studies have had more varied results. A prospective study of 186 pregnancies showed a two to three times greater risk of spontaneous abortions in women who consumed alcohol at the time of pregnancy conception[97]. The risk was statistically significant when women who consumed ten or more drinks per week were compared to women who consumed no alcohol. The effects of only high alcohol consumption being a risk factor have been demonstrated in other studies, finding little effect from moderate consumption[98].

1.10.2.3 Prematurity

Premature delivery (before 37 weeks of gestational age) is associated with heavy alcohol consumption. In a retrospective cohort study of 18,000 births, women who drank greater than ten units of alcohol per week were almost three times as likely (OR 2.93, 95% CI: 1.52, 5.63) to give birth prematurely compared with women who drank under 1 unit of alcohol per week[99]. The relationship between low to moderate levels of alcohol and prematurity is unclear, and some studies have shown that light alcohol intake may be associated with reduced levels of preterm birth[100,101]. In a meta-analysis of cohort and case-control studies (12 studies, 280,443 mothers), women who drank up to 1.5 units of alcohol per day did not have an increased risk of premature birth. This relationship was non-linear, and there was an increasing dose-response relationship once greater than 1.5 units per day were consumed[102].

1.10.2.4 Low birthweight and small for gestational age

A population-based study of 1.2 million births from Denmark demonstrated that heavy drinkers have an increase in risk of having offspring with Small for Gestational Age (SGA) (adjOR 2.20 [95% CI: 1.97, 2.45]) and prematurity (adjOR 1.32 [95% CI: 1.19, 1.46]) [103]. However, this study only compared heavy drinkers (0.4% of women) to non-drinkers, thus providing limited evidence for the effects of small amounts of maternal consumption. A 2011 meta-analysis of 36 studies examined alcohol consumption in a more representative sample, finding limited evidence of harm specific to alcohol, especially at low levels[102]. This limited evidence was supported by further meta-analysis in 2017 which directly investigated consumption of 4 units of alcohol per week (32g of ethanol) to no alcohol consumption in prospective cohort and quasi-experimental studies. The

authors reported concerns about a lack of research but did find an increased risk of SGA (adjOR 1.08, 95% CI: 1.02, 1.14) in the 7 studies that could be analysed[104].

1.10.2.5 Fetal alcohol spectrum disorder

Fetal alcohol spectrum disorder (FASD) is defined as the presence of cognitive impairment and behavioural defects related to ante-natal alcohol consumption and is associated with 428 comorbid conditions. The most common conditions include peripheral nervous system, conduct disorder, receptive language disorders, chronic serous otitis media, and expressive language disorders[105]. FASD represents a spectrum of diseases, including Fetal Alcohol Syndrome (FAS), Partial Fetal Alcohol Spectrum (PFAS), Alcohol-Related Birth Defect (ARBD), and Neurobehavioral Disorders associated with Prenatal Alcohol Exposure (ND-PAE).

Due to its heterogeneous presentation and poor diagnosis rates, no large study has studied the incidence of FASD at a population level. In a report by the Scottish Intercollege Guideline Network (SIGN), the lack of universal screening and assessments was highlighted, but it was estimated that FASD could affect as many as 32 per 1,000 pregnancies (95% CI: 20, 49) [106]. Until a comprehensive diagnostic criteria pathway exists, the incidence of FASD will likely remain unknown at a population level. At present, there is no routinely collected data on the diagnosis of FASD in the UK despite its potentially high prevalence.

1.10.2.6 Mediators in alcohol-related harm in pregnancy

The effects of alcohol in pregnancy on offspring outcomes are mediated by the quantity of alcohol consumed, the consumption pattern, genetics, and environmental factors. The variation in these mediating factors partly explains the differences in the expression of alcohol-related harm seen in offspring. These mediators can be classified into maternal factors, alcohol exposure and environmental factors; Figure 1-6 outlines these factors[107].

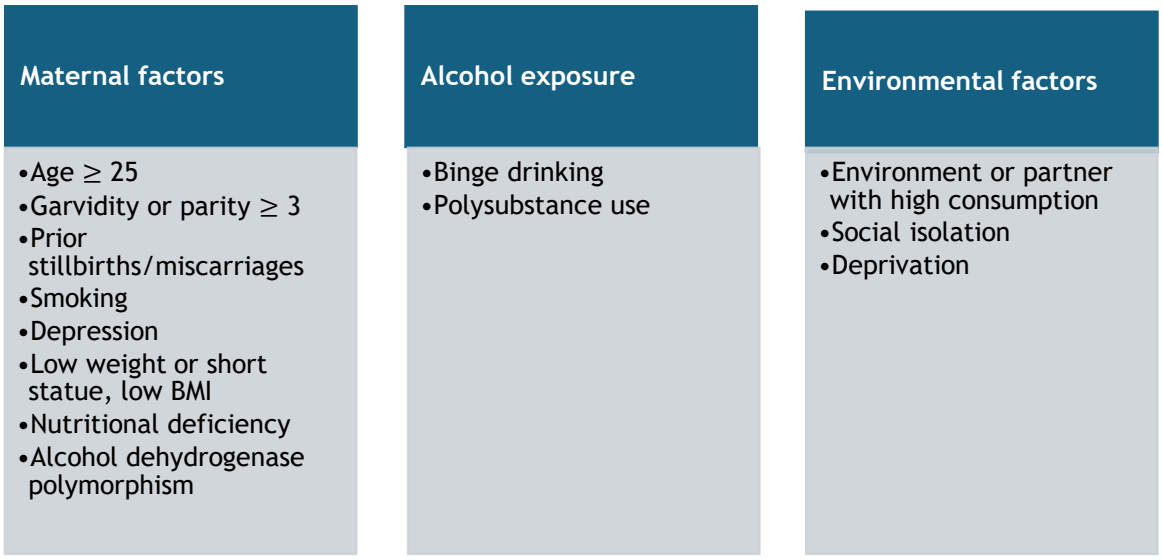


Figure 1-6: Modifiers of alcohol-related harm.
Own work adapted publication from May et al. [107]

The more alcohol a woman consumes during pregnancy, the greater the risk to the offspring's health [88,108,109]. As the dose of alcohol consumed increases, the harm associated with alcohol increases, but this increase is not linear. There is a "J" shaped curve to most offspring outcomes, with light drinkers having better outcomes than non-drinkers. These effects on offspring outcomes might be impacted by a failure to account for residual confounding differences between mothers who consume low amounts of alcohol and those who do not[108]. Prior studies have demonstrated that those who consume alcohol have different demographic characteristics (e.g. age, smoking rates, BMI), and failure to account for this could bias non-adjusted outcome studies[110,111].

Whilst heavy drinking in pregnancy is irrefutably associated with adverse offspring outcomes, the lower level of alcohol needed to cause harm remains unclear, and current evidence is inconclusive. As described in the previous section (on SGA outcomes) a meta-analysis in 2017 investigated 26 observational

studies and highlighted a lack of evidence on the effects of drinking under 32g of ethanol per week (4 UK units) on offspring outcomes[104]. Whilst they reported an increase in SGA births and low birth weight, heterogeneity in study design and sample sizes precluded definitive conclusions on other important birth outcomes. The authors concluded that there was some evidence that even light alcohol consumption in pregnancy was associated with SGA and prematurity[104]. A recent update of that systematic review, which focused on evidence from RCTs and quasi-experimental studies, further concluded that there was some evidence that prenatal alcohol consumption could lead to low birth weight and adverse cognitive outcomes[112]. The authors noted that none of the 23 included studies had a low risk of bias across all domains.

There are several possible explanations of why no change can be seen in some outcomes in studies examining low levels of alcohol intake. It is possible that there is no harm associated with low alcohol intake, or that women who drink have other favourable characteristics which reduce their risk of poor outcomes. Furthermore, there may be limitations in the ability to study the topic due to a lack of data. The limitations can occur for any reason, such as lack of data collection, including heterogeneity and lack of precision when recording alcohol intake, biased self-reporting of alcohol consumption, and heterogeneity of outcome data. Furthermore, women who drink low levels of alcohol during pregnancy are more likely to be from a higher socioeconomic position, which is associated with improved birth outcomes. The different characteristics of women who drink means that adjustment for critical confounding factors is vital when looking at population data on alcohol consumption and perinatal outcomes. A failure to account for patterns of drinking can limit studies' ability to measure outcomes following maternal drinking[113]. Whilst there is clear evidence that binge drinking is harmful in the general population, there is no consistent research to show that binge drinking is harmful in pregnancy[114]. An association between congenital disabilities and the prevalence of binge drinking has been reported, with countries with high binge drinking rates (e.g. South Africa) having high levels of birth defects compared to areas with lower binge drinking rates (e.g. Italy) [107].

1.10.3 Confounding factors – opioids, smoking, and deprivation.

Alcohol is not the only factor that impacts maternal and offspring health. Some of the most significant factors affecting perinatal outcomes are concurrent drug use, smoking, and deprivation. The combination of these factors is poorly understood due to interactions and confounding, but it can be assessed that multiple adverse factors combine to lead to greater harm.

1.10.3.1 Opioids

There are approximately 62 million non-medical opioid users globally, with more than 11 million people injecting drugs in 2019[115]. Opioid use in people of childbearing age and consequently in pregnancy is increasing and represents a growing public health challenge[116]. It has been estimated that opioids affect 30,000 births in regions of Europe each year[117]. During pregnancy, continued opioid use is associated with obstetric and neonatal complications such as stillbirth, intrauterine growth restriction, placental abruption, preterm labour, prolonged hospital admission, maternal cardiac arrest, and congenital defects. The primary neonatal adversity directly linked to opioids is neonatal abstinence syndrome (NAS), characterised by autonomic, neurological, gastrointestinal, and respiratory system disturbances. Following opioid exposure and NAS, offspring have higher rates of developmental delay in childhood and an increased risk of addictions, criminal activity, and poor health in adulthood[118]. In addition to the harm to offspring, a mother who has a neonate diagnosed with NAS has an 11-12 fold increased risk of death in the ten years following delivery compared with a mother whose neonate does not have NAS[119]. The harm to mother and offspring is most likely a result of a combination of direct and indirect harm from social determinants of health.

To reduce the harm associated with opioid use, opioid substitution programs during pregnancy have been introduced. These programs stop the cycle of intoxication and withdrawal associated with illicit drug use, reducing the incidence of blood-borne virus infections, reducing criminal activity, and increasing engagement with health care services [120-123]. The two main drugs used for opioid substitution therapy are methadone and buprenorphine, with both recommended for use in pregnancy by international guidelines. However, little is

known regarding which is superior as studies comparing methadone and buprenorphine in pregnancy are complicated by differences in prescription practices (in cohort studies) and by small study sizes (in randomised control trials)[124-126].

1.10.3.2 Smoking

Smoking is a further major confounder of offspring outcomes. Maternal smoking leads to harm due to nicotine and carbon monoxide exposure. Nicotine decreases uterine artery blood flow (due to vasoconstriction), reduces placental blood flow (due to reduced maternal blood pressure) and alters acid-base homeostasis[127]. Carbon monoxide is transferred to the fetal circulation and equilibrates at 15% of maternal levels, resulting in a left-hand shift in oxygen dissociation and reduced oxygen delivery to the fetus[128]. Continued smoking in pregnancy is associated with 46 conditions in offspring, including stillbirth, low birth weight and prematurity[129]. Smoking 6-10 cigarettes a day is associated with a reduction of 320.41g (95% CI: 535.4g, 105.32g) in the birth weight in full term offspring[130]. The combination of both smoking and drinking in pregnancy has an effect more significant than would be predicted by the presence of both individual exposures. The Safe Passage Study monitored 11,892 pregnancies in South Africa and the USA and observed that combined smoking and drinking are associated with a greater risk of adverse birth outcomes than just smoking or drinking alone. When stillbirths were investigated, the adjusted risk ratio for stillbirth if a woman smoked and drank was 2.78 (95% CI: 1.12, 6.67), while for drinkers, it was 2.22 (95% CI: 0.78, 6.18) and smokers, 1.60 (95% CI: 0.64, 3.98) [131]. When the Safe Passage Study team investigated sudden infant death syndrome, they found the adjusted risk ratio of dual exposure was 14.75 (95% CI: 4.28, 50,87) compared to drinking of 3.96 (95% CI 95: 0.66, 23.71) or smoking alone 6.39 (95% CI: 1.70, 24.07). It is unknown how the physiological interaction between smoking and drinking occurs. Still, it is clear from this research that smoking has harmful effects on the developing fetus, and that this is worse when drinking also occurs.

1.10.3.3 Genetics

Genetics can influence alcohol-related harm. Women with a lower tolerance to alcohol consume less alcohol in pregnancy and are less likely to have offspring with facial abnormalities and low IQ[132,133]. There is also an association between maternal FAS and offspring FAS, with mothers in a higher drinking group in South Africa demonstrating signs of possible FAS themselves[107]. However, this association is subject to confounding due to the similar environmental exposure and risks.

1.10.3.4 Socioeconomic

Socioeconomic position is a further important confounding factor, with greater harm associated with a given alcohol intake in women and offspring when from lower socioeconomic groups. For example, for a given volume of maternal alcohol consumption, there is less growth impairment observed in more affluent compared with less affluent families[134]. In the USA, there is a 15-fold increase in FAS rates in communities with the highest deprivation indices compared with the lowest[107].

1.11 Alcohol regulation worldwide

There is a considerable variation in alcohol regulation worldwide. Alcohol regulation is enacted by international bodies, governments, regional authorities, and Non-Governmental Organisations (NGOs), with the overarching international policy monitored by the World Health Organisation (WHO). The WHO has a focus on harm reduction following a 2010 resolution that gave the organisation a mandate to reduce harm and monitor global alcohol harm[135]. The United Nation's (UN) sustainable development goals (SDH) overlap with the WHO harm reduction goals[136]:

- Ending poverty (SDG 1)
- Quality education (SDG 4)
- Gender equality (SDG 5)
- Economic growth (SDG 5)
- Reducing inequalities between and within countries (SDG 10)

As well the goals listed above, there is a specific target for:

> "strengthening the prevention and treatment of substance abuse, including the harmful use of alcohol" and "preventing drinking in pregnancy and preventing fetal alcohol spectrum disorders (FASD)." [137]

The WHO aims to reduce alcohol-related harm by advocating for public health, supporting the development of policies and laws, and producing evidence-based use resources in low and middle-income countries. One of the main elements of the WHO alcohol risk reduction policy is the SAFER initiative[138].

- Strengthen restrictions on alcohol availability.
- Advance and enforce drink-driving countermeasures.
- Facilitate access to screening, brief interventions, and treatment.
- Enforce bans or comprehensive restrictions on alcohol advertising, sponsorship, and promotion.
- Raise prices on alcohol through excise taxes and pricing policies.

As part of the WHO public health measures, alcohol risk reduction "best buys" are[139]:

- Increase taxes

- Bans/restrictions on advertising
- Restrictions on availability
- Enforce drink-driving laws
- Provide brief psychosocial interventions for hazardous drinkers
- Regular review of prices
- Establish minimum prices
- Restrict / ban sponsorship in connection with activities targeting young people
- Provide treatment and care for those with alcohol disorders and provide consumer information on packaging

The benefit of this intervention is to improve health and the economy. For every dollar spent on a comprehensive policy package for alcohol harm prevention, there are $16 in economic savings[139]. The Scottish government has accepted the recommendations of the WHO, and the following section will outline its response.

1.12 Alcohol policy in Scotland

Scotland has a long history of alcohol consumption and production with corresponding evolution in control and regulation. Restrictions to alcohol sales in Scotland began with alcohol licences in 1756 but significantly changed during the 19th and 20th centuries [140,141]. In the 19th century, there was the development of on-sale (e.g., pubs and clubs) and off-sale (e.g. supermarkets) licencing. During the 20th century, there has been a steady progression in the increasing regulation of alcohol sales, reducing access to alcohol and lowering limits for "low-risk" drinking to improve public health and social cohesion.

The first measure to improve public health via alcohol regulation came in the 20th century via the temperance movement. This social movement campaigned against the recreational use and sale of alcohol and promoted abstinence. In 1931, the MacKay Commission aimed to gain a "better understanding of the laws of health and a general desire to conform to those laws". They believed that counter attractions such as sports, outdoor pursuits, motoring, better education, updated licensing laws, improved housing, and increased taxation would improve public health and reduce alcohol use. In 1973, the Clayton Commission continued this work with further reforms to alcohol sales in Scotland. Unfortunately, in the years following the Clayton Commission, harm from alcohol increased significantly with a rise in binge drinking[140].

The 21st century was a time for significant reform of alcohol sales in Scotland. During the first ten years of the century, multiple reviews and commissions established the modern policy of alcohol controls in Scotland. In 2001, the Nicholson Commission established Scottish licencing regulations, focussing on the implications for the health and public order of alcohol consumption. The five provisions to be included in licensing regulation were preventing crime and disorder, public safety, preventing public nuisance, protecting children from harm, and protecting and improving public health[142]. The 2005 Licensing (Scotland) Act enshrined many of these elements into law. The key elements, from a healthcare perspective, were measures to reduce harmful consumption of alcohol as well as improve public safety[142].

In 2009, the Scottish Government produced a new strategy for alcohol use in Scotland; "Changing Scotland's Relationship with Alcohol: A Framework for Action" [143]. The strategy changed Scottish policy from individual responsibility to a population approach with targeted interventions for high-risk groups. The entire population approach aimed to change social norms around alcohol and reduce and prevent harm while supporting people to stop risky or harmful drinking. Sir Harry Burns, Scotland's Chief Medical Officer, outlined the requirement for action due to the doubling of alcohol-related deaths in the 15 years before the report. The report proposed:

- Regulations to end irresponsible promotions and below-cost selling of alcoholic drinks on licensed premises.
- Pursuance of the establishment of a minimum price per unit of alcohol through regulation review.
- Placing a duty on Licensing Boards to consider raising the age for off-sales purchases to 21 years of age.
- Establishing a legislative power to charge some alcohol retailers a social responsibility fee and propose regulations restricting the use of marketing material or activity on licensed premises.

This strategy led to legislation in the 2010 Licensing (Scotland) Act[144]. There were many changes in the 2010 Licensing Act, but the three key policies and actions were introduced.

- Reform of Sales and Licencing Law, with local control and challenge to anyone who looks younger than 21 years old - 2012
- Reduced drink driving limits - 2014
- Minimum unit pricing (MUP) – 2018

The licensing reform was implemented progressively. Following the 2012 reform in Scotland, on-sales could occur in "happy hours," pricing had to be linear (multiple packs the same cost as singles), restrictions were placed on off-sales locations, advertising was restricted, and local communities had greater input into planning and licencing. These reforms were consistent with the WHO SAFER interventions[138].

1.12.1 Driving and alcohol limits in Scotland

Driving a vehicle whilst intoxicated has been illegal since the late 19th century, but motor vehicles have long replaced horses, and as such, the rules were strengthened to align with the dangers of road use[145,146]. The alcohol and driving laws in Scotland have progressed as follows:

- 1872 – 1960: illegal to drive (motor or animal-controlled vehicle) whilst intoxicated
- 1960 – 2014: 80mg alcohol /100mls in blood
- 2014 – current: 50mg alcohol /100mls in blood

On the 5th of December 2014, the limit for driving and blood alcohol level was reduced to 50mg/100mls in Scotland. This reduction followed a recommendation by the European Commission in 2001 and the North Report in 2010[145,146]. A decrease in alcohol consumption was advised due to an exponential increase in road traffic collisions as blood alcohol levels incease from zero. The increased risk is as follows [146]:

- Three times risk of road traffic collision at 50mg/100mls
- Six times at 80mg/100mls
- Eleven times at 100mg/100mls
- Fifty times at 125mcg/100mls
- Five hundred times at 200mcg/100mls

Following the legislation change in 2014, research has been conducted into the effects of these reductions in the blood alcohol limit. A study by the University of Glasgow used road traffic data and alcohol sales taxes to study the effects of the change in Scotland[147]. This study found no statistically significant improvements in drink-driving rates, road traffic collisions, or other dangerous behaviours observed since the 2014 change. The study did, however, report a slight (<1%) reduction in on-trade sales. According to this study, Police Scotland said there was a reduction of 12.5% in drink driving offences in the nine months post-reduction of the legal blood alcohol limit, but this could have been further influenced by changes in enforcement and policing priorities[148]. A meta-analysis of 21 studies (not including the prior research in Scotland) found that regions which had reduced alcohol to 50mg/100mls, led to an 11.1% decline in fatal road traffic collisions[149]. The meta-analysis could not elucidate a change in self-

reported alcohol consumption, attitudes or prosecutions following the change. Work has yet to be conducted on the effects of changes to drink-driving legalisation on subgroups of the population, with most research focusing on either legal aspects (convictions and road traffic collisions) or samples of drivers.

1.12.2 Minimum unit pricing

Minimum unit pricing for alcohol has been a Scottish government priority since 2007, with the Scottish National Party campaigning on this issue to reframe public health policy towards a population based approach[150]. In 2009, a bill was proposed, but this was only passed on 24th of May, 2012, and the new pricing modelling was introduced on 1st of May, 2018. The delay in implementing MUP was due to legal challenges by the Scottish Whisky Association leading to reviews in Scottish, British, and European courts [151].

The modelling commission by the Scottish Government estimated that MUP at 50p per unit would lead to 3.5% less alcohol consumed, 121 fewer deaths and 2,042 fewer hospital admissions per year[152]. Time series analysis has shown that the implication of the MUP has led to a 13% reduction in fatalities attributed to alcohol (156 deaths per year) and a 4% reduction in hospitalisations (411 per year) [153]. This study found that the change was most significant in the regions with higher indices of deprivation. There are yet to be any investigations into the effects of MUP on the pregnant population.

1.12.3 The future of alcohol policy in Scotland

In 2018, the latest Scottish government alcohol policy was released: "The Population Health Directorate Alcohol Framework" [154] builds on the work of the 2009 report with the fundamental principles of:

- Reducing consumption
- Positive attitudes, positive choices
- Supporting families and communities

The Scottish government outlined 20 actions to be implemented in line with the SAFER approach from WHO, focusing on reducing inequality and protecting children and young people. This framework also recognised that alcohol policy must integrate with other issues,

> "Enabling and supporting positive mental health; reducing poverty and tackling inequalities at source; providing good quality housing and ending homelessness; enabling the best starts in life for our children, including recognising the impact of adverse childhood experiences; improving the life circumstances of children, young people and families at risk; improving social connectedness, community cohesion and safety and evolving our justice system to improve outcomes for individuals, families and communities." [138]

This continues the Scottish Government's trend of harm reduction through reduced consumption, especially in the highest-risk groups. On the 8th of February 2024, the Scottish Health Minister published plans to increase the cost of a unit of alcohol in Scotland from 50 pence per unit to 65 pence per unit[155]. The increase was due to inflation and a desire to maintain the impact of the cost that had been planned on the MUP induction. The continued support of MUP after its sunset period (six years since it was initially introduced) shows ongoing commitment to this policy from the Scottish Government.

1.13 Guidelines relating to alcohol intake in pregnancy.

International policy on alcohol consumption in pregnancy is variable, with many countries lacking any formal policies and others having varying degrees to which alcohol is discouraged. In the 2022-2030 Global Alcohol Action Plan, the WHO stated member states should:

> "… advocate for the development and implementation of high-impact strategies and interventions and other actions to prevent and reduce alcohol-related harm. This includes placing a special emphasis on protecting at-risk populations and those affected by the harmful drinking of others; preventing the initiation of drinking among children and adolescents; preventing drinking in pregnancy; and preventing FASDs, including by providing information about the risks of drinking when planning pregnancy or breastfeeding." [156]

This document was controversial as the first draft (sent for public debate) included the action area of:

> "Prevention of drinking among pregnant women and women of childbearing age, and protection of people from pressures to drink, especially in societies with high levels of alcohol consumption" [137]

This inclusion of "women of childbearing age" aimed to minimise the harm associated with drinking alcohol when the pregnancy is unplanned. As 16.2% (95% CI: 13.1-19.9) of UK pregnancies are not planned, reducing alcohol consumption in women of childbearing age could potentially reduce harm for many pregnancies[9]. As reported by the UK charity Full Fact, the media reaction to this was largely adverse and framed the working as banning alcohol for women only, and therefore sexist[157]. When speaking about their policy to the Full Fact organisation, the WHO clarified that the intention was harm reduction. Following the media reports, subsequent versions of 2022-2030 guidelines did not include mention of women of childbearing age. There are no reports on why the wording was dropped, but one might assume that it was due to the negative perception in the media and desire to represent the view of the WHO member states.

The controversy around WHO wording and perception of being too prescriptive to all women differs from European and US policy. The European Council Health Executive recommends complete abstinence from alcohol during

pregnancy. Still, communication for health care occurs at the state level, and adherence to this central European health message is variable[158,159]. In the US, the Centers for Disease Control and Prevention (CDC) recommends that women of reproductive age avoid alcohol entirely when they are pregnant, are attempting to be pregnant, or could be pregnant[160]. US State laws differ, with some having a legal requirement for health care professionals to report alcohol use in pregnancy, with many of these reports leading to social work involvement[161].

1.13.1 Scottish Guidelines relating to alcohol intake in pregnancy

Scotland has a long history of advice to reduce alcohol consumption around the time of pregnancy. The contemporary guidelines for alcohol in Scotland date back to 1995 and the publication of "Sensible Drinking" by the UK Department of Health[162]. The Sensible Drinking report outlines alcohol policy in the UK with specific advice for pregnant women recommending that:

> "Women who are trying to become pregnant or are at any stage of pregnancy should not drink more than 1 or 2 units of alcohol once or twice a week and should avoid episodes of intoxication." [162]

The report's authors detailed the lack of any clear evidence of harm when 1-2 units of alcohol per week were consumed with the final recommendation stressing the importance of moderation in alcohol intake, given the apparent dose-related effect and harm from episodes of binge drinking. The full guidelines stress the lack of high-quality evidence and the difficulties in interpreting associations with harm when potential confounders are not accounted for. The limit of 1-2 drinks per week is related to findings of increased risk of SGA above this level[162]. The report also recommends that advice should be framed around units of alcohol consumed per week to include those who binge drink and that:

> "To any new advice which may be formulated on sensible drinking limits, a caveat should be added to the effect that women who are pregnant or who are likely to become pregnant should keep their alcohol intake substantially below limits suggested for non-pregnant women." [162]

In 2007, the UK government updated the "Sensible Drinking" report with a new publication titled "Safe. Sensible. Social. The next steps in the National Alcohol Strategy" [163]. The report recommended that the same advice should be given as the 1995 report but include an additional phase:

> "Pregnant women or women trying to conceive should avoid drinking alcohol. If they do choose to drink, to protect the baby, they should not drink more than 1–2 units of alcohol once or twice a week and should not get drunk." [163]

The change in wording to add advice to abstain from alcohol followed a 2005 literature review from the National Perinatal Epidemiology Unit[164]. The literature review found no evidence of harm due to low to moderate consumption during pregnancy, but that binge drinking was harmful. The Department of Health felt the previous wording could have been easier to interpret, so it clarified the wording as above.

In 2008, guidance from The National Institute of Health and Care Excellence (NICE) expanded on previous reports with additional advice explaining that advice to abstain from alcohol in the first three months of pregnancy is to reduce the risk of miscarriage[165]. The report further highlights a lack of evidence of harm from low-level intake but clear harm from higher intakes.

Scottish health policy regarding alcohol intake in pregnancy diverged from UK policy in 2010. In 2010, Sir Harry Burns (Chief Medical Officer for Scotland) submitted written evidence to the House of Commons Science and Technology Committee on Alcohol[166]. The committee was holding a hearing on the UK policy regarding alcohol, and Sir Burns said:

> "Current advice on alcohol and pregnancy is that there is no "safe" time for drinking alcohol during pregnancy and there is no "safe" amount." [166]

In 2016, the UK's chief medical officers reviewed alcohol policy in pregnancy and presented this new standard approach across the UK [167]. The policy had the intent of harm minimisation and a desire to provide clarity and consistency in messaging:

> "If you are pregnant or think you could become pregnant, the safest approach is not to drink alcohol at all, to keep risks to your baby to a minimum. Drinking in pregnancy can lead to long-term harm to the baby; the more you drink, the greater the risk." [167]

The advice also stressed the importance of keeping alcohol consumption as low as possible to avoid risk, and to reassure women who have already consumed alcohol before knowledge of pregnancy that the risk of harm is low and to encourage abstinence going forward. This guidance aimed to provide a careful balance between advising women regarding the safest approach of abstaining from alcohol in pregnancy without misrepresenting current evidence and avoiding the stigmatisation of women who consumed alcohol before they realised they were pregnant. Publication of the 2016 report from the Government was extensively covered in the UK media, with 997 articles published on the topics (largely factual). Still, there was little promotion from the Government, NHS or NGOs[168]. The updated wording on the NHS literature, such as the "Better Health – Start for Life" website, states,

> "Your baby cannot process alcohol as you can, and too much can be extremely harmful to their development. Drinking alcohol, especially in the first three months of pregnancy, increases the risk of miscarriage, premature birth and low birth weight". [169]

Following the CMO's advice, the Institute for Health surveyed 74,388 adults living in England and found that the new guidelines were not associated with a change in drinking, and the trend of increased consumption continued, however this project, did not include Scotland[168]. In 2021, the Scottish Government published a report on the awareness of the units per week guidelines (also updated in the 2016 CMO report) [170]. The guideline showed that 82% of Scots were aware of the existence of policies on alcohol, but only 21% of these Scots knew there was an advised upper limit of 14 units per week for non-pregnant persons. There was no assessment of knowledge of advice for pregnancy or measurement of alcohol use.

The awareness of the CMO 2016 advice surrounding alcohol consumption in pregnancy has also been studied in health care professionals. In a survey of 842 practising midwives, 58% (n = 484) were aware of the CMO advice, and 91% of those respondents (n = 438) knew that its direction was to avoid alcohol altogether[171]. This survey did not explore the understanding of alcohol recommendations in midwives who were not aware of the CMO advice. No

studies have examined the effects of particular governmental advice on the pregnant population.

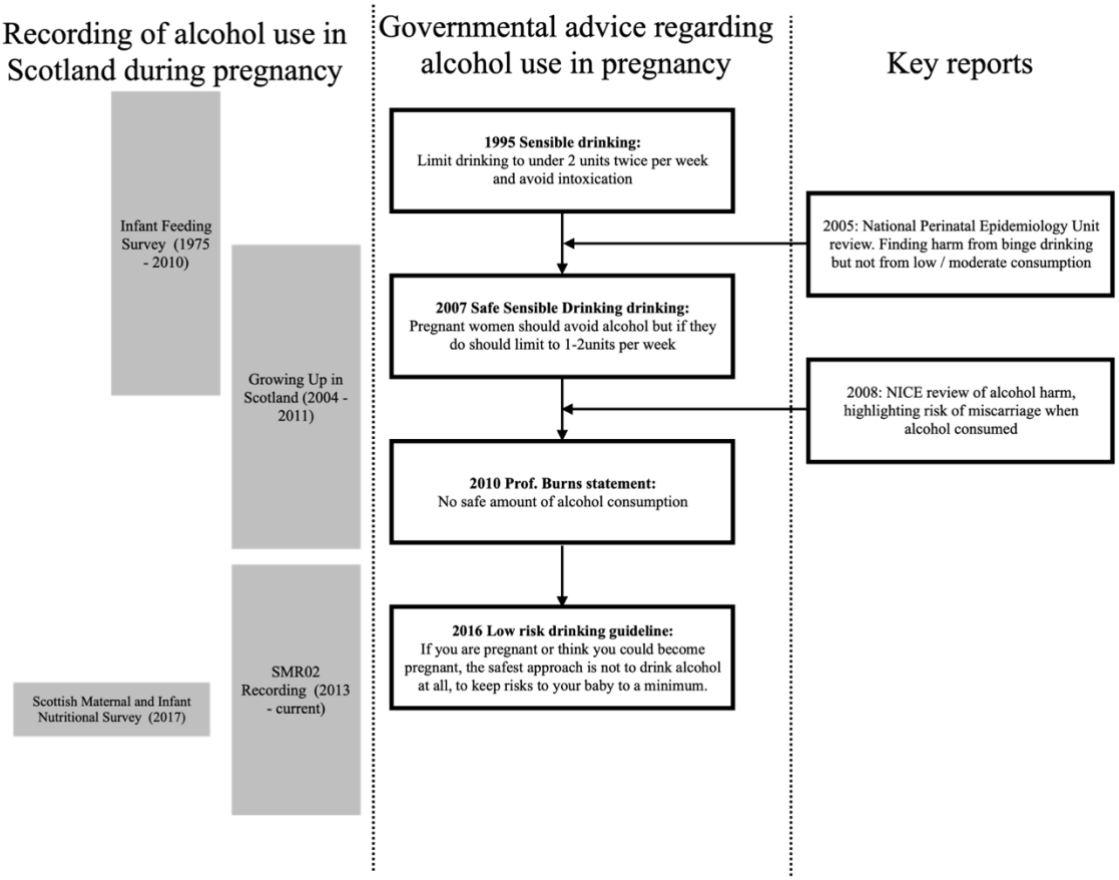


Figure 1-7: Alcohol advice in pregnancy over time with critical reports and monitoring.

1.14 Chapter Summary

This chapter highlights that most health outcomes are determined not by the health care a person receives, but by the environment in which they are born and live. Despite alcohol consumption being responsible for five per cent of worldwide morbidity and mortality, little is known about the prevalence of consumption in pregnancy and on the influence of public health interventions on maternal alcohol consumption. Interventions such as the introduction of lower permissible drink-drive limits in 2014, Minimum Unit Pricing (MUP) in 2018, and the UK Chief Medical Officers advice to pregnant women to abstain from alcohol (2016) could affect maternal alcohol use. In addition, whilst there is good evidence that heavy alcohol consumption in pregnancy can result in adverse perinatal outcomes, the impact of low and modest consumption is unclear, and causal evidence of effects at these levels is challenging to ascertain. Consequently, the UK CMOs invoked the 'precautionary principle' for their recommendation that women should abstain from any alcohol consumption during pregnancy. The availability of detailed linked data in Scotland, including on alcohol consumption in pregnancy, together with the implementation of general, as well as pregnancy-specific, alcohol reduction policies, provides a unique opportunity to add to the sparse evidence on the effects of alcohol in pregnancy on maternal and perinatal health.

This chapter also explores that alcohol alone is not responsible for adverse outcomes in pregnancy. Health is determined and mediated by a range of factors, including smoking, social deprivation, and drug use. Opioid substitution therapies have developed and evolved, but little is known about which therapy is superior for women of childbearing age. Given that adverse behaviours tend to cluster, improvement in health will come from addressing multiple aspects affecting maternal and offspring health.

1.15 Aims and objectives of this thesis

As outlined in this chapter, alcohol and opioid drug consumption in pregnancy has a potentially profound impact on both maternal and offspring health outcomes. Yet, there is relatively little research on prevalence and population interventions affecting these behaviours. Combining routinely collected, accessible health records from the NHS and population health measures can lead to novel research and understanding of population health. In this thesis, I will evaluate alcohol consumption in pregnancy, measure the change in alcohol consumption following three distinct public health interventions as individual entities and cumulatively across all three interventions, and measure any associated changes in perinatal outcomes in Scotland. I will investigate if birth outcomes are affected by low-level alcohol consumption, compared to no reported alcohol consumption or higher-level consumption. In order to support shared decision making, I will also investigate whether there is a level of alcohol consumption in which harm appears to increase.

Furthermore, I will systematically review and appraise the evidence for both methadone and buprenorphine opioid substitution therapy in pregnancy, with an emphasis on maternal, neonatal, and longer-term childhood outcomes, and provide contemporary meta-analysis of perinatal outcomes relating to these different opioid agonist therapies. A systematic review of opioid substitutes in pregnancy affords vital evidence to decision-makers supporting improved maternal and offspring outcomes.

Chapter 2 Effect of public health interventions on alcohol consumption

This work is currently undergoing peer review with BMJ public health.

2.1 Chapter Abstract

Background: Alcohol consumption during pregnancy is associated with adverse maternal and perinatal outcomes. This chapter will evaluate the individual and cumulative impact of three alcohol-related interventions on maternal alcohol use and perinatal outcomes in Scotland.

Methods: 346,360 births in Scotland (1st April 2013 - 31st December 2019) using interrupted time-series analyses to assess individually and cumulatively: 1) change in drink-driving legislation [5th December 2014], 2) UK Chief Medical Officers' (CMO) advice to abstain from alcohol during pregnancy [6th January 2016], and 3) Alcohol Minimum Unit Pricing (MUP) [1st May 2018], on drinking behaviour during pregnancy. Multivariable regression models quantified associations of these interventions with perinatal outcomes.

Findings: Of 346,360 antenatal care initiates, 92.8% had alcohol consumption data. By 2019, 26.1% reported alcohol use during pregnancy. In women who consumed alcohol during pregnancy, 55.2% consumed greater than four units per week. The introduction of Minimum Unit Pricing led to a significant reduction in consumption by -0.59 (95% CI: -0.99, -0.18) units per week, contributing to an overall decrease of -0.69 (95% CI: -0.90, -0.48) units per week following all interventions. Additionally, we observed improvements in perinatal outcomes, including reduced small for gestational age (adjRR 0.87, 95% CI: 0.84, 0.90), neonatal unit admission (adjRR 0.92, 95% CI: 0.89, 0.96), and stillbirth (adjRR 0.77, 95% CI: 0.62, 0.94), but not preterm birth (adjRR 1.08, 95% CI: 1.04, 1.13) following the implementation of these collective public health interventions.

Conclusions: One in four women self-reported alcohol consumption during early pregnancy. Only MUP was associated with lower consumption among pregnant

women. The public health measures were collectively associated with improvement in select perinatal outcomes, highlighting the potential effectiveness of universal interventions.

2.2 Introduction

Alcohol consumption accounts for five percent of worldwide morbidity and mortality, constituting a significant global public health challenge[25]. During pregnancy, 12-41% of mothers report consuming alcohol, despite no safe lower limits being established and the potential detrimental impact on their offspring [28,103,172]. After reaching historically high levels of alcohol-related harm, the Scottish Government instituted a comprehensive national strategy incorporating a range of interventions, policies, and legislation[143]. This included the introduction of a lower permissible drink-drive limit in 2014 and more recently Minimum Unit Pricing (MUP) in 2018[147,155]. In 2016 the United Kingdom Chief Medical Officers (CMO) also specifically advised pregnant women to completely abstain from alcohol for the first time[173]. The effectiveness of these, and similar public health interventions, are increasingly being established, with regulations related to drink driving reducing the number of road traffic injuries and deaths, and the introduction of MUP associated with a decline in alcohol sales[149,174,175]. The availability of detailed linked data in Scotland, including on alcohol consumption in pregnancy, together with the implementation of general and pregnancy-specific alcohol reduction policies, provides a unique opportunity to add to the sparse evidence on the effects of public health policy on maternal and perinatal health.

This chapter will evaluate alcohol consumption in pregnancy, measure the change in alcohol consumption following three distinct public health interventions both as individual entities and cumulatively across all three interventions, and measure any associated changes in perinatal outcomes in Scotland.

2.3 Methods

Four Scotland-wide administrative databases were linked. These were the: Scottish Morbidity Record-2 (SMR02); Scottish Morbidity Record-1 (SMR01); Scottish Birth Record (SBR); and National Records of Scotland (NRS). The SMR02 records all maternity in-patient and day case admissions, including maternal and infant characteristics, maternal alcohol consumption, and pregnancy outcomes. The SMR01 records all in-patient and day-case admissions. Both record diagnoses according to the International Classification of Diseases 9th or 10th revision (ICD-9/ICD-10) [176,177]. SBR records all neonatal care, and the NRS registers all births, stillbirths, and infant deaths in Scotland. Public Health Scotland reported 99% completeness for SMR02 in 2020/21[178]. Data governance procedures were approved by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (1920-0097), and NHS Greater Glasgow and Clyde Research and Development (GN20PH059). The NHS Scotland electronic Data Research and Innovation Service (eDRIS) linked and de-identified data prior to analysis.

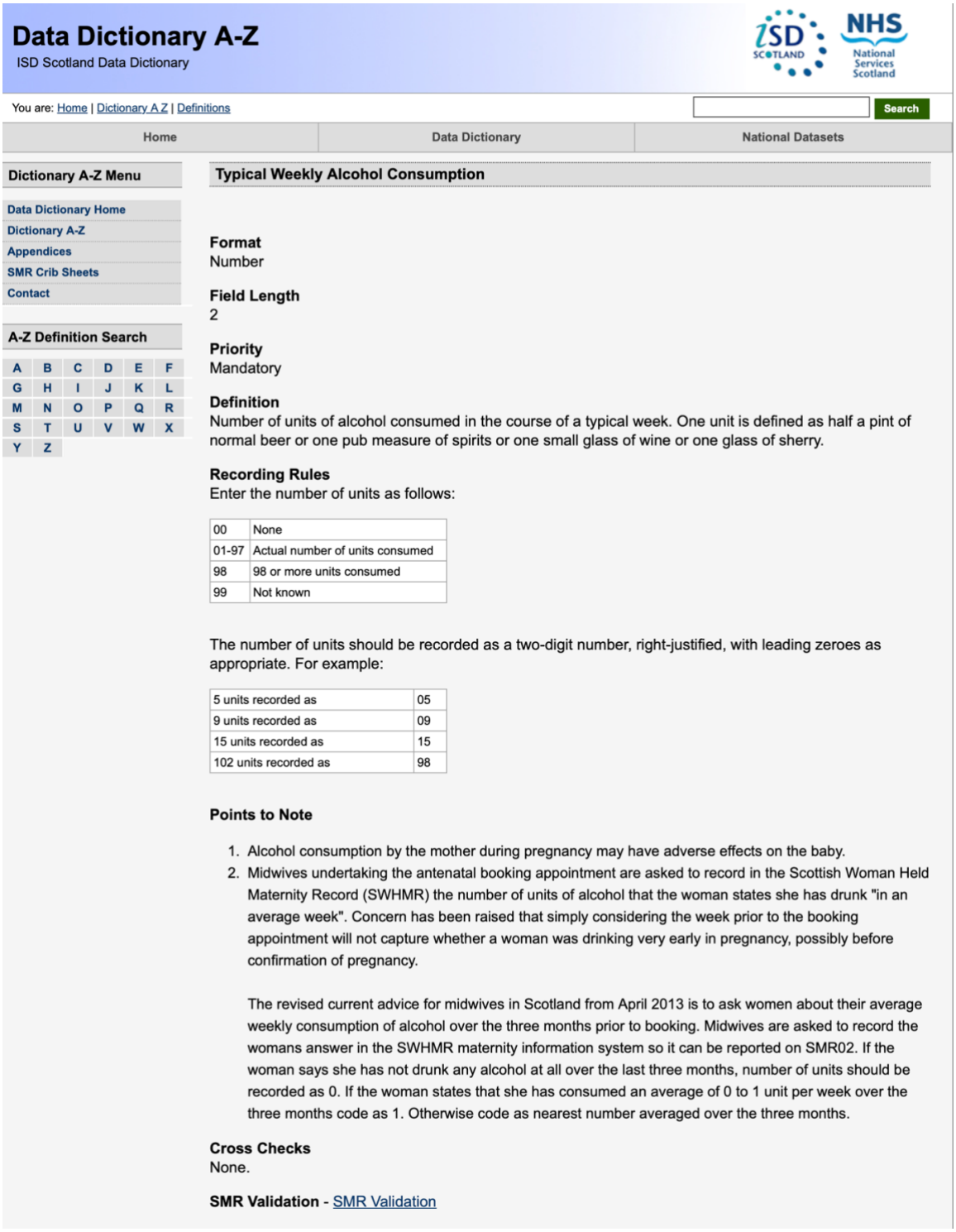
2.3.1 Inclusion criteria

The data obtained in this chapter relates to pregnancies in Scotland between 1st April 2013 and 31st December 2019 inclusive from SMR02. This seven-year period reflects a time with detailed recording of alcohol consumption at the initiation of antenatal care. All pregnant women in Scotland are routinely provided with antenatal care, which is free at the point of access, and for over 75% of patients, obstetric care is initiated in the first trimester[179].

2.3.2 Maternal alcohol consumption

The primary outcome was self-reported units of alcohol consumption per week by pregnant women (defined as average units consumed per week in the preceding three-month period), at the initiation of antenatal care obtained from the SMR02 dataset. In the United Kingdom, one unit of alcohol is defined as ten millilitres (ml), or eight grams of pure ethanol. Alcohol consumption of greater than zero and less than one unit per week was recorded as one unit, with all other values reported to the nearest whole unit up to 97 units per week (Figure 2-1). Women who drank alcohol were further subdivided into those who

consumed Alcohol 1-4 units of alcohol per week, and those who consumed greater than 4 units of alcohol per week. The 4 units of alcohol per week threshold was defined a priori and represents the previous upper limit for alcohol consumption in pregnancy[163].



Data Dictionary A-Z

ISD Scotland Data Dictionary

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A-Z Definition Search

A B C D E F
G H I J K L
M N O P Q R
S T U V W X
Y Z

Typical Weekly Alcohol Consumption

Format
Number

Field Length
2

Priority
Mandatory

Definition
Number of units of alcohol consumed in the course of a typical week. One unit is defined as half a pint of normal beer or one pub measure of spirits or one small glass of wine or one glass of sherry.

Recording Rules
Enter the number of units as follows:

00	None
01-97	Actual number of units consumed
98	98 or more units consumed
99	Not known

The number of units should be recorded as a two-digit number, right-justified, with leading zeroes as appropriate. For example:

5 units recorded as	05
9 units recorded as	09
15 units recorded as	15
102 units recorded as	98

Points to Note

1. Alcohol consumption by the mother during pregnancy may have adverse effects on the baby.
2. Midwives undertaking the antenatal booking appointment are asked to record in the Scottish Woman Held Maternity Record (SWHMR) the number of units of alcohol that the woman states she has drunk "in an average week". Concern has been raised that simply considering the week prior to the booking appointment will not capture whether a woman was drinking very early in pregnancy, possibly before confirmation of pregnancy.

   The revised current advice for midwives in Scotland from April 2013 is to ask women about their average weekly consumption of alcohol over the three months prior to booking. Midwives are asked to record the womans answer in the SWHMR maternity information system so it can be reported on SMR02. If the woman says she has not drunk any alcohol at all over the last three months, number of units should be recorded as 0. If the woman states that she has consumed an average of 0 to 1 unit per week over the three months code as 1. Otherwise code as nearest number averaged over the three months.

Cross Checks
None.

SMR Validation - SMR Validation

Figure 2-1: Informative Service Division (ISD) Data Dictionary extract for weekly alcohol consumption [180].

2.3.3 Maternal data and confounding variables

Data on maternal characteristics and prior obstetric history were obtained from SMR02. Variable were defined as follows: maternal age in years at the time of booking, Body Mass Index (BMI) as calculated from booking weight and height measurements, and parity coded as ordinal data. Self-reported drug misuse was coded as "yes / no". Socioeconomic status was measured using a person's Scottish Index of Multiple Deprivation (SIMD) derived from the area of residence at the time of delivery. SIMD is a score calculated from 33 indicators covering seven domains (income, employment, health, education, access to services, crime, and housing). SIMD was stratified into quintiles with one being most deprived and five being least deprived. Self-reported ethnicity was classified per the 2011 Scotland census[181]. Smoking status was based on self-classification at the initiation of antenatal care and comprised current smokers or non-smokers (never / former smokers).

2.3.4 Perinatal outcomes

Linked offspring outcomes were obtained from SMR02, SBR and NRS and included preterm birth (<37 weeks of estimated gestation), small for gestational age (SGA, birth weight below the 10th centile), neonatal unit admission, and stillbirth (intrauterine death after 24 weeks of estimated gestation).

2.3.5 Interventions

We investigated three distinct alcohol-related interventions. Two represented universally applicable, enforceable statutory policies affecting the Scottish population, with the third intervention targeted directly at pregnant women. These interventions were:

1. A lower permissible drink-driving limit of 0.05 g/dl reduced from 0.08 g/dl: 5th December 2014[147].
2. United Kingdom Chief Medical Officers' (CMO) advice to all pregnant women to avoid alcohol consumption during pregnancy: 6th January 2016[173].
3. The introduction of minimum unit alcohol pricing: 1st May 2018[155].

2.3.6 Statistical analyses

Interrupted time-series analysis was performed to quantify changes in alcohol consumption reported at the initiation of antenatal care after implementing each of the three government interventions, with a three-month lag to all measures to take effect on reported alcohol intake. The data were divided into four periods for analysis: (i) pre-existing trends (April 2013 to December 2014), (ii) post-drink-driving legislation (January 2015 to January 2016), (iii) post-UK CMOs' advice to abstain from alcohol during pregnancy (February 2016 to May 2018), and (iv) following MUP implementation (June 2018 to December 2019). Any woman for whom data on alcohol consumption was missing, or where alcohol consumption greater than the upper limit of recording (98 units per week or greater), was excluded from the Interrupted time-series. Analysis was conducted with the following cohort: Analysis cohort (0 – 97 units of alcohol per week), Drinkers cohort (1-97 units of alcohol per week), 1-4units of alcohol per week, >4 units of alcohol per week. The 4 units of alcohol per week threshold was defined a priori and represents the previously advised upper limit for alcohol consumption in pregnancy[163].

Interventions were assessed for both step changes and trend changes. A step-change was defined as the change in the mean units of alcohol consumed per week per woman from the month preceding the intervention to three months following the intervention. A trend change was defined as the monthly change in the mean reported units of alcohol consumed per week following the intervention. The analysis for each intervention was performed using a stacked additive approach (i.e. the first and second interventions versus the pre-intervention period, and the second and third interventions versus all preceding periods), and cumulatively to include all interventions (Figure 2-2).

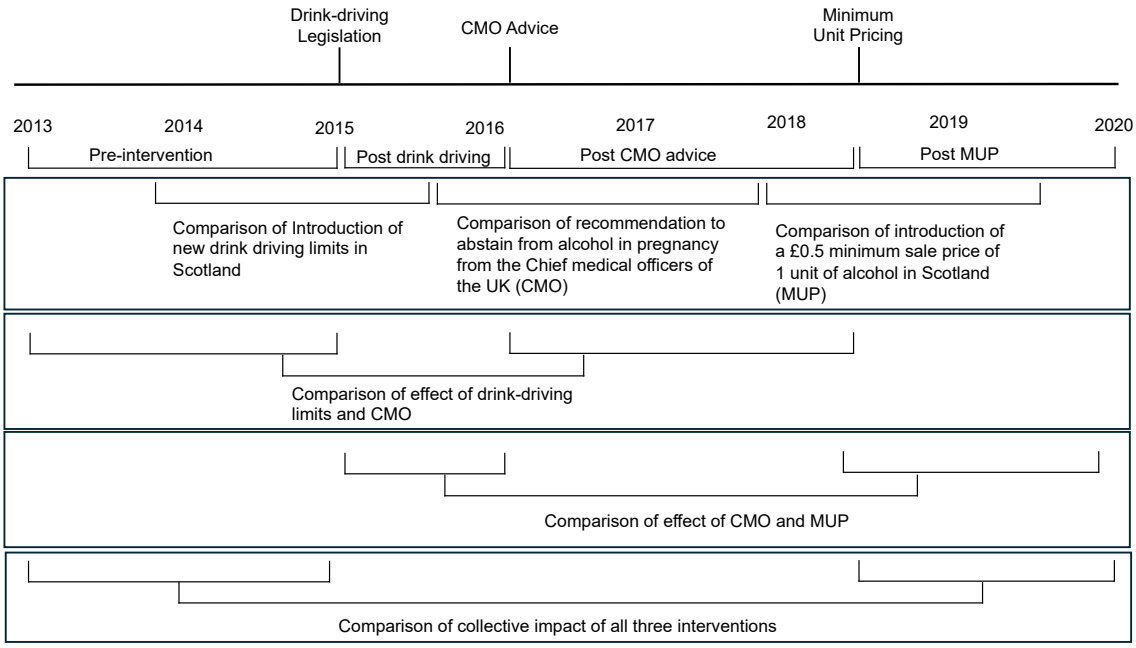


Figure 2-2 Comparisons of epochs in public health interventions during time series analysis. Interventions compared to epoch prior (blue), epoch prior to first intervention (green and pink) or pre-intervention period (grey)

To model the time-series data and to account for autocorrelation, trends, and seasonality, an Auto-Regressive Integrated Moving Average (ARIMA) technique was used[182]. ARIMA models were used both to adjust to auto-correlation of residuals in ITS analysis and also to forecast trends and thus allow analysis of cumulative interventions. The benefits of this approach include that it allows investigation of the relations between observations and explore changes relative to the underlying background trends in the data and has been recommended for routine health data. To estimate the autoregressive, differencing, and moving average components of the data, Akaike Information criterion (AIC) was used, with the lowest AIC statistic indicating the model with the best fit[183].

Offspring outcomes were analysed using adjusted and non-adjusted models. Adjustments were made for, maternal age, maternal BMI, ethnicity, parity, SIMD, smoking status, alcohol consumption, drug misuse and booking date (earlier [<9 week estimated gestation] or later [≥9 week estimated gestation]). Listwise deletion was employed to account for missing data within the adjusted modelling process. Risk ratios (RR) were calculated for outcomes using the immediate epoch before each intervention as a reference, using a stacked additive approach to include different combinations of interventions, and then

for the cumulative effect of the three interventions on pregnancies after 1 May 2018 referenced to those before December 2014 (Figure 2-2). Multivariable Poisson regression models with cluster robust sandwich estimators under the generalized estimation equation framework was used. These models were chosen in place of log-binomial models to avoid problems with convergence. The robust estimator was utilised to correct the inflated variance typically found in standard Poisson models and to account for the clustering effect of sequential births in the same women. This regression model produced adjusted relative risks (adjRR) and 95% confidence intervals (95% CI). To understand the incidence of the adverse perinatal outcomes within the pre-intervention, incidence and trends were calculated.

We performed the following additional sensitivity analyses to further evaluate the robustness of our findings. We measured the effect if no three-month lag phase was included (immediate change) and then we extended our lag period from three months to six months to account for a potentially slower impact of policy changes. We also analysed results for smoker and non-smokers separately. In addition, we addressed the variation in alcohol consumption reporting observed in the final year of the seven-year study period. Although the question regarding alcohol consumption remained unchanged, there was enforcement of interpretation and recording policies during the latter period. As a result, we assumed that the later period's data more accurately reflected the true prevalence of alcohol consumption, with potential under-reporting in the earlier years. To correct for this under-reporting, we randomly reassigned non-drinking women from the earlier period into the overall prevalence categories observed in the later periods. This adjustment was performed in three stages. Initially, with no alcohol adjustment, followed by an adjustment to 50% of the prevalence of the later time-period (50% normalised). In the final stage of analysis alcohol consumption was brought from the earlier period's data to the later periods' prevalence rates (normalised).

Analyses were conducted on the R software platform (version 4.4.1) and included modelling using the "forecast" package (version 8.16) [184,185].

2.4 Results

Between 1st April 2013 and 31st December 2019, 346,360 women initiated antenatal care, of whom 321,333 (92.8%) had data recorded for alcohol consumption (Figure 2-3, Tables 2-1, Table 2-2). Initiation of antenatal care remained consistent at around ten weeks gestation throughout the study period (Table 2-3). 36,208 (11.3%) women reported drinking alcohol (drinkers), and 281,125 (88.7%) women reported consuming no alcohol during pregnancy (non-drinkers). Of women who drank alcohol, 16,207 (44.8%) reported consumption between 1 and 4 units of alcohol per week and 20,001 (55.2%) reported consumption of greater than 4 units of alcohol per week (Table 2-4). Women who drank were more likely to be; older, white, have lower BMI, misuse drugs, and live in less socioeconomically deprived areas. Women from the most deprived areas were more likely to consume greater than 4 units of alcohol per week (Table 2-4). Reporting of alcohol consumption varied throughout the study period from 2,373 per year (5.8%) in 2013 to 12,225 women per year (26.1%) in 2019 (Table 2-2). Maternal characteristics were broadly similar during each of the intervention epochs (Table 2-5).

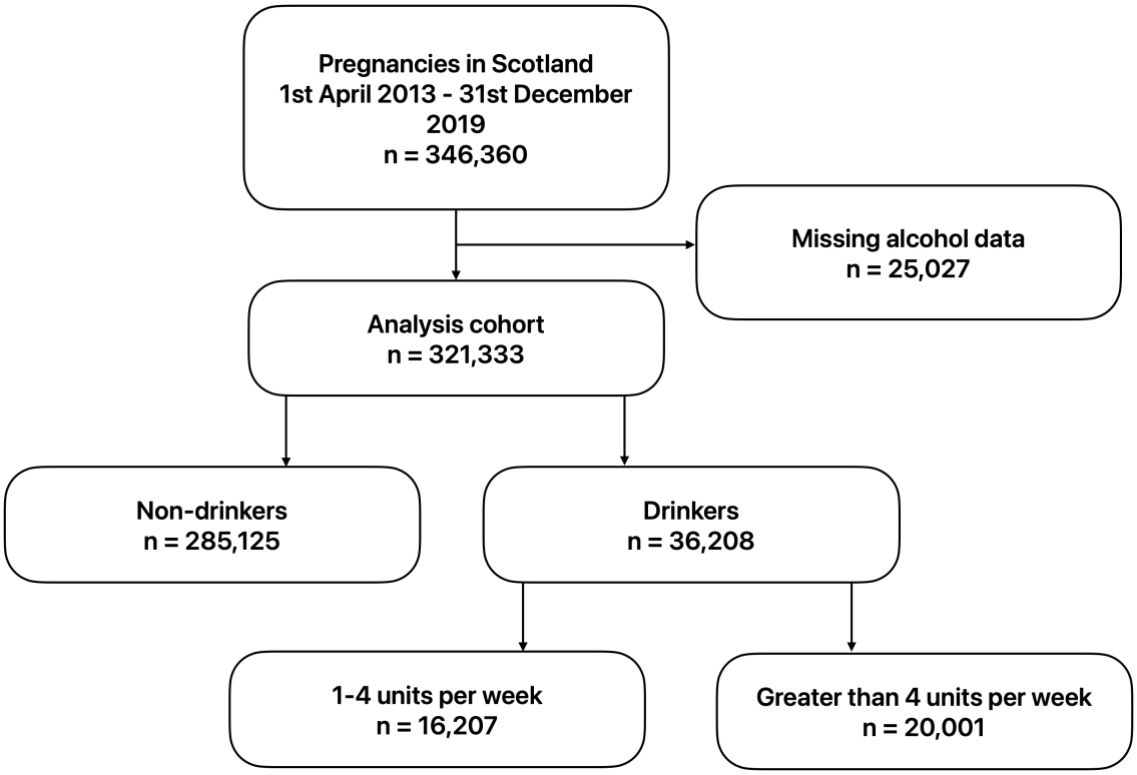


Figure 2-3: Consort flow of analysis cohort in study

Characteristic	Known alcohol intake, n = 321,333[1]	Unknown alcohol intake, n = 25,027[1]	p-value[2]
Maternal age, years (IQR)	30.00 (26.00, 34.00)	30.00 (25.00, 34.00)	<0.001
Maternal BMI, kg/m^2 (IQR)	25.16 (22.21, 29.48)	26.08 (22.72, 31.22)	<0.001
Missing	6,347	9,293	
Maternal height, cm (IQR)	165.00 (160.00, 169.00)	164.00 (160.00, 168.00)	<0.001
Missing	5,571	5,820	
Maternal weight, kg (IQR)	68.00 (60.00, 80.00)	71.00 (61.00, 87.00)	<0.001
Missing	4,852	8,596	
Ethnicity, n (%)			0.005
Black	3,816 (1.5%)	276 (1.5%)	
Mixed	1,551 (0.6%)	82 (0.4%)	
White	235,746 (92%)	16,885 (93%)	
Other	2,933 (1.1%)	242 (1.3%)	
Asian	11,068 (4.3%)	740 (4.1%)	
Missing	66,219	6,802	
SIMD Quintile, n (%)			<0.001
01	78,891 (25%)	8,325 (33%)	
02	68,494 (21%)	4,927 (20%)	
03	58,415 (18%)	4,076 (16%)	
04	59,946 (19%)	4,485 (18%)	
05	55,006 (17%)	3,145 (13%)	
Missing	581	69	
Smoker during pregnancy, n (%)	52,140 (17%)	4,117 (22%)	<0.001
Missing	7,338	6,439	
Drug misuse, n (%)	4,685 (1.7%)	335 (8.6%)	<0.001
missing	43,449	21,111	
Parity, n (IQR)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	<0.001
Missing	825	1,744	

Median (IQR); n (%).
Wilcoxon rank sum test; Pearson's Chi-squared test

Table 2-1: Maternal characteristics of women who booked pregnancies between April 2013 and December 2019, by reported drinking status

Year	**Total yearly pregnancies, n**	**Pregnancies reporting alcohol use, n (%)**	**Pregnancies reporting no alcohol use, n (%)**	**Missing data on alcohol use, n (%)**
2013[1]	40,598	2,373 (5.8%)	35,275 (86.9%)	2,950 (7.3%)
2014	54,703	3,605 (6.6%)	47,226 (86.4%)	3,872 (7.1%)
2015	53,057	3,435 (6.5%)	46,689 (88.0%)	2,933 (5.5%)
2016	51,797	3,508 (6.8%)	45,568 (88.0%)	2,721 (5.3%)
2017	50,544	3,573 (7.7%)	42,187 (83.5%)	4,784 (5.5%)
2018	48,941	7,459 (15.2%)	37,914 (77.5%)	3,568 (7.3%)
2019	46,720	12,225 (26.1%)	30,266 (64.8%)	4,199 (9.0%)

1) Start date 01/04/2013

Table 2-2: Recording of alcohol consumption during pregnancy as recorded in SMR02, by year.

Year	Births, n	Estimated gestation at booking: mean (SD), weeks	Estimated gestation at booking: 95% confidence interval, weeks	Estimated gestation at booking: median (Q1, Q3), weeks
2013[1]	40,421	10.6 (1.98)	10.6, 10.7	9.6 (8.0, 11.4)
2014	54,290	10.4 (2.03)	10.4, 10.5	9.3 (7.9, 11.3)
2015	52,689	10.1 (1.99)	10.0, 10.1	9.0 (7.7, 10.7)
2016	51,415	10.1 (2.00)	10.1, 10.1	9.1 (7.9, 10,7)
2017	50,333	9.8 (2.02)	9.8, 9.9	8.9 (7.6, 10.6)
2018	48,895	9.8 (2.02)	9.8, 9.9	9.0 (7.6 10.4)
2019	46,691	10.0 (1.97)	9.9, 10.0	9.0 (7.6, 10.4)

1) Start date 01/04/2013

Table 2-3: Estimated gestation at booking appointment as recorded in SMR02, by year.

Characteristic	Non-drinker N = 285,125[1]	Drinker N = 36,208[1]	p-value[2]	1-4 units of alcohol per week. N = 16,207[1]	> 4 units of alcohol per week N = 20,001[1]	p-value[2]
Maternal age, years (IQR)	30.00 (26.00, 34.00)	31.00 (27.00, 34.00)	<0.001	31.00 (27.00, 34.00)	31.00 (26.00, 34.00)	<0.001
SD [99 centile]	5.68 [18.00, 42.00]	5.53 [17.71, 43.91]		5.32 [20.00, 39.00]	5.68 [20.00, 39.00]	
Maternal BMI, kg/m^2 (IQR)	25.16 (22.21, 29.62)	25.10(22.27, 29.30)	0.029	24.91 (22.10, 29.04)	25.30 (22.41, 29.38)	0.15
SD [99 centile]	6.02 [17.43, 45.12]	5.69 [17.71, 43.94]		5.69 [19.27, 37.46]	5.69 [19.47, 37.37]	
Missing	5,905	442		95	347	
Maternal height, cm (IQR)	165.00 (160.00, 169.00)	165.00 (161.00, 169.00)	<0.001	165.00 (161.00, 169.00)	165.00 (161.00, 169.00)	<0.001
SD [99 centile]	6.49 [150.00, 180.00]	6.42 [150.35, 180.00]		6.43[155.00, 175.00]	6.42 [155.00, 176.00]	
Missing	5,199	372		79	293	
Maternal weight, kg (IQR)	68.00 (60.00, 80.00)	69.00 (60.00, 80.00)	0.003	68.00 (60.00, 80.00)	69.00 (61.00, 80.00)	<0.001
SD [99 centile]	17.08 [45.00, 125.00]	16.30 [46.00, 122.00]		16.19(51.00, 103.00)	16.38 [52.00, 103]	
Missing	4,537	315		68	247	
Ethnicity, n (%)			<0.001			<0.001
Black	3,672 (1.6%)	144 (0.5%)		87 (0.7%)	57 (0.4%)	
Mixed	1,431 (0.6%)	120 (0.4%)		66 (0.5%)	54 (0.3%)	
White	207,395 (92%)	28,351 (98%)		12,433 (97%)	15,918 (98%)	
Other	2,828 (1.3%)	105 (0.4%)		60 (0.5%)	45 (0.3%)	
Asian	10,740 (4.8%)	328 (1.1%)		197 (1.5%)	131 (0.8%)	
Missing	59,059	7,160		3,364	3,796	
SIMD Quintile, n (%)			<0.001			<0.001
01	70,222 (25%)	8,669 (24%)		3,482 (22%)	5,187 (26%)	
02	61,217 (22%)	7,277 (20%)		3,114 (19%)	4,163 (21%)	
03	52,050 (18%)	6,365 (18%)		2,998 (19%)	3,367 (17%)	
04	53,351 (19%)	6,595 (18%)		3,170 (20%)	3,425 (17%)	
05	47,742 (17%)	7,264 (20%)		3,420 (21%)	3,844 (19%)	
Missing	543	38		23	15	
Smoker during pregnancy, n (%)	46,265 (17%)	5,875 (17%)	0.7	1,925 (12%)	3,950 (21%)	<0.001
Missing	6,339	999		217	782	
Drug misuse, n (%)	4,012 (1.6%)	673 (2.0%)	<0.001	202 (1.3%)	471 (2.6%)	<0.001
missing	40,517	2,932		974	1,958	
Parity, n (IQR)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	<0.001	1.00 (0.00, 1.00	1.00(0.00, 1.00)	<0.001
SD [99 centile]	1.10 [0.00, 5.00]	1.02 [0.00, 4.00]		1.02 [0.00, 3.00]	1.02 [0.00, 3.00]	
Missing	700	100		515	1,125	
Year, n (%)			<0.001			<0.001
2013[a]	35,275 (12%)	2,373 (6.6%)		1,051 (6.5%)	1,322 (6.6%)	
2014	47,226 (17%)	3,605 (10%)		1,493 (9.2%)	2,112 (11%)	
2015	46,689 (16%)	3,435 (9.5%)		1.492 (9.2%)	1,943 (9.7%)	
2016	45,568 (16%)	3,508 (9.7%)		1,554 (9.6%)	1,953 (9.8%)	
2017	42,187 (15%)	3,573 (9.9%)		1,554 (9.6%)	2,019 (10%)	
2018	37,914 (13%)	7,459 (21%)		3,385 (21%)	4,074% (20%)	
2019	30,266 (11%)	12,255 (34%)		5,678 (35%)	6,577 (33%)	

a) Start date 1st April 2013

1)Median (IQR), Standard Deviation (99 centile); n (%).

2) Wicoxon rank sum test; Pearson's Chi-Squated test

Table 2-4: Maternal characteristics of women who booked pregnancies between April 2013 and December 2019, by reported alcohol intake

Characteristic	Pre-intervention, N = 97,936[1]	Post drink driving, N = 54,678[1]	Post CMO advice, N = 107,725[1]	Post MUP, N = 60,994[1]
Cohort group				
Non-drinker, n (%)	91,238 (93%)	50,934 (93%)	99,204 (92%)	43,749 (72%)
Alcohol 1-4 units, n (%)	2,859 (2.9%)	1,628 (3.0%)	3,750 (3.5%)	7,970 (13%)
Alcohol > 4 units, n (%)	3,839 (3.9%)	2,116 (3.9%)	4,771 (4.4%)	9,275 (15%)
Maternal age, years (IQR)	30.00 (25.00, 34.00)	30.00 (26.00, 34.00)	30.00 (26.00, 34.00)	31.00 (27.00, 34.00)
Maternal BMI, kg/m^2 (IQR)	24.98 (22.07, 29.15)	25.07 (22.15, 29.39)	25.28 (22.31, 29.74)	25.40 (22.32, 29.76)
Missing	1,630	728	3,080	909
Maternal height, cm (IQR)	164.00 (160.00, 169.00)	165.00 (160.00, 169.00)	165.00 (160.00, 169.00)	165.00 (160.00, 169.00)
Missing	1,441	611	2,731	788
Maternal weight, kg (IQR)	68.00 (59.00, 79.00)	68.00 (60.00, 80.00)	69.00 (60.00, 81.00)	69.00 (60.00, 82.00)
Missing	794	514	2,733	811
Ethnicity, n (%)				
Black	1,266 (1.6%)	644 (1.5%)	1,247 (1.5%)	659 (1.4%)
Mixed	455 (0.6%)	241 (0.5%)	507 (0.6%)	348 (0.7%)
White	71,322 (92%)	40,733 (92%)	79,128 (93%)	44,563 (92%)
Other	716 (0.9%)	550 (1.2%)	1,030 (1.2%)	637 (1.3%)
Asian	3,544 (4.6%)	1,892 (4.3%)	3,559 (4.2%)	2,073 (4.3%)
Missing	20,633	10,618	22,254	12,714
SIMD Quintile, n (%)				
01	24,132 (25%)	13,302 (24%)	26,457 (25%)	15,000 (25%)
02	20,796 (21%)	11,718 (21%)	22,970 (21%)	13,010 (21%)
03	17,952 (18%)	9,935 (18%)	19,552 (18%)	10,976 (18%)
04	17,675 (18%)	10,130 (19%)	20,484 (19%)	11,657 (19%)
05	17,172 (18%)	9,496 (17%)	18,084 (17%)	10,254 (17%)
Missing	209	97	178	97
Smoker during pregnancy, n (%)	16,293 (17%)	8,315 (15%)	17,650 (17%)	9,882 (16%)
Missing	1,883	713	3,777	965
Drug misuse, n (%)	1,273 (1.5%)	673 (1.5%)	1,695 (2.0%)	1,044 (1.8%)
missing	11,090	8,302	21,121	2,936
Missing	146	43	287	76
Parity, n (IQR)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)	1.00 (0.00, 1.00)
Missing	213	66	404	142

a) start date 1 April 2013

1) Median (IQR), Standard Deviation (99 centile); n (%).
2) Wicoxon rank sum test; Pearson's Chi-Squated test

Table 2-5: Maternal characteristics of women who booked pregnancies between April 2013 and December 2019, by public health phase

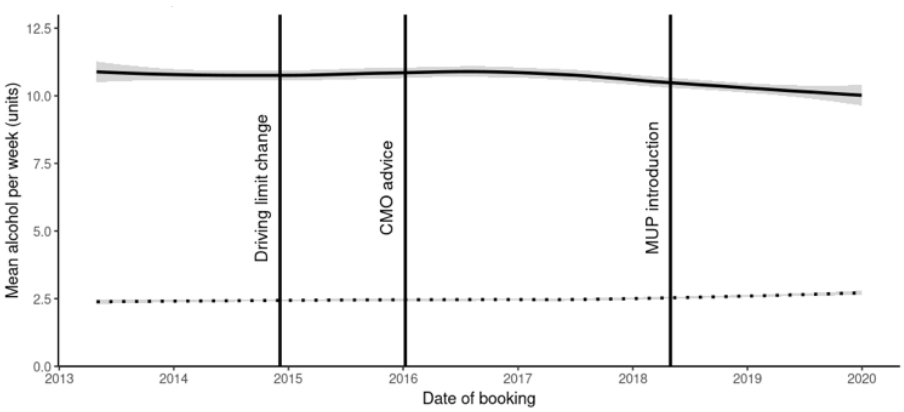
2.4.1 Maternal alcohol consumption

Over the study period, there was a small decrease in the mean alcohol consumption of women who reported drinking alcohol, from 7.09 (95% confidence interval [95% CI]: 6.71,7.47) units per week in 2013 to 6.70 (95% CI: 6.55,6.84, p <0.001) units per week in 2019 (Table 2-6). In women who drank 1-4 units of alcohol per week, alcohol consumption increased from 2.38 (95% CI: 2.31,2.45) in 2013 to 2.66 (95% CI: 2.63,2.69, p <0.001) units of alcohol per week in 2019 (Table 2-6, Figure 2-4). Contrastingly, alcohol consumption in women who drank > 4 units of alcohol per week decreased from 10.87 (95% CI: 10.46,11.27) units of alcohol per week in 2013 to 10.18 (95% CI: 10.01,10.35, p <0.001) units of alcohol per week in 2019 (Table 2-6, Figure 2-4). Alcohol consumption was greatest in women who reported drinking from the most deprived residential areas (SIMD1 in 2019, 7.46 [95% CI: 7.20,7.73] units of alcohol per week versus the least deprived residential area (SIMD5 in 2019, 5.93 [95% CI: 5.74, 6.12] units of alcohol per week, p <0.001) (Table 2-7, Figure 2-5,). There was limited evidence of a reduction of this socioeconomic gradient in alcohol consumption over the study period (Figure 2-5). Women who smoked during pregnancy consistently consumed more alcohol across the study period (9.43 [95% CI: 8.90, 9.96] units of alcohol per week in 2019 versus non-smokers (6.16 [95% CI: 6.04, 6.28], p <0.001], units of alcohol per week) (Table 2-8, Figure 2-6).

Year	Mean alcohol consumption (units of alcohol per week) in all women (excluding missing data), units per week (95% CI)	Mean alcohol consumption (units of alcohol per week) in all drinkers, units per week (95% CI)	Mean alcohol consumption (units of alcohol per week) in those who consume 1-4 units of alcohol per week, units per week (95% CI)	Mean alcohol consumption (units of alcohol per week) in those who consume > 4 units of alcohol per week, units per week (95% CI)
2013[1]	0.44 (0.39, 0.50)	7.09 (6.71, 7.47)	2.38 (2.31, 2.45)	10.87 (10.46, 11.27)
2014	0.52 (0.49, 0.54)	7.30 (7.09, 7.51)	2.44 (2.36 2.53)	10.73 (10.46, 11.00)
2015	0.48 (0.45, 0.52)	7.15 (5.66, 7.43)	2.42 (2.37, 2.48)	10.75 (10.42, 11.08)
2016	0.51 (0.48, 0.61)	7.21 (6.95, 7.49)	2.50 (2.41, 2.59)	10.96 (10.62, 11.31)
2017	0.56 (0.51, 0.61)	7.10 (6.78, 7.41)	2.43 (2.40, 2.46)	10.69 (10.45, 10.94)
2018	1.12 (0.73, 1.51)	6.89 (6.58, 7.19)	2.59 (2.53, 2.64)	10.33 (9.99, 10.67)
2019	1.93 (1.88, 1.98)	6.70 (6.55, 6.84)	2.66 (2.63, 2.69)	10.18 (10.01, 10.35)

1) Start date 1/4/2013

Table 2-6: Mean alcohol consumption over time by alcohol intake group



>4units of alcohol per week (solid black line)
1-4units of alcohol per week (dashed line)
Grey shaded area represents 95% Confidence interval

Figure 2-4: Mean alcohol consumption (units of alcohol per week) in those who consume alcohol, over time (stratified by consumption group).

Year	Mean alcohol consumption (units per week) in women in SIMD 1, in those who drink alcohol, units per week (95% CI)	Mean alcohol consumption (units per week) in women in SIMD 2 in those who drink alcohol, units per week (95% CI)	Mean alcohol consumption (units per week) in women in SIMD 3 in those who drink alcohol, units per week (95% CI)	Mean alcohol consumption (units per week) in women in SIMD 4 in those who drink alcohol, units per week (95% CI)	Mean alcohol consumption (units per week) in women in SIMD 5 in those who drink alcohol, units per week (95% CI)
2013[1]	8.55 (7.23, 9.87)	7.69 (7.17, 8.22)	6.51 (5.66, 7.37)	6.50 (5.88, 7.12)	6.52 (5.88, 7.15)
2014	8.75 (7.95, 9.54)	8.09 (7.40, 8.78)	6.86 (6.32, 7.40)	6.51 (6.15, 6.86)	6.32 (6.05, 6.60)
2015	9.05 (8.36, 9.74)	7.31 (6.85, 7.78)	6.73 (6.20, 7.27)	6.41 (5.99, 6.81)	6.15 (5.76, 6.54)
2016	9.36 (9.30, 10.43)	7.49 (7.05, 7.93)	6.25 (5.84, 6.65)	6.39 (5.78, 7.00)	6.39 (5.97, 6.81)
2017	8.23 (7.51, 8.95)	7.73 (6.91, 8.55)	6.77 (6.07, 7.47)	6.14 (5.79, 6.58)	6.42 (5.96, 6.89)
2018	8.04 (7.37, 8.70)	6.92 (6.39, 7.44)	6.53 (6.16, 6.89)	6.17 (5.77, 6.58)	6.43 (5.96, 6.91)
2019	7.46 (7.20, 7.73)	7.03 (6.55, 6.81)	6.54 (6.28, 6.81)	6.12 (5.82, 6.42)	5.93 (5.74, 6.13)

1) Start date 1/4/2013

The degree of social deprivation was categorised using deciles according to the Scottish Index of Multiple Deprivation (SIMD) with quintiles of 1 (most deprived) to 5 (least deprived).

Table 2-7: Mean alcohol consumption stratified by Scottish Index of Multiple Deprivation (SIMD) over time.

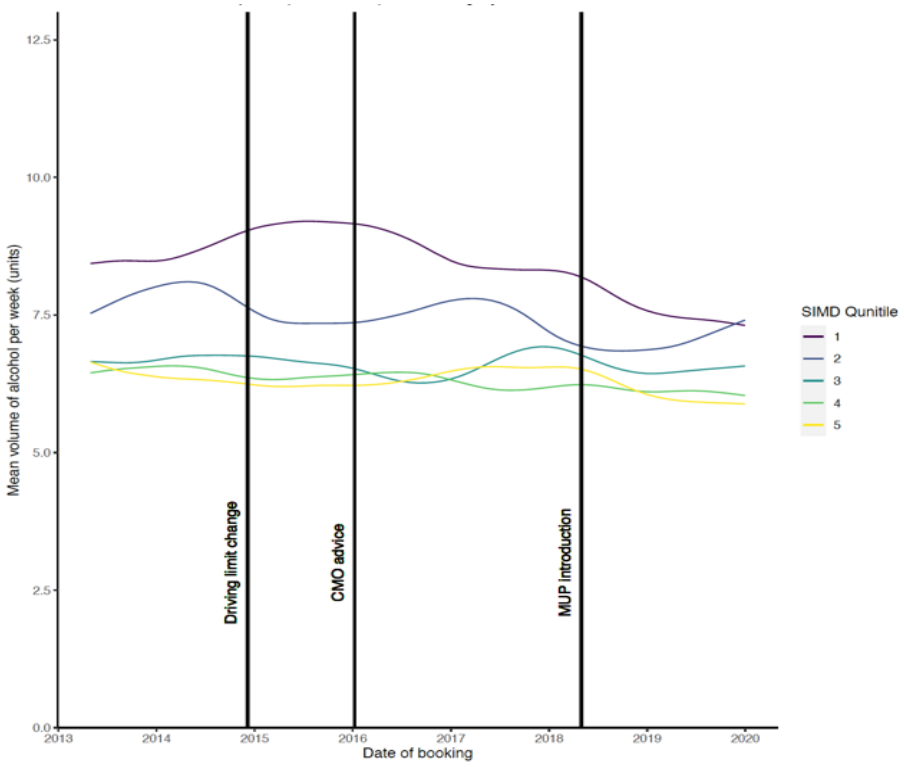
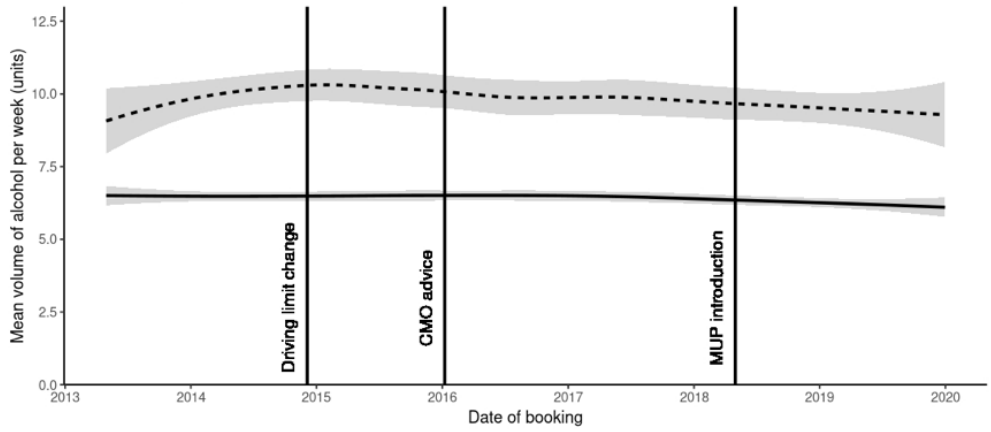


Figure 2-5: Mean alcohol consumption (units of alcohol per week) stratified by socioeconomic status in drinkers.

The degree of social deprivation was categorised using deciles according to the Scottish Index of Multiple Deprivation (SIMD) with quintiles of 1 (most deprived) to 5 (least deprived).



Non-smokers (solid black line)
Smokers (dashed line)
Grey shaded area represents 95% Confidence interval

Figure 2-6: Mean alcohol consumption (units of alcohol per week) stratified by smoking status in drinkers

Year	Mean alcohol consumption (units of alcohol per week) of non-smokers, in those who drink alcohol, units per week (95% CI)	Mean alcohol consumption (units of alcohol per week) of smokers, in those who drink alcohol, units per week (95% CI)
2013[1]	6.45 (5.95, 6.94)	9.42 (8.28, 10.55)
2014	6.50 (6.25, 6.74)	10.54 (9.54, 11.54)
2015	6.50 (6.25, 6.75)	10.10 (9.27, 10.94)
2016	6.52 (6.27, 6.77)	10.18 (8.95, 11.42)
2017	6.41 (6.16, 6.67)	10.01 (8.95, 10.08)
2018	6.36 (6.09, 6.64)	9.43 (8.64, 10.23)
2019	6.16 (6.04, 6.28)	9.43 (8.90, 9.96)

1) Start date 1/4/2013

Table 2-8: Mean alcohol consumption stratified by smoking status, by year.

2.4.2 Impact of public health interventions on maternal alcohol consumption

Neither the introduction of the drink-driving legislation on the 5th of December 2014, nor the United Kingdom's Chief Medical Officers' (CMO) advice to all pregnant women to avoid alcohol consumption during pregnancy on the 6th of January 2016, had any discernible effect on self-reported alcohol consumption in pregnant women who drank either when considered as individual interventions or cumulatively (Table 2-9). In contrast, the introduction of the MUP in Scotland in 2018 led to a fall in alcohol consumption in pregnant drinkers by a mean of -0.59 (95% CI: -0.99, -0.18) units per week, when compared to the epoch before the intervention (i.e. when both the drink-driving legislation and CMO advice were already in place) (Table 2-9). By the end of the study period, following all three interventions, there was evidence of a step change in alcohol consumption, with a reduction of -0.69 (95% CI: -0.90, -0.48) units per week in pregnant drinkers, though there was no trend change (-0.01 [95% CI: -0.15x10^{-2}, 0.04] units of alcohol per week per month) (Table 2-9). The results were similar after removing the 3-month lag period (Table 2-10) or extending to six-months (Table 2-11) and when stratified by smoking status (Table 2-12 and Table 2-13)

Drinking status	Step or trend change	Introduction of new drink driving limits in Scotland	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)	Effect of drink-driving limits and CMO	Effect of CMO and MUP	Collective impact of all three intervention
Analysis cohort (n = 321,33)	**Step change[a], units of alcohol per week change (95% CI)**	-0.13 (-0.25, -0.01)	-0.02 (-0.15, 0.12)	1.06 (0.88, 1.25)	-0.02 (-0.14, 0.11)	1.09 (0.97, 1.21)	0.14 (-0.11, 0.39)
	Trend change[b], units per week per month (95% CI)	0.02 (-0.03, 0.05)	$-0.02x10^{-2}$ (-0.03, 0.03)	-0.02 (-0.03, 0.06)	$-0.25x10^{-2}$ (-0.03, 0.02)	0.02 ($-0.36x10^{-2}$, 0.04)	0.01 (-0.05, 0.07)
Drinker cohort (n= 36,208)	**Step change[a], units of alcohol per week change (95% CI)**	-0.29 (-0.86, 0.29)	0.08 (-0.37, 0.53)	-0.59 (-0.99, -0.18)	-0.07 (-0.02, 0.01)	-0.33 (-0.53, -0.13)	-0.69 (-0.90, -0.48)
	Trend change[b], units per week per month (95% CI)	0.04 (-0.04, 0.13)	-0.01 (-0.03, 0.02)	0.01 (-0.02, 0.05)	0.01 (-0.15, 0.29)	-0.01 (-0.03, -0.01)	-0.01 ($-0.15x10^{-2}$, 0.04)
>4units of alcohol per week (n = 20,001)	**Step change[a], units of alcohol per week change (95% CI)**	-0.35 (-1.01, 0.29)	0.11 (-0.38, 0.60)	-0.83 (-1.27, 0.37)	0.48 (0.10, 0.86)	-0.46 (-0.70, -0.22)	-0.23 (-0.61, 0.14)
	Trend change[b], units per week per month (95% CI)	0.06 (-0.04, 0.16)	-0.02 (-0.05, 0.15)	0.02 (-0.02, 0.06)	-0.02 (-0.04, $0.32x10^{-2}$)	-0.01 (-0.03, 0.01)	0.01 (-0.03, 0.05)
1-4 units of alcohol per week (n = 16,583)	**Step change[a], units of alcohol per week change (95% CI)**	-0.06 (-0.21, 0.08)	-0.02 (-0.14, 0.10)	0.18 (0.07, 0.30)	-0.06 (-0.14, 0.02)	0.18 (-0.07, 0.18)	0.24 (0.17, 0.32)
	Trend change[b], units per week per month (95% CI)	0.01 (-0.01, 0.03)	$0.12 x10^{-2}$ (-0.01, 0.01)	0.00 (-0.01, 0.01)	$0.20 x10^{-2}$ (-0.01, 0.01)	0.01 ($-0.01x10^{-2}$, 0.02)	$0.07x10^{-2}$ ($-0.86x10^{-2}$, $0.99x10^{-2}$)

[a]Step change – a change of mean alcohol units per week in the month before and compared to the three months after the intervention.

[b]Trend change – a change in the mean alcohol units per week per month after the intervention when compared to change in the mean alcohol units per week per month prior to the intervention, starting at three months post-intervention.
CMO = Chief Medical Officers MUP = Minimum Unit Pricing for Alcohol

Table 2-9: Step and trend changes in reported alcohol consumption in pregnancy following public health intervention.

Drinking status	Step or trend change	Introduction of new drink driving limits in Scotland	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)	Effect of drink-driving limits and CMO	Effect of CMO and MUP	Collective impact of all three intervention
Analysis cohort (n = 321,33)	**Step change[a], units of alcohol per week change (95% CI)**	0.32 (-0.95, 1.59)	0.01 (-0.13, 0.15)	-0.04 (-0.31, 0.21)	-0.05 (-0.14, 0.03)	-0.09 (-0.29, 0.11)	0.01 (-0.17, 0.20)
	Trend change[b], units per week per month (95% CI)	-0.02 (-0.37, 0.33)	$-0.13x10^{-2}$ (-0.03, 0.03)	0.07 (-0.01, 0.13)	$0.35x10^{-2}$ (-0.01, 0.01)	0.07 (-0.03, 0.12)	0.07 (-0.03, 0.20)
Drinker cohort (n= 36,208)	**Step change[a], units of alcohol per week change (95% CI)**	0.09 (-0.61, 0.41)	0.02 (-0.40, 0.44)	-0.31 (-0.70, 0.08)	0.10 (-0.20, 0.22)	0.17 (-0.35, 0.70)	-0.56 (-0.76, -0.36)
	Trend change[b], units per week per month (95% CI)	0.01 (-0.05, 0.07)	$-0.3x10^{-2}$ (-0.02, 0.2)	-0.01 (-0.03, 0.02)	0.01 (-0.01, 0.01)	-0.02 (0.06, 0.02)	0.01 (-0.01, 0.02)
>4units of alcohol per week (n = 20,001)	**Step change[a], units of alcohol per week change (95% CI)**	-0.10 (-0.62, 0.42)	0.22 (-0.24, 0.67)	-0.42 (-0.86, 0.01)	0.41 (0.03, 0.78)	-0.31 (-0.61, -0.01)	-0.23 (-0.62, 0.15)
	Trend change[b], units per week per month (95% CI)	0.01 (-0.05, 0.07)	-0.01 (-0.03, 0.01)	-0.01 (-0.05, 0.02)	-0.02 (-0.32, $0.57x10^{-2}$)	-0.01 (-0.04, 0.01)	$-0.48x10^{-2}$ (-0.04, 0.03)
1-4 units of alcohol per week (n = 16,583)	**Step change[a], units of alcohol per week change (95% CI)**	-0.10 (-0.61, 0.41)	0.07 (-0.04, 0.19)	0.10 (-0.01, 0.21)	0.05 (-0.14, 0.03)	0.01 (-0.10, 0.11)	-0.06 (-0.13, 0.02)
	Trend change[b], units per week per month (95% CI)	-0.01 (-0.05, 0.07)	$0.11x10^{-2}$ ($-0.68x10^{-2}$, $-0.47x10^{-2}$)	$0.58x10^{-2}$ ($-0.68x10^{-2}$, -0.01)	$0.16x10^{-2}$ ($0.53x10^{-2}$, $0.85x10^{-2}$)	0.62x10-2 (0.37x10-2, 0.02)	$0.20x10^{-2}$ ($0.55x10^{-2}$, $0.94x10^{-2}$)

[a]Step change – a change of mean alcohol units per week in the month before and compared to the month after the intervention. [b]Trend change – a change in the mean alcohol units per week per month after the intervention when compared to change in the mean alcohol units per week per month prior to the intervention, starting at the month post-intervention.

CMO = Chief Medical Officers MUP = Minimum Unit Pricing for Alcohol

Table 2-10: Step and trend changes in reported alcohol consumption in pregnancy following public health interventions without lag period.

Drinking status	Step or trend change	Introduction of new drink driving limits in Scotland	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)	Effect of drink-driving limits and CMO	Effect of CMO and MUP	Collective impact of all three intervention
Analysis cohort (n = 321,33)	**Step change[a], units of alcohol per week change (95% CI)**	-0.16 (-0.28,-0.04)	-0.07 (-0.21, 0.07)	1.34 (1.15, 1.52)	$0.34x10^{-2}$ ($-0.80x10^{-4}$, $0.77x10^{-3}$)	1.06 (0.94, 1.18)	-0.16 (-0.28, -0.04)
	Trend change[b], units per week per month (95% CI)	-0.02 (-0.03, 0.06)	0.18 (-0.03, 0.03)	$0.42x10^{-2}$ (-0.05, 0.05)	$0.34x10^{-2}$ (-0.08, 0.04)	0.02 ($-0.97X10^{-2}$, 0.05)	-0.02 (-0.03, 0.06)
Drinker cohort (n= 36,208)	**Step change[a], units of alcohol per week change (95% CI)**	0.33 (-0.32, 0.98)	-0.02 (-0.52, 0.48)	-0.57 (-1.04, -0.11)	0.08 (-0.15, 0.30)	-0.57 (-0.83, -0.32)	0.33 (-0.32, 0.98)
	Trend change[b], units per week per month (95% CI)	-0.06 (-0.20, 0.08)	$-0.55x10^{-2}$ (-0.04, 0.33)	0.02 (-0.04, 0.07)	$-0.01x10^{-2}$ (-0.03, $0.6x10^{-2}$)	0.01 (-0.01, 0.04)	-0.06 (-0.20, 0.08)
>4units of alcohol per week (n = 20,001)	**Step change[a], units of alcohol per week change (95% CI)**	0.33 (-0.38, 1.04)	0.08 (-0.46, 0.61)	-0.68 (-1.19, -0.17)	-0.02 (-0.42, 0.37)	-0.66 (-0.96, -0.37)	0.33 (-0.38, 1.04)
	Trend change[b], units per week per month (95% CI)	0.08 (-0.19, 0.11)	-0.02 (-0.06, 0.02)	0.02 (-0.05, 0.03)	$-0.50x10^{-2}$ (-0.05, 0.04)	$0.69x10^{-2}$ (-0.02, 0.04)	0.08 (-0.19, 0.11)
1-4 units of alcohol per week (n = 16,583)	**Step change[a], units of alcohol per week change (95% CI)**	0.02 (-0.08, 0.12)	0.02 (-0.08, 0.12)	0.19 (0.07, 0.32)	0.06 (-0.02, 0.14)	0.25 (0.21, 2.81)	0.02 (-0.08, 0.12)
	Trend change[b], units per week per month (95% CI)	$0.11x10^{-2}$ ($-0.65x10^{-2}$, $0.88x10^{-2}$)	$0.39x10^{-2}$ ($-0.65x10^{-2}$, $0.88x10^{-2}$)	$0.72x10^{-2}$ (-0.02, $0.12x10^{-2}$)	$3x10^{-4}$ ($-0.56x10^{-2}$, $0.62x10^{-2}$)	$-0.26x10^{-2}$ ($-0.66x10^{-2}$, $0.14x10^{-2}$)	$0.11x10^{-2}$ ($-0.65x10^{-2}$, $0.88x10^{-2}$)

[a]Step change = A change of mean alcohol per unit per week in the month before and compared to the six months after the intervention
[b]Trend change = A change in the mean alcohol units per week per month after the intervention when compared to the change in the mean alcohol units per week per month prior to the intervention, starting at three months post-intervention
CMO = Chief Medical Officers, MUP = Minimum Unit Pricing for Alcohol

Table 2-11: Step and trend changes in reported alcohol consumption in pregnancy following public health interventions with six month lag period

Drinking status	Step or trend change	Introduction of new drink driving limits in Scotland	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)	Effect of drink-driving limits and CMO	Effect of CMO and MUP	Collective impact of all three intervention
Analysis cohort (n = 276,326)	**Step change[a], units of alcohol per week change (95% CI)**	-0.10 (-0.22, 0.03)	-0.05 (-0.16, 0.06)	1.32 (1.15, 1.48)	-0.02 (-0.07, 0.03)	1.35 (1.26, 1.46)	1.30 (1.19, 1.41)
	Trend change[b], units per week per month (95% CI)	0.01 (-0.04, 0.06)	-0.41×10^{-2} (-0.02, 0.03)	0.15×10^{-2} (-0.04, 0.05)	0.43×10^{-2} (0.85×10^{-3}, 0.77×10^{-2})	0.01, (-0.03, 0.03)	0.15×10^{-2} (-0.03, 0.03)
Drinker cohort (n= 29,334)	**Step change[a], units of alcohol per week change (95% CI)**	0.43 (-0.34, 1.20)	-0.28 (-0.69, 0.14)	-0.41 (-0.81, $-0.19\times^{-2}$)	-0.10 (-0.39, 0.19)	-0.37 (0.59, -0.15)	-0.49 (-0.73, -0.25)
	Trend change[b], units per week per month (95% CI)	-0.07 (-0.24, 0.09)	0.02 (-0.01, 0.05)	0.01 (-0.03, 0.06)	0.48×10^{-2} (-0.02, 0.03)	0.01 (-0.01, 0.03)	0.02 (-0.80×10^{-2}, 0.04)
>4units of alcohol per week (n = 15,269)	**Step change[a], units of alcohol per week change (95% CI)**	0.32 (-0.73, 1.37)	-0.05 (-0.61, 0.51)	-0.61 (-1.18, -0.05)	0.15 (-0.36, 0.66)	-0.31, (-0.73, 0.12)	-0.18 (-0.71, 0.33)
	Trend change[b], units per week per month (95% CI)	-0.08 (-0.31, 0.15)	0.01 (-0.03, 0.06)	0.85×10^{-2} (-0.05, 0.07)	0.28×10^{-2} (-0.03, 0.04)	0.04 (-0.05, 0.09)	-0.10 (-0.71, 0.33)
1-4 units of alcohol per week (n = 14,065)	**Step change[a], units of alcohol per week change (95% CI)**	0.03 (-0.18, 0.24)	-0.18×10^{-2} (-0.11, 0.11)	0.23 (0.09, 0.37)	0.03 (-0.05, 0.11)	0.23 (0.17, 0.30)	0.02 (-0.19, 0.24)
	Trend change[b], units per week per month (95% CI)	-0.26×10^{-2} (-0.05, 0.04)	0.10×10^{-2} (-0.70×10^{-2}, 0.91×10^{-2})	-0.47×10^{-2} (0.09, 0.36)	0.05×10^{-3} (-0.62×10^{-2}, 0.52×10^{-2})	-0.25×10^{-2} (-0.96×10^{-2}, 0.46×10^{-2})	-0.18×10^{-2} (-0.07, 0.07)

[a]Step change = A change of mean alcohol per unit per week in the month before and compared to the six months after the intervention

[b]Trend change = A change in the mean alcohol units per week per month after the intervention when compared to the change in the mean alcohol units per week per month prior to the intervention, starting at three months post-intervention

CMO = Chief Medical Officers, MUP = Minimum Unit Pricing for Alcohol

Table 2-12: Step and trend changes in reported alcohol consumption in pregnancy following public health interventions with six month lag period for non-smokers

Drinking status	Step or trend change	Introduction of new drink driving limits in Scotland	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)	Effect of drink-driving limits and CMO	Effect of CMO and MUP	Collective impact of all three intervention
Analysis cohort (n = 56,257)	**Step change[a], units of alcohol per week change (95% CI)**	-0.35 (-0.71, $0.40x10^{-2}$)	-0.04 (-0.60, 0.11)	1.49 (0.87, 2.11)	-0.07 (-0.10, 0.23)	1.24, (0.85, 1.63)	1.17 (0.58, 1.50)
	Trend change[b], units per week per month (95% CI)	0.04 (-0.10, 0.16)	-0.01 (-0.14, 0.11)	0.01 (-0.15, 0.18)	$-0.03x10^{-2}$ (-0.02, 0.01)	0.05 (-0.09, 0.12)	0.01 (-0.07, 0.10)
Drinker cohort (n= 5875)	**Step change[a], units of alcohol per week change (95% CI)**	0.04 (-2.42, 2.51)	0.96 (-0.75, 2.67)	-0.75 (-2.51, 1.01)	0.72 (-0.21, 1.65)	-1.04 (-1.95, -0.13)	-0.15 (-1.09, 0.77)
	Trend change[b], units per week per month (95% CI)	0.01 (-0.48, 0.51)	0.07 (0.23, 0.03)	0.01 (-0.17, 0.21)	0.03 (-0.11, 0.02)	0.02 (-0.08, 0.13)	-0.03 (-0.15, 0.08)
>4units of alcohol per week (n = 3,950)	**Step change[a], units of alcohol per week change (95% CI)**	0.28 (-2.58, 3.16)	0.55 (-1.54, 2.64)	-0.68 (-2.55, 1.19)	0.85 (-0.74, 2.43)	-1.43 (-2.66, -0.20)	1.83 (0.26, 3.39)
	Trend change[b], units per week per month (95% CI)	-0.02 (-0.60, 0.64)	-0.08 (-0.24, 0.08)	-0.02 (-0.23, 0.19)	-0.01 (-0.12, 0.10)	-0.02 (-0.16, 0.11)	-0.10 (-0.28, 0.09)
1-4 units of alcohol per week (n = 1,925)	**Step change[a], units of alcohol per week change (95% CI)**	0.27 (-0.16, 0.69)	-0.05 (-0.12, 0.02)	0.17 (-0.17, 0.50)	0.31 (-0.03, 0.64)	0.23 (0.17, 0.28)	0.02 (-0.36, 0.41)
	Trend change[b], units per week per month (95% CI)	-0.06 (-0.15, 0.03)	0.01 ($0.21x10^{-2}$, 0.01)	0.01 (-0.03, 0.05)	$0.38x10^{-2}$ (-0.02, 0.03)	$0.82x10^{-2}$ (0.17, 0.28)	0.02 (-0.10, 0.14)

[a]Step change = A change of mean alcohol per unit per week in the month before and compared to the six months after the intervention
[b]Trend change = A change in the mean alcohol units per week per month after the intervention when compared to the change in the mean alcohol units per week per month prior to the intervention, starting at three months post-intervention
CMO = Chief Medical Officers, MUP = Minimum Unit Pricing for Alcohol

Table 2-13: Step and trend changes in reported alcohol consumption in pregnancy following public health interventions with six-month lag period for smokers

2.4.3 Impact of Alcohol-related public health interventions on perinatal outcomes

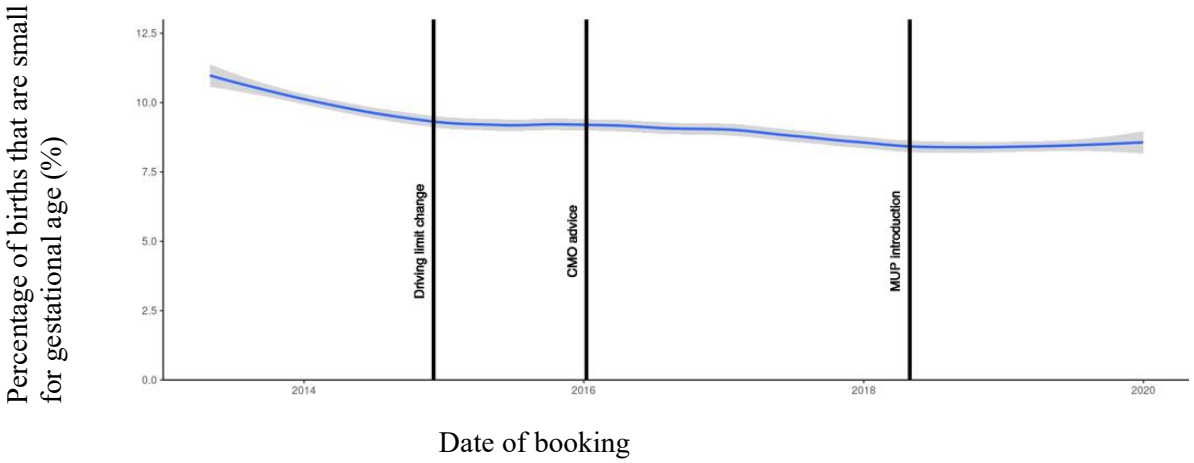
Over the period of the three public health interventions, the incidence of SGA decreased from 9.9% to 8.5%, and stillbirths from 4 per 1000 pregnancies to 3 per 1000 pregnancies, whilst the prevalence of preterm births increased from 7.0% to 7.7% (Table 2-14, Figures 2-7 to 2-9). This was not accompanied by a change in neonatal unit admissions, which was maintained at around 8.6% (Table 2-14, Figure 2-10). Adjusted multivariable analyses were used to assess the effect of the individual alcohol-related interventions while accounting for the changes in the underlying maternal population (Table 2-15). For SGA, the introduction of the drink-driving ban (adjRR 0.95 [95% CI: 0.91,0.99]); CMO advice to abstain from alcohol (adjRR 0.96 [95% CI: 0.93-1.00]); and MUP (adjRR 0.91 [95% CI: 0.87, 0.95]) were associated with a reduced risk of SGA when considered both individually, and cumulatively across all three interventions (adjRR 0.87 [95% CI: 0.84, 0.90]) (Table 2-15). The prevalence of preterm birth increased following all interventions (adjRR 1.08 [95% CI: 1.04, 1.13]). The public health interventions were associated with a reduction in the prevalence of neonatal unit admissions after CMO advice (adjRR 0.94 [95% CI: 0.90, 0.98]) and MUP (adjRR 0.90 [95% CI 0.86, 0.94]). For stillbirth, only CMO advice to abstain from alcohol was associated with a reduction in stillbirth risk (adjRR 0.72 [95% CI: 0.57, 0.91]), with this maintained when all three interventions were considered cumulatively (adjRR 0.77 [95% CI: 0.62, 0.94]) (Table 2-15). Results were similar in unadjusted analyses (Table 2-16), when gestational age at booking was removed from the analysis (Table 2-17), with adjustment for alcohol (Table 2-18), as well as alcohol consumption 50% normalised to post-MUP drinking levels (Table 2-19), and normalised to the post-MUP period (Table 2-20)

Characteristic	Pre-intervention N = 105,360[1]	Post drink driving limits N = 57,747[1]	Post CMO advice N = 104,727[1]	Post MUP N = 78,526[1]	p-value[2]
Small for Gestational Age	10,439 (9.9%)	5,368 (9.3%)	9,240 (8.8%)	6,669 (8.5%)	<0.001
Missing[3]	580	506	861	103	
Premature	7,381 (7.0%)	4,269 (7.4%)	7,974 (7.6%)	6,064 (7.7%)	<0.001
Missing	472	417	418	61	
Requirement for neonatal unit	9,022 (8.7%)	5,125 (9.0%)	8,677 (8.8%)	6,133 (8.6%)	0.078
Missing	1,062	580	6,136	7,240	
Stillbirth	376 (0.4%)	207 (0.4%)	344 (0.3%)	243 (0.3%)	0.3

1) N (%).
2) Wilcoxon rank sum test; Pearson's Chi-squared test
3) Calculated missing from missing gestational age or birthweight

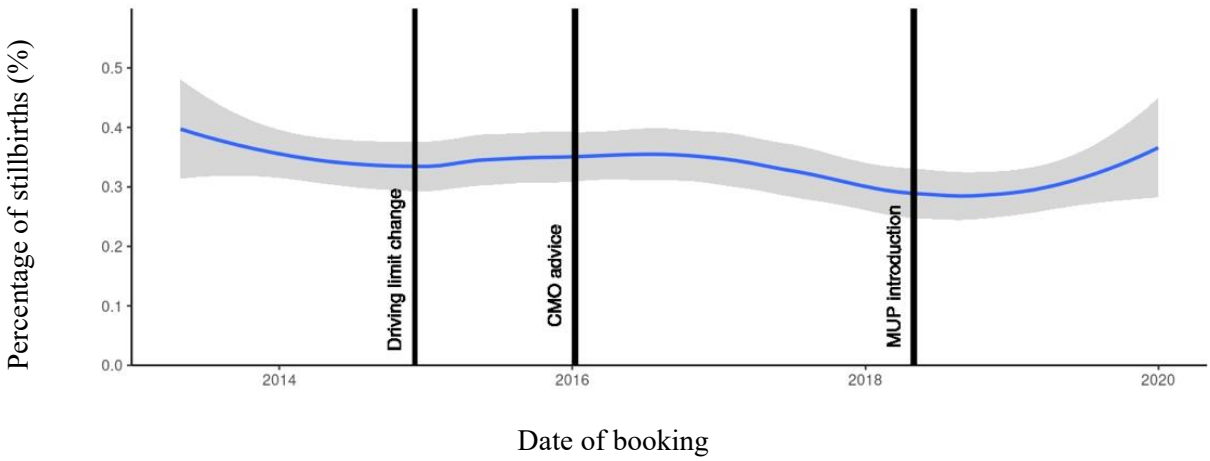
CMO = Chief Medical Officers, UK. MUP = Minimum Unit Pricing for alcohol

Table 2-14: Perinatal outcomes of booked pregnancies between April 2013 and December 2019 by public health phase.



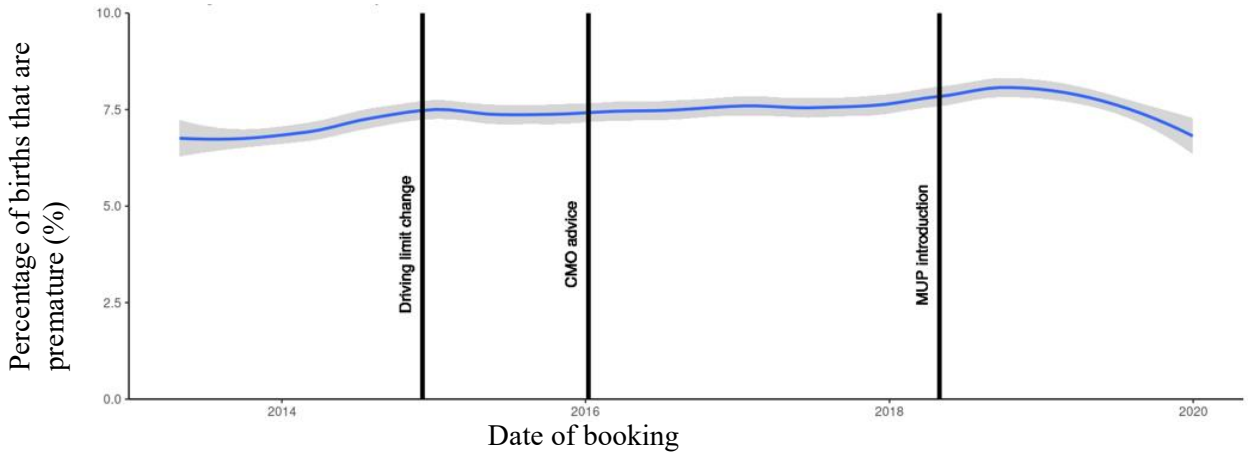
Gray shaded area represents 95% Confidence interval

Figure 2-7: Percentage of births that are small for gestational age in Scotland, overtime (unadjusted).



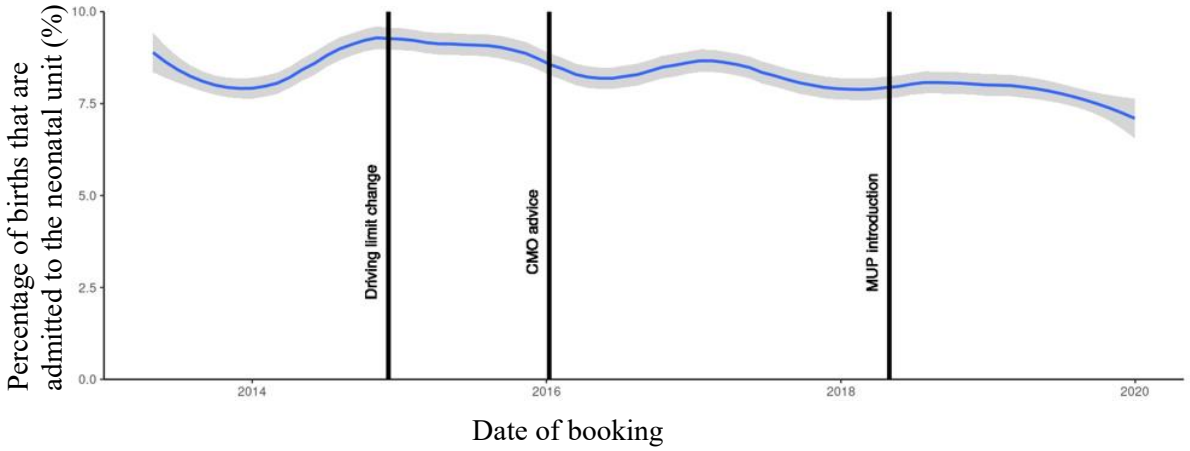
Gray shaded area represents 95% Confidence interval.

Figure 2-8: Percentage of booking visits that have pregnancies that result in stillbirths, overtime (unadjusted).



Gray shaded area represents 95% Confidence interval

Figure 2-10: Percentage of births that are premature in Scotland, overtime (unadjusted).



Gray shaded area represents 95% Confidence interval

Figure 2-9: Percentage of births that are admitted to a neonatal unit in Scotland, overtime (unadjusted).

Outcome	Pre-intervention. Starting incidence, End incidence (trend) [1] [2]	Introduction of new drink driving limits in Scotland[3], adj[a] Risk Ratio (95% CI), p value	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK(CMO)[3], adj[a] Risk Ratio (95% CI), p value	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[3], adj[a] Risk Ratio (95% CI), p value	Effect of drink-driving limits and CMO[3], adj[a] Risk Ratio (95% CI), p value	Effect of CMO and MUP[3], adj[a] Risk Ratio (95% CI), p value	Collective impact of all three intervention[4], adj[a] Risk Ratio (95% CI), p value
Small for gestational	6.3%, 5.6%, ($-2.3x10^{-2}$ %/day)	0.95 (0.91, 0.99), <0.01	0.96 (0.93, 1.00), 0.05	0.95 (0.92, 0.99), <0.01	0.91 (0.88, 0.94), <0.01	0.92 (0.88, 0.95), <0.01	0.87 (0.84, 0.90), <0.01
Prematurity	5.5%, 5.6%, ($1.4x10^{-4}$ %/day)	1.07 (1.00, 1.14), 0.05	1.02 (0.97, 1.07), 0.50	1.01 (0.97, 1.05), 0.60	1.11 (1.01, 1.23), 0.03	1.03 (0.98, 1.09), 0.25	1.16 (1.00, 1.35), 0.05
Neonatal unit admission	6.9%, 6.8%, ($-4.2x10^{-4}$ %/day)	1.03 (0.97, 1.09), 0.30	0.94 (0.90, 0.98), <0.01	0.96 (0.92, 0.99), 0.02	0.98 (0.90, 1.08), 0.08	0.90 (0.86, 0.94), <0.01	0.96 (0.84, 1.11), 0.59
Stillbirth	0.2%, 0.2%, ($-2.1x10^{-3}$ %/day)	1.05 (0.85, 1.31), 0.64	0.73 (0.58, 0.92), <0.01	1.00 (0.80, 1.26), 0.98	0.77 (0.63, 0.95), 0.01	0.72 (0.57, 0.92), 0.01	0.77 (0.62, 0.95), 0.02

a) Adjusted for: Estimated gestation at booking, smoking, drug use, age of mother, maternal BMI, Ethnicity, Parity, and SIMD.
1) Estimated incidence of outcome at start and end of pre-intervention period and estimated change in incidence per day of study, over pre-intervention period. % (%/day)
2) Estimate incidence controlled for: maternal BMI (26.48kg/m2), Ethnic group (White), Smoking status (No), Drug use (No), Parity (0.98 births), SIMD (5)
3) Relative to the epoch prior
4) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014
CMO = Chief Medical Officers, UK MUP = Minimum Unit Pricing for Alcohol

Table 2-15: Adjusted perinatal outcomes following public health interventions

Outcome	Introduction of new drink driving limits in Scotland[1], Risk Ratio (95% CI)	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK (CMO)[1], Risk Ratio (95% CI)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[1], Risk Ratio (95% CI)	Effect of drinking driving limits and CMO advice[1], Risk Ratio (95% CI)	Effect of CMO advice and MUP[1], Risk Ratio (95% CI)	Collective impact of all three intervention[2], Risk Ratio (95% CI)
Small for gestational	0.95 (0.91, 0.97)	0.95 (0.92, 0.98)	1.02 (0.98, 1.05)	0.89 (0.86, 0.91)	0.91 (0.88, 0.94)	0.85 (0.83, 0.88)
Prematurity	1.06 (1.02, 1.10)	1.03 (0.99, 1.06)	1.01 (0.98, 1.04)	1.09 (1.05, 1.11)	1.03 (1.00, 1.08)	1.10 (1.06, 1.34)
Neonatal unit admission	1.03 (1.00, 1.07)	0.93 (0.90, 0.96)	0.94 (0.91, 0.97)	0.97 (0.94, 1.00)	0.88 (0.85,0.91)	0.91 (0.88, 0.94)
Stillbirth	1.00 (0.94, 1.19)	0.94 (0.77, 1.09)	0.94 (0.91, 0.97)	0.92 (0.79, 1.07)	0.86 (0.71, 1.04)	0.87 (0.73, 1.02)

1) Relative to immediate preceding epoch
2) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014
CMO = Chief Medical Officer, UK. MUP = Minimum Unit Pricing for alcohol

Table 2-16: Unadjusted perinatal outcomes by public health phase

Outcome	Introduction of new drink driving limits in Scotland[1], adj[a] Risk Ratio (95% CI)	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK(CMO)[1], adj[a] Risk Ratio (95% CI)	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[1], adj[a] Risk Ratio (95% CI)	Effect of drink-driving limits and CMO[1], adj[a] Risk Ratio (95% CI)	Effect of CMO and MUP[1], adj[a] Risk Ratio (95% CI)	Collective impact of all three intervention[2], adj[a] Risk Ratio (95% CI)
Small for gestational	0.95 (0.91, 0.98)	0.96 (0.92, 1.00)*	0.96 (0.92, 0.99)	0.91 (0.88, 0.94)	0.91 (0.87, 0.95)	0.86 (0.83, 0.89)
Prematurity	1.04 (1.00, 1.09)	1.03 (0.98, 1.07)	1.04 (0.99, 1.09)	1.07 (1.03, 1.11)	1.03 (0.98, 1.08)	1.07 (1.03, 1.12)
Neonatal unit admission	1.02 (0.98, 1.06)	0.94 (0.90, 0.98)	0.90 (0.86, 0.94)	0.96 (0.93, 1.00)*	0.90 (0.86, 0.94)	0.92 (0.89, 0.96)
Stillbirth	1.05 (0.84, 1.30)	0.72 (0.57, 0.91)	0.72 (0.56, 0.93)	0.75 (0.61, 0.95)	0.72 (0.57, 0.91)	0.76 (0.61, 0.95)

a) Adjustments for : Estimated gestation at booking, smoking, drug use, age of mother, maternal BMI, Ethnicity, Parity, and SIMD
1) Relative to immediate preceding epoch
2) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014
* Upper 95% CI CI <1.00 (but rounded to 2 decimal places)
CMO = Chief Medical Officers, UK MUP = Minimum Unit Pricing for Alcohol

Table 2-17: Adjusted perinatal outcomes following public health interventions (without adjustment for estimated gestational age at booking)

Outcome	Pre-intervention. Starting incidence, End incidence (trend) [1] [2]	Introduction of new drink driving limits in Scotland[3], adj[a] Risk Ratio (95% CI), p value	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK(CMO)[3], adj[a] Risk Ratio (95% CI), p value	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[3], adj[a] Risk Ratio (95% CI), p value	Effect of drink-driving limits and CMO[3], adj[a] Risk Ratio (95% CI), p value	Effect of CMO and MUP[3], adj[a] Risk Ratio (95% CI), p value	Collective impact of all three intervention[4], adj[a] Risk Ratio (95% CI), p value
Small for gestational	6.4%, 5.6%, ($-2.3x10^{-2}$ %/day)	0.95 (0.91, 0.99), <0.01	0.96 (0.93, 1.00), 0.05	0.91 (0.87, 0.95), <0.01	0.92 (0.89, 0.95), <0.01	0.91 (0.88, 0.95), <0.01	0.87 (0.84, 0.90), <0.01
Prematurity	5.1%, 5.6%, ($1.7x10^{-2}$ %/day)	1.04 (1.00, 1.09), 0.07	1.02 (0.98, 1.07), 0.38	1.01 (0.97, 1.05), 0.60	1.06 (1.02, 1.11), 0.02	1.04 (0.99, 1.09), 0.16	1.08 (1.04, 1.13), <0.01
Neonatal unit admission	6.6%, 6.8%, ($3.6x10^{-3}$ %/day)	1.02 (0.98, 1.07), 0.30	0.94 (0.90, 0.98), <0.01	0.90 (0.86, 0.94), <0.01	0.96 (0.93, 1.00), 0.04	0.90 (0.86, 0.94), <0.01	0.92 (0.89, 0.96), <0.01
Stillbirth	0.2%, 0.2%, ($2.7x10^{-4}$ %/day)	1.05 (0.85, 1.31), 0.64	0.72 (0.57, 0.91), <0.01	0.73 (0.56, 0.94), 0.01	0.76 (0.62, 0.94), 0.01	0.73 (0.57, 0.94), 0.01	0.77 (0.62, 0.94), 0.01

a) Adjusted for: Estimated gestation at booking, alcohol, smoking, drug use, age of mother, maternal BMI, Ethnicity, Parity, and SIMD

1) Estimated incidence of outcome at start and end of pre-intervention period and estimated change in incidence per day of study, over pre-intervention period. % (%/day)

2) Estimate incidence controlled for: maternal BMI (26.48kg/m2), Ethnic group (White), Smoking status (No), Drug use (No), Parity (0.98 births). Weekly alcohol use (0.48units per week), SIMD (5)

3) Relative to the epoch prior

4) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014

CMO = Chief Medical Officers, UK, MUP = Minimum Unit Pricing for Alcohol

Table 2-18: Birth outcomes following public health interventions, with adjustment for alcohol

Outcome	Pre-intervention. Starting incidence, End incidence (trend) [1 2]	Introduction of new drink driving limits in Scotland[3], adj[a] Risk Ratio (95% CI), p value	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK(CMO)[3], adj[a] Risk Ratio (95% CI), p value	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[3], adj[a] Risk Ratio (95% CI), p value	Effect of drink-driving limits and CMO[3], adj[a] Risk Ratio (95% CI), p value	Effect of CMO and MUP[3], adj[a] Risk Ratio (95% CI), p value	Collective impact of all three intervention[4], adj[a] Risk Ratio (95% CI), p value
Small for gestational	6.4%, 5.6% ($-3.2x10^{-2}$ %/day)	0.95 (0.91, 0.99), <0.01	0.96 (0.93, 1.00), 0.06	0.91 (0.87, 0.95), <0.01	0.92 (0.89, 0.95), <0.01	0.91 (0.88, 0.95), <0.01	0.87 (0.84, 0.90), <0.01
Prematurity	5.1%, 5.6%, ($1.9x10^{-2}$ %/day)	1.04 (1.00, 1.09), 0.07	1.02 (0.98, 1.07), 0.38	1.03 (0.98, 1.08), 0.13	1.06 (1.02, 1.11), <0.01	1.04 (0.99, 1.09), 0.14	1.08 (1.03, 1.12), <0.01
Neonatal unit admission	6.7%, 6.8%, ($2.1x10^{-2}$ %/day)	1.02 (0.98, 1.07), 0.28	0.94 (0.90, 0.98), <0.01	0.91 (0.87, 0.95), <0.01	0.96 (0.93, 1.00), 0.03	0.90 (0.86, 0.94), <0.01	0.92 (0.89, 0.96), 0.49
Stillbirth	0.2%, 0.2%,($8.1x10^{-5}$ %/day)	1.05 (0.85, 1.31), 0.64	0.72 (0.57, 0.91), <0.01	0.72 (0.56, 0.94), 0.01	0.76 (0.62, 0.94), 0.01	0.73 (0.57, 0.94), 0.01	0.77 (0.62, 0.96), 0.02

a) Adjusted for: Estimated gestation at booking, smoking, drug use, age of mother, maternal BMI, Ethnicity, Parity, and SIMD
1) Estimated incidence of outcome at start and end of pre-intervention period and estimated change in incidence per day of study, over pre-intervention period. % (%/day)
2) Estimate incidence controlled for: maternal BMI (26.48kg/m2), Ethnic group (White), Smoking status (No), Drug use (No), Parity (0.98 births), SIMD (5)
3) Relative to the epoch prior
4) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014

CMO = Chief Medical Officers, UK, MUP = Minimum Unit Pricing for Alcohol

Table 2-19: Birth outcomes following public health interventions, with 50% normalised pre-MUP drinking levels

	Pre-intervention Starting incidence, End incidence (trend) [1 2]	Introduction of new drink driving limits in Scotland[3], adj[a] Risk Ratio (95% CI), p value	Recommendation to abstain from alcohol in pregnancy from the Chief medical officers of the UK(CMO)[3], adj[a] Risk Ratio (95% CI), p value	Introduction of a £0.5 minimum sale price of 1 unit of alcohol in Scotland (MUP)[3], adj[a] Risk Ratio (95% CI), p value	Effect of drink-driving limits and CMO[3], adj[a] Risk Ratio (95% CI), p value	Effect of CMO and MUP[3], adj[a] Risk Ratio (95% CI), p value	Collective impact of all three intervention[4], adj[a] Risk Ratio (95% CI), p value
Small for gestational	6.4%, 5.6%, (-3.2×10^{-2} %/day)	0.95 (0.91, 0.99), <0.01	0.96 (0.93, 1.00), 0.06	0.91 (0.87, 0.95), <0.01	0.92 (0.89, 0.95), <0.01	0.91 (0.88, 0.95), <0.01	0.87 (0.84, 0.90), <0.01
Prematurity	5.1%, 5.6%, (1.9×10^{-2} %/day)	1.04 (1.00, 1.09), 0.07	1.02 (0.97, 1.07), 0.38	1.03 (0.98, 1.08), 0.13	1.06 (1.02, 1.11), <0.01	1.03 (0.99, 1.08), 0.17	1.08 (1.04, 1.13), <0.01
Neonatal unit admission	6.7%, 6.8%, (2.1×10^{-2} %/day)	1.02 (0.98, 1.07), 0.28	0.94 (0.90, 0.98), <0.01	0.90 (0.86, 0.94), <0.01	0.96 (0.93, 1.00), 0.08	0.90 (0.86, 0.94), <0.01	0.92 (0.89, 0.96), 0.59
Stillbirth	0.2%, 0.2%, (3.3×10^{-5} %/day)	1.05 (0.85, 1.31), 0.64	0.72 (0.57, 0.91), <0.01	0.72 (0.56, 0.93), 0.01	0.76 (0.62, 0.94), 0.01	0.72 (0.56, 0.93) 0.01	0.77 (0.61, 0.96), 0.02

a) Adjusted for: Estimated gestation at booking, smoking, drug use, age of mother, maternal BMI, Ethnicity, Parity, and SIMD
1) Estimated incidence of outcome at start and end of pre-intervention period and estimated change in incidence per day of study, over pre-intervention period. % (%/day)
2) Estimate incidence controlled for: maternal BMI (26.48kg/m2), Ethnic group (White), Smoking status (No), Drug use (No), Parity (0.98 births), SIMD (5)
3) Relative to the epoch prior
4) Comparison of pregnancies after 1 May 2018 relative to April 2013 – December 2014
CMO = Chief Medical Officers, UK, MUP = Minimum Unit Pricing for Alcohol

Table 2-20: Birth outcomes following public health interventions, with normalised pre-MUP drinking levels

2.5 Discussion

This chapter demonstrates that by 2019, up to one in four pregnant women in Scotland reported drinking on average, six to eight units of alcohol per week in early pregnancy, up from 7% in 2013. Although drink-driving legislation and specific guidance to pregnant women to abstain from alcohol, were not individually or collectively associated with a sustained reduction in the amount of alcohol consumed by pregnant drinkers, the introduction of alcohol minimum unit pricing (MUP) was associated with a small reduction of approximately half a unit per week (4g ethanol) when compared to the preceding period. Cumulatively, the effect of all three interventions was a reduction of almost 0.7 units per week. During this study there was a trend to improvements in birth outcomes, with the prevalence of SGA, neonatal admissions and stillbirths all declining. In contrast, the prevalence of preterm births increased throughout the study period.

MUP compared to the existing drink-driving legislation and CMO advice to abstain from alcohol in pregnancy, was associated with a small decline in alcohol consumption in pregnant drinkers and in the risk of SGA in all pregnancies. The reduction in alcohol consumption is in accordance with the known reduction in alcohol-related sales in Scotland and other countries on the introduction of MUP[186,187]. The success of MUP, particularly in women who consume greater than four units per week, is likely to relate to its mandatory and comprehensive implementation and the clarity of the underlying message. The reduction in SGA with the introduction of MUP is consistent with two previous reviews of RCTs and quasi-experimental studies suggesting that greater alcohol consumption in pregnancy does cause an increase in SGA[104,112]. That a population-level intervention such as MUP contributed toward reducing maternal alcohol consumption in women who drink during pregnancy and improved key perinatal outcomes in the obstetric population is an important finding and supports the introduction of population-based measures.

Drink-driving legislation was originally introduced in Scotland in 1967, and the legislation in 2014 further lowered the permissible drink-driving limit from 0.08 g/dl to the lowest detectable concentration 0.05g/dl[146,148]. Despite this “zero tolerance” approach, there was no observable change in mean maternal

alcohol consumption in pregnant drinkers following this legislation nor following the UK CMOs' advice to abstain completely from alcohol. This was despite broad awareness by midwives of these policies and wide adoption of alcohol product labels to discourage drinking or state "it is safest not to drink alcohol when pregnant" [188]. Whether the failure of the CMO advice to impact alcohol consumption was due to the lack of targeted intervention programmes and/or the limited effectiveness of labelling in reducing alcohol consumption is unclear.

It has been recognised for many decades that low birth weight and being born small for gestational age pose a risk factor for immediate perinatal and long-term adverse health outcomes[189]. There was an identified reduction in SGA following MUP and a trend to reduce throughout the study period. Heavy alcohol consumption has previously been associated with an increased risk of SGA[102]. Although the prevalence of consumption of greater than four units per week reduced over the studied period, we cannot exclude the possibility that other contemporary improvements in maternal health may have contributed. For example, wider use of low-dose aspirin, which is protective against SGA, with the effect estimates from randomised controlled trials similar to those reported here[190]. Our finding of an overall reduction in stillbirths across the study period is consistent with reported national trends and is likely to reflect general improvements in maternal healthcare[191]. The CMO advice on maternal alcohol consumption was strongly associated with a reduction in stillbirths across all pregnant women. This is potentially due to variations due its low incidence (<0.5%), or other factors not measured in study, as alcohol consumption was largely stable at the time of the intervention (January 2016)[173].

The increasing prevalence of preterm birth is likely to reflect altered obstetric care pathways rather than a biological effect, particularly given the known tocolytic mechanisms related to alcohol[192]. Many risk factors for preterm birth, including the proportion of mothers aged 40 years or over at delivery, obesity and socioeconomic deprivation, are common in Scotland and continue to increase, with obstetric interventions also increasing the risk of iatrogenic preterm birth[193].

There are several limitations to this research, including the reliance on self-reported alcohol consumption, which is generally underestimated in women

who drink more heavily, and may bias our results, particularly for the 1-4 units of alcohol per week cohort[16]. However, our effect estimates for MUP are similar to those reported for alcohol sales which are regulated and reported in accordance with statutory legislation[155,194,195]. There were temporal differences in data collection (5.8% vs 26.2% women reporting alcohol consumption in 2013 and 2019 respectively) raising the potential of under-reporting of drinking in the early epochs of the data. This variation is specifically why non-drinkers were not included in our analyses of mean alcohol consumption and public health interventions, and we acknowledge that this may have resulted in underestimation of mean alcohol consumption. However, when units of alcohol were compared over time, we found that this did not differ between time periods. The additional sensitivity analysis on offspring data brought the earlier period's data both 50% and fully in line with the later periods' prevalence rates, giving similar results. There are multiple potential explanations for the temporal change in alcohol consumption reported in this study. These include a change in data input/validation, change in questioning from midwives, or a change in drinking patterns. There is no definitive evidence to support any one particular theory, but the adoption of new digital systems could have been a significant factor. The issues were highlighted in a report by eDRIS and site-specific measures were implemented around the time of digital roll-out[178]. It was not possible to control for digital record keeping due to a heterogeneity of implementation and lack of recording of manual to digital change over dates from the digital service provider. It should be acknowledged that there were missing data for alcohol consumption, though this remained relatively constant throughout the study period. Women with missing data were more likely to have adverse characteristics (smoking, socioeconomic deprivation, drug use), which will contribute to the uncertainty of the outcome estimates, however, the rate of missing data, in other variables was similar between drinkers and non-drinkers. These missing data could lead to selection bias and impact alcohol consumption trends and offspring outcomes. It is possible that women with missing data for alcohol intake may have higher alcohol consumption, higher incidence of other adverse features and higher risk of adverse outcomes, but without control of data collection we were unable to reduce the rate of missing data. Self-reported alcohol consumption was solely recorded at the initiation of antenatal care, which was predominantly in the first trimester. To adjust for the

minor variations in gestational age at booking throughout the cohort's time period, gestational age at booking was included in the models, with results similar to those where it was not included. Subsequent changes in alcohol consumption, as well as other confounding factors, across gestation or time period may have occurred, but alcohol consumption is likely to reduce across gestation due to societal pressure and therefore only likely to have attenuated the results, and we adjusted our results across the study period. Smoking and alcohol consumption are frequently linked behaviours; however, our results were similar in non-smokers. Given the established adverse effect of smoking on pregnancy, future strategies may target reducing the combination of smoking and alcohol consumption in pregnancy. While the National Institute of Clinical Excellence guidance for antenatal care did not change during the study period, it should be recognised that concomitant public health interventions and local changes in obstetric care practices may have contributed to our findings. It should be appreciated that the study was unable to determine the individual effects of all of the interventions; however, the observed cumulative effect may suggest that small individual shifts in behaviour may have accumulated, and the three interventions were eventually synergistic. Similarly, this study was unable to assess alternative outcomes, like miscarriage, which have been associated with alcohol consumption in some studies[196]. Lastly, our findings are restricted to the pregnant population and, as such, cannot be generalised to the wider Scottish population or to other countries with different legislative and public health alcohol-related interventions.

2.6 Chapter Summary

This chapter has demonstrated that maternal alcohol consumption in pregnancy is common, with around one in four women self-reporting alcohol consumption in early pregnancy. The amount of alcohol consumed by pregnant drinkers in Scotland has decreased by around 0.7 units per week during this study and with the introduction of MUP, though not drinking-driving legislation nor CMO advice. We observed an overall reduction in the key perinatal outcomes of SGA, neonatal unit admission and stillbirth despite an underlying increase in preterm births. Given the lack of evidence of safety even at lower levels of alcohol consumption, comprehensive education and continued public policy efforts reinforcing low alcohol consumption for people embarking on pregnancy is warranted.

In the subsequent chapter, there will be an exploration of the association of low amounts of alcohol consumption in pregnancy (less than 4 units of alcohol per week) on perinatal outcomes, and whether this differs in women who abstain from alcohol altogether.

Chapter 3 Association between alcohol consumption and perinatal outcomes

3.1 Chapter Abstract

Background: Alcohol consumption during pregnancy is known to be harmful at high volumes. Current UK Chief Medical Officers' guidance recommends complete abstinence during pregnancy, based primarily on the precautionary principle rather than clear evidence of harm from consuming 1-4 units of alcohol per week. We aimed to determine whether consumption of 1-4 units of alcohol per week was associated with adverse perinatal outcomes compared to abstinence or consumption of over 4 units per week.

Methods: Scottish health records between 1st April 2013 and 31st December 2019 were analysed for associations between self-reported alcohol consumption and perinatal outcomes. Multivariable regression models quantified relationships between alcohol intake and outcomes including small for gestational age, very small for gestational age, low birth weight, prematurity, spontaneous prematurity, neonatal unit admission, and stillbirths. Given the collinearity between alcohol consumption and smoking, analyses were stratified by smoking status.

Results: Among 341,239 singleton pregnancies, 35,719 (10.7%) reported alcohol consumption, with 44.8% (n=15,988) consuming 1-4 units of alcohol per week. Consumption of 1-4 units of alcohol per week was associated with improved offspring outcomes in premature births (adjOR 0.81, 95% CI: 0.79, 0.93), low birthweight (adjOR 0.82, 95% CI: 0.76, 0.89), and neonatal unit admission (adjOR 0.87, 95% CI: 0.82, 0.93) compared to non-drinkers. Consumption of >4 units of alcohol per week was associated with non-significant increases in adverse outcomes. The risk of adverse perinatal outcomes increased with additional units consumed, particularly among smokers.

Conclusions: This study found no evidence of adverse perinatal outcomes associated with consumption of 1-4 units of alcohol per week. However, the risk of adverse perinatal outcomes increased as consumption levels increased, especially when combined with smoking. While these findings suggest minimal

risk from consuming 1-4 units of alcohol per week, they support public health messaging to limit alcohol consumption during pregnancy to the lowest possible amount.

3.2 Introduction:

This chapter investigates the association between differing levels of alcohol consumption during pregnancy and perinatal outcomes. While alcohol consumption at high volumes during pregnancy is associated with clear harm, women have historically received mixed advice regarding whether they should abstain completely or limit consumption to no more than 4 units of alcohol per week during pregnancy. The UK Chief Medical Officer's (CMO) advice is heavily based on the precautionary principle and has remained unchanged since 2016:

> "If you are pregnant or think you could become pregnant, the safest approach is not to drink alcohol at all" [167].

This diverges from previous recommendations that permitted consumption of up to 4 units of alcohol per week during pregnancy, or up to 14 units of alcohol per week outside pregnancy[163,197,198]. Previous systematic reviews have failed to demonstrate whether there is a threshold where alcohol is harmful and whether alcohol effects are linear[104,112].

There is overwhelming evidence that alcohol consumption at high volumes during pregnancy is harmful to offspring[73,164,199,200]. Alcohol is neurotoxic and leads to direct and indirect harm to the developing fetus[201]. Alcohol consumption in pregnancy is associated with Fetal Alcohol Spectrum Disorder (FASD), characterised by impairments across multiple domains: motor development, cognition, communication, academic achievement, memory processing, attention, executive functions, and affect regulation[202]. There is no established lower limit for the risk of having an offspring with FASD, but risk increases with higher alcohol consumption during pregnancy[199].

In addition to FASD, alcohol consumption is associated with adverse perinatal outcomes, including prematurity, low birthweight, Small for Gestational Age (SGA), and pregnancy loss (stillbirths, spontaneous abortions, miscarriage) [88,95,96,98,99,102,103,203]. A population-based study of 1.2 million births from Denmark demonstrated that heavy drinkers have an increase in risk of having offspring with SGA (adjOR 2.20 [95% CI: 1.97, 2.45]) and prematurity (adjOR 1.32 [95% CI: 1.19, 1.46])[103]. However, this study only compared heavy

drinkers (0.4% of women) to non-drinkers, thus providing limited evidence for the effects of small amounts of maternal consumption. A 2011 meta-analysis of 36 studies examined alcohol consumption in a more representative sample, finding limited evidence of harm specific to alcohol, especially at low levels[102]. However, a dose effect was observed, with an increased risk for low birthweight and SGA at one drink per day, and for preterm birth at 1.5 drinks per day. Studies investigating pregnancy loss (stillbirths and spontaneous abortions) report a stronger association between drinking and adverse outcomes. A meta-analysis of 231,000 pregnancies found that alcohol consumption increases the risk of miscarriage (OR 1.19, 95% CI 1.12, 1.28) compared to abstinence, and that every additional drink (from one to five units per week) was associated with a six percent increase in miscarriage risk (OR 1.06, 95% CI 1.01, 1.10) [96]. These estimates need to be interpreted with caution as this meta-analysis included studies with different methodologies (prospective and retrospective), and with variable levels of adjustments for confounders. A failure to fully adjust for confounders such as deprivation and smoking, could impact effect estimates significantly[104,112]. Of particular concern is the association between smoking and drinking, as they often co-occur, and both are linked to adverse perinatal outcomes. Their combined effects may influence observed associations, but this has been poorly studied[7,93].

To provide further information to women about the risk of alcohol consumption at low levels, researchers at The University of Bristol conducted two reviews on the effects of low alcohol intake on perinatal outcomes[104,112]. The first meta-analysis directly compared up to four units of alcohol per week (32g of ethanol) to no alcohol consumption in prospective cohort and quasi-experimental studies[104]. This review was published in 2017 and included 26 studies demonstrating an increased risk of SGA (adjOR 1.08, 95% CI: 1.02 to 1.14; 7 studies) in women who drank up to four units of alcohol per week. In their discussion, the authors noted the limited number of prospective studies specifically addressing the question of whether up to 4 units of alcohol per week has any causal effect (adverse or beneficial) on perinatal outcomes. The authors concluded that guidance should explain the paucity of evidence. The second review was published in 2020 and consisted of a systematic review of RCTs and quasi-experimental studies, concluding that there is a likely causal detrimental

role of prenatal alcohol exposure on cognitive outcomes, plus weaker evidence for a role in low birth weight, thus confirming results seen in observational studies[112]. These two systematic reviews provide further evidence that the precautionary approach is merited but could not provide evidence on whether the effect of alcohol exposure is linear, or whether there is a threshold for harm when drinking in pregnancy.

This chapter uses a whole-population dataset with contemporaneous recording of alcohol consumption and confounders to further determine: 1) if consumption of 1-4 units of alcohol per week during pregnancy is associated with perinatal harm, and 2) if perinatal harm demonstrates a dose-related effect, and 3) if there is a threshold at which alcohol consumption during pregnancy leads to perinatal harm.

3.3 Methods

Four Scotland-wide administrative databases were linked: Scottish Morbidity Record-2 (SMR02), Scottish Morbidity Record-1 (SMR01), Scottish Birth Record (SBR), and National Records of Scotland (NRS). The SMR02 records all maternity inpatient and day case admissions, including maternal and infant characteristics, maternal alcohol consumption, and pregnancy outcomes. The SMR01 records all inpatient and day-case admissions. Both record diagnoses according to the International Classification of Diseases 9th or 10th Revision (ICD-9/ICD-10) [176,177]. SBR records all neonatal care, and the NRS registers all births, stillbirths, and infant deaths in Scotland. Public Health Scotland reported 99% completeness for SMR02 in 2020/21[178]. Data governance procedures were approved by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care (1920-0097) and NHS Greater Glasgow and Clyde Research and Development (GN20PH059). The NHS Scotland electronic Data Research and Innovation Service (eDRIS) linked and de-identified data prior to analysis. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[204].

3.3.1 Definition of Alcohol Consumption

Maternal alcohol consumption was self-reported and defined as the average number of units consumed per week in the preceding 3-month period. In the UK, one unit equals 8g of pure alcohol, equivalent to approximately half a pint of ordinary strength beer (3.5% ABV) or a small glass (125ml) of wine (12% ABV) [14]. Women who reported consuming no alcohol were recorded as ‘non-drinkers”. Women who consumed less than one but more than zero units per week were recorded as having consumed one unit. Women who consumed alcohol were categorised into those who consumed 1-4 units of alcohol per week or >4 units of alcohol per week. The 4 units of alcohol per week threshold was defined a priori and represents the previous upper limit for alcohol consumption in pregnancy[173].

3.3.2 Inclusion criteria

All registered singleton pregnancies in Scotland between 1st of April 2013 and 31st December 2019 were included in this study. The seven-year study period reflects a time with detailed recording of alcohol consumption at the initiation of antenatal care. All pregnant women in Scotland are routinely provided with antenatal care, which is free at the point of access. For over 75% of patients, obstetric care is initiated in the first trimester[179].

3.3.3 Maternal data and confounding variables

Maternal characteristics and prior obstetric history were obtained. The confounding variables included maternal age and body mass index (BMI), calculated from booking weight and height measurements. Drug misuse was defined as use of illegal drugs or receipt of opioid replacement therapy. Socioeconomic status was measured using the Scottish Index of Multiple Deprivation (SIMD) derived from the area of residence at the time of delivery. SIMD is a score calculated from 33 indicators covering seven domains (income, employment, health, education, access to services, crime, and housing) [205]. SIMD was stratified into quintiles, with quintile one being allocated to regions with the highest indicators of deprivation and quintile five the least deprivation indicators. Ethnicity was classified according to the 2011 Scotland census[181]. Pre-eclampsia was defined as a recording of pre-eclampsia in SMR02. Smoking status was based on self-classification at the initiation of antenatal care and comprised current smokers or non-smokers (never/former smokers). As smoking and alcohol consumption in pregnancy are collinear, this was analysed separately in strata of women who smoked and women who did not smoke[93,206].

3.3.4 Perinatal outcomes

Linked offspring outcomes were obtained from SMR02, SBR, and NRS. These included:

- Preterm birth (<37 weeks of estimated gestation)
- Spontaneous preterm birth (<37 weeks of estimated gestation and not born by induction of labour or elective caesarean section)

- Small for gestational age (SGA, birth weight below the 10th centile)
- Very small for gestational age (vSGA, birth weight below the 3rd centile)
- Low birth weights (less than 2500 grams)
- Neonatal care unit admission
- Stillbirth (intrauterine death after 24 weeks of estimated gestation)

3.3.5 Statistical analyses

As this study analysed the entire Scottish population of pregnant women during the study period, formal sample size calculations were not required. Baseline characteristics were summarised using median values with interquartile ranges for continuous variables and frequencies with percentages for categorical variables. Between-group comparisons were conducted using Wilcoxon Rank Sum tests for continuous variables and Pearson's Chi-squared tests for categorical variables.

To address missing data, we performed multiple imputation using chained equations (MICE) to create 10 imputed datasets. Predictive Mean Matching (PMM) methodology was employed to maintain the distributional characteristics of the variables[207].

The primary analysis employed multivariable logistic regression models with cluster robust sandwich estimators within a generalised estimation equation framework. To account for women with multiple pregnancies during the study period, we clustered analyses on the maternal identifier[208]. All models were adjusted for potential confounders including maternal age, BMI, ethnicity, parity, socioeconomic status (SIMD), smoking status, drug misuse, and pre-eclampsia. We calculated adjusted odds ratios (OR) comparing three groups: non-drinkers, 1-4 units of alcohol per week and >4 units of alcohol per week.

Dose-response analysis was performed to examine the potential dose-response relationships. We modelled alcohol consumption as a continuous variable using generalized additive models with cubic spline functions. This approach allowed for non-linear relationships between alcohol consumption and outcomes. Thin plate spline functions were fitted using restricted maximum

likelihood (REML). We calculated adjusted odds ratios for the risk of each outcome per additional unit of alcohol consumed.

We conducted several sensitivity analyses to test the robustness of our findings:

- Analysis of complete cases (non-imputed data)
- Unadjusted analyses to assess the impact of our confounder selection
- Stratified analyses by smoking status to examine potential effect modification

All analyses were performed using R software (version 4.4.1) [184].

3.4 Results

This study included 346,360 women who initiated antenatal care in Scotland over a seven-year period (April 2013 - December 2019). Among these pregnancies, 316,645 (92.8%) were singleton births with documented alcohol consumption status, establishing our primary study cohort (Figure 3-1). Comparing women with and without alcohol consumption data revealed important demographic differences. Women with missing alcohol data demonstrated higher risk indicators across multiple domains: higher rates of smoking (22% versus 17%), increased drug use (8.6% versus 1.7%), and higher likelihood of residing in areas of highest deprivation (SIMD 1: 33% versus 22%) (Table 3-1). These systematic differences suggest that women with missing alcohol data may represent a population with increased maternal risk factors, thus requiring additional attention in future research as well as in clinical practice.

Analysis of maternal characteristics revealed distinct demographic patterns across alcohol consumption groups. Women who reported consumption of 1-4 units per week generally demonstrated more favourable health and socioeconomic indicators compared to non-drinkers. These women had lower rates of smoking (12% versus 17%) and drug use (1.3% versus 1.7%), were older (median age 31years versus 30 years) and had lower BMI (24.9kg/m^2 versus 25.2kg/m^2). However, this group was less ethnically diverse (white: 97% versus 92%), demonstrating the known cultural differences in alcohol consumption patterns.

In contrast, women consuming greater than 4 units of alcohol per week showed markers of increased vulnerability compared to low-level drinkers. This higher-consumption group had nearly double the smoking rate (21% versus 12%), twice the rate of drug use (2.6% versus 1.3%), higher BMI (25.3 kg/m^2 versus 24.9 kg/m^2) and were more likely to live in areas of highest deprivation (SIMD 1: 26% versus 22%). These patterns suggest that higher alcohol consumption clusters with other risk factors that may independently affect perinatal outcomes (Table 3-2).

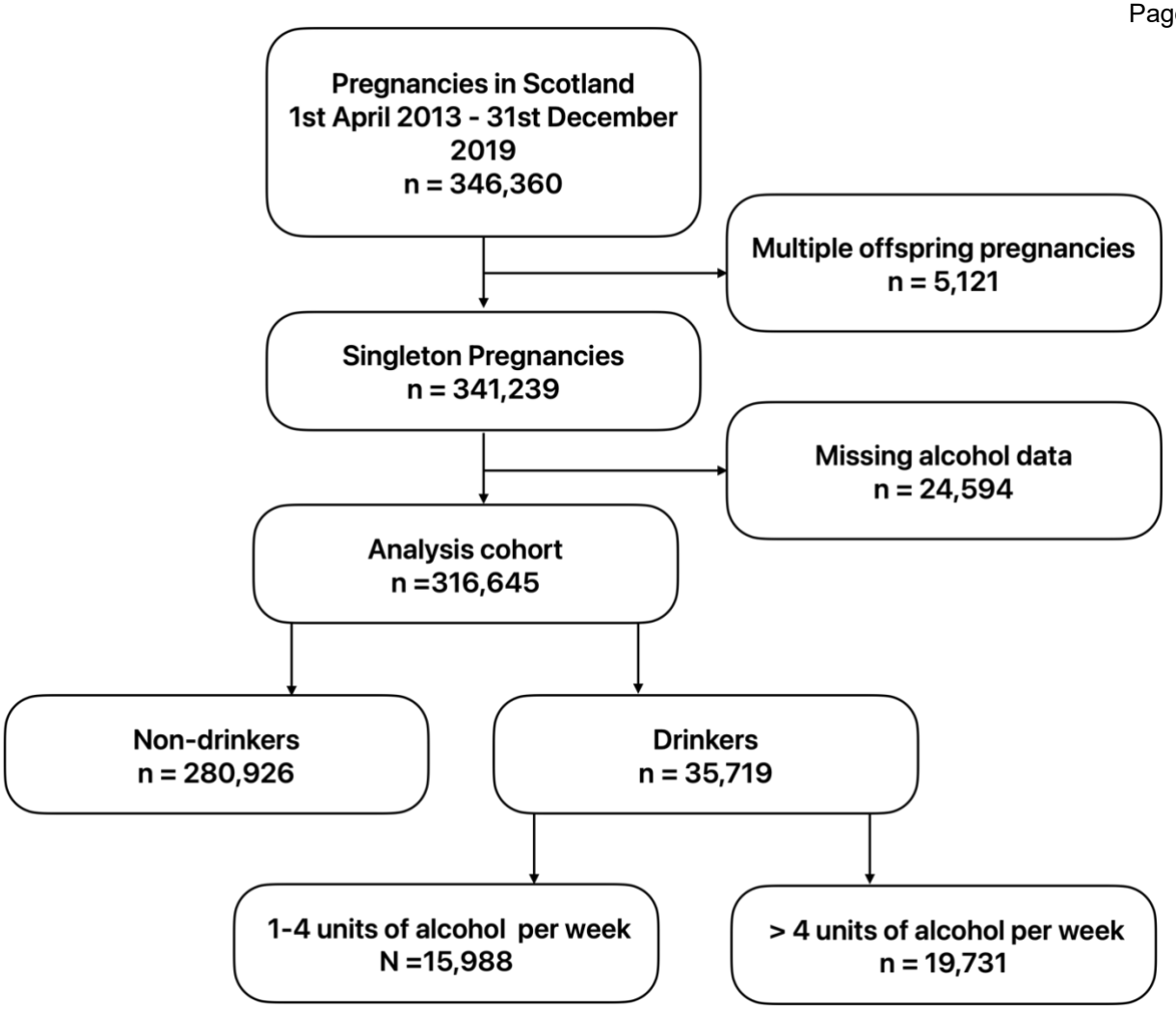


Figure 3-1: CONSORT flow for analysis

Characteristic	Known alcohol intake, N = 316,645[1]	Unknown alcohol intake, N = 24,594[1]	p-value[2]
Maternal age, years (IQR)	30.00 (26.00, 34.00)	30.00 (25.00, 34.00)	<0.001
Maternal BMI, Kg/m^2 (IQR)	25.15 (22.21, 29.41)	26.06 (22.72, 31.22)	<0.001
missing	6,216	9,099	
Ethnicity, n (%)			0.005
Black	3,734 (1.5%)	271 (1.5%)	
Mixed	1,531 (0.6%)	81 (0.5%)	
White	232,298 (92%)	16,611 (93%)	
Other	2,895 (1.2%)	238 (1.3%)	
Asian	10,927 (4.3%)	727 (4.1%)	
missing	65,260	6,666	
SIMD Quintile, n (%)			<0.001
01	77,874 (25%)	8,200 (33%)	
02	67,544 (21%)	4,855 (20%)	
03	57,520 (18%)	3,991 (16%)	
04	59,051 (19%)	4,392 (18%)	
05	54,087 (17%)	3,091 (13%)	
missing	569	65	
Smoker during pregnancy, n(%)	51,447 (17%)	4,049 (22%)	<0.001
missing	7,201	6,307	
Drug misuse, n(%)	4,630 (1.7%)	333 (8.6%)	<0.001
missing	42,737	20,744	
Year, n (%)			<0.001
2013	37,119 (12%)	2,901 (12%)	
2014	50,072 (16%)	3,794 (15%)	
2015	49,413 (16%)	2,879 (12%)	
2016	48,311 (15%)	2,684 (11%)	
2017	45,127 (14%)	4,700 (19%)	
2018	44,700 (14%)	3,503 (14%)	
2019	41,903 (13%)	4,133 (17%)	

1) Median (IQR); n (%)

2) Wilcoxon rank sum test; Pearson's Chi-squared test

Table 3-1: Maternal characteristics of women who booked pregnancies between April 2013 and December 2019, by reported alcohol intake

Characteristic	Non-drinker, N = 280,926[1]	1-4 units alcohol of per week, n = 15,988[1]	> 4 units alcohol of per week, n = 19,731[1]	1-4 units alcohol of per week versus Non-drinker p-value[2]	> 4 units alcohol of per week versus 1-4 units alcohol of per week p-value[2]
Maternal age, years (IQR)	30.00 (26.00, 34.00)	31.00 (27.00, 34.00)	31.00 (26.00, 34.00)	<0.001	<0.001
Maternal BMI, Kg/m^2 (IQR)	25.16 (22.21, 29.59)	24.91 (22.07, 29.03)	25.28 (22.41, 29.38)	<0.001	<0.001
missing	5,788	91	337		
Ethnicity, n (%)				<0.001	<0.001
Black	3,593 (1.6%)	85 (0.7%)	56 (0.4%)		
Mixed	1,413 (0.6%)	64 (0.5%)	54 (0.3%)		
White	204,339 (92%)	12,251 (97%)	15,708 (98%)		
Other	2,792 (1.3%)	59 (0.5%)	44 (0.3%)		
Asian	10,606 (4.8%)	195 (1.5%)	126 (0.8%)		
missing	58,183	3,334	3,743		
SIMD Quintile, n (%)				<0.001	<0.001
01	69,296 (25%)	3,443 (22%)	5,135 (26%)		
02	60,357 (22%)	3,076 (19%)	4,111 (21%)		
03	51,245 (18%)	2,955 (19%)	3,320 (17%)		
04	52,548 (19%)	3,124 (20%)	3,379 (17%)		
05	46,949 (17%)	3,367 (21%)	3,771 (19%)		
missing	531	23	15		
Smoker during pregnancy, n(%)	45,643 (17%)	1,898 (12%)	3,906 (21%)	<0.001	<0.001
missing	6,228	216	757		
Drug misuse, n(%)	3,964 (1.6%)	201 (1.3%)	465 (2.6%)	0.004	<0.001
missing	39,861	962	1,914		
Year, n (%)				<0.001	<0.001
2013	34,770 (12%)	1,040 (6.5%)	1,309 (6.6%)		
2014	46,517 (17%)	1,475 (9.2%)	2,080 (11%)		
2015	46,020 (16%)	1,471 (9.2%)	1,922 (9.7%)		
2016	44,851 (16%)	1,535 (9.6%)	1,925 (9.8%)		
2017	41,598 (15%)	1,533 (9.6%)	1,996 (10%)		
2018	37,342 (13%)	3,341 (21%)	4,017 (20%)		
2019	29,828 (11%)	5,593 (35%)	6,482 (33%)		

1) Median (IQR); n (%) 2) Wilcoxon rank sum test; Pearson's Chi-squared test

Table 3-2: Maternal characteristics of women who booked pregnancies between April 2013 and December 2019 by alcohol intake

3.4.1 Perinatal outcomes

Analysis of perinatal outcomes revealed several unexpected patterns in relation to maternal alcohol consumption (Table 3-3). Women who consumed 1-4 units alcohol of per week demonstrated more favourable outcomes compared to non-drinkers, with reduced risk of low birth weight (adjOR 0.82, 95% CI: 0.76, 0.89). This pattern extended to gestational outcomes, where low-level drinkers showed lower rates of both overall prematurity (adjOR 0.81, 95% CI: 0.79, 0.93) and spontaneous premature births (adjOR 0.87, 95% CI: 0.79, 0.93). Additionally, their offspring were less likely to require neonatal unit admission (adjOR 0.87, 95% CI: 0.82, 0.93).

When examining women who consumed greater than 4 units alcohol per week, there was no statistically significant differences in rates of SGA, vSGA, or low birth weight compared to those who consumed 1-4 units alcohol of per week. Similarly, there were no significant differences in prematurity or neonatal unit admission rates between these groups.

Analysis of stillbirths showed no significant differences between any of the groups, though interpretation of this finding requires caution given the relative rarity of these events.

	Event rate[1]			1-4 units alcohol of per week versus non-drinker[2]		> 4 units alcohol of per week versus 1-4 units alcohol of per week [2]	
	Non-drinker, n = 280,926[1]	1-4 units alcohol of per week, n = 15,988[1]	> 4 units alcohol of per week, n = 19,731[1]	Unadjusted	Adjusted[3]	Unadjusted	Adjusted[3]
Small for Gestational age	25,730 / 280,322 (9.18%) [9.1%, 9.3%]	1,249 / 15,978 (7.82%) [7.4%, 8.2%]	1,751 / 19,724 (8.88%) [8.5%, 9.3%]	0.84 (0.79, 0.89) 0.001	0.96 (0.90, 1.02) 0.2	1.15 (1.06, 1.24) <0.001	1.04 (0.96, 1.12) 0.3
Very Small for Gestational age	5,771 / 280,322 (2.06%) [2.0%, 2.1%]	250 / 15,978 (1.56%) [1.4%, 1.8%]	410 / 19,724 (2.08%) [1.9%, 2.3%]	0.76 (0.66, 0.86) <0.001	0.91 (0.80, 1.03) 0.14	1.34 (1.14, 1.57) <0.001	1.15 (0.98, 1.35) 0.086
Low Birth weight	15,415 / 280,322 (5.50%) [5.4%, 5.6%]	690 / 15,978 (4.32%) [4.0%, 4.6%]	1,024 / 19,724 (5.19%) [4.9%, 5.5%]	0.77 (0.72, 0.84) <0.001	0.82 (0.76, 0.89) <0.001	1.21 (1.10, 1.34) <0.001	1.08 (0.97, 1.19) 0.2
Premature	18,403 / 280,073 (6.57%) [6.5%, 6.7%]	863 / 15,971 (5.40%) [5.1%, 5.8%]	1,172 / 19,706 (5.95%) [5.6%, 6.3%]	0.81 (0.76, 0.87) <0.001	0.81 (0.76, 0.87) <0.001	1.11 (1.01, 1.21) 0.024	1.04 (0.95, 1.14) 0.4
Spontaneous Premature	12,266 / 273,822 (4.48%) [4.4%, 4.6%]	629 / 15,761 (3.99%) [3.7%, 4.3%]	885 / 19,454 (4.55%) [4.3%, 4.9%]	0.85 (0.78, 0.91) <0.001	0.86 (0.79, 0.93) <0.001	1.14 (1.03, 1.26) 0.011	1.07 (0.97, 1.18) 0.2
Neonatal care unit admission	22,210 / 269,687 (8.24%) [8.1%, 8.3%]	1,057 / 14,863 (7.11%) [6.7%, 7.5%]	1,479 / 18,593 (7.95%) [7.6%, 8.4%]	0.85 (0.80, 0.91) <0.001	0.87 (0.82, 0.93) <0.001	1.12 (1.04, 1.21) 0.005	1.05 (0.96, 1.13) 0.3
Stillbirth	929 / 280,926 (0.33%) [0.31%, 0.35%]	44 / 15,988 (0.28%) [0.20%, 0.37%]	54 / 19,731 (0.27%) [0.21%, 0.36%]	0.83 (0.61, 1.13) 0.2	0.93 (0.69, 1.27) 0.7	0.99 (0.67, 1.48) >0.9	0.83 (0.55, 1.24) 0.4

[1] Incidence (percentage) [95% Confidence interval]

[2] Odd ratio (95% Confidence interval), P value

[3]Adjustment: Age, BMI, drug use, SIMD, Ethnicity, Smoking, Pre-eclampsia.

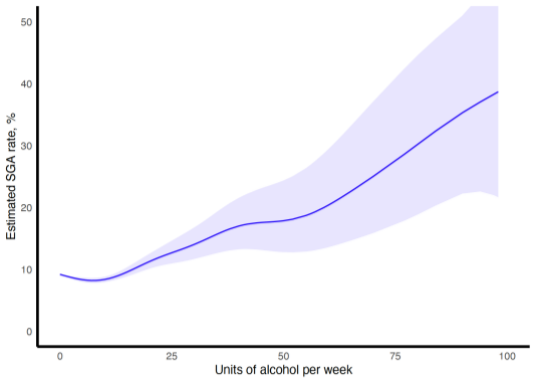
Table 3-3: Perinatal outcomes of booked pregnancies between April 2013 and December 2019 by alcohol intake

3.4.2 Dose related effect

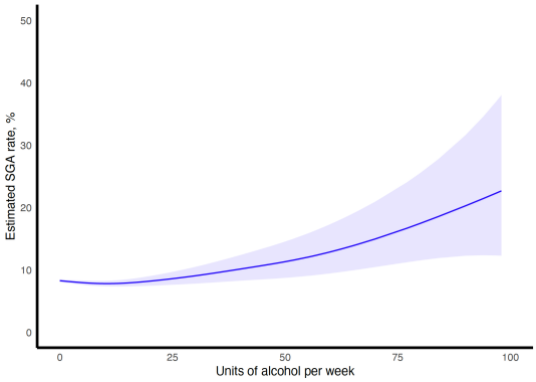
The risk of adverse perinatal outcomes increased with higher levels of alcohol consumption. There was an increased risk of SGA, vSGA, low birth weight, prematurity, spontaneous prematurity, and admission to neonatal unit (Figure 3-2 and Table 3-4).

Growth-related birth outcomes (SGA and birth weight) demonstrated an exponential relationship with alcohol consumption, while outcomes related to gestational age and neonatal unit admission exhibited a sigmoid relationship (Figure 3-2).

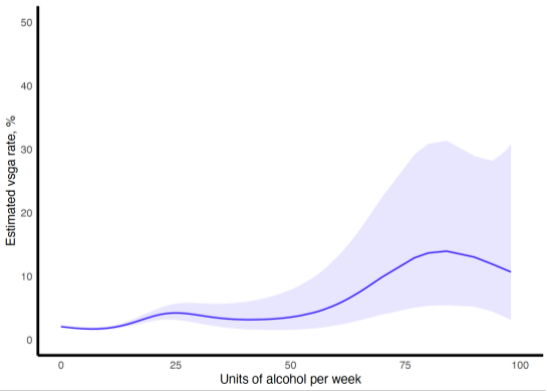
Analysis of stillbirths revealed no significant dose effect, though confidence intervals were wide due to low incidence (Figure 3-2 and Table 3-4).



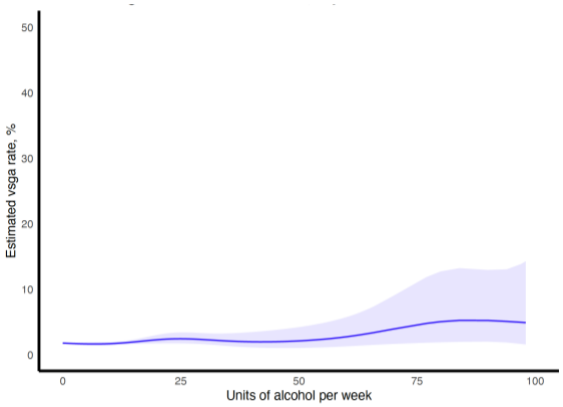
a) Estimated SGA rate over alcohol intake – unadjusted



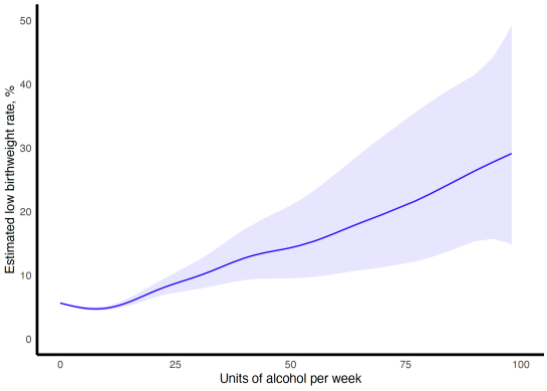
b) Estimated SGA rate over alcohol intake – adjusted[1]



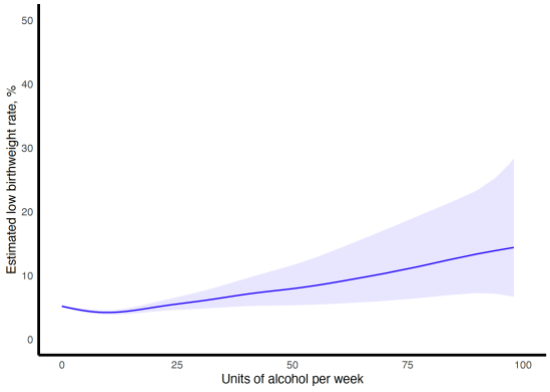
c) Estimated vSGA rate over alcohol intake – unadjusted



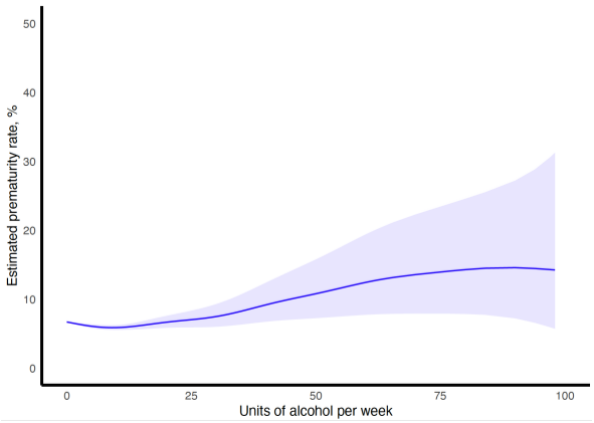
d) Estimated vSGA rate over alcohol intake – adjusted[1]



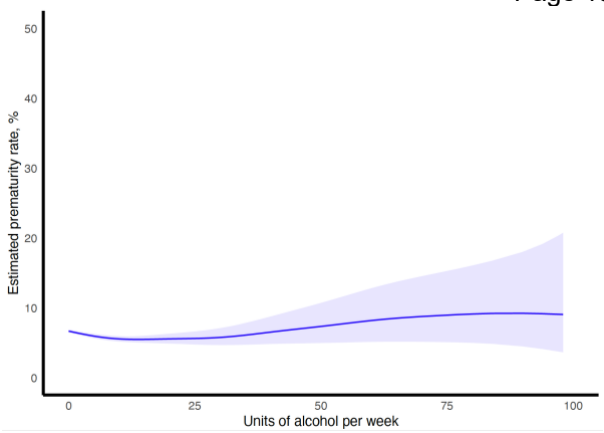
e) Estimated low birthweight rate over alcohol intake – unadjusted



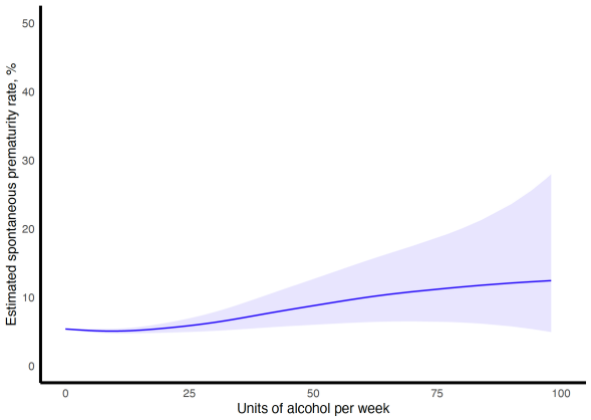
f) Estimated low birthweight rate over alcohol intake – adjusted[1]



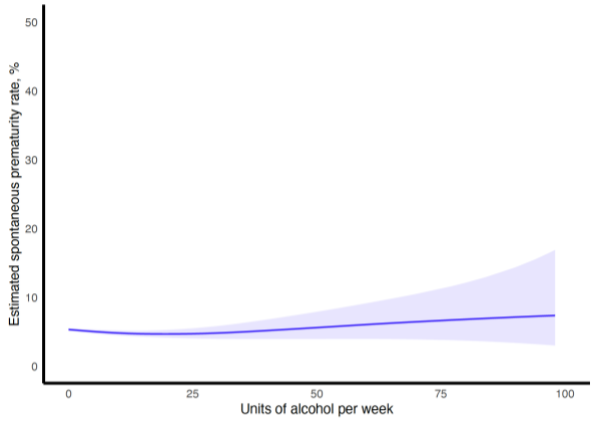
g) Estimated prematurity rate over alcohol intake – unadjusted



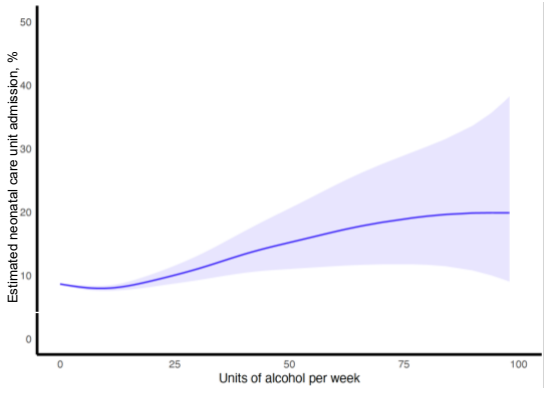
h) Estimated prematurity rate over alcohol intake – adjusted[1]



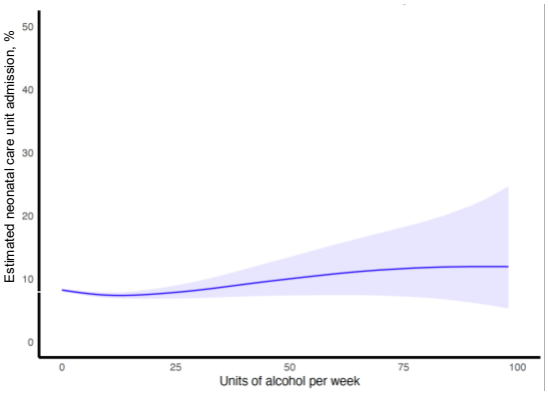
i) Estimated spontaneous prematurity rate over alcohol intake – unadjusted



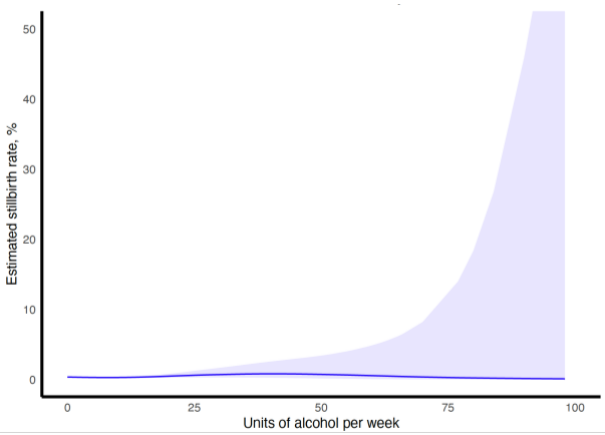
j) Estimated spontaneous prematurity rate over alcohol intake – adjusted[1]



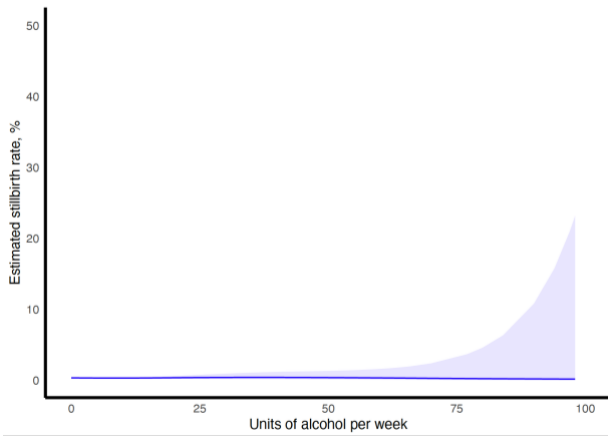
h: Estimated admission to Neonatal care unit admission over alcohol intake – unadjusted



i) Estimated admission to Neonatal care unit rate over alcohol intake – adjusted[1]



j: Estimated stillbirth rate over alcohol intake – unadjusted



k: Estimated stillbirth rate over alcohol intake – adjusted[1]

1) Adjustment: Age, BMI, Drug use, SMID, Ethnicity, Smoking, Pre-eclampsia.

Figure 3-2: Estimated perinatal outcomes by reported consumption, adjusted.

Characteristic	Unadjusted[1]	Adjusted[1,2]
Small for gestational age	1.02 (1.02, 1.03) <0.001	1.02 (1.01, 1.02) <0.001
Very small for gestational age	1.03 (1.02, 1.04) <0.001	1.01 (1.00, 1.02) 0.10
Low birth weight	1.03 (1.02, 1.03) <0.001	1.02 (1.01, 1.03), <0.001
Premature	1.01 (1.01, 1.02) <0.001	1.01 (1.00, 1.02) <0.034
Spontaneous premature	1.01 (1.01, 1.02) <0.001	1.01 (1.00, 1.02) 0.036
Neonatal care unit admission	1.02 (1.01, 1.02) <0.001	1.01 (1.00, 1.02) 0.008
Stillbirth	1.02 (1.01, 1.04) 0.008	0.99 (0.96, 1.02) 0.06

1) Odd ratio (95% Confidence Interval), P value,

2) Adjustments for Age, BMI, drug use, SMID, Ethnicity, Smoking, Pre-eclampsia.

Table 3-4: Change in odds of perinatal outcomes per additional unit of alcohol reported in booked pregnancies who reported consumption of alcohol

3.4.3 Sensitivity analysis

Sensitivity analysis conducted on non-imputed data yielded similar results (Table 3-5). Stratified analysis of smokers and non-smokers demonstrated the same direction of effect as the non-stratified analysis (Tables 3-3 and 3-5). Women who consumed 1-4 units of alcohol per week had more favourable outcomes when compared to both non-drinkers and those who consumed more than 4 units alcohol per week. When outcomes were plotted by units of alcohol consumption, smokers demonstrated consistently higher risks of adverse outcomes, and these risks increased at lower levels of consumption.

Characteristic	1-4 units alcohol of per week versus non-drinkers[1]		Alcohol greater than 4 units versus 1-4 units alcohol of per week [1]	
	Unadjusted	Adjusted[2]	Unadjusted	Adjusted[2]
Small for Gestational age	0.84	0.94	1.15	1.07
	(0.79, 0.89)	(0.88, 1.01)	(1.07, 1.24)	(0.97, 1.17)
	<0.001	0.10	<0.001	0.2
Very Small for Gestational age	0.75	0.93	1.34	1.17
	(0.66, 0.85)	(0.79, 1.07)	(1.15, 1.58)	(0.97, 1.41)
	<0.001	0.3	<0.001	0.11
Low Birth weight	0.77	0.82	1.21	1.07
	(0.71, 0.83)	(0.74, 0.90)	(1.10, 1.34)	(0.95, 1.21)
	<0.001	<0.001	<0.001	0.2
Premature	0.81	0.86	1.11	1.06
	(0.76, 0.87)	(0.79, 0.93)	(1.01, 1.21)	(0.94, 1.20)
	<0.001	<0.001	0.028	0.6
Spontaneous Premature	0.89	0.92	1.15	1.02
	(0.82, 0.96)	(0.84, 1.01)	(1.03, 1.27)	(0.93, 1.13)
	0.004	0.094	0.011	0.4
Neonatal care unit admission	0.85	0.90	1.13	1.02
	(0.80, 0.91)	(0.83, 0.97)	(1.04, 1.23)	(0.93, 1.13)
	<0.001	0.005	0.004	0.7
Stillbirth	0.83	1.01	0.99	0.78
	(0.61, 1.11)	(0.68, 1.43)	(0.67, 1.49)	(0.48, 1.28)
	0.2	>0.9	>0.9	0.3

1 - Odd ratio (95% Confidence Interval), P value,

2 – Adjustment for: Age, BMI, drug use, SMID, Ethnicity, Smoking, Pre-eclampsia.

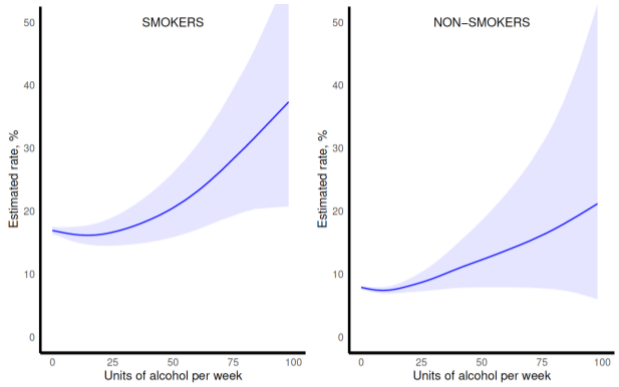
Table 3-5: Perinatal outcomes of booked pregnancies between April 2013 and December 2019 by alcohol intake non-imputed data

Characteristic	Non-smoker		Smokers	
	1-4 units of alcohol per week Versus non-drinker[1] Adjusted[2]	> 4 units of alcohol per week Versus 1-4 units of alcohol per weeek[1] Adjusted[2]	1-4 units of alcohol per week versus non-drinker[1] Adjusted[2]	> 4 units of alcohol per wekk versus Alcohol 1-4 units[1] Adjusted[2]
Small for Gestational age	0.94	1.08	1.04	0.93
	(0.88, 1.01)	(0.98, 1.18)	(0.91, 1.17)	(0.80, 1.09)
	0.089	0.11	0.6	0.4
Very Small for Gestational age	0.92	1.04	0.92	1.29
	(0.79, 1.07)	(0.85, 1.28)	(0.73, 1.18)	(0.97, 1.70)
	0.3	0.7	0.5	0.077
Low Birth weight	0.83	1.04	0.76	1.15
	(0.76, 0.91)	(0.92, 1.18)	(0.65, 0.90)	(0.95, 1.40)
	<0.001	0.5	0.001	0.15
Premature	0.81	1.04	0.81	0.99
	(0.75, 0.88)	(0.93, 1.15)	(0.68, 0.95)	(0.81, 1.21)
	<0.001	0.5	0.012	>0.9
Spontaneous Premature	0.86	1.06	0.79	1.09
	(0.79, 0.95)	(0.94, 1.19)	(0.65, 0.95)	(0.87, 1.37)
	0.001	0.3	0.013	0.4
Neonatal careUnit admission	0.85	1.05	0.96	0.97
	(0.80, 0.92)	(0.96, 1.15)	(0.82, 1.11)	(0.81, 1.16)
	<0.001	0.3	0.6	0.7
Stillbirth	0.80	0.83	1.57	0.71
	(0.54, 1.19)	(0.48, 1.46)	(0.91, 2.72)	(0.36, 1.40)
	0.3	0.5	0.11	0.3

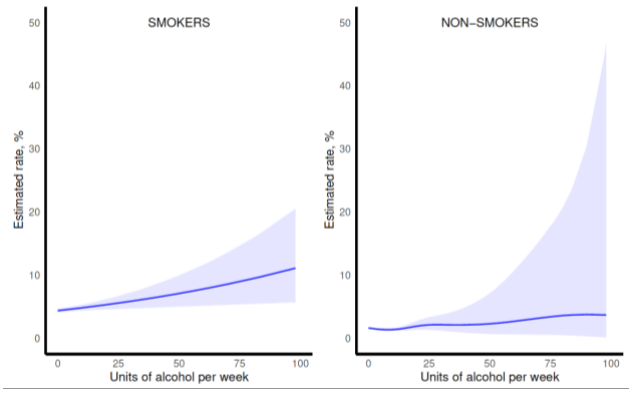
1) Odd ratio (95% Confidence Interval), P value,

2) Adjustment for: Age, BMI, drug use, SMID, Ethnicity, Pre-eclampsia.

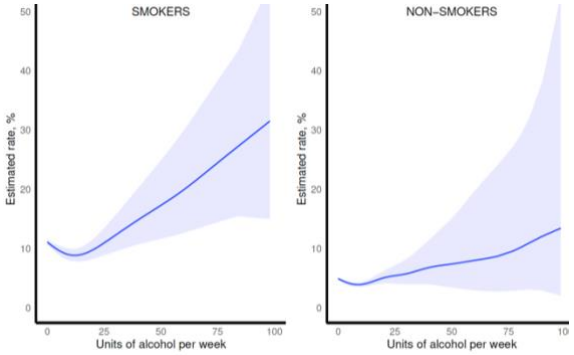
Table 3-6: Perinatal outcomes of booked pregnancies between April 2013 and December 2019 by alcohol intake stratified by smoking status



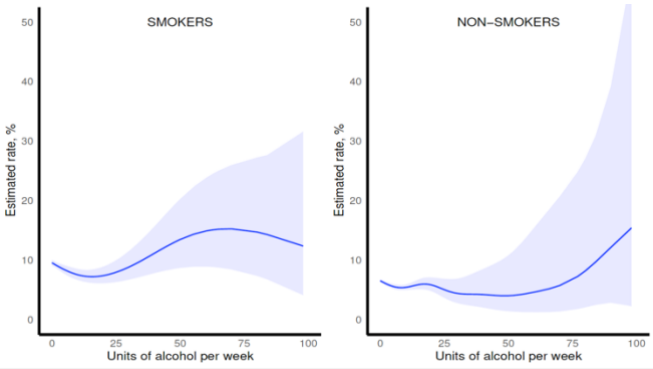
b) Estimated SGA rate over alcohol intake by smoking status



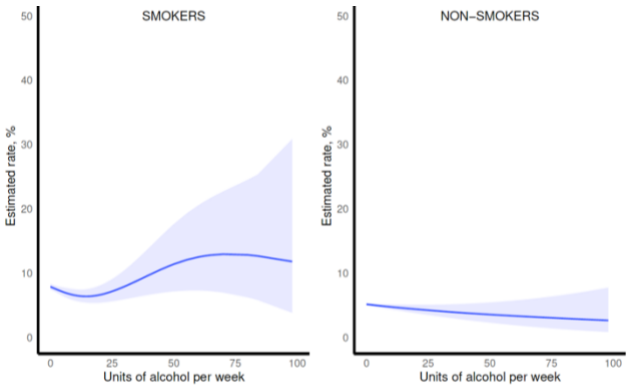
b) Estimated vSGA rate over alcohol intake by smoking status



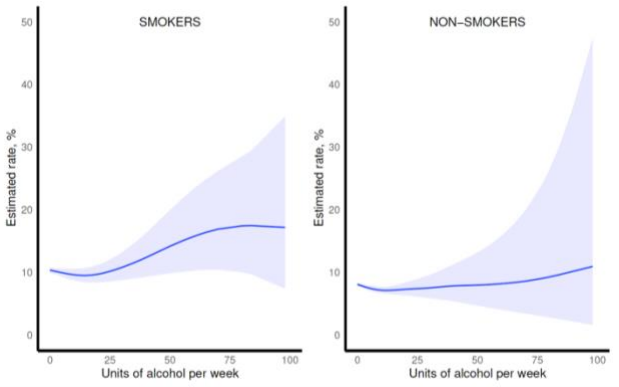
c) Estimated low birth weight rate over alcohol intake by smoking status



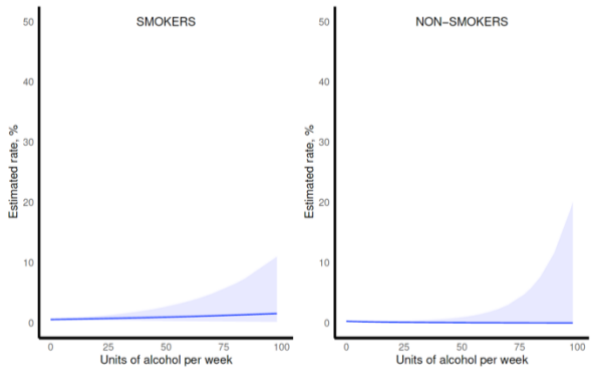
d) Estimated prematurity rate over alcohol intake by smoking status



e) Estimated spontaneous prematurity rate over alcohol intake by smoking status



f) Estimated requirement for neonatal unit rate over alcohol intake by smoking status



Estimated stillbirth rate over alcohol intake by smoking status

Adjustment for: Age, BMI, drug use, SMID, Ethnicity, Pre-eclampsia.
Figure 3-3: Adjusted estimates of perinatal outcomes by smoking status.

3.5 Discussion

This study demonstrates no clear evidence of adverse perinatal outcomes associated with consuming 1-4 units of alcohol per week in early pregnancy compared to no alcohol consumption. As alcohol consumption increases, the risk of adverse outcomes also increases. Furthermore, the study reveals that smoking combined with alcohol consumption appears to exert a synergistic effect on adverse outcomes, underscoring the public health message to abstain from smoking during pregnancy.

This research addresses limitations of previous studies which did not investigate dose effects or adequately control for confounding factors. This study examined data from an entire country with a high prevalence of alcohol consumption over multiple years, incorporating estimated weekly intake measurements. Through comprehensive data linkage and careful control of confounders, distinct patterns in maternal characteristics across different levels of alcohol consumption have emerged.

Women who consumed 1-4 units of alcohol per week demonstrated more favourable characteristics compared to non-drinkers, including fewer indices of deprivation and lower smoking rates. This is in keeping with the “healthy drinker” hypothesis where people who consume low to moderate levels of alcohol also possess other favourable characteristics such as higher socioeconomic status. Conversely, adverse factors were more prevalent among women who consumed >4 units of alcohol per week. This group showed almost double the prevalence of drug misuse (2.6% versus 1.3%), higher smoking rates (21% versus 12%), and increased likelihood of residing in areas of Scotland with the 20% highest levels of deprivation (26% versus 22%).

Prior research by Mamluk et al. indicated potential harm from up to 4 units of alcohol per week but was unable to demonstrate a dose effect or fully control for confounding factors[104, 112]. The two meta-analyses published by this group indicated that consumption of up to 4 units of alcohol per week was associated with small for gestational age, adverse cognitive outcomes, and low birth weight. This study builds upon these findings by demonstrating that while alcohol consumption may be associated with some adverse birth outcomes, the

relationship is more nuanced when additional factors are considered. The analysis reveals that risk increases with alcohol dose, but when a greater number of confounders, such as smoking and deprivation, are adjusted for, there is greater attenuation of alcohol-associated harm.

This study has several strengths, including comprehensive data coverage, enquiry about dose of alcohol, and linkage of maternal and offspring outcomes. The use of health records from the entire Scottish population eliminates risk of sampling bias, recall biases and loss to follow-up, which can affect studies such as the Growing Up in Scotland and Scottish Feeding Survey project that enquire about alcohol post-partum[15,16,39,40]. A further methodological strength derives from the consistency of Scottish antenatal care delivery (excluding the pandemic period). The majority of women attend their "booking" visit between eight and twelve weeks of gestation (as demonstrated in Chapter 2), providing standardised timing for data collection. This temporal consistency enables a reliable trend analysis across the study period. Additionally, the linkage between maternal and offspring records minimised missing data for those who reported alcohol consumption, enhancing the completeness and reliability of the dataset.

Limitations of the study include missing data and potential recording inaccuracies. As demonstrated, patients with missing data had more characteristics associated with adverse outcomes (e.g., drug use and smoking) compared to those with recorded alcohol intake. Missing alcohol intake data may indicate less engagement with obstetric services and consequently poorer data recording. Another limitation involves potential underreporting of alcohol consumption, where individuals might report no alcohol intake rather than actual volumes consumed. While this may dilute the results to show alcohol as less harmful than possible, this is preferable to demonstrating harm where none exists. In addition we could access only booking appointment alcohol recordings, and not at other time points including late pregnancy or at the time of a pregnancy loss, is a further limitation. We did not have control of data collection methods or standardisation of questions asked during clinic appointments and assumptions were made regarding consistency in midwife questioning, and as explored in Chapter 2, there was an increase in alcohol recording in the later years of this study. The increase in data recording is believed to reflect improved capture rates, as the recorded intake has moved toward other study

estimates, but this is an assumption. The impact of this increase in alcohol consumption reporting over time resulted in a higher proportion of women in the drinking cohort coming from the later years of the study. As outlined in Chapter 2, these is a general improvement in outcomes over time, thus the adverse. effects of alcohol could have been reduced, as women in the alcohol drinker cohort may have benefited from these improvements in obstetric care.

There has been no oversight of data collection however, there is no reason to suspect midwives would record alcohol use differently, when disclosed, from the start of the study to the end. The analysis has not examined the full spectrum of alcohol-related harms in pregnancy, particularly FASD, maternal morbidities, and psychosocial effects. Future research may benefit from the implementation of national guidelines and diagnostic algorithms, combined with improved data recording, to support large-scale FASD research, which is currently lacking[202].

3.5.1 Policy Implications

This research should be considered when national messaging on maternal health is next reviewed. Currently, there is precautionary guidance from the Chief Medical Officers due to insufficient evidence. This precautionary approach contrasts with alcohol intake advice for the general population, which is framed around individual choices. The UK advice currently advises women to stop drinking entirely during pregnancy “as a precaution” while recommending the non-pregnant population to avoid weekly intakes of above 14 units of alcohol per week. The UK "low-risk drinking guidance” states that "risks [of developing cancer] start from any level of regular drinking" but the shift toward a more paternalistic approach to pregnancy health is stark [167]. This policy change shifts the perception of women from having agency over their own behaviour (i.e., the choice to drink) to being viewed as proxies for the well-being of their offspring (i.e., pregnant women who drink risk affecting their child's health) [209]. Changing this risk framework may result in women feeling they have less autonomy regarding their health, with the well-being of their fetus prioritised over their own. Moreover, recommending abstinence from alcohol without clear evidence of harm from low alcohol intake can undermine women's trust in healthcare advice overall[210]. Since recommendations to abstain from alcohol are not made

in isolation, and pregnant women receive guidance on various health and social factors, efforts to promote zero alcohol intake may inadvertently divert attention from other behaviours (such as smoking) that could pose greater risks. Another potential consequence of the precautionary principle is its adverse impact on social interactions. In Scotland, it is common for women, particularly in communities with higher levels of deprivation, to socialise at home over alcohol [210]. *Restriction on alcohol consumption could potentially unintentionally harm women's mental health and social functioning, an area which needs further research, and possible mitigation prior to policy implementation. There is little research on alcohol consumption in pregnancy and mental health, but pregnant women have reported social pressure and negative experiences due to government recommendations and labelling*[211]. Given that mental health-related deaths are the leading cause of death between six weeks and one year postpartum, it is essential to consider the impacts of maternal mental health and social interactions in all public policy discussions[212].

This study has shown that, across a narrow spectrum of perinatal outcomes, there is no significant harm associated with low-level alcohol consumption. We have confirmed previous research indicating that harm occurs with increased alcohol levels. Our study should reassure pregnant women who have consumed small amounts of alcohol in early pregnancy, as well as those who have done so in prior pregnancies. We believe that pregnant women should carefully consider the Chief Medical Officers' advice; if they choose to drink alcohol, they should limit their intake to the lowest possible amount to minimise perinatal harm. For healthcare professionals and policymakers, there should be a concerted effort to incorporate further evidence, such as presented in this chapter, into developing evidence-based guidance for pregnant women, similar to the approach taken for non-pregnant women.

Chapter Summary

This study has demonstrated that across a narrow spectrum of perinatal outcomes, no significant harm was associated with consuming 1-4 units of alcohol per week. The findings confirm previous research showing that harm occurs when alcohol consumption increases. These results should reassure pregnant women who have consumed small amounts of alcohol in early pregnancy or in previous pregnancies. While pregnant women should strongly consider the CMO's advice, those who choose to consume alcohol should limit consumption to the lowest possible amount to minimise perinatal harm.

For healthcare professionals and policymakers, there should be a concerted effort to incorporate more evidence, such as presented in this chapter, into developing evidence-based guidance for pregnant women, similar to the approach taken for non-pregnant women.

Chapter 4 Opioid substitution narrative review

4.1 Chapter Abstract

The work presented in this chapter has been published in the Journal of Substance Use[213]*.* Kinsella M, Capel Y, Nelson SM, & Kearns RJ. Opioid substitution in pregnancy a narrative review: contemporary evidence for use of methadone and buprenorphine in pregnancy. *J Subst Use. 2022*; 28(6): 919–924.

Illicit opioid use is a growing public health emergency and is associated with adverse medical and social outcomes. Opioid use in the pregnant population is increasing globally, and optimal management incorporates opioid substitution programs with improved concurrent engagement in medical care. This chapter is a narrative reviews opioid replacement management during pregnancy.

The two main drugs used in opioid substitution programs are methadone and buprenorphine. Methadone has been used since the 1970s and provides treatment stability leading to improved engagement with obstetric services. Buprenorphine is a newer treatment, has greater dosing flexibility, and may be associated with fewer neonatal adverse effects. Direct comparisons of methadone and buprenorphine treatments are limited but suggest that buprenorphine is associated with less severe neonatal withdrawal; however, it is not universally well-tolerated and tends to be prescribed to less severely affected mothers. Given the lack of clear evidence to support one opioid substitution therapy over another, the principal aim of therapy should be to stabilise treatment and promote more comprehensive engagement with multidisciplinary services.

4.2 Introduction

There are approximately 62 million non-medical opioid users globally, with more than 11 million people injecting drugs in 2019[115]. Opioid use in people of childbearing age and consequently in pregnancy is increasing and represents a growing public health challenge[116].

Opioid dependence is associated with socioeconomic disadvantage, poly-substance use, and mental and physical co-morbidities [214-217]. During pregnancy, continued opioid use is associated with obstetric and neonatal complications such as stillbirth, intrauterine growth restriction, placental abruption, preterm labour, prolonged hospital admission, maternal cardiac arrest, congenital defects, and fetal alcohol syndrome[116,218]. Furthermore, abrupt cessation of neonatal opioid exposure at birth can result in neonatal abstinence syndrome (NAS), characterised by autonomic, neurological, gastrointestinal, and respiratory system disturbances. A mother who has a neonate diagnosed with NAS has an 11-12-fold increased risk of death in the ten years following delivery compared with a mother whose neonate does not have NAS[119]. Opioid exposure in utero has been associated with developmental delay in childhood and an increased risk of addictions, criminal activity, and poor health in adulthood[118].

Maternal treatment with an opioid substitution regime during pregnancy has numerous advantages compared to ongoing illicit drug use. These include stopping the cycle of intoxication and withdrawal associated with illicit drug use, reducing the incidence of blood-borne virus infections, reducing criminal activity, and increasing engagement with health care services[120-123]. The two main drugs used for opioid substitution therapy are methadone and buprenorphine, with both recommended for use in pregnancy by international guidelines [124-126]. Studies comparing methadone and buprenorphine in pregnancy are complicated by differences in prescription practices (in cohort studies) and by small study sizes (in randomised control trials).

Mothers taking buprenorphine are more likely to be older, married, in employment, have a higher level of education and have a history of prescription rather than illicit opioids than those on methadone [219]. This tendency to prescribe buprenorphine to mothers with less severe addictions may bias

observational studies[220]. The lack of high-quality evidence has led national guidelines to stress clinical equipoise regarding the optimal opioid replacement regime in pregnancy, stating that if a mother is stable on one medication, this should be continued[121,125,126].

Maternal illicit opioid use has been identified as a research priority by the World Health Organization in 2014 [126]. During pregnancy, mothers are in frequent contact with their healthcare providers, making this a powerful 'teachable moment' for promoting positive behavioural change. This review appraises the evidence for both methadone and buprenorphine in pregnancy, with a focus on maternal, neonatal, and longer-term childhood outcomes.

4.3 Methods

We conducted a literature search without language restriction of published scientific articles on online databases (EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL, and the Cochrane Central Registry of Controlled Trials (CENTRAL)) from inception to April 2020. Eligible studies were full-text RCTs and observational cohort studies comparing methadone and buprenorphine and reporting maternal and or neonatal outcomes. Search terms were "pregnancy", "infant", "neonate", "opiate substitution treatment", "methadone", and "buprenorphine". Relevant articles were obtained, and the reference sections were reviewed to identify additional relevant literature. The population of interest was mothers receiving opioid substitution therapy during pregnancy. All obstetric, maternal, neonatal, and early childhood outcomes were considered. This article was prepared using the Scale of the quality of Assessment of Narrative Review Articles (SARNA) guidelines for quality assessment of narrative review articles[221].

4.4 Methadone

Methadone is a full mu-opioid receptor agonist which has been used to treat opioid dependence in pregnancy since the 1970s[222]. As its half-life is around 36-48 hours, it is generally administered once daily, in supervised clinics or pharmacies, with 'take-home' doses generally limited to dates when the premises are closed or if compliance with treatment can be assured. Methadone remains a popular choice of opioid substitution due to its lower risk of neuropsychiatric toxicity, lack of active metabolites, minimal accumulation in renal failure, good bioavailability, and long duration of action. As methadone is bound to alpha-1-glycoprotein in the plasma, free concentrations of the drug can change at times of stress. Furthermore, drug-related liver enzyme induction (e.g., rifampicin), inhibition (e.g., omeprazole), and enzyme polymorphism may lead to altered methadone metabolism and necessitate changes to the drug dose [223-225].

A typical starting dose of methadone during pregnancy is between 10-20mg per day, increasing to 60-120mg per day with dose adjustments of 5-10mg increments[226]. As pregnancy progresses, methadone clearance increases and plasma concentrations reduce, resulting in the potential need for increased daily dose or split dosing throughout the day[227].

4.4.1 Maternal outcomes

The risk-benefit profile of methadone has been widely studied in both obstetric and non-obstetric populations, with treatment retention found to be improved on flexible higher dose programs compared with fixed lower dose programs [228]. The advantages/benefits associated with methadone use include; stabilisation of opioid levels and reduction in illicit drug use, improved HIV risk scores, reduced criminal activity, reduced mortality, and improved engagement with healthcare when compared to ongoing illicit opioid use[120,122-124,229-231]. Disadvantages of methadone include the risk of maternal respiratory depression, QT prolongation due to cardiac ion channel inhibition, drug interactions, and lifestyle restrictions reflecting the need for supervised intake [223,232].

4.4.2 Birth outcomes

Methadone-exposed neonates generally have a lower birthweight than neonates born to non-opioid-using mothers (approximately 279g lighter) but greater birth weight than neonates born to heroin-using mothers[233]. Furthermore, methadone crosses the placenta, affecting fetal heart rate, motor activity, and parasympathetic tone due to altered fetal neurodevelopment[234-237]. Such fetal neurobehavioral change does not necessarily imply longer-term impairment, and there is a lack of association between NAS severity and later developmental outcomes [238].

NAS is common, with a reported incidence of 48-94% in offspring of mothers taking opioids [239], and this risk increases with in utero co-exposure to other drugs (e.g. nicotine, benzodiazepines) [240]. Compared with neonates born to heroin-using mothers, neonates of mothers on opioid replacement programs have a later onset of NAS, lower peak NAS severity, and shorter length of hospital stay[240,241]. In a meta-analysis of 29 studies, methadone dose was not related to the incidence or severity of NAS. However, many studies were not blinded, and most did not control for other confounding factors[242]. Management of NAS includes close monitoring, supportive care, and reducing opioid regimes. The use of methadone in pregnancy is associated with lower neonatal mortality when compared to heroin and methadone (uncontrolled drug use) where both are used in pregnancy, relative risk, RR: 1.47 (95% CI: 0.81, 2.33) versus RR: 3.26 (95% CI: -0.95, 9.60), respectively[243]. The recent advances in treatment have reduced short-term neonatal mortality to be comparable with offspring without withdrawal symptoms[244-247].

4.4.3 Childhood outcomes

The effects of methadone on childhood development have not been investigated in large trials, with meta-analyses pooling opioid use (methadone, buprenorphine, or heroin) to achieve adequate sample sizes to assess the potential impact on a range of diverse developmental outcomes. These studies have shown impairments in multiple childhood outcome measures for opioid-exposed compared to non-opioid-exposed offspring[248]. The domains negatively

associated with opioid exposure include cognitive scores (standardised mean difference, SMD: -0.77, 95% CI: -1.06, -0.48); psychomotor scores (SMD: -0.52, 95% CI: -0.78, -0.25); IQ (SMD: -0.76, 95% CI: -1.25, -0.28); expressive language scores (SMD: -0.65, 95% CI: -0.97, -0.34); and receptive language scores (SMD: -0.74, 95% CI: -1.12, -0.3). A single-centre study showed that methadone exposure is associated with a higher risk of abnormal visual assessment at 27 weeks of age (RR: 5.1, 95% CI: 1.3, 20) when compared to matched non-drug exposed offspring[249]. The potential mechanism underlying this developmental delay has been investigated in animal studies, which show alterations in neurotransmitters across multiple systems and altered dendric length, synaptic plasticity, neuronal proliferation, and cholinergic function[250,251].

4.5 Buprenorphine

Buprenorphine was licensed for use by the Federal Drug Administration (FDA) in the USA in 2002 and is a potent partial mu-receptor agonist, an opioid receptor-like-1 receptor (ORL-1) agonist with weak binding affinity, and a delta and kappa receptor antagonist with high binding affinity. The differential receptor activity of buprenorphine is favourable as it produces potent analgesia (meaning that doses can be given on alternate days), with a ceiling effect for respiratory depression and euphoria and a reduction in opioid-related side effects such as constipation, anxiety, respiratory depression, and addiction[232,252]. Buprenorphine has a high first-pass metabolism; it is mostly administered via the sublingual or buccal routes and may be co-administered combined with naloxone to discourage intravenous injection. The starting dose for buprenorphine at a dose of between 0.8 - 4mg per day increased to 32mg per day, with a typical range of 12 - 24mg per day[253].

4.5.1 Maternal outcomes

Despite its clear pharmacological advantages, the requirement to dissolve buprenorphine under the tongue for 10-15 minutes may be poorly tolerated by some users and can impact treatment retention. Three randomised trials have investigated treatment retention rates[254-256]. The 223 mothers in these studies had a higher relative risk for drop-out on buprenorphine versus methadone (RR:

0.66, 95% CI: 0.37 -1.20) [257]. This concern regarding retention on buprenorphine therapy was further supported by a meta-analysis of 1,391 non-pregnant drug users, which showed higher treatment dropouts (RR 0.83, 95% CI: 0.73 - 0.95) on buprenorphine compared to methadone[258].

4.5.2 Birth outcomes

Three meta-analyses have compared the relationship between methadone and buprenorphine and neonatal outcomes[257,259,260]. Each meta-analysis had a different approach to analysis. The study by Minozzi et al. included only RCTs (223 mothers), and found no statistically significant differences in the primary outcomes of NAS treatment, maternal retention on treatment, primary substance use, or adverse events[257]. Birthweight was higher in the buprenorphine group, but the quality of the evidence was moderate to very low due to inconsistent outcomes, high drop-out rates, and small sample sizes. The authors concluded that "There is still a need for randomised controlled trials of adequate sample size comparing different maintenance treatments" [257].

Two further meta-analyses by Zedler et al. in 2016 (including both RCTs and cohort studies) and Brogly et al. in 2014 (presenting the results adjusted for confounding factors in both RCTs and cohort studies) found greater gestation, larger head circumference, and lower risk of being pre-term with buprenorphine [259,260]. These cohort studies increase the sample size of the comparison but could add biases due to a lack of control for confounding factors. Overall, the effect sizes were attenuated, though they still favoured buprenorphine after adjustment for confounding.

4.5.3 Childhood outcomes

Few studies have investigated the neurodevelopment of children exposed to buprenorphine, with those which have been undertaken primarily focusing on comparing buprenorphine to methadone. Following birth, offspring exposed to buprenorphine have fewer signs of stress, arousal, and excitability compared to those exposed to methadone [261]. In a three-year follow-up of the Jones et al. 2010 RCT, no differences were observed between opioid therapies for childhood development (cognition, language, sensory, and temperament) or maternal

outcomes (parenting stress, home environment and addiction severity), with the results of the development assessment for both groups within standard ranges [255,262]. Furthermore, there were no differences in outcomes between offspring who had NAS and those who did not. This suggests that the type of opioid exposure in utero does not differentially affect development. Consistent with this, when visual pathways were examined in 30 offspring exposed to buprenorphine, no differences were observed between the buprenorphine group and the non-opioid exposed control group[263].

4.6 Other treatments

Other opioid substitution regimes include buprenorphine-naloxone in combination, naltrexone, and oral morphine. A meta-analysis of 5 observational studies (1,875 mothers) investigating the safety of buprenorphine-naloxone combination therapy compared to other opioid substitution regimes found a reduced risk of requiring treatment for NAS with buprenorphine-naloxone but no difference in other outcomes[264]. More extensive studies in the obstetric population are needed to make definitive conclusions. Naltrexone, an opioid receptor antagonist, is rarely used, except in countries where methadone/buprenorphine are not prescribed[265]. A cohort study (n=107) investigating naltrexone compared with methadone in the obstetric population found naltrexone to have a favourable profile regarding birth weight, gestation, and Apgar score at one minute[266]. This small study supports the idea that naltrexone may be a potential alternative to buprenorphine or methadone. The lack of regulated programs in pregnancy and the high risk of defaulting off-program may limit its use, as it does in the general population.

One small, randomised control trial (n = 48) investigated morphine compared to methadone, finding reduced benzodiazepine and additional opioid consumption in the morphine arm, though no other differences were observed[267]. The limitations of morphine for withdrawal therapy include difficulty in monitoring for additional illicit opioid use, lack of established treatment programs, and diversion risk.

4.7 Guidelines for the management of mothers with opioid addiction

Several national and international organisations provide guidelines on the treatment of opioid dependency in pregnancy. These include the National Institute for Health and Clinical Excellence, the American College of Obstetricians and Gynaecologists, the American Society of Addiction Medicine, and the World Health Organization[228,268-270]. These guidelines provide valuable and freely available resources for managing opioid addiction during pregnancy. Fundamental tenets of all guidelines include personalised and supportive treatment tailored to individual needs, use of opioid substitution therapies rather than withdrawal programs, encouragement of breastfeeding in those not using illicit drugs or without other contraindications, postpartum psychological support, and discussion surrounding ongoing contraception.

These guidelines provide a valuable evidence base for treating this complex condition. However, they are limited by low levels of evidence and a need for studies explicitly examining the obstetric population.

4.8 Chapter Summary

Treatment of opioid addiction during pregnancy is challenging, and maintaining trust and engagement in services should remain the priority, irrespective of which drug treatment is used. Health professionals should be sensitive to mothers' physical, psychological, and social needs, provide appropriate support and optimise good health practices. This review has shown opioid replacement therapy in pregnancy is preferable to ongoing illicit drug use and, when combined with specialist obstetric care, can improve birth outcomes.

Both methadone and buprenorphine can be safely used in pregnancy, and there is some evidence that buprenorphine can improve neonatal outcomes, but this has not been recently studied in meta-analysis. Further work is required to systematically study any differences between buprenorphine and methadone, as well as different formulations of opioid replacement, on longer-term childhood outcomes to delineate how best to manage mothers who choose to abstain from illicit opioids during pregnancy.

Chapter 5 Opioid substitution therapies meta-analysis

5.1 Chapter Abstract

The work presented in this chapter has been published in the Journal of Substance Use and Misuse [271]. A post publication review (page 200) has been added to discuss results in the context of more recent work published after our publication. Kinsella M, Halliday LOE, Shaw M, Capel Y, Nelson SM, Kearns RJ. Buprenorphine Compared with Methadone in Pregnancy: A Systematic Review and Meta-Analysis. *Subst Use Misuse.* 2022;57(9):1400-1416.

Introduction: Illicit opioid use in pregnancy is associated with adverse maternal, neonatal, and childhood outcomes. Opioid substitution is recommended, but whether methadone or buprenorphine is the optimal agent remains unclear.

Methods: A search was conducted on EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL and the Cochrane Central Registry of Controlled Trials (CENTRAL) from inception to April 2020 for randomized controlled trials (RCTs) and cohort studies comparing methadone and buprenorphine treatment for opioid-using mothers. Included studies assessed maternal and or neonatal outcomes. We used random-effects meta-analyses to estimate summary measures for outcomes and report these separately for RCTs and cohort studies.

Results: The meta-analysis included 408 abstracts screened, 20 papers were included (4 RCTs, 16 cohort, 223 and 7028 participants respectively). All RCTs (4/4) had a high risk of bias and median (IQR) Newcastle Ottawa Scale for cohort studies was 7.5 (6-9). In both RCTs and cohort studies, buprenorphine was associated with; greater offspring birth weight (weighted mean difference [WMD] 343 g (95% CI: 40-645 g) in RCT and 184 g (95% CI: 121-247 g) in cohort studies); body length at birth (WMD 2.28 cm (95% CI: 1.06-3.49 cm) in RCTs and 0.65 cm (95% CI: 0.31-0.98 cm) in cohort studies); and reduced risk of prematurity (risk ratio [RR] 0.41 (95% CI: 0.18-0.93) in RCTs and 0.63 [95% CI: 0.53-0.75] in cohort studies) when compared to methadone. All other clinical outcomes were comparable.

Conclusion: Compared to methadone, buprenorphine was consistently associated with improved birthweight and gestational age, however given potential biases, results should be interpreted with caution.

Post publication review: The results of the meta-analysis were supported by a large cohort study published in the New England Journal of Medicine following our publication[272].

5.2 Introduction

Opioid use is common worldwide and is a growing public health challenge. In the United States of America, there are approximately 10 million people (3.7% of the adult population) who use opioids for non-medical reasons every year[273]. Of those individuals, it has been estimated that 745,000 (0.3% of the total adult population) consumed heroin. The widespread adverse effects of illicit opioid use on maternal and child health are widely recognised[240]. A multi-faceted public health response to opioid use in pregnancy is required to achieve the World Health Organization's sustainability development goals of improving maternal and offspring health[274].

Pregnancy is recognised as an opportunity to change lifestyle behaviours[275], and whilst abstinence from opioids during pregnancy is ideal, withdrawal from opioids during pregnancy is not recommended[121,126]. Opioid pharmacotherapy programs were established in the 1960s to integrate controlled opioid therapy with obstetric care and social health interventions and have led to reductions in overdoses, reduced recidivism, and reduced blood-borne virus transmission[276]. Opioid use in pregnancy carries a risk of Neonatal Abstinence Syndrome (NAS), a collection of gastrointestinal, neurological, and behavioural symptoms following the abrupt cessation of opioids after delivery[270]. The balance between the risk of NAS and uncontrolled illicit opioid use favours opioid agonist therapies in pregnancy[122,126,228].

Methadone is commonly used as an opioid agonist medication. Methadone therapy aims to provide stability in opioid levels, prevent withdrawal cycles, and improve engagement with obstetric care and neonatal outcomes. Still, it is limited by stringent observation protocols and the risk of overdose[124,222]. Buprenorphine is a more recently developed opioid agonist therapy and is an alternative to methadone. Buprenorphine is a partial opioid receptor agonist which has a ceiling effect on respiratory depression (limiting harm following overdose), a more flexible dosing design, and may have a more favourable neonatal opioid withdrawal profile when compared to methadone [232].

Previous meta-analyses have investigated differences between opioid agonist therapies but have included only RCTs, or RCTs plus cohort studies from over five years ago[257,259,260]. Since 2015, five large cohort studies (~3000

patients) have been published[277-281]. Including these cohort studies will enable further triangulation of evidence, given the limited evidence available from RCTs and previous smaller observational cohorts. The objective of this review was to systematically review all the published evidence to determine the optimal opioid substitution therapy in pregnancy.

5.3 Methods

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist was followed to report this systematic review and meta-analysis and is displayed in Table 5-1[282].

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.

Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

Table 5-1 Preferred Reporting Items for Systematic Review (PRISMA)

The protocol was registered with PROSPERO (CRD42020173882). We defined the research question in accordance with the PICO format (Population, Intervention, Comparator, and Outcomes) (Table 5-2).

Population	Mothers who are pregnant and prescribed opioid substitutes and offspring that were exposed to opioids during their gestation
Intervention	Buprenorphine drug therapy (with or without naloxone)
Comparator	Methadone drug therapy
Outcomes	Maternal outcomes: death, side-effects associated with treatment, maintenance on treatment, illicit drug use, and mode of delivery. Offspring outcomes: death, stillbirth, birthweight, small for gestational age, length (at birth), head circumference (at birth), prematurity, opioid withdrawal treatment, hospital stay, congenital anomalies and childhood development

Table 5-2: PICO format (Population, Intervention, Comparator, and Outcomes)

The population of interest was patients taking opioid agonists whilst pregnant and their offspring. The intervention was buprenorphine drug therapy (with or without naloxone), and the comparator was methadone drug therapy. Maternal outcomes were side effects associated with treatment, maintenance of treatment, illicit drug use, death, and mode of delivery. Offspring outcomes were stillbirth, birthweight, growth (total body length at birth and head circumference at birth, small for gestational age), prematurity, opioid withdrawal treatment, hospital admission duration, death, congenital anomalies, and childhood development. Full details of outcomes are shown in Table 5-3.

Outcomes	Definition
Maternal death	Loss of life of mother
Side effects of medication	Maternal side effects associated with treatment
Maintenance on treatment	Maintenance on specific opioid replacement treatment
Mode of delivery	Type of delivery – SVD, assisted vaginal or caesarean section
Additional Opioid use	Use of illicit opioids through pregnancy
Stillbirths	Stillbirth offspring
Offspring death	Post-partum death of offspring
Birth weight	Total body weight at birth in grams
Length	Total body length at birth in centimetres
Head circumference	Head circumference at birth in centimetres
Small for gestational age	Rate of small for gestational age, definitions as per study
Prematurity	Birth before completion of 37 weeks gestation
NAS (Neonatal Abstinence Syndrome) Treatment	Requirement for treatment of neonatal withdrawal
Hospital stay	Duration of neonatal hospital admission in days

Congenital anomalies	Structural, metabolic, or functional defect present at birth or diagnosed as a neonate
Childhood development	Cognitive, functional, or behavioural development assessment

Table 5-3: Definitions of outcomes of the meta-analysis

We conducted a systematic search of EMBASE, PubMed, Web of Science, Scopus, Open Gray, CINAHL and the Cochrane Central Registry of Controlled Trials (CENTRAL) from inception for April 2020. The search strategy was led by a senior university librarian, and is shown in Table 5-4.

Medline	Embase
(((((opiate substitution treatment [MeSH Major Topic]) OR buprenorphine) OR methadone) AND Humans [Mesh])) AND (((((infant[MeSH Major Topic]) OR neonat*[MeSH Major Topic]) OR neonat*) OR pregnan*[MeSH Major Topic]) OR pregnan*) Filters: Humans	Pregnancy OR newborn AND methadone OR buprenorphine OR "drugs used in treatment of addiction"
Web of Science	Scopus
(("opiate substitution treatment" OR buprenorphine OR m ethadone) AND (infan* OR neonat* OR pregnan*)	(Infan* OR neonat* OR pregnan*) AND (opiate substation treatment OR buprenorphine OR methadone)
Cinahl	Central
Pregnancy OR infant OR Neonate AND Opiate Substitution treatment OR methadone OR buprenorphine	Pregnancy OR Infant AND Opiate substitution treatment OR Methadone OR Buprenorphine
Cochrane Database of Systematic Reviews	Open Gray
(MeSH (Pregnancy) OR MeSH(infant)) AND (MeSH Opiate Substition Treatment) OR (Methadone) OR (Buprenorphine))	(buprenorphine OR methadone) AND pregnant

Table 5-4: Search terms used in each online repository

Eligible studies were full-text RCTs and observational cohort studies comparing methadone and buprenorphine and reporting maternal and or neonatal outcomes. We included cohort studies in accordance with Cochrane guidance [283]. To provide evidence of the effects (benefit or harm) of interventions for which only a small number of randomised trials are available (or are likely to be available). We excluded case reports, case series, case-control studies, and editorials. We limited our results to human studies. Non-English studies were translated using Google Translate.

Screening of titles was conducted using the Covidence software platform[284]. One reviewer (Dr M Kinsella) searched and removed duplications. Two reviewers (Dr M Kinsella and Dr Y Capel) independently reviewed studies for eligibility by screening titles, abstracts, and full texts. Any disagreement was settled by discussion with a third reviewer (Dr L Halliday). One reviewer conducted data extraction and assessment of bias (Dr M Kinsella). A second reviewer (Dr L Halliday) independently extracted data for a sample of the trials (3 RCTs and 2 cohort studies) to verify data entry standards. No significant differences were seen in data entry. The data were extracted into an Excel spreadsheet and analysed in R (version 4.0.3) using the package "meta" [184].

The risk of bias was assessed using the Newcastle Ottawa Score Field (24) for cohort studies and the revised Cochrane Risk-of-Bias (RoB 2) tool for the RCTs [285]. The Newcastle Ottawa Score consists of three domains to assess the quality and risk of bias. These are selection, comparability, and outcome assessment. Each cohort study was given a star rating for each domain with a maximum star rating of 4 for selection, 2 for comparability, and 3 for outcome, with a more significant number of stars reflecting a lower risk of bias. For RCTs, the RoB 2 reporting template was used to score each outcome as: "low risk", "some concern", or "high risk". The overall risk of bias is "low" if all domains are low risk, "some concerns" if some concerns are raised but these are not high risk, and "high risk" if any domain has a high risk or there are multiple domains with some concerns. Data on risk of bias and overall quality assessment is presented.

Results for RCT and cohort studies were analysed separately [283]. Due to heterogeneity between studies, we used a random effects model (DerSimonion & Laird model). For binary outcomes, we calculated risk ratios. For continuous

outcomes, we used weighted mean differences. Uncertainty of the estimates (relative risk [RR] and weighted mean difference [WMD]) was expressed by calculating the 95% confidence interval [CI]. The I^2 statistic was used to assess study heterogeneity. The I^2 represents the percentage of variance across studies attributable to heterogeneity rather than change and is presented alongside each forest plot for RCTs and cohort studies. To investigate publication bias, we produced a funnel plot if the number of pooled studies was greater than ten. We used adjusted estimates where they were available for cohort studies. As adjusted estimates were only available for 8 of 16 cohort studies, we present the primary results as unadjusted analyses for a total of four outcomes. Estimates for the pooled, adjusted analyses (where available) are included in the study.

5.4 Results

Our search strategy identified 803 studies. After the removal of duplicates, 404 studies were screened for inclusion. Four additional papers were added following screening of citations in previously published papers in the field. Four hundred and eight studies were screened by title and abstract, 129 of which were selected as potentially includible and evaluated as full-text articles. Twenty papers met the criteria for inclusion in the meta-analysis. Two papers were included in the results for development outcomes only, as birth and maternal outcomes were reported from these populations in other documents in this meta-analysis[286,287]. The CONSORT flow diagram is shown in Figure 5-1.

The 20 studies in this meta-analysis included 7,251 patients (methadone n = 4,146, buprenorphine n = 3105) in four RCTs and 16 cohort studies [254-256,262,263,277-281,287-296]. The location of the studies was Europe (eight), North America (ten) and Oceania (two). Of the 16 cohort studies, eight provided adjusted results for four outcomes (small for gestational age, prematurity, duration of hospital admission, and NAS treatment). Characteristics of each study are given in Appendix 1, and results of pooled estimates for both adjusted (where available) and unadjusted analyses for cohort studies are presented.

The risk of bias was high for all the randomised trials (4/4). The median (IQR) Newcastle Ottawa score was 7.5 (6-9) for cohort studies (Tables 5-5 and 5-6). A funnel plot was produced for outcomes with more than ten studies, and there was no apparent asymmetry in these plots.

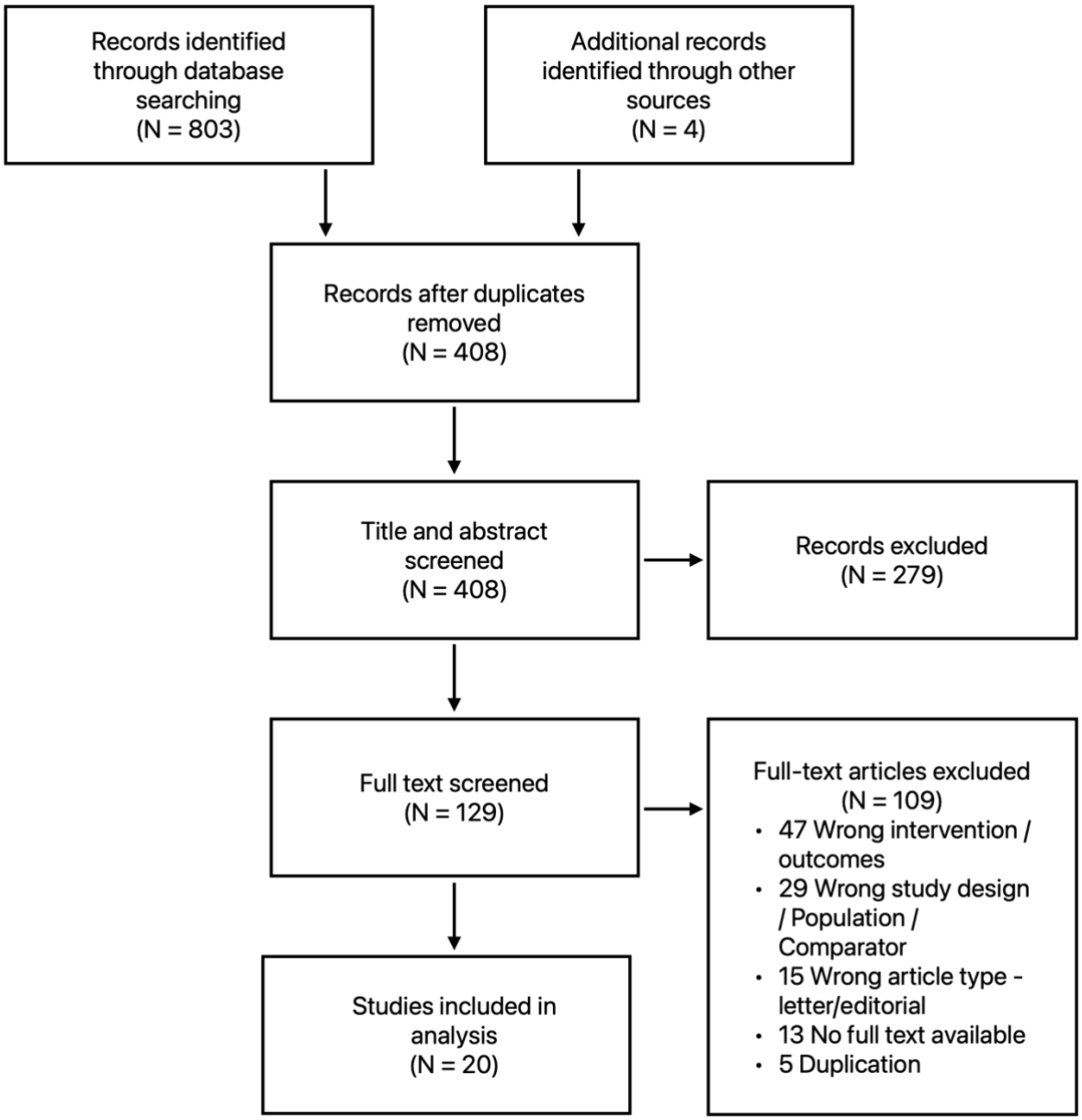


Figure 5-1: CONSORT flow diagram of studies included in analysis

Study (year of publication)	Selection	Comparability	Outcome	Total stars
Beir (2015)	****	0 star	***	7
Brogly (2017)	***	**	***	8
Colombini (2008)	****	0 star	**	6
Ebner (2007)	****	0 star	**	6
Gawronski (2014)	****	0 star	***	7
Kakko (2008)	**	0 star	***	5
Konijnenberg (2014)	****	**	**	8
Lacroix (2011)	**	0 star	**	4
Lejeune (2006)	****	0 star	**	6
Meyer (2016)	****	**	***	9
Nechanska (2017)	****	**	***	9
Norgaargd (2015)	****	**	**	8
Pritham (2013)	****	**	***	9
Tolia (2018)	**	**	***	7
Whitham (2010)	****	**	***	9
Wiegard (2015)	****	**	***	9

Table 5-5: Risk of bias for cohort studies

Study	Outcome	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Jones (2010)	Length at birth	+	+	-	+	+	-
Jones (2010)	Birth weight	+	+	-	+	+	-
Jones (2010)	Head circumference	+	+	-	+	+	-
Jones (2010)	Gestational age	+	+	-	+	+	-
Jones (2010)	Neonatal abstinence syndrome	+	+	-	+	+	-
Jones (2010)	Duration of hospital admission	+	+	-	!		-
Jones (2010)	Maternal outcomes	+	+	-	+	!	-
Jones (2010)	Prematurity	+	+	-	+	+	-
Jones (2010)	Caesarean section	+	+	-	+	+	-
Jones (2005)	Birth weight	+	+	-	+	!	-
Jones (2005)	Length at birth	+	+	-	+	!	-
Jones (2005)	Head circumference	+	+	-	+	!	-
Jones (2005)	Gestational age	+	+	-	+	!	-
Jones (2005)	Neonatal abstinence syndrome	+	+	-	+	!	-
Jones (2010)	Stillbirth	+	+	-	+	!	-
Jones (2005)	Hospital stay	+	+	-	+	!	-
Jones (2005)	Prematurity	+	+	-	+	!	-
Jones (2005)	Caesarean section	+	+	-	+	!	-
Jones (2005)	Stillbirth	+	+	-	+	!	-
Kaltenbach	Childhood outcomes	+	+	-	+	+	-
Fischer	Prematurity	+	+	-	+	!	-
Fischer	Gestational Age	+	+	-	+	!	-
Fischer	Stillbirth	+	+	-	+	!	-

Table 5-6: Risk of bias for RCTs, per outcome. Green = Low, Yellow = Some Concerns, Red = High.

5.4.1 Growth Outcomes

Birthweight was reported in 14 studies (12 cohort, 2 RCTs). The weighted mean difference in offspring birth weight was 184g (95% CI: 121, 247) in cohort studies and 343g (95% CI: 40, 645) in RCTs favouring buprenorphine (Figure 5-2, Figure 5-3). One paper (Pritham et al., 2012) reported a standard deviation of 2695g (4 times greater than other studies)[295]. When this study was excluded from the results, the weighted mean difference was 186g (95% CI: 122, 250) in cohort studies (Figure 5-4).

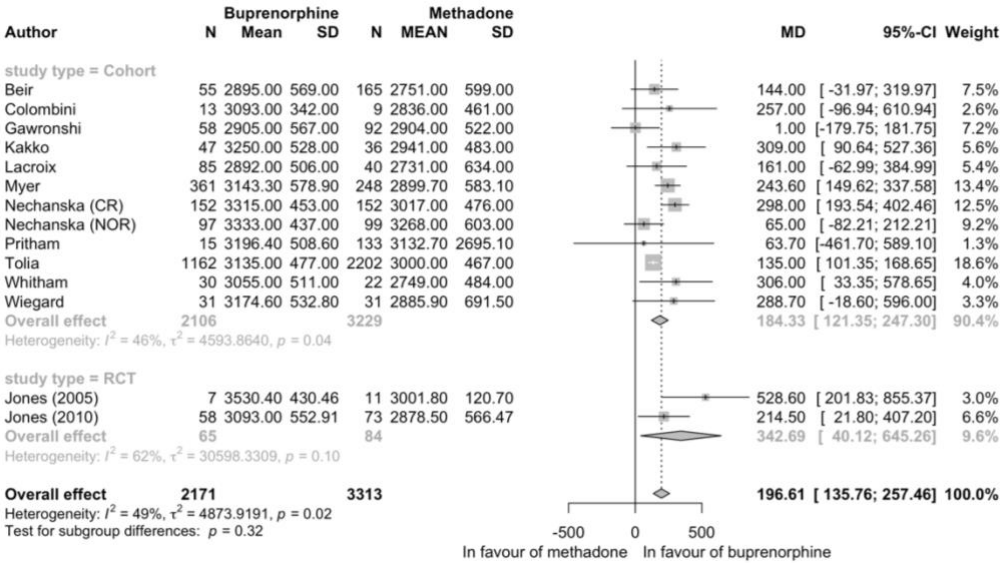


Figure 5-2: Forrest plot of exposure to buprenorphine versus methadone and weighted mean difference in offspring birthweight (grams)

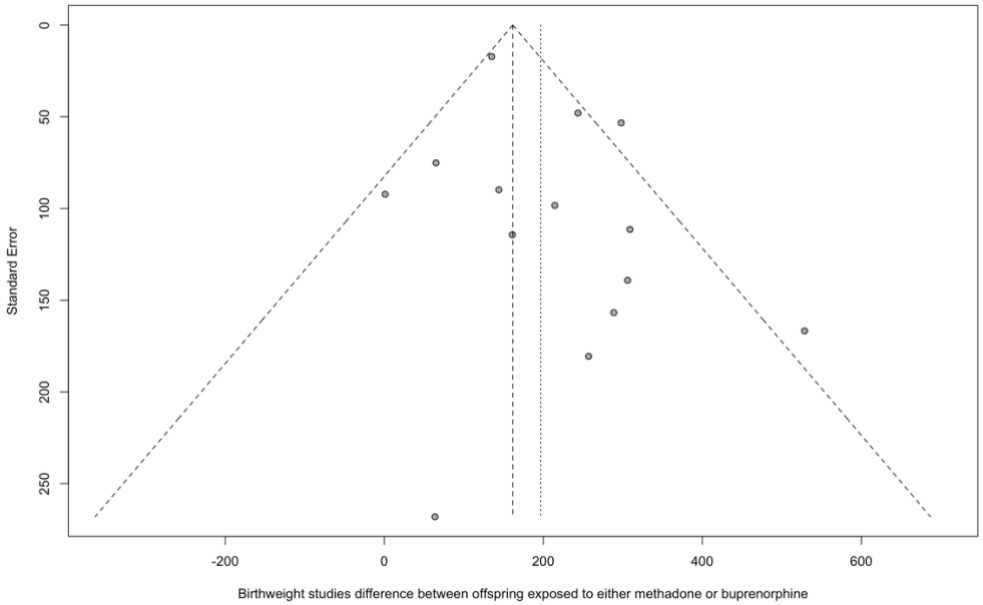


Figure 5-3: Funnel plot of standard error for studies reporting birthweight of offspring following exposed buprenorphine or methadone.

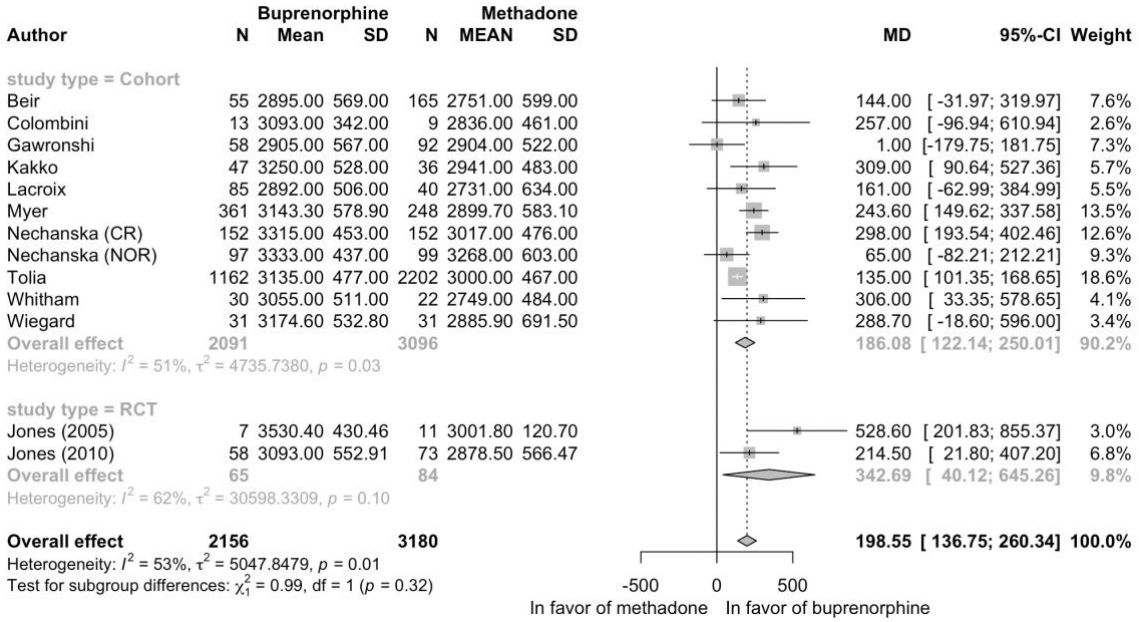


Figure 5-4: Forrest plot of weighted mean difference of offspring's birth weight in those exposed to buprenorphine or methadone during gestation with outlier removed (grams)

Length at birth was measured in 9 studies (7 cohort, 2 RCTs), and was 0.65cm (95% CI: 0.31, 0.98) greater in the cohort studies and 2.28cm (95% CI: 1.06, 3.49) greater in RCTs with buprenorphine compared to methadone (Figure 5-5).

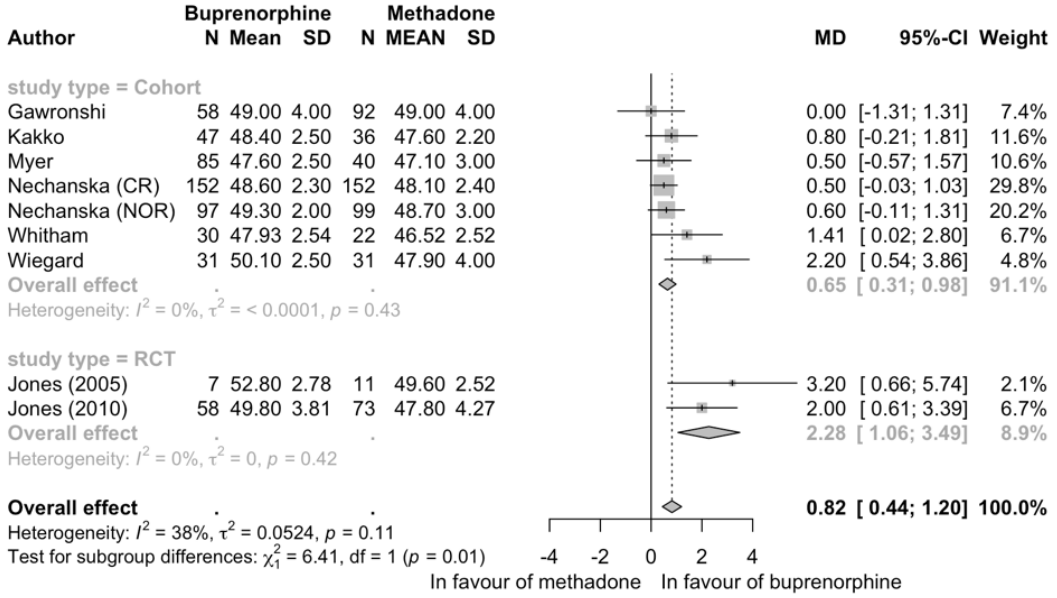


Figure 5-5: Forrest plot of exposure to buprenorphine versus methadone during pregnancy and weighted mean difference in offspring total body length (centimetres)

Head circumference was measured in 9 studies (7 cohort, 2 RCTs). Buprenorphine was associated with a 0.42cm (95% CI: 0.20, 0.64) increase in head circumference in the cohort studies and no change in RCTs (weighted mean difference of 0.80cm (95% CI: -0.03, 1.63) (Figure 5-6). None of the cohort studies reporting birth weight or length at birth provided adjusted estimates.

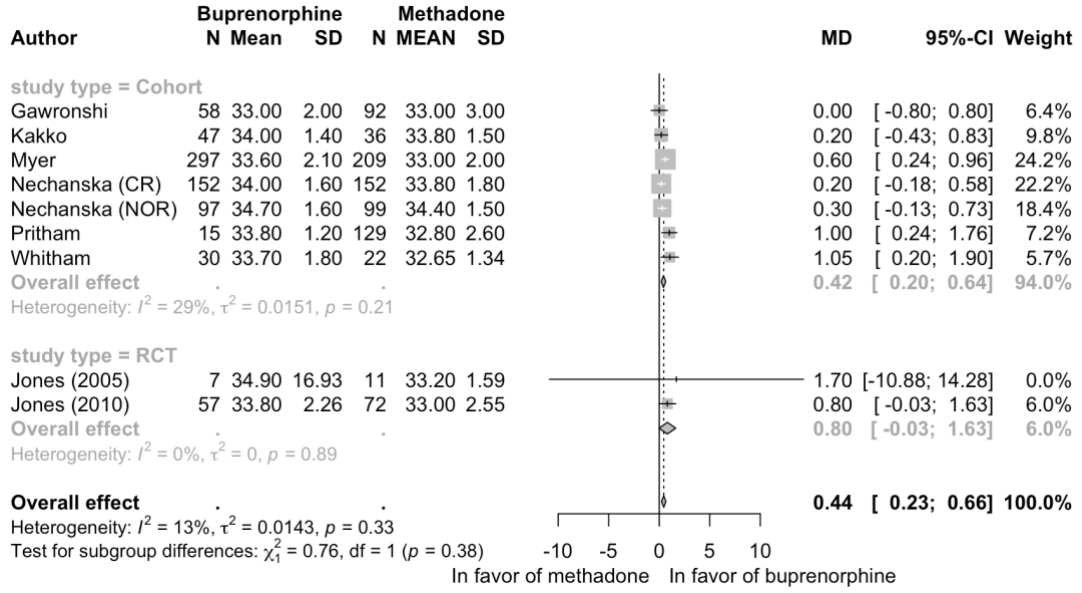


Figure 5-6: Forrest plot of the weighted mean difference of offspring's head circumference after exposure to buprenorphine or methadone during gestation (centimetres).

5.4.2 Gestational outcomes

Small for gestational age (SGA) was investigated in 5 studies (all cohort studies). The risk ratio for SGA was 0.76 (95% CI: 0.66, 0.88), in favour of buprenorphine (Figure 5-7). When this analysis was restricted to the three studies where the outcome was adjusted for confounding or when both adjusted and unadjusted estimates were pooled, the risk ratio was no longer significant (Table 5-7)

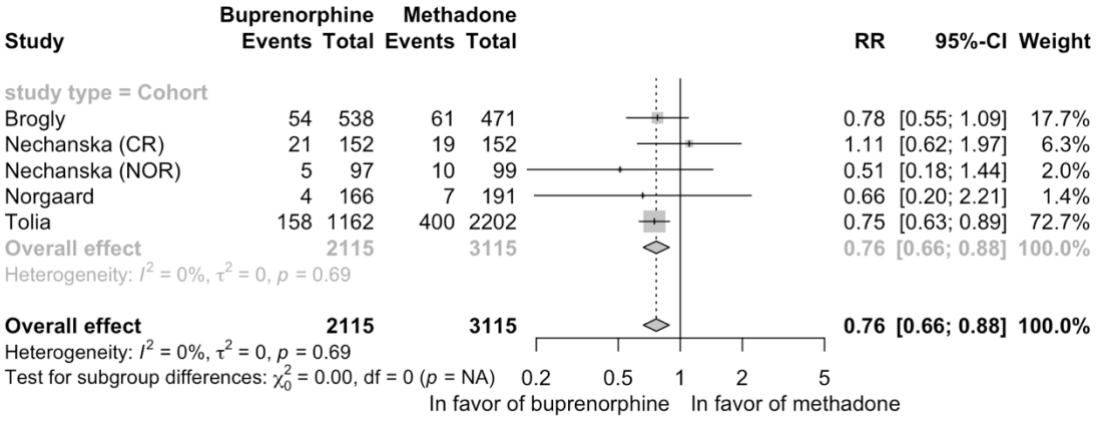


Figure 5-7: Forrest plot of the relative risk of small for gestation age after exposure to buprenorphine or methadone during gestation.

Outcome	Studies with adjusted estimates for outcomes	Pooled results (adjusted outcomes)[1]	Pooled results (unadjusted outcomes, all studies)	Pooled results (adjusted where available plus unadjusted for remaining studies)
Small for gestational age	Brogly (2017) Nechanska [CR] (2017) Nechanska [Nor] (2017)	adjRR 1.10 (95% CI: 0.79, 1.52)	RR 0.76 (95% CI: 0.66 to 0.88)	RR 0.88 (95% CI: 0.67, 1.15)
Prematurity	Brogly (2017) Nechanska [CR] (2017) Nechanska [Nor] (2017)	adjRR 0.66 (95% CI: 0.42, 1.04)	RR 0.62 (95% CI: 0.53, 0.74)	RR 0.60 (95% CI: 0.50, 0.73)
Duration of hospital admission	Brogly (2017)	WMD −3.66 days (95% CI: -5.46, -1.87)	WMD -6.84 days (95% CI: -11.37, -2.32)	NA[2]
NAS (Neonatal Abstinence Syndrome) Treatment	Lacroix (2010)[3] Nechanska [Nor] (2017) Wiegard (2015)	adjRR 1.18 (95% CI: 0.78, 1.79)	RR 0.58 (95% CI: 0.40, 0.82)	RR 0.60 (95% CI: 0.50, 0.73)

1) Results of buprenorphine compared to methadone, with methadone as reference group
2) Adjusted and non-adjusted estimates not pooled as data could not be combined to form total estimate of effect
3) Adjustment of NAS requirements given maternal heroin use.

Table 5-7: Studies with adjusted analysis and comparison to unadjusted of perinatal outcomes.

5.4.3 Gestational age

Gestation was measured in 11 studies (9 cohort, 2 RCTs). Buprenorphine was associated with an increase in gestational age of 0.55weeks (95% CI: 0.25, 0.84) in cohort studies (unadjusted estimates only), but no difference in RCTs (WMD 0.9weeks (95% CI: -0.13, 1.92) (Figure 5-8). No cohort studies provided adjusted estimates for this outcome.

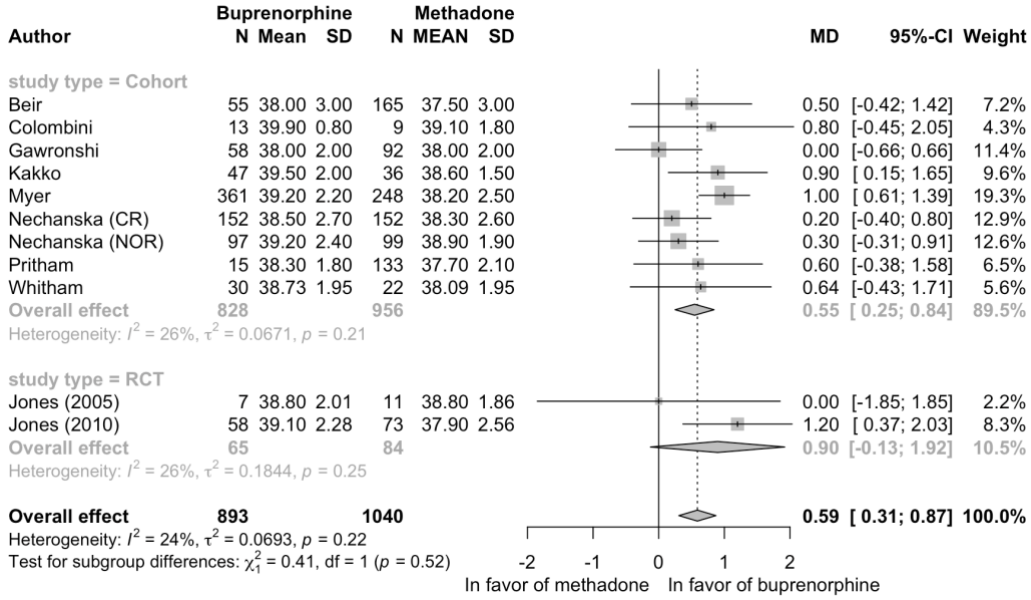


Figure 5-8: Forrest plot of the weighted mean difference in gestational age of offspring exposure to buprenorphine or methadone.

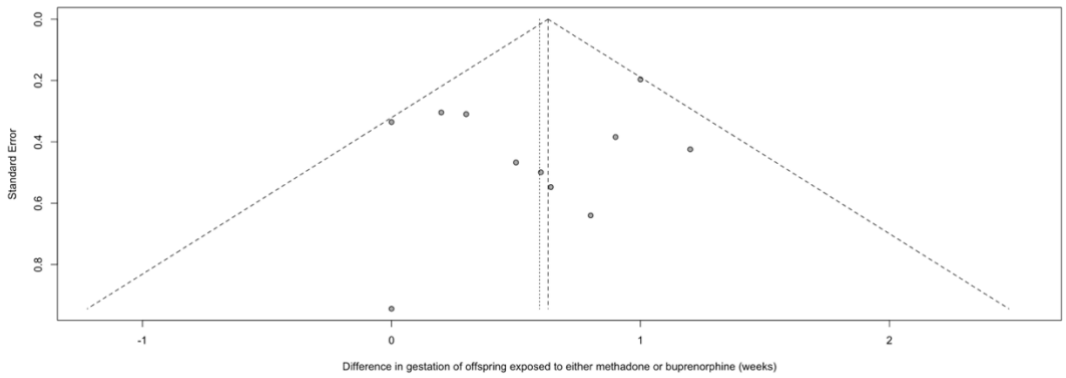


Figure 5-9: Funnel plot of standard error for studies reporting gestation of offspring following exposed buprenorphine or methadone

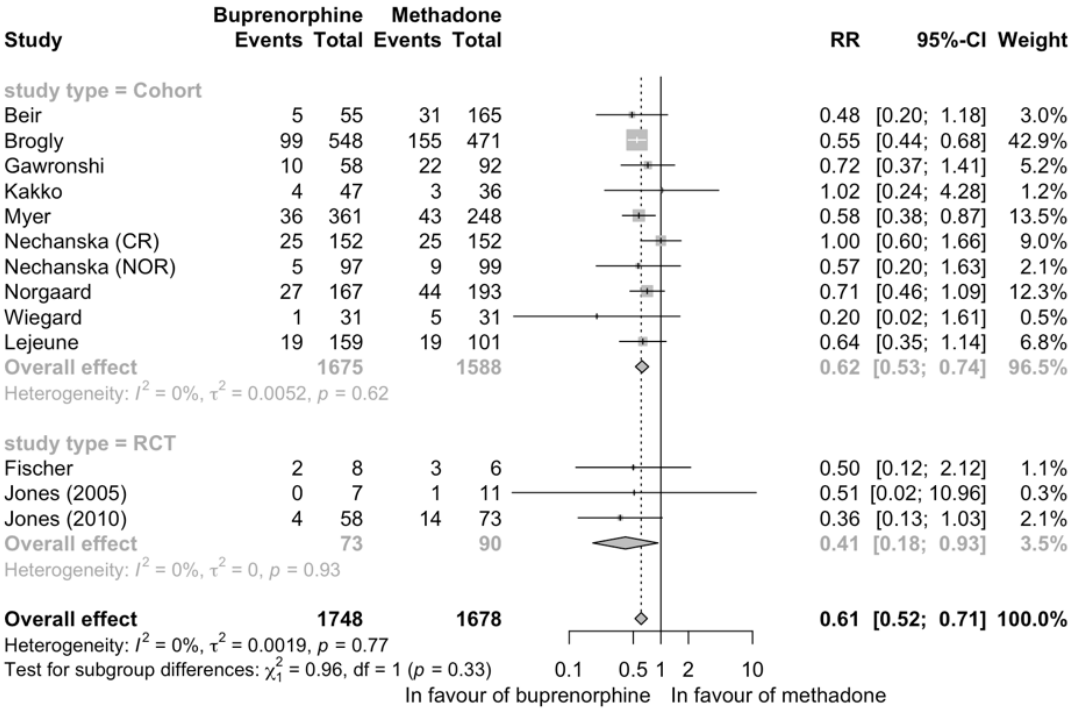


Figure 5-10: Forrest plot of exposure to buprenorphine versus methadone during pregnancy and risk ratio for prematurity

Prematurity was reported in 12 studies (9 cohort, 3 RCTs). Buprenorphine treatment was associated with a reduced risk of prematurity in both cohort (RR 0.62, 95% CI: 0.53, 0.74) and RCTs (RR 0.41, 95% CI: 0.18, 0.93). (Figure 5-11, Figure 12)

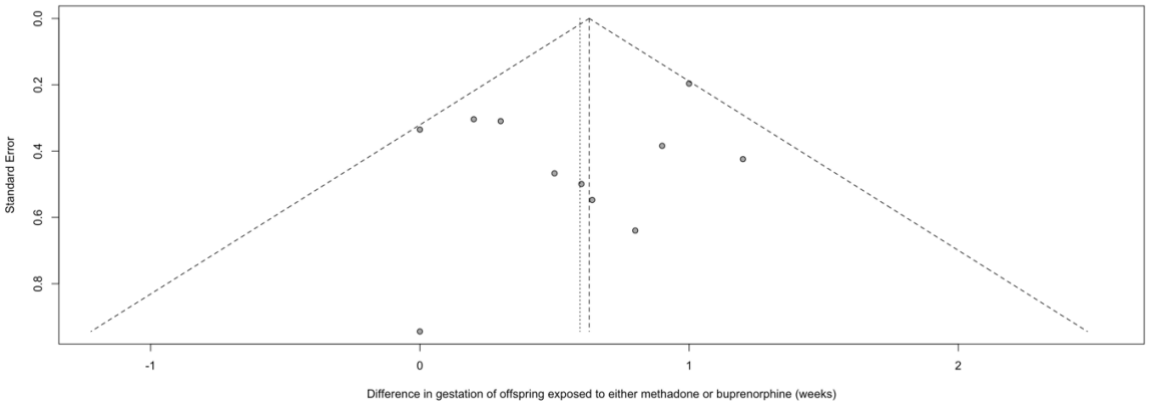


Figure 5-11: Funnel plot of standard error for studies reporting gestation of offspring following exposed buprenorphine or methadone

5.4.4 Neonatal abstinence syndrome

Fifteen studies (12 cohort, 3 RCTs) reporting treatment for NAS showed a reduction in the relative risk of requiring treatment in mothers receiving buprenorphine in cohort studies (RR 0.58, 95% CI: 0.40. 0.82), but not RCTs (RR 0.84, 95% CI: 0.62, 1.15) (Figure 5-12, Figure 5-13). When the analysis of cohort studies was restricted to those providing adjusted estimates (3 studies) [280,292,296], this difference was no longer statistically significant (Table 5-7).

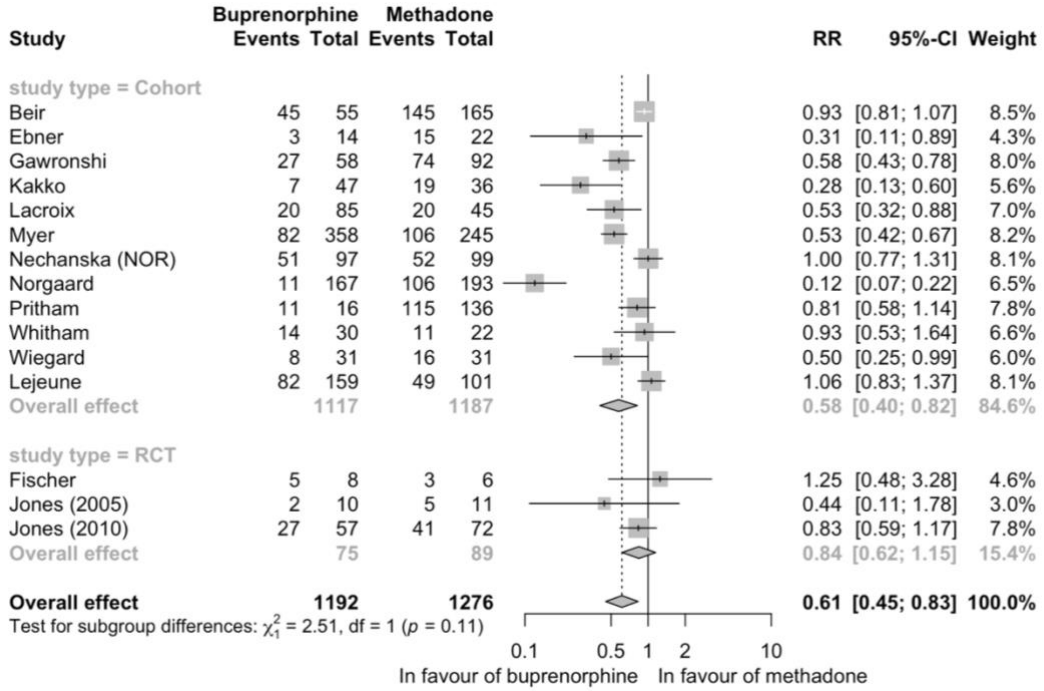


Figure 5-12: Forrest plot of exposure to buprenorphine versus methadone during pregnancy and risk ratio for NAS treatment

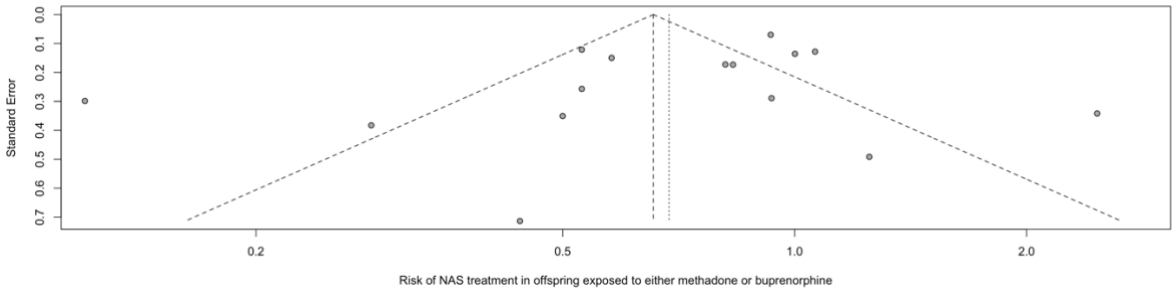


Figure 5-13: Funnel plot of standard errors of studies reporting percentage per group treated for NAS

5.4.5 Duration of hospital admission

The duration of hospital admission was measured in 9 studies (7 cohort and 2 RCTs). Buprenorphine was associated with a reduction of 6.84 days (95% CI: -11.37, -2.32) in cohort studies and no change in RCTs (-4.21 days, 95% CI: -10.28, 1.85). Only one study provided adjusted estimates for this outcome (mean difference -3.66 days, 95% CI: -5.46, -1.87) [278].

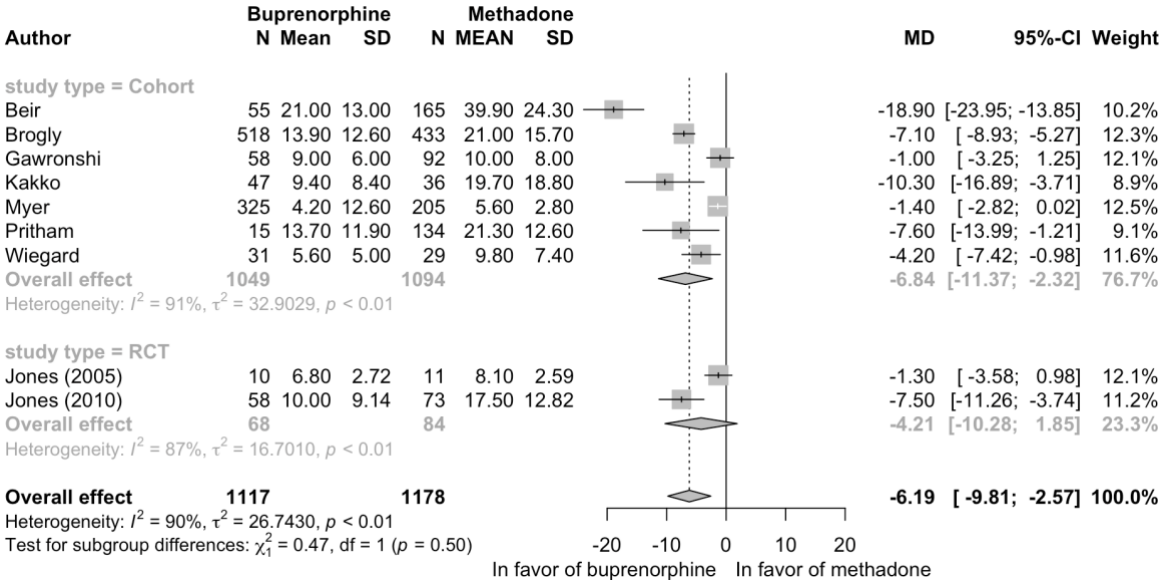


Figure 5-14: Forrest plot of the weighted mean difference in duration of hospital admission for offspring exposure to buprenorphine or methadone.

5.4.6 Congenital anomalies

Three cohort studies (all reporting unadjusted outcomes) reported congenital anomalies (486 methadone-exposed and 618 buprenorphine-exposed offspring). There were 23 (4.7%) malformations in methadone-exposed neonates and 20 (3.2%) malformations in buprenorphine-exposed neonates. When results were pooled, there was no difference between groups (RR 0.85, 95% CI: 0.47, 1.54).

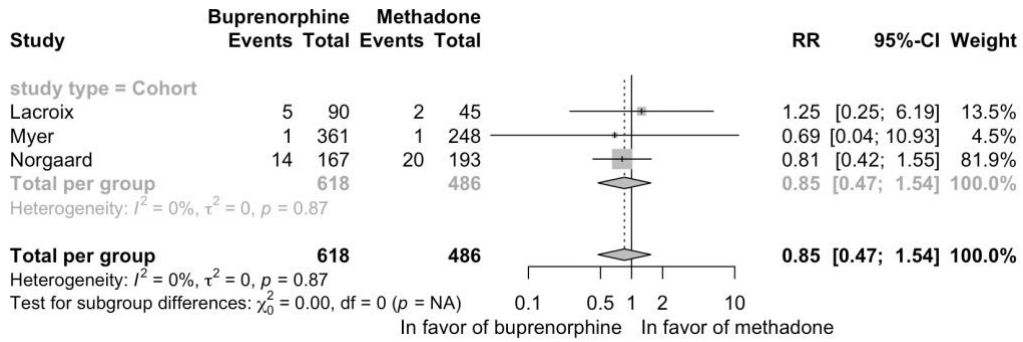


Figure 5-15: Forrest plot of relative risk of congenital malformation required after exposure to buprenorphine or methadone during gestation.

The malformations reported in the methadone group included poly-malformation, absent hand, and dextrocardia. In the buprenorphine group, malformations reported included tragus appendix, nasal septum deviation, short neck, gastroschisis, facial abnormalities, microcephaly, and cleft palate. One study reported a malformation rate of 39,934 (4.2%) in a reference group of non-opioid users (n = 945,569) [294].

5.4.7 Stillbirths

Seven studies reported stillbirths (596 methadone-exposed and 759 buprenorphine-exposed offspring), with the relative risk of stillbirth lower in cohort studies (RR 0.38, 95% CI: 0.12, 1.20), however the confidence intervals included unity. There was one stillbirth (methadone group) in the three RCTs (86 buprenorphine exposed, 89 methadone exposed), and a relative risk could not be calculated. No offspring deaths were reported in either cohort or RCTs.

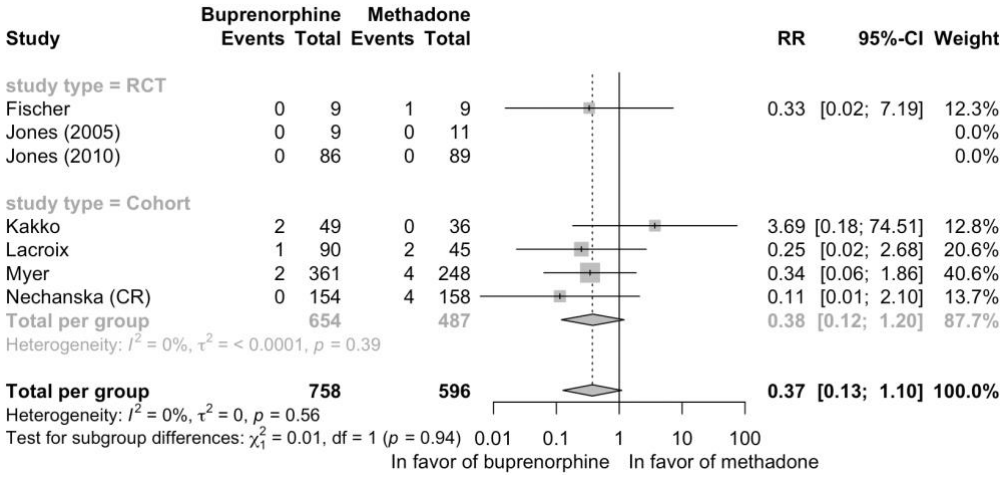


Figure 5-16: Forrest plot of relative risk of stillbirth after exposure to buprenorphine or methadone during gestation.

5.4.8 Childhood development

Three studies reported development outcomes; however, these results could not be pooled due to heterogeneity in outcome measures. Bier et al. investigated development at four months with the Bayley Mental Developmental Index (MDI) and the Alberta Infant Motor Scale (AIMS) [297]. There were no significant differences in Bayley MDI scores between methadone (high and low dose groups) and buprenorphine [277]. AIMS scores were different between groups, with buprenorphine-exposed offspring having higher scores compared to methadone (low and high-dose groups). The proportion of infants with the suspected or abnormal neurological examination was not significant between low-dose methadone (n=19 [23%]), high-dose methadone (n = 17 [21%]) and buprenorphine-exposed groups (n = 7 [13%]). Whitham et al. measured visual evoked potential at four months old; infants exposed to methadone (n = 22) had prolonged latency compared to controls and buprenorphine-exposed offspring (n = 30) [263]. Kaltenbach et al. followed up participants (n = 96, methadone n = 52, buprenorphine n = 44) of the 2010 Jones et al. trial[255,262]. It was observed that these offspring had normal development at 36 months.

5.4.9 Maternal outcomes

One RCT (175 patients) systematically measured and documented maternal outcomes[255]. There were 14 (16%) serious adverse events, 83 (93%) non-serious adverse events in the methadone arm, 8 (9%) serious adverse events, and 66 (77%) non-serious events in the buprenorphine arm. Three RCTs reported retention rates[254-256]. In the methadone arms, 23/113 (20%) mothers dropped out, while in the buprenorphine arms, 35/110 (32%) dropped out of the studies. The relative risk (RR) of drop-out from treatment was 1.60 (95% CI: 1.00 – 2.55) when taking buprenorphine compared with methadone.

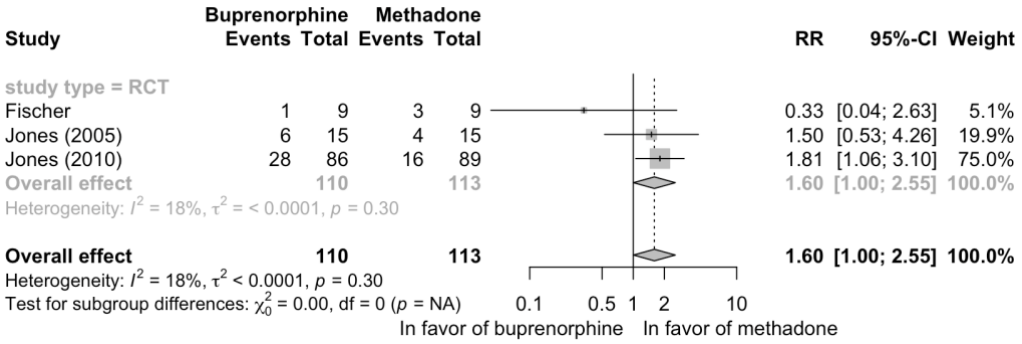


Figure 5-17: Forrest plot of relative risk of dropout use after exposure to buprenorphine or methadone.

Two cohort studies reported measures of additional opioid use throughout pregnancy (unadjusted analyses). Lacroix reported that 15/90 (17%) of women used heroin in the buprenorphine group versus 20/45 (44%) in the methadone group[292]. Pritham et al. reported 14/16 (88%) patients using additional opioids in the buprenorphine group and 128/136 patients (94%) of patients in the methadone group[295]. When the results of these two studies were pooled, there was no difference between groups (RR 0.61, 95% CI: 0.25, 1.49).

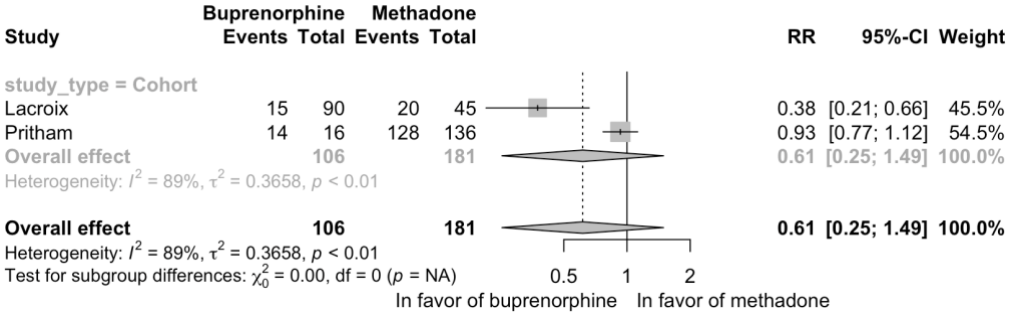


Figure 5-18: Forrest plot of relative risk of opioid use after exposure to buprenorphine or methadone.

The caesarean section rate was measured in 11 studies (8 cohort studies and 3 RCTs). Buprenorphine treatment was associated with a reduced rate of caesarean sections in cohort studies (unadjusted analyses), with relative risk of 0.90 (95% CI: 0.84, 0.98). There was no difference in RCTs (RR 0.84 (95% CI: 0.52, 1.36).

No maternal deaths were reported in the studies.

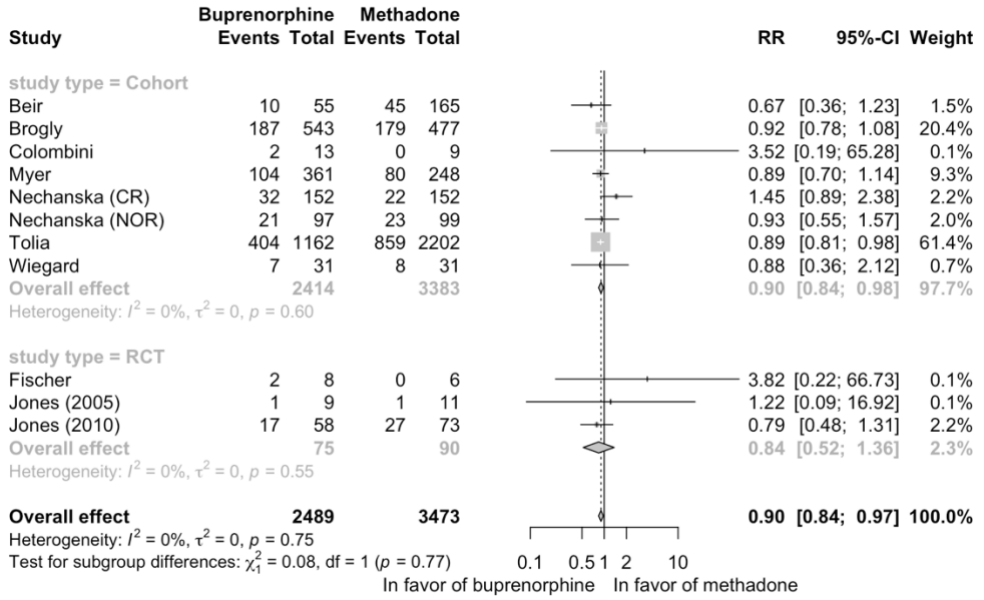


Figure 5-19: Forrest plot of relative risk of caesarean section after exposure to buprenorphine or methadone during gestation.

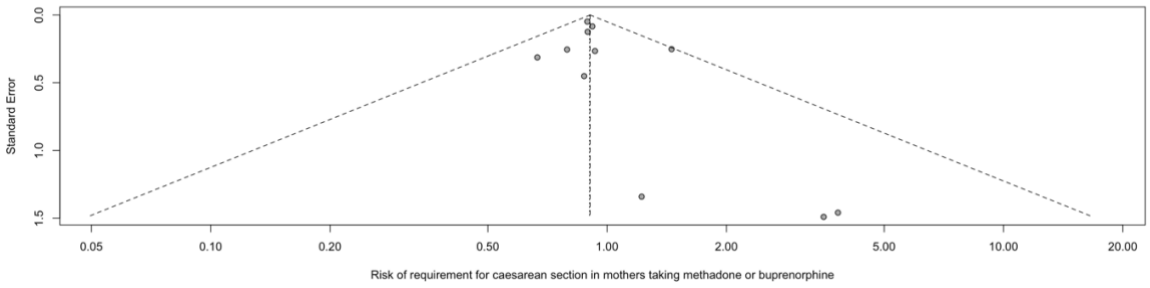


Figure 5-20: Funnel plot of standard errors for caesarean section rate in mothers taking methadone or buprenorphine.

5.5 Discussion

This meta-analysis shows that offspring exposed to buprenorphine, compared to methadone, have greater birth weight, longer length at birth, and lower risk of prematurity in both RCTs and cohort studies. In RCTs, there was a greater risk of maternal adverse events with methadone but higher drop-out rates with buprenorphine. Analysis of the cohort studies demonstrated greater head circumference, longer gestation, lower requirements for NAS treatment, shorter neonatal hospital stay, and reduced risk for caesarean section. However, these differences were not observed in the RCTs. There was no difference in risk of congenital malformations, small for gestational age, stillbirths or additional maternal opioid use in cohort studies, with insufficient data to analyse these outcomes in RCTs. There was insufficient data to make firm conclusions on longer-term childhood outcomes. Similarly, adjusted estimates accounting for potential confounders were only available in half of the cohort studies and for only four outcomes. Of these, only the duration of hospital admission remained statistically significant in adjusted analyses. Collectively, these data would suggest that buprenorphine may be beneficial compared to methadone. However, larger, more robust studies are required.

This meta-analysis updates existing literature to include all available evidence from both RCTs and observational cohort studies comparing methadone and buprenorphine for opioid-using mothers. Our findings confirm the results of previous meta-analyses regarding the beneficial effects of buprenorphine on growth. Three smaller meta-analyses (n = 271 to 2146) have been published on this topic[257,259,260]. Two meta-analyses[259,260] included RCTs and observational studies, while a third meta-analysis[257] was conducted including only RCTs (3 studies[254-256] comparing methadone to buprenorphine). The meta-analysis of RCTs and observational studies by Brogly et al. reported an association between lower NAS treatment risk and treatment duration and shorter hospital stay in neonates exposed to buprenorphine compared with methadone in a sample of 1,370 patients[259]. Buprenorphine was associated with greater mean gestational age, higher birthweight, longer length at birth, and larger head circumference at birth, and reduced illicit maternal opioid use near delivery. Adjustment for bias, including confounding by indication, attenuated these findings, but there was

still clinically and statically significant improvement in the buprenorphine group. In 2016, a meta-analysis including three RCTs and 15 cohort studies (2,146 patients) reported similar results, with buprenorphine-exposed offspring having a lower risk of preterm birth, greater birth weight, and larger head circumference compared with methadone-exposed offspring but did not adjust for confounding[260]. A 2020 Cochrane review by Minozzi et al. included four randomised controlled trials (271 patients), three of which directly compared buprenorphine to methadone; this analysis found no significant differences in maternal or neonatal outcomes between treatments[257]. Evidence was considered of moderate or low quality due to small sample sizes and high drop-out rates, as well as a lack of reporting of smoking status and inconsistencies in results. Long-term development outcomes were not included in these meta-analyses.

In our meta-analysis, we estimate a weighted mean increase in birthweight of 184 grams in cohort studies and 343 grams in RCTs in buprenorphine-exposed, compared to methadone-exposed offspring. This compares favourably to the 174 grams reduction in birthweight seen in offspring of women who smoke during pregnancy to those who do not smoke cigarettes[298]. The magnitude of improvement should be interpreted cautiously due to possibilities of bias, especially as our meta-analysis could not control for differences in smoking rates between groups.

There are several strengths to this study. We included both cohort studies and RCTs, used comprehensive search terms, and reported a wide range of maternal and offspring outcomes, including longer-term childhood development. We report pooled results, separately for both RCTs and observational studies, reflecting what we believe is the totality of research directly comparing methadone and buprenorphine in pregnancy. The main limitation of this study is that we did not adjust for confounding by indication in the included observational studies, which may predispose to bias. It is believed that higher-risk opioid-using mothers may preferentially be treated with methadone rather than other agents[220]. Higher-risk patients are expected to have neonates with poorer outcomes due to differences in opioid substitution use as well as other drug use, increased maternal stress and smoking rates.

When correction for confounding by indication was accounted for in a previous meta-analysis, indices of growth differences were no longer significant,

but the level of NAS treatment remained reduced[259]. A further meta-analysis by Zedler et al. did not correct for confounding, arguing that any corrections were based on largely "subjective" and potentially severe assumptions for key parameter values[220,260,299]. Similarly, to Zedler and colleagues, we did not correct for bias in this study as it is unclear to what direction or extent bias can exist. We were concerned that introducing a correction factor based on prior beliefs might introduce further bias. It is also possible that any existing bias due to differences in prescription practices, training, and familiarisation may change over time. Whilst we agree that, ideally, correction for confounding would be performed, this methodology requires further development before being widely implemented. We have reported analyses using adjusted estimates where these are available. However, we accept that these are reported in only half of the included cohort studies and for only a minority of outcomes.

A further limitation of this study was the significant risk of bias due to high drop-out rates and lack of *a priori*-published protocols in randomised trials. These limitations are substantial but expected when investigating the topics of opioid replacement in pregnancy due to the population studied and side-effects of treatment programs.

This meta-analysis has highlighted that further research is required into longer-term childhood development, specifically looking at any differences between drug groups and formulations. Few studies have investigated developmental outcomes, and meta-analysis has not been performed. Opioid replacement (buprenorphine or methadone), compared to no opioid replacement, is negatively associated with a range of offspring developmental outcomes, but differences between specific opioids have not been thoroughly investigated[118,186,251,300-303]. The measurement of developmental effects is complicated by a multitude of factors, including type and timing of testing, pre-existing differences between groups, and difficulties in recruiting participants. Development concerns are increased in the first year of life [263], only to recede in later years[262,304]. Different drug formulations, such as buprenorphine-naloxone in combination, may have additional advantages, such as decreasing the risk of diversion and misuse. A recent meta-analysis of buprenorphine combined with naloxone compared with other opioid replacement regimes (methadone, buprenorphine, or long-acting opioids) showed no difference between groups but

did not include any longer-term follow-up[305].

Further randomised controlled trials, including larger populations and with less loss to follow-up, are aspirational but may not be feasible. Larger cohort studies using routinely collected healthcare data allow larger sample sizes than RCTs but are limited by their observational nature and potential confounding. Further efforts to control for confounding may be achieved by the collection of detailed data on demographics, social factors, other determinants of health, and other drug use, including smoking and alcohol.

This meta-analysis shows that buprenorphine is associated with improvements in growth when compared to methadone. The priority for opioid replacement care programs remains the delivery of non-judgmental support, addressing individual needs and maintenance of stability of treatment.

5.6 Post-publication review

Since the publication of our meta-analysis in the journal Substance Use & Misuse[271], a further large cohort study comparing methadone with buprenorphine treatment for opioid use disorder in pregnant women was published in the New England Journal of Medicine [272]. The authors analysed a cohort of 16,328 pregnancies where the mother was treated with either methadone or buprenorphine over eight years (2010-2018) in 47 US states and Washington, D.C. The sample was defined using Medicaid data. As most opioid-dependent patients are insured via Medicaid in the United States, this provided a representative sample. Neonatal outcomes were neonatal abstinence syndrome, preterm birth, small for gestational age, and low birth weight defined using validated algorithms. Maternal outcomes were caesarean section and severe maternal complications, defined as a composite of potentially life-threatening conditions caused or aggravated by pregnancy. All outcomes were ascertained at birth or in the 30 days following birth, and risk ratios for neonatal and maternal outcomes were calculated after adjusting for confounding variables using propensity-score weights.

The results of this large cohort study support our meta-analysis findings. Those on buprenorphine were more likely to be white and be diagnosed with depression, anxiety, or non-opioid substance use. Methadone users were more likely to take other opioids. A lower risk of adverse neonatal outcomes was seen in patients taking buprenorphine (adjRR 0.73 (95 CI: 0.71, 0.75). This compares with our meta-analysis's non-adjusted relative risk of 0.61 (95% CI: 0.45, 0.83). The risk of prematurity in the study by Suarez et al. was 0.58 (95% CI: 0.53, 0.62) in early pregnancy and 0.57 (95% CI: 0.53, 0.62) in late pregnancy. This compares to a relative risk of 0.61 (95% CI: 0.52, 0.71) in our analysis. The risk of small for gestational age was low in the 2022 study for the buprenorphine group with an adjusted relative risk of 0.72 (95% CI: 0.66, 0.80) in early pregnancy and 0.75 (95% CI: 0.69, 0.82) in late pregnancy. Again, this is similar to our analysis's relative risk of 0.76 (95% CI: 0.66, 0.88). Contrary to our results, there was no reduction in caesarean sections in the study by Suarez et al. In contrast, we demonstrated a slight reduction in the risk of caesarean section for those on buprenorphine (RR 0.90, 95% CI: 0.84, 0.97). However, this was due to

a risk reduction seen in a single study[281]. Similarly to our work, there was no analysis of any longer-term childhood developmental outcomes and this remains an area where further research is required.

The large sample size and adjustment for a range of potentially confounding covariates and the use of a propensity-score analysis for each exposure window are strengths of this study. Furthermore, sensitivity analyses assessing possible exposure and outcome misclassification and unmeasured residual confounding did not change the interpretation of the findings. This study adds to the growing body of literature supporting a reduction in adverse neonatal outcomes without detriment to maternal outcomes favouring buprenorphine over methadone. That effect estimates were similar for important clinical outcomes in our summary of the available evidence to this point, and in this large cohort study, the findings were strengthened. As we conclude in our article, the clinical priority remains providing patient-centred care with shared decision-making to facilitate stability in treatment.

5.7 Chapter summary

This meta-analysis of opioid replacement in pregnancy demonstrates that buprenorphine is associated with increased offspring growth, and gestation, and reduced length of stay in hospital compared with methadone. Following publication of our study, these results have been supported by an independent cohort study published in the New England Journal of Medicine.

This chapter builds on the findings of the narrative review in the prior chapter that showed buprenorphine is potentially favourable, compared to methadone. These chapters, and their related publications, allow a more evidence-based approach to the prescriptions of opioids in pregnancy that can potentially improve maternal and offspring health.

Chapter 6 Summary and future directions

6.1 Introduction

This MD investigated the impact of policies on alcohol and opioid substitution on maternal and offspring health, demonstrating that routinely collected medical data can be used to provide novel insights with which to inform patients, healthcare professionals and policymakers. In this final chapter of the MD, I will summarise the key results of this original research, as well as reflect on my own learning and possibilities for future work.

6.2 Results of this MD

Chapter one outlined how social determinants of health can result in inequalities in health outcomes across Scotland. Living in an area with higher indices of deprivation is associated with poorer health outcomes, including increased levels of alcohol and drug use, and their associated complications. A comprehensive outline of the public health measures introduced to combat alcohol related harm in the Scottish population was provided. The different health effects resulting from maternal alcohol and opioid use were explored.

In chapter two, it was demonstrated that the adoption of routinely collected national data has afforded a unique opportunity to create a linked dataset encompassing maternal and offspring outcomes across the population of Scotland, giving important insights into the health of hundreds of thousands of individuals over multiple years. A cohort of three hundred sixty thousand pregnancies were investigated to measure reported alcohol use and offspring outcomes, demonstrating that minimum unit pricing, but not other policies, was associated with a reduction in maternal alcohol consumption as well as a reduction in babies born small for gestational age, requiring admission to neonatal unit, and being stillborn over time. This chapter highlights that the data quality of SMR02 could be further improved (e.g. by including alcohol consumption data at different time-points throughout pregnancy) to facilitate alcohol related research and evidenced-based practice and policy.

Chapter three investigated whether alcohol consumption during pregnancy of between one and four units per week was associated with adverse perinatal outcomes compared to no alcohol or high-levels of alcohol consumption. In an analysis of over 340,000 pregnancies over a six year period, it demonstrated significantly improved outcomes (gestational age, birthweight and neonatal unit admission) in the low alcohol group compared to both non-drinking and high-level consumption groups. Increasing the volume of alcohol consumed per week increased the risk of perinatal harm, but there was no clear threshold at which harm started to occur.

Chapters four and five focused on the effects of opioid substitution therapies on maternal outcomes, comparing methadone and buprenorphine for maternal opioid substitution therapy. In a narrative review, I highlighted pharmacological reasons why buprenorphine might be beneficial to mothers and offspring due to improved stability on treatment and receptor modulation. In the subsequent meta-analysis, I demonstrated that the published body of evidence supports the use of buprenorphine over methadone. Subsequently, a large cohort study published in the New England Journal of Medicine has cited this work and supported these conclusions.

6.3 Strengths and limitations

The work presented in this thesis represents original research on alcohol and drug intake in pregnancy and has several strengths. The analysis on alcohol intake is the largest study of its kind and is based on a comprehensive dataset from an entire nation. The use of these data allows for the control of multiple confounding factors and has allowed for the measurement of impacts of interventions over time. This research has afforded a greater understanding of the effect of landmark policies such as reducing drink-driving limits, introducing minimum unit pricing, and advising complete abstinence from alcohol during pregnancy. Improved awareness of the effects of these interventions may lead to a more informed policy debate, directing allocation of resources in the most effective manner. The use of a routinely collected NHS administrative data improves reproducibility, allowing for further iterations of this work as new policies are implemented at minimal additional cost to future researchers.

The access to contemporaneously recorded alcohol intake in volume per week for each mother in the analysis is a major strength of this work. The data that this provides allows investigation of the dose-response relationship between alcohol consumption and perinatal outcomes, thus helping to support informed decisions framed on risk. Previous research which has mainly compared high levels of alcohol consumption to abstinence has been unable to further inform our understanding of the effects relating to alcohol consumption of under four units of alcohol per week. This thesis will contribute towards informing clinical recommendations and future public health messaging.

The systematic review and meta-analysis on opioid substitution demonstrated that buprenorphine can have beneficial effects compared to the older therapy of methadone. The use of a meta-analysis allows us to inform care using a systematic summation and appraisal of the available evidence without the requirement to wait for further large cohort or randomised controlled trials. The results of this meta-analysis will help to improve outcomes for those with complex health needs in pregnancy.

Whilst this thesis has several strengths, there are some limitations, mainly relating to the accuracy of alcohol reporting and generalisability of the findings. In the analysis of alcohol consumption, there is a recognition of a reliance on self-reported intake, with no direct control on data collection. This dependency on self-reported consumption could have biased the results. It is possible that there was inaccurate disclosure or recording of amounts, leading to the study failing to demonstrate changes in perinatal outcomes when they did exist, or vice versa. We addressed this using a variety of sensitivity analyses outlined in Chapters two and three. In addition, due to the single time point at which alcohol consumption was recorded, we were unable to measure effects of alcohol in early pregnancy. Further, the study was not able to measure the effects of alcohol on neurological or developmental outcomes due to limitations in the data available. The meta-analysis on opioid substitution therapies is limited by the high risk of bias in the studies analysed. The lack of blinding, high attrition rates, small sample sizes and lack of control for potential confounding factors all effect the validity of the studies. Nevertheless, there is a clear physiological basis for why buprenorphine should have more favourable effects, and the meta-analysis supports this.

6.4 What this MD means

This thesis has many implications for the health of pregnant women, healthcare staff, and policymakers. The following section will highlight the learning points in terms of alcohol policy and drug policy both at a national level, and in an international context.

6.4.1 Implications for women

Women who are pregnant should be reassured by many of the findings of this research. We have demonstrated that there is relatively little impact of low-level alcohol consumption in pregnancy on birth outcomes. As one in four women drink in early pregnancy (in some cases prior to them being aware that they are pregnant), this should provide reassurance that birth outcomes are unlikely to be significantly affected by low level consumption. Parents should however bear in mind that FASD remains a risk, and that this was not investigated in this study.

This work has also demonstrated benefit in continuing established opioid replacement therapy if this is working well for the woman. We have shown that stability of opioid replacement therapies is the key factor, but if tolerated, then buprenorphine might have an optimal profile. As a significant proportion of new patients on opioid replacement will take buprenorphine, this work should provide reassurance should they become pregnant, that perinatal outcomes are better than on older therapies such as methadone or no opioid replacement.

The combination of these results highlights that stability and moderation is key in terms of opioid substitution and alcohol consumption. We know that pregnancy is a time of many stressors, but women should be reassured that significant changes in stable therapies is not required.

6.4.2 Implications for healthcare workers

Midwives and other healthcare workers should be equally reassured by these results. This MD has increased the evidence base for both the effects of alcohol and drugs in pregnancy. With a shift to a higher level of continuity of care from midwives in Scotland, midwives should continue to listen to their patients,

developing plans for care based on shared goals and priorities. As outlined in the 2024 MBRRACE-UK maternal health report, mental health and access to care remains difficult for some women[212]. Women with complex care needs require additional support, and the use of evidence based individualised care alongside effective public health strategies is key in optimising outcomes.

6.4.3 Implications for policy makers

For policymakers, this MD adds evidence towards a focus on health improvement, particularly in women who have higher levels of adverse social factors. Addressing clusters of adverse health behaviours such as smoking and alcohol consumption, and educating women in the additional harms caused by these behaviours (particularly if concurrent) is important.

The work presented in chapters 4 and 5 strengthen the evidence base for buprenorphine role out as viable opioid replacement therapy during pregnancy. There is a lack of data on the precise numbers of pregnant women in Scotland taking methadone compared to buprenorphine. It is possible that the number are increasing following smaller pilot studies of longer acting buprenorphine in the non-pregnant general and prison populations[306]. It is known that buprenorphine is now the most prescribed opioid substitute used in pregnant women in the US[307]. The work presented in this MD could support NICE, Scottish Medicines consortium and regional health boards to update their recommendations to support the optional opioid replacement therapy in pregnancy.

Finally this MD supports evidenced based decision making, demonstrating that routinely collected data relating to healthcare interactions can have additional benefits for society, and lead to unique insights into population health and policy.

6.5 Future work

In this thesis, I have demonstrated that maternal alcohol recording can provide insights into the both the prevalence and outcomes associated with early alcohol intake in pregnancy. A modified version of chapter two is being prepared for submission to the BMJ. We aim to publish the results to share our finding with a wide audience. Following the communication of these results, the data used in this MD can continue to be used to monitor alcohol intake with particular focus on long term trends as well as changes associated with the increase in MUP to 65p from September 2024. I hope that the Scottish Government will continue to use these data to monitor maternal health in a similar way to the recording of alcohol outside pregnancy. This MD has highlighted a lack of data on FASD and I would recommend that the accuracy of FASD diagnosis should be improved, thus allowing for enhanced monitoring of this condition similar to the more robustly recorded peri-natal outcomes.

With regards to drug policy, our meta-analysis yielded similar results to a large US cohort study and supports that Buprenorphine may have benefits for perinatal outcomes. From my discussions with patients with lived experience of drug uses, depot injections are well tolerated and may allow for improved quality of life. Research on the impact of depot injection of buprenorphine compared to sub-lingual use in the obstetric population is warranted.

During the time period of this MD, I have transitioned into working as a full-time critical care clinician. The insights I have gained in completing this MD will support my wider understanding of the impact of chronic health conditions, associated medication burden and social determinants of health. We know that 53% of patient discharged from ICU will be admitted to hospital in the following year and that there are multiple risk factors for this[308]. Due to the heterogeneity of our patients, there is not a good predictor score for individual patients, but the use of large data cohort might allow us to find patterns and trends that are adjustable[309]. I am keen to support further development with more data that could culminate in the development of a business case for the implementation of additional resources to look at a diverse range of patients. In my clinical role, I have started to work with critical care follow up and drug addiction teams in Tayside. I have seen first-hand the impact critical illness has on patients and the

lack of investment that is being placed into health improvement. I hope that I can make good use of the skills that I have developed to support a transition towards a health care model that is more proactive in facilitating health and less dependent on treating illness, often at times of crisis for patients and families.

6.6 My development

This MD marks the end of the beginning of my research career. During this time, I have developed my skills in team working, dealing with uncertainty, organisation, data management and development of hypotheses. I am fortunate to have had access to grant funding support from Wellbeing of Women as well as from the team of researchers who have supported me to develop the concepts of the MD into the thesis that you have read.

When I started as a student in early 2019, the COVID pandemic was just about to emerge, and this stress tested my idea that a dataset can be used to develop insights into public health. The pandemic showed us how health (or illness) can be traced on a national scale and how systems can adapt to this data in near real time. This MD has allowed me to develop a detailed understanding on how this works, in a practical sense and as well as the associated issues and limitations. My belief is that with large scale health dataset we can explore health behaviours in more detail that we can in sampling for a study.

This MD has developed my understanding of the complexity around health care and researching its effects. The underlying theme of this MD relates to the importance of the social determinants of health, and that health (or illness) is largely determined via life events, conditions, and stressors in the communities in which we all live. The work on this MD has cemented my belief that that the social determinants of health are the keystone of health policy. I believe that I now have the skills to lead areas of research outlined in the section on future work. I will use these insights to add to the discussion about public health in a meaningful way, acting as an advocate for the health of my patients on an individual level as well as nationally.

Appendix 1: Studies included in Meta-Analysis

Study	Period	Type	Sample (N)	Location	Inclusion criteria	Results	Adjusted results
Bier, 2015, USA	1996 – 2014	Retrospective cohort study	220 165 methadone 55 buprenorphine	Developmental Paediatric clinic, USA	Inclusion: All offspring born in clinic during study period Exclusion: Not specified	Total birth weight of offspring: methadone 2751g (SD ± 599), buprenorphine 2895g (SD ± 569) Gestational age at birth: methadone 37.5weeks (SD ± 3), buprenorphine 38weeks (SD ± 3) Prematurity: methadone 31 (19%), buprenorphine 5 (9%) Treatment for NAS: methadone 145 (88%), buprenorphine 45 (82%) Length of offspring hospital admission: methadone 39.9 (SD ± 24.3) buprenorphine 21 (SD ±13) Caesarean section rate: methadone 45 (27%), buprenorphine (18%) Development assessment: Bayley Mental Development Index Low dose methadone: 96.6(SD ±7), high dose methadone 94.3(SD ± 9) buprenorphine 95.7(SD ± 7). Alberta Infant motor score: Low dose methadone: 44.8(SD ±24), High dose methadone 38.1(SD ±24), buprenorphine 53.5 (SD±2). Suspect or abnormal neurological exam Low dose methadone: 19 (23%), high dose methadone 17 (21%), buprenorphine 7 (13%) Methadone group divided into low dose (<100mg / day) methadone (n=84) or high dose (n=81) during this study. Meta-analysis conducted as one group (methadone) compared to buprenorphine.	No adjusted results published.

Brogly, 2017, USA	2006-2011 & 2015-2016	Retrospective cohort study	1020 477 methadone, 543 buprenorphine	Massachusetts Medicaid Analytic eXtract (MAX) dataset (2006-2011) and Boston dataset (2015 – 2016)	Inclusion: Age over 14yrs, delivered between 2006 – 2011 and had a Medicaid claim with opioid (or other drug) dependency. Exclusion: not specified	Prematurity: methadone 155 (32.9%), buprenorphine 99 (18.4%) Small for gestational age: methadone 61 (13%), buprenorphine 54 (10.9%) Length of offspring hospital admission: methadone 21.4days (SD ±15.7) buprenorphine 13.9days (SD ±12.6) Caesarean Section: methadone 179 (37.5%), buprenorphine 187 (34.3%)	Adjustments for maternal age, race/ethnicity, year of delivery, pre-natal selective serotine reuptake inhibitors or benzodiazepine before opioid substitution therapy. Buprenorphine compared to methadone. Prematurity: Risk ratio (RR) 0.53 (95% CI 0.39, 0.71) Small for gestational age: RR 1.13 (95% CI 0.77, 1.69) Length of hospital stay (days): -3.66 (-5.46, -1.87)
Colombini, 2008, France	1998 – 2004	Prospective cohort study	21 9 methadone 13 buprenorphine	Single addiction centre in Marseille France.	Inclusion: Offspring exposure to buprenorphine or methadone in pregnancy (mothers on established programs) Exclusion: not specified	Total birth weight of offspring: methadone 2826g (SD ± 461), buprenorphine 3093g (SD ± 342) Gestational age at birth: methadone 39.1weeks (SD±1.8), buprenorphine 39.9weeks (SD± 0.8) Treatment for NAS: methadone 9 (100%) and buprenorphine 13 (100%) Caesarean section: methadone 90 (0%), buprenorphine 2 (15%) Onset of NAS (range – hrs): methadone 6-24hrs, buprenorphine 24-168hrs. Not analysed in meta-analysis as only range presented.	No adjusted results published.

Ebner, 2007, Austria	Not specified	Prospective cohort study	36 22 methadone 14 buprenorphine	Single Specialist clinic in Austria	Inclusion: All neonates born to women who met criteria for opioid dependence during pregnancy (DSM-IV 304.0) and were enrolled in opioid maintenance therapy. Exclusion: Neonates born to mothers with alcohol and/or benzodiazepine co-dependency and twin pregnancies	Treatment for NAS: methadone 7(32%), buprenorphine 11 (74%) Time to develop NAS: methadone 57.5hrs (SD ± 37.5), buprenorphine 34.4hrs (SD ± 5.3) Birth weight, total length at birth and head circumference were reported to be not statistically significantly different between groups, due to lack of groups. Not including in meta-analysis due to lack of report of means or variation.	No adjusted results published.

Fischer, 2006, Austria	2000 - 2002	Randomised control trial	18 9 methadone 9 buprenorphine	Single addiction clinic at the Medical University of Vienna, Austria	Inclusion: Opioid-dependent pregnant women diagnosis (DSM-IV = 304.0), older than 18 years, who presented at the addiction clinic of the Medical University Vienna. Informed consent and were willing to follow the protocol and to avoid use of illegal drugs whenever possible. Exclusion: outside recruitment window of 24 and 29 of pregnancy, positive drugs test for cocaine, benzodiazepine and severe somatic or other severe psychiatric diseases or a high-risk pregnancy.	Pre-term delivery (<37 weeks): methadone 3, buprenorphine 2, Treatment for NAS: 8 required treatments 3 in methadone group (50%), 5 in buprenorphine group (63%) Start of Treatment for NAS methadone 60hrs (SD11.3), buprenorphine 72hrs (SD 35.2) Caesarean section: methadone group 0, buprenorphine group 0 Dropouts of treatment: methadone 3, buprenorphine 1 Total birth weight of offspring mean: 2820g – not reported per group except for “no difference” therefore not analysed.	No adjusted results published.

Gawronski,2014, USA	2010 – 2011	Retrospective cohort study	150 92 methadone 58 buprenorphine	Single centre medical centre Ohio (USA).	Inclusion: 18 years of age with a history of opioid dependence currently enrolled in a treatment program and stabilized on buprenorphine/naloxone or methadone Exclusion: not specified	Total birth weight of offspring: methadone 2905g (SD ± 567), buprenorphine 2904(SD ± 522) Total body length of offspring at birth: methadone 49cm (SD ± 4), buprenorphine 49 cm (SD ± 4) Head Circumference: methadone 33cm (SD ± 3), buprenorphine 33cm (SD±3) Preterm birth: methadone 22 (24%), buprenorphine 10 (17%). Gestational age at birth: methadone 37weeks (SD ± 2), buprenorphine 38weeks (SD ± 2) Treatment for NAS: methadone 74 (80%), buprenorphine 37 (64%) Time to NAS onset: methadone 2days (range 1-9), buprenorphine 2 days (range 1-6). No analysed in meta-analysis due to unit of measure not being hours and only ranges presented. Length of offspring hospital admission: 10 days (SD ± 8), buprenorphine 9days (SD ± 6) Caesarean section: 20% - not analysed in meta-analysis as no group break down.	No adjusted results published.

Jones, 2005,USA	2000 – 2003	Randomised control trial	30 15 methadone 15 buprenorphine	Single centre - Centre for Addiction and Pregnancy, USA.	Inclusion: 21–40 years of age; estimated gestational age (EGA) by sonogram of 16–30 weeks; DSM-IV diagnosis of current opioid dependence; requesting maintenance pharmacotherapy; recent self-reported opioid use (more than 4 days of use in the past 7 days); and an opiate positive urine specimen at intake. Exclusion: a urine positive for undocumented methadone during intake; a current DSM-IV diagnosis of alcohol abuse or dependence; self-reported use of benzodiazepines (more than seven times per month and/or more than once a week); currently taking medication for another Axis I disorder; presence of a serious concurrent medical illness contraindicating study participation; diagnosis of pre-term	Total birth weight of offspring: methadone 3001.8g(SE ± 120.7), buprenorphine 3530.4g(SE ± 162.7) Head circumference: methadone 33.2cm (SE ± 0.48), buprenorphine 34.9cm (SE ± 6.40) Gestation: methadone 38.8weeks (SE ± 0.56), buprenorphine 38.8 weeks (SE ± 0.76) Preterm births: methadone 1 (9.1%), buprenorphine 0(0.0%) Treatment for NAS: methadone 5(45%), buprenorphine 2 (20%) Duration of hospital stay: methadone 8.1days (SE ±0.78), buprenorphine 6.8 days (SE ± 0.86) Caesarean section: methadone 1 (9%), buprenorphine 1 (11%) 20 completed (11 methadone, 9 buprenorphine) Dropouts from treatment: methadone 4 (3 missed doses, 1 elective withdrawal), buprenorphine 6 (1 medical condition, 4 missed doses, 1 elective withdrawal)	No adjusted results published.

					labour; evidence of foetal malformation; positive HIV test; or positive sickle cell trait		

Jones, 2010, Multi - centre (USA + Austria)	2005 – 2008	Randomised control trial	175 89 methadone 86 buprenorphine	Multiple centres in North America and Europe	Inclusion: prescription of opioid replacement Exclusion: medical or other conditions contraindicating participation, pending legal action that might prevent their participation, disorders related to the use of benzodiazepines or alcohol, and birth planned outside the hospital at the study site.	Total birth weight of offspring: methadone 2878g (SE ± 66.3), buprenorphine 3092g (SE ±72.6) Total body length of offspring at birth: methadone 47.8cm (SE ± 0.5), buprenorphine 49.8cm (SE ± 0.5) Infant head circumference: methadone 33.0cm (SE ± 0.3), buprenorphine 33.8cm (SE ± 0.3) Prematurity: methadone 14(19%), buprenorphine 4(7%) Gestation age: methadone 37.9weeks (SE ± 0.3), buprenorphine 39.1weeks (SE ± 0.3) Treatment for NAS: methadone 41 (57%), buprenorphine 27 (47%) Duration of hospital stay methadone 17.5days (SE ± 1.5), buprenorphine 10.0days (SE ± 1.2) Foetal abnormalities: 1 case of dextrocardia reported (as surgical correction documented), no other reports but several other surgical procedures performed. Not analysis due to uncertain regarding incidence per group. Maternal adverse events: methadone 83 (93%) nonserious maternal events, and 14 (16%) serious. Buprenorphine 66 (77%) nonserious maternal events, and 8 (9%) serious. Caesarean section: Methadone 27 (37%) and Buprenorphine 17 (29%) Drop out from treatment: Methadone 16 (voluntary withdraw 10, involuntary 6) buprenorphine 28 (voluntary 26, involuntary 2)	No adjusted results published.

Kakko,2008,Sweden	1982 – 2006	Cohort study (Mixed – retrospective and prospective)	56 26 methadone 39 buprenorphine	Hospital ante-natal clinic in Stockholm, Sweden.	Inclusion: Prescription of methadone or prescription of buprenorphine and a DSM-IV criteria for drug dependency for at least 1 year. Exclusion: not specified	Intra-uterine deaths: methadone 0, buprenorphine 2 (5% Gestational age at birth: methadone 38.6 weeks (SD ± 1.5), buprenorphine 39.5weeks (SD +- 2.0) Total birth weight of offspring: methadone 2941g (SD ± 483), buprenorphine 3250g (SD ± 528) Total body length at birth: methadone 47.6cm (SD ± 2.2), buprenorphine 48.4cm (SD ±2.5) Head Circumference: methadone 33.8cm (SD ± 1.5), buprenorphine 34.0cm (SD±1.4) Treatment for NAS: methadone 19 (52.8%), buprenorphine 7(14.9%) Length of offspring hospital admission: methadone 19.7days (SD ± 18.8) buprenorphine 9.4days (SD ± 8.4)	No adjusted results published.
Kaltenbach, 2018, Multi-centre (North America + Europe)	2005 – 2008	Randomised control trial	Randomised control trial	Multicentre in North America and Europe	Inclusion: Recruited in Jones 2010, with same inclusion criteria. Exclusion: as per Jones 2010.	Offspring development at 3-36months within normal range, no difference between buprenorphine and methadone.	No adjusted results published.

Konijnenberg, 2014, Norway	2005 – 2007	Prospective Cohort study	66 24 methadone 11 buprenorphine 31 controls	Multiple opioid maintenance therapy centres throughout Norway	All women in Norway during time period who gave informed consent.	No non adjusted results published.	Resulted adjusted for maternal education and employment. Executive function was lower in exposure neonatal compared to none exposed but mean group scores fell within the normal range of development. No difference demonstrated between methadone and buprenorphine.
Lacroix, 2011, France	1998 – 2006	Prospective cohort study	135 45 methadone 90 buprenorphine	French maternity hospitals, maintenance therapy centres, and general practitioners involved in addiction care.	Inclusion: opioid replacement therapy. Exclusion Exclusion: multiple substitution therapies in the same pregnancy.	Total birth weight methadone 2,892g (SD± 506), buprenorphine 2,731g (SD ± 634) Length methadone 47.6cm (SD ± 2.5) buprenorphine 47.1cm (SD ± 3) Prematurity methadone 4 (9%), buprenorphine 16 (18%) Treatment for NAS methadone 20 (80%) buprenorphine 20 (23%) Onset of NAS: methadone 2.0days (SD ± 1.8), buprenorphine 2.8days (SD ±1.8) Maternal opioid use (Heroin): methadone 20 (44.4%), buprenorphine (16.7%) Malformations: methadone 2 offspring, buprenorphine 5 offspring Stillbirths: methadone 2 buprenorphine 1	Adjustments of requirement for treatment for NAS during concurrent heroin use and benzodiazepine. Requirement for NAS treatment controlled for heroin use: odd ratio (OR) 1.8 (95% CI 0.8 – 4.1). Requirement for NAS treatment controlled for benzodiazepines use: OR 1.49 (0.94 - 2.35)

Lejeune, 2006, France	1998 – 1999	Prospective cohort case control study	259 100 methadone 159 buprenorphine	35 French perinatal centres and public hospitals	Inclusion: Receiving drug substitution that had started before or during this pregnancy Exclusion: not specified	Treatment for NAS: methadone 50 (49%), buprenorphine 78 (52%) Duration of hospital admission: methadone 28days, buprenorphine 16 days (not analysis as no presentation of distribution), Total birth weight of offspring (2822g), gestation (38.6weeks) or prematurity (14.6%) not analysis in meta-analysis as no per group analysis. Mean duration of treatment methadone 17days, buprenorphine 16 days (not analysed as not presentation as distribution not reported).	No adjusted results published.

Meyer, 2016, USA	2000 - 2012	Retrospective cohort study	609 248 methadone 361 buprenorphine	Single addiction centre in USA	Inclusion: All subjects in the centre between 2000 – 2012 with exposure to methadone or buprenorphine Exclusion: Enrolment in the MOTHER study (Jones 2010), not on opioid replacement, on opioid for other reason that addiction, delivered outside intuition or APGAR score of 0 (stillbirth)	Total birth weight of offspring: methadone 2899.7g (SD ± 583.1), buprenorphine 3143.3g (SD ± 578.9) Head circumference at birth: methadone 33.0cm (SD ± 2.0), buprenorphine 33.6cm (SD ± 2.1) Gestational age at birth: methadone 38.2weeks (SD ± 2.5), buprenorphine 39.2weeks (SD ± 2.2) Treatment for NAS: methadone 106 (42%), buprenorphine 82 (23%) Duration of treatment for NAS: methadone 133days (SD ± 83), buprenorphine 82days (SD ± 60) Length of offspring hospital admission (if EGA ≥ 37 weeks): methadone 5.6days (SD ± 2.8), buprenorphine 4.2days (SD ± 12.6) Stillbirths: methadone 4, buprenorphine 2 (1 mother in methadone group had twins, this is recorded as 1 still birth) Congenital deformity: methadone 1, buprenorphine 1 Total birth weight of offspring <5th Percentile: methadone 32 (13%), buprenorphine 40 (11%) – not analysed under SGA in meta-analysis due to difference to standard definition of 10th percentile.	No adjusted results published.

Nechanská, 2018, Norway	2004 – 2013	Retrospective cohort study	23599 methadone 97 buprenorphine	Entire Norwegian population	Inclusion: All patients prescribed of methadone or buprenorphine in Norway. Birth data from Medical Birth Registry of Norway (MBRN) and prescription from Norwegian Prescription Database (NorPD). Exclusion: not specified	Total birth weight of offspring: methadone 3268g (SD ± 603), buprenorphine 3333g (SD ± 437) Birth length: methadone 48.7com (SD ± 3.0), buprenorphine 49.3 (SD ± 2.0) Head circumference: methadone 34.4cm (SD ± 1.5), buprenorphine 34.7cm (SD ±1.6) Gestational age at birth: methadone 38.9weeks (SD ± 1.9), buprenorphine 39.2weeks (SD ± 2.4) Stillbirths: methadone <4, buprenorphine 0 (incidence recorded as less than 4 due to data-protection legislation) Preterm birth: methadone 9 (9.3%), buprenorphine 5 (5.2%) Small for gestational age at birth: methadone 10 (10.3%), buprenorphine 5 (5.2%) Treatment for NAS: methadone 55 (44.2 – 64.9) buprenorphine 51 (43.2-63.9) Caesarean section: methadone 23 (23.7%), buprenorphine 21 (23.7%)	Adjusted for maternal age, marital status, education, and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group. Preterm birth: Odds Ratio (OR) 0.73 (95% CI: 0.16 to 3.36) Small for gestational age: OR 0.83 (95% CI: 0.22 to 3.20) Treatment for NAS 0.94 (95% CI: 0.46 - 1.92) Linear regression performed for continuous dependant variables. Not analysed as unable to pool published results. Gestational age age Beta-coefficient (ß) 0.48 (95% CI: 0.29 to 1.25), Total Birth weight of offspring: ß 83.1 (95% CI:-100.8 to 267.0), birth Length: ß 0.47 (95% CI: 0.35 to 1.29), Head circumference: ß 0.57 (95% CI: 0.04 to 1.18)

Nechanská, 2018, Czech Republic	2000 - 2014	Retrospective cohort study	333 152 methadone 152 buprenorphine	Entire Czech Republic population	Inclusion: All patients in Czech Republic prescribed OAT as taken from National Register of Reproduction Health (NRRH) and National Register of Addiction Treatment (NRAT) datasets. Exclusion: not specified.	Total birth weight of offspring: methadone 3017g (SD ± 476), buprenorphine 3115g (SD ± 453) Small for gestational age at birth: methadone 19 (12.8%), buprenorphine 21 (13.8%) Birth length: methadone 48.1cm (SD ± 2.4), buprenorphine 48.6cm (SD ± 2.3) Head circumference at birth: methadone 33.8cm (SD ± 1.8) buprenorphine 34.0cm (SD ± 1.6) Gestational age at birth: methadone 38.3weeks (SD ± 2.6) buprenorphine 38.5weeks (SD ± 2.7) Stillbirth: methadone 4 (2.6%) buprenorphine 0 (0%) Preterm births: methadone 25 (16.9%) buprenorphine 25 (16.4%) Caesarean Section: methadone 23 (14.6%), buprenorphine 32 (22.1%) After adjustment for maternal age, marital status, education, and tobacco smoking during pregnancy	Adjusted for maternal age, marital status, education and tobacco smoking during pregnancy published. Buprenorphine compared to methadone, with methadone being the reference group. Preterm birth OR:0.92 (95% CI 0.48 to 1.74) Small for gestational age at birth OR 1.07 (95% CI: 0.52 to 2.21) Linear regression performed for continuous dependant variables. Not analysed as unable to pool published results. Gestational age ß: 0.05 (95% CI: 0.68 to 0.59), Total birth weight of offspring ß 111.6 (95% CI: 10.5 to 233.6). Birth length: ß 0.45 (95% CI: - 0.17 to 1.08), Head circumference at birth ß 0.12 (95% CI: 0.41 to 0.65).

Nørgaard, 2015, Denmark	1997 – 2011	Retrospective cohort study	Total 364 197 methadone 167 buprenorphine	Entire Danish population	Inclusion: Danish population between 1997 – 2011 in the Danish Medical Birth Registry. Exclusion: not specified	Pre-term birth: methadone 41(21.2%), buprenorphine 25(15%) Small for gestational age at birth: methadone 7(3.6%), buprenorphine 4 (2.4) Treatment for NAS: methadone 106 (54.9%), buprenorphine 11 (6.6%) Congenital malformation: methadone 20 (10.4%), buprenorphine 14 (8.4%)	No adjusted results published.
Pritham, 2013, USA	2005 – 2007	Retrospective cohort study	152 136 methadone 16 buprenorphine	Neonatal ICU, USA	Inclusion: Infants of mothers who received methadone or buprenorphine prescription in pregnancy and over 27 weeks' gestation Exclusion: None specified	Maternal use of opioids: methadone 128 (94%), buprenorphine 14 (93%). Gestational age at birth: methadone 37.6weeks (SD ± 2.1), buprenorphine 38.2weeks (SD ± 1.8) Birth weight: methadone 3132.7g (SD ± 2695.1), buprenorphine 3196.5g (SD ± 508.6) Head circumference: methadone 32.9cm (SD ± 2.6), buprenorphine 33.8cm (SD ±1.2) Small for gestation age at birth: methadone 14 (10.5%), buprenorphine 0 (0%) Treatment for NAS: methadone 115, 84.6%), buprenorphine 11 (68.8%) Age treatment started: methadone 1.84days (SD ±1.35), buprenorphine 1.87days (SD ±1.88) Length of hospital stay: methadone 21.3days (12.6), buprenorphine 13.7days (11.9)	Regression model used to examine methadone exposed offspring and length of stay not analysed as no comparison to buprenorphine published.

Tolia, 2018, USA	2011 – 2014	Retrospective cohort study	3364 2202 methadone 1162 buprenorphine	Pediatrix Clinical Data from neonatal ICUs across the USA (241 centres)	Inclusion: singleton infants born ⩾36 weeks' gestation and diagnosed with NAS at or before 7 days of age. Exclusion: not specified	Total birth weight of offspring: methadone 3047g (SD ±474) buprenorphine 3000g (SD ± 467) Gestational age at birth: methadone median 39weeks (range 38-39), buprenorphine median 39weeks (range 37-39) – no meta-analysis due to medium / range provided not standard deviation. Small for gestational age at birth: methadone 400 (18%), buprenorphine 158 (14%) Caesarean section: methadone 859 (40%), buprenorphine 404 (36%)	Adjusted results for maternal age, parity, race and ethnicity, prenatal care, smoking status, use of antidepressants, use of benzodiazepines, gestational age, small for gestational age status, caesarean delivery, sex, out born status, type of pharmacotherapy, breast milk use, year and controlled for centre with robust sandwich variances) Not analysed as unable to pool published results. Small for gestational age at birth: Hazard Ratio (HR) 0.87 (0.78, 0.97, 95% CI 0.78, 0.97). Caesarean delivery HR 0.98 (0.90, 1, 1.07)

Whitham, 2010, Australia	2002 - 2006	Open-label non-randomised flexible-dosing longitudinal study	52 22 methadone 30 buprenorphine	2 specialist drug and alcohol antenatal clinics Adelaide, South Australia.	Inclusion: prescription of methadone o buprenorphine and <28 weeks gestational and mothers aged between 16-40yrs. Exclusion: medical illness requiring medication that interacted with the maintenance drug or was known to affect pregnancy outcomes; alcohol consumption greater than seven standard drinks per week; multiple pregnancy; any signs of congenital foetal malformations on admission; participation in another clinical research project that interfered with the present study.	Total birth weight of offspring: methadone 2749.09g (SD ± 484.32), buprenorphine 3055.52 (SD ±511.65) Birth length: methadone 46.52cm (SD ±3.21), buprenorphine 47.93 (SD ± 2.54) Head circumference: methadone 32.65cm (SD ± 1.34), buprenorphine 33.7cm (SD ± 1.81) Gestational age at birth: methadone 38.09weeks (SD ± 1.95, buprenorphine 38.73weeks (SD ± 1.95) NAS treatment required: methadone 11(50%), buprenorphine 14 (47%)	Adjustment for age, family income, Marijuana use, and adjustment used for visual studies (not analysed as not relevant outcome for this meta-analysis).

Wiegand, 2015, USA	2011 – 2013	Retrospective cohort study	62 patients (31 methadone, 31 buprenorphine + naloxone)	Single addiction centre Northern Carolina Chapel Hill, USA.	Inclusion: prescription of opioid replacement Exclusion: treatment started less than 30day before delivery, delivery at an outside hospital, multiple gestations, intrauterine fetal demise or still-birth, or an anomalous foetus or new-born and multiple births.	Treatment for NAS: methadone 16 (51%), buprenorphine 8 (21%) Duration of NAS: methadone 11.4days (SD ± 3.4), buprenorphine 10.6 (SD ± 3.1) Head Circumference at birth: methadone 32.9 (SD ± 2.5), buprenorphine 34.4 (SD ± 1.4) Total birth weight of offspring: methadone 2885.9 (SD ± 691.2), buprenorphine 3174g (SD ± 532.8) Total length of offspring at birth: methadone 47.9cm (SD ± 4.0), buprenorphine 50.1 (SD ± 2.5) Preterm: methadone 5(16.1%), buprenorphine 1(19.4%) Length of hospital admission: methadone 9.8days (SD ± 7.4), buprenorphine 5.7 (SD ± 5.0) Caesarean Section: methadone 8 (25.8%), buprenorphine 7 (22.6%)	Adjustment for gestational age and maternal indication for opiates. Buprenorphine compared to methadone, with methadone being the reference group. Treatment for NAS: OR 2.55 (95% CI: 1.31 - 4.98)

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