Stillbirths in High-Income Countries: Lifestyle, Environmental and Sociodemographic Risk Factors

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First Author Presentations Related to this Thesis

Bowman, A, A review of the impact of lifestyle risk factors on Stillbirth risk, *SAHMRI Foodplus/Healthy Mothers Babies and Children Symposium, October 2017:* Adelaide Australia

Bowman, A, Reducing the rate of stillbirths and inequalities in Australia, *Australian College of Midwives Annual Conference, October 2017:* Adelaide Australia

Bowman, A. Lifestyle factors and social complexity for stillbirth risk, *Women's Healthcare Australasia Forum, November 2017:* Melbourne Australia

Bowman A, A review of the evidence for the impact of lifestyle factors on stillbirth risk, *University of Adelaide, School of Medicine Seminar Series, December 2017:* Adelaide Australia

Bowman A, Lifestyle risk factors and stillbirth risk in high-income countries, *Stillbirth Centre of Research Excellence workshop, August 2018:* Brisbane Australia

Bowman A, PhD 3-minute thesis - We need to talk (about stillbirth), South Australian Health and Medical Research Institute Annual Scientific Meeting October 2018, Adelaide Australia

Bowman A, Preventing stillbirth with wisdom and grace, *NHMRC Centre for Research Excellence in Stillbirth; Annual National Stillbirth forum, August 2019:* Brisbane Australia

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Abbreviations

95% CI	95% confidence intervals
aOR	Adjusted odds ratio
ART	Assisted reproductive therapy
BMI	Body Mass index
CINAHL	Medical database – Cumulative Index to Nursing and Allied Health Literature.
CRE	Centre of Research Excellence
GA	Gestational age
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
H1N1	Hemagglutinin1 and neuraminidase1 (swine influenza)
HAA	Haloacetic acid (pollutant)
HPV	Human Papillomavirus
ICSI	Intracytoplasmic sperm injection
IPI	Interpregnancy interval
IUFD	Intrauterine fetal demise
IUI	Intrauterine insemination
IVF	In vitro fertilisation
NHMRC	National Health and Medical Research Council
NO_2	Nitrogen dioxide
NOx	Nitrogen oxide
NRT	Nicotine replacement therapy
O3	Ozone
PAF	Population attributable fractions
PCE	Perchloroethylene (pollutant)
PM 10	Particulate matter 10 micrometres or less
PM 2.5	Particulate matter 2.5 micrometres or less
SA	South Australia
SAHMRI	South Australian Health and Medical Research Institute
SES	Socioeconomic status
SGA	Small for gestational age
UK	United Kingdom
USA	United States of America
USSR	United Socialist Soviet Republic (1922-1992)
WHO	World Health Organization

Thesis Abstract

Background

Stillbirth rates in high-income countries have shown little improvement over the last decade. However, many lifestyle, sociodemographic and environmental factors are modifiable, and may help reduce stillbirth rates. Systematic review, meta-analysis and cohort studies identifying lifestyle, sociodemographic and environmental factors are powerful methods for guiding stillbirth prevention in high-income countries. Better understanding of potentially modifiable risk factors of stillbirth at a global level as well as a local level will enable more effective prevention of stillbirth.

Aims

1. To systematically review case-control and cohort studies to identify lifestyle, environmental and sociodemographic risk factors, and their association with stillbirth within high-income countries.
2. To use data contained with the perinatal dataset of South Australia (SA) to identify lifestyle, environmental and sociodemographic risk factors of stillbirth relevant to the Australian population.
3. To inform and recommend individual, local community, national policy, and practice changes to prevent stillbirths.

Methods

To following methods were employed to address the identified aims of this research;

1. Systematic review of cohort and case-control studies published between 1998-2020 examining factors of interest associated with stillbirth were identified through database searches. The primary outcome of interest, stillbirth, is defined as a birth with no signs of life ≥20 weeks gestational age (GA) or ≥400 grams birthweight. Adjusted odds ratios were calculated through random effects meta-analysis for individual risk factors and stratified by GA where possible.
2. All births registered in the SA routine data collection over the period of 1998-2016 were included in a cohort study of stillbirth risk in SA. Associations between stillbirth risk and lifestyle, environmental and social determinant factors were explored, using multivariable logistic regression. Population Attributable Fractions (PAF) were calculated for factors demonstrating the strongest associations with stillbirth in SA.

Results

1. The systematic review and meta-analysis included 390 studies assessing relevant risk factors of stillbirth in high-income countries. Strongest associations with stillbirth were seen for inadequate or no antenatal care, maternal assault during pregnancy, supine sleep position, maternal age ≥45 years, maternal body mass index ≥40, and pre-existing diabetes. Other factors showing an increase in stillbirth risk were; unmarried status, low household income, advanced paternal age, pre-existing hypertension, nulliparity or ≥3 previous births, small or large interpregnancy interval, drug, alcohol, caffeine or cigarette use, unplanned place of birth, parental occupation, maternal ethnicity or country of birth, high exposure to tap water pollution, public or uninsured insurance status and remote/regional living. Maternal university education,

H1N1 vaccination, and residential segregation, showed preventative associations with stillbirth odds.

2. From the SA perinatal database, a total of 363,959 births were included in a large cohort study investigating stillbirth risk factors. An inadequate number of antenatal visits was associated with the strongest odds of stillbirth. Other factors found to have important associations with stillbirth odds were: pregnant plant or machine operators, maternal age ≥40 years, paternal pensioners, South Asian country of birth and Aboriginal/Torres Strait Islander women. Odds of stillbirth were increased in regional and remote areas in association with inadequate antenatal care visits, maternal age 35-40 years, Aboriginal and/or Torres Strait Islander women, paternal occupations; tradesperson or unemployed.

Discussion and conclusion

Comprehensive systematic review and detailed SA cohort data have identified risk factors that potential actions and strategies can target to prevent stillbirth and to decrease rates within high-income countries. Although there is a lack of global consensus on definitions of stillbirth, it is clear that the identified risk factors need to be addressed at local and national policy levels. Risk factors found to have the largest impact on stillbirth odds such as maternal assault, inadequate antenatal care, supine sleep position, and occupation are all factors that may be modified to mitigate the risk of stillbirth. Knowledge of these preventive factors will help families to decrease their risk of stillbirth and to also address and reduce inequity.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Chapter 1 Introduction

Stillbirth: a map of the landscape

Each year globally an estimated 2.6 million babies are stillborn ≥28 weeks gestation[1]. This figure underestimates the true burden of stillbirth due to poor data quality, exclusion of stillbirths from 22 to 27+6 weeks gestation (excluded from the WHO definition of stillbirth), and poor termination of pregnancy reporting in later gestations[2, 3]. Obtaining accurate numbers of stillborn babies is a global challenge as a result of poor registration systems[3, 4], and in some regions, fear of blame, stigma, social rejection and litigation decreasing formal acknowledgment of a stillborn baby[5]. Although the stillbirth of a baby is far more common in low and middle-income countries, data from high-income countries has demonstrated that widespread inequity causes disparity between stillbirth rates at a community level[6]. Disadvantaged women, and women with specific risk factors within high-income countries are reported to experience double the risk of stillbirth than their advantaged counterparts[2, 5, 6].

Stillbirth is one of the most stressful life events experienced by families, which is often associated with lack of community recognition of loss, and in some instances, shunning of the grieving family leading to disenfranchised grief[7]. Within families who experience pregnancy loss, one in five mothers experience long term depression, anxiety or post-traumatic stress disorder[5]. Both parents express feelings of disenfranchised grief; a feeling that grief of their stillborn baby is not recognised or acknowledged by society[8]. Recently, bereavement care research has acknowledged the need for bereavement training of healthcare staff, and ongoing access to psychological support for families following the stillbirth of their baby[9]. The cost of subsequent care has been estimated as approximately $4200/stillborn baby in Australia for investigations alone[10], and £4191 in the UK[11] for care related to the stillbirth and subsequent pregnancy. The economic burden combined with the social burden experienced by families may be averted if effective primary preventions based on strong evidence are implemented.

Agendas to reduce the burden of stillbirth within high-income countries, although now prominent, were previously neglected by international forums. In 2000, the United Nations and World Health Organization (WHO), through the United Nations Millennium Declaration, focused their core efforts on maternal and infant health, thereby neglecting stillbirth[12]. To raise awareness of stillbirth, and to highlight is lack of priority in global development goals, the *Lancet* stillbirth series of 2011 was published through international perinatal research collaborations[4, 5, 13-16]. The series outlined action that needed to be taken at an international level to decrease stillbirth rates[4, 5, 13-16] Since the 2011 Lancet stillbirth series, there has been an increasing trend of publications and media discussions highlighting the importance of recognising perinatal death as a devastating, and in many cases preventable, pregnancy outcome[17]. The *Lancet* published a second stillbirth series in 2016[6, 18], and reported that if preventative action were implemented it would result in a triple return on financial investment, and potentially save 1.1 million lives per year worldwide, but the chance to implement change was missed[6, 18] and progress slow. In 2020, Women and Birth published a series summarising research and progress to date, highlighting efforts and future goals to reduce stillbirth rates in Australia. The main focus of the series being education and training, awareness and prioritising research[19-24].

Stillbirth: risk factors and opportunities for prevention

Flenady et al found in their 2011 systematic review that many of the risk factors for stillbirth in high-income countries are fully or partly avoidable[5]. Factors with an

increased odds of stillbirth were maternal BMI, maternal smoking, maternal age, primiparity, interpregnancy interval, previous stillbirth, small size for gestational age, placental abruption, and pre-existing maternal diabetes or hypertension[5]. The results of this high-quality synthesis of evidence, and the *Lancet* series, have been used to inform multiple care guidelines globally[25-30]. Following the identification of risk factors in their large systematic review, a number of recent publications have implicated new risk factors such as poor adherence to antenatal care recommendations[31] as well as sleep position during pregnancy[32, 33] and pollution[34-36]. Through a family's reproductive years, exposure to risk factors associated with their sociodemographic characteristics, environment and lifestyle affect the odds of stillbirth. Many of the risk factors prevalent within high-income countries disproportionately affect disadvantaged women[24], and there exists an opportunity for stillbirth prevention following up to date systematic review and evaluation of major risk factors affecting high-income countries.

Identification and subsequent modification of risk factors during the preconception and antenatal period offers an opportunity to reduce the risk of stillbirth. Preconception health refers to the health status of both parents during pregnancy planning prior to conception. Preconception health factors related to poor pregnancy outcomes are closely related to parental morbidity and lifestyle as well as and socioeconomic status. Increasingly, women are delaying pregnancy to a later age than previous generations[37]. This is due to a combination of lifestyle and medical factors including; underlying fertility issues, socioeconomic demands, and multiparous women continuing to bear children into later life [38, 39]. Increasing maternal age nearly doubles the risk of stillbirth for women >35 years of age at birth[38]. Marital status also affects stillbirth risk, and can reflect the economic status of the maternal household with either one or two sources of income, as well as reflect the support a women has during her pregnancy[40-43]. Obesity is the most prevalent modifiable risk factor of stillbirth, contributing to 10% of stillbirths worldwide[5, 6, 44]. Almost 30% of women entering pregnancy were obese in the USA in 2019[45], ~25% in the UK[46], and in Australia, almost half of the women giving birth in 2016 were overweight or obese[37]. Increasing rates of obesity may be a factor in the stalled progress in reducing stillbirth rates. The link between obesity and stillbirth is unclear, however diseases related to obesity increase risk including diabetes and hypertensive disorders[47, 48]. Preconception care programs are designed to improve health indicators, and where implemented, have been shown to significantly improve pregnancy outcomes by risk factor prevention, and offering support programs[49, 50]. Optimisation of preconception health indicators aids and supports parents to ensure the best possible outcomes from their pregnancy[50]. Ensuring that risk factors of stillbirth are minimised by optimising a healthy BMI, socioeconomic status, parental age and interpregnancy interval as well as monitoring and treating pre-existing conditions such as diabetes or hypertension all aid in stillbirth prevention. Pregnancy planning plays a vital role in mitigating stillbirth risk associated with these factors, indeed; over 4000 stillbirths could be prevented by decreasing maternal age at conception across all high-income countries to <35 years at birth[5]. Obesity has also been implicated as the most prevalent modifiable risk factor, contributing to 10% of stillbirths worldwide, and between 8-18% of stillbirths within high-income countries[5, 6, 44]. In the face of these risk factors, and the changing landscape of sociodemographic characteristics, exposures, and lifestyles, it is imperative that we provide up-to date, quality evidence to inform families and carers of their risk before entering pregnancy.

Following the preconception period, effective and appropriate antenatal care remains the cornerstone of stillbirth prevention. The antenatal period is a time of frequent health intervention to monitor, assess and apply preventative strategies to mitigate risky behaviours such as smoking and drug use. Smoking and drug use combined are associated with 2.5 times greater odds of stillbirth[5, 51], while antenatal vaccination programs and maternal education levels have been shown to reduce the risk of stillbirth[52-54]. Pregnancy health incentive campaigns and action plans for stillbirth prevention are aimed at increasing education and awareness within high-income countries[6, 21]. For campaigns, national police, and translation of research findings to be effective within target populations, the underlying pillars of evidence must be current[23].

Families at risk of stillbirth are not only affected by modifiable risk factors, but also as part of vulnerable populations within high-income countries. Sociodemographic characteristics of a populations aid in identifying vulnerable families that are at increased risk due to inequity and disadvantage. Maternal and paternal occupation, remoteness and socio-economic status all serve to shape the family's sociodemographic characteristics. Certain occupations and their associated exposures to chemicals, lifting, and rotating shift work have been shown to increase the rates of stillbirth in high-income countries[55-58]. For mothers, the association between occupational exposure and stillbirth rates is often associated with antenatal exposure to occupational hazards such as chemicals, lifting activities and radioactive exposure. For fathers, exposures such as radioactive chemical exposure and occupations such as deep sea diving, are commonly explored at the time of, or just prior to, conception[59-61]. Remoteness and rural living determines the access that women have to services during pregnancy, and inequity of service provisions has been identified as a contributor to poor pregnancy outcomes. In Australia and Canada, remote living has been shown to contribute to stillbirth rates[62-64], owing to the lack of access to nearby health care and barriers associated with access[5]. Indigenous women have been highlighted as a vulnerable population in high-income countries, and experience nearly double the odds of stillbirth than Caucasian women[65-68]. Higher rates of stillbirth within Indigenous populations have been attributed to numerous factors, including lack of culturally appropriate care, institutionalised racism, as well as socioeconomic disadvantage. Research from high-income countries has also identified that women of diverse ethnic groups have differing stillbirth rates[42, 69-71]. Women of South Asian or African ethnicities have consistently higher rates of stillbirth[69-71]. Disparities due to barriers such as lack of cultural sensitivity within health care system, lack of access to interpreters, and social deprivation have all been shown to play a role in poorer health outcomes for women from minority ethnic groups[72, 73].

All environmental, lifestyle and sociodemographic risk factors have not, to date, been cohesively examined through systematic review and meta-analysis. As the landscape of risk exposure changes quickly, it is imperative to stay abreast of new and emerging risk factors of disease to ensure that strategies to reduce stillbirth are based on the best available evidence.

Research questions and thesis aims

1. What are the parental, and pregnancy lifestyle and social determinant factors which are independently associated with an increased risk of stillbirth in high-income countries?

The purpose of this research will be to identify all risk factors concerning lifestyle, sociodemographic characteristics and environment of families, of stillbirth. The identification and analysis of factors will complement the robust information collected by

Flenady et al's 2011 systematic review[5] of stillbirth risk factors, and will serve to inform guideline and policy development to aid stillbirth rate reduction in high-income countries.

2. How relevant are risk factors identified for stillbirth in high-income countries to a South Australian population?

The lifestyle and sociodemographic stillbirth risk factors in South Australia study (ILSSA study) is analysis of the perinatal data collected by midwives across South Australia (SA). Results will provide information regarding risk factors of stillbirths in SA for the period of 1998 to 2016. The information collected within this dataset correlates well with known lifestyle, environmental and geographical remoteness patterns of risk factors for stillbirth. To date, the data from SA has not been examined per these risk associations collectively alongside geographic area of remoteness within South Australia.

Chapter 2 Systematic Review and Meta-Analysis of Lifestyle, Sociodemographic and Environmental Risk Factors for Stillbirth in High-Income Countries

Abstract

Background

Stillbirths in high-income countries have shown little improvement over the last decade. More attention to lifestyle, sociodemographic and environmental factors is likely to help reduce stillbirth rates. This systematic review and meta-analysis identifies lifestyle, sociodemographic and environmental factors contributing to, or preventing stillbirth in high-income countries.

Methods

Cohort and case-control studies published between 1998-2020 examining lifestyle, sociodemographic and environmental factors were identified through database searches. Adjusted odds ratios were calculated through random effects meta-analysis for individual risk factors and stratified by gestational age (GA) where possible.

Results

We included 390 studies assessing potential risk factors of stillbirth from pre-conception onwards. Strongest associations with stillbirth were seen for inadequate or no antenatal care (aOR 3.24 (95% CI 3.12, 3.36) and aOR 3.51 (95% CI 1.79, 6.89) respectively), supine sleep position (aOR 3.00 (95% CI 1.92, 4.70)), assault during pregnancy (aOR 3.16 (95% CI 2.31, 4.32)), maternal age ≥45 years (aOR 2.65 (95% CI 2.06, 3.39)) or maternal BMI≥40 (aOR 2.60 (95% CI 1.96, 3.45)), pre-existing diabetes (aOR 2.59 (95% CI 2.02, 3.30)). Other factors showing an increase in stillbirth risk were; unmarried status, low household income, advanced paternal age, pre-existing hypertension, nulliparity or ≥3 previous births, small or large interpregnancy interval, drug, alcohol, caffeine or cigarette use, unplanned place of birth, parental occupation, maternal ethnicity or country of birth, high exposure to tap water pollution, public or uninsured insurance status and remote/regional living. Maternal university education (aOR 0.66 (95% CI 0.60, 0.74)), H1N1 vaccination (aOR 0.79 (95% CI 0.68, 0.94)), residential segregation 0.81 (95% CI 0.71, 0.93)), showed lower rates of stillbirth for women giving birth in high-income countries.

Discussion and conclusion

These impacts of lifestyle, environmental and sociodemographic risk factors in high-income countries on stillbirths need to be addressed at individual and national policy levels within high-income countries.

Introduction

Since the 1990s, several global perinatal research groups have been the driving force behind placing stillbirth, and the associated burden, into the spotlight and firmly onto national agendas. Yet global estimates reveal that 38,516 babies at or over 28 weeks' gestational age (GA) are stillborn each day within high-income countries, and many are associated with preventable risk factors. The recent release of The Global Patient Safety Action Plan 2021-2030[74], from the World Health Organization, promotes the provision of safe, respectful and quality care to prevent and decrease perinatal mortality, including stillbirth and highlights the need for effective preventative care to decrease stillbirth rates.

Over the last two decades, the stillbirth rate across high-income countries has decreased by just under one stillbirth per 1000 births[75]. Current estimates indicate that the stillbirth rate for high-income countries is 3.0 stillbirths per 1000 births (≥28 weeks GA)[75]. Large disparities are evident across high-income countries as stillbirth rates vary from 1.42 stillbirths per 1000 births in Monaco to 13.12 per 1000 births in Nauru[1]. That the top five countries have achieved a stillbirth rate of less than 2 stillbirths per 1000 births demonstrates that reduction is achievable across all high-income countries (Appendix A).

In 2011, Flenady et al published a comprehensive summation of risk factors associated with stillbirth in high-income countries[5]. Cited over 700 times, this has informed multiple preventative campaigns and action plans internationally. However, data included in the review are now more than a decade old. Since 2009, demographic profiles of families birthing in high-income countries have shifted - the average maternal age at birth is older, an increased percentage of women are obese, and migratory patterns globally have seen new sub-populations in high-income countries[76, 77]. New risk factors have been identified as contributors to stillbirth risk, and globally, perinatal data collection has improved in risk factor capture, and comprehensiveness, to allow analysis of risk association[78-81]. This has resulted in increased publications of stillbirth causes and risk factors using robust datasets.

National strategies to decrease stillbirth in high-income countries should be based on current evidence and to incorporate changes in technology, healthcare programs and new emerging risks in high-income countries.

Objective of this systematic review.

To identify the environmental, sociodemographic and lifestyle risk factors for stillbirth relevant to the high-income populations, and to assess risk factors by GA (where possible).

Methods

Literature Search Strategy

To identify relevant publications a systematic literature search of the medical literature was conducted using assistance from the University of Adelaide Senior Research Librarian (Michael Draper). The term “fetal death” was first searched in the MeSH database in order to identify MeSH terms indexed to correspond with this term. This led to identification of four MeSH headings for use within our search; “stillbirth”, “fetal death”, “perinatal mortality”, and “perinatal death”. Search terms were also encompassed into the strategy in order to capture un-indexed publications. Search strategy can be found in Appendix B.

We used a methodological filter in order to restrict study results to prognostic and aetiological designs. The methodological filter was written by Senior Research Librarian (Michael Draper) from the University of Adelaide. We searched CINAHL, PubMed, Ovid, Embase, and the Cochrane Database of systematic reviews for relevant studies published between 1998 -2020. Initially, literature searches were conducted for the period 1998-2017, with a language restriction to the English literature only. Top-up searches were conducted in July 2020 to supplement the original search with recent literature using the same inclusion/exclusion criteria. Studies where the reported last date of data collection was prior to 1988 were excluded.

Inclusion criteria

All identified published papers which report either risk factors, predictors and risk for stillbirth including reviews, or peer reviewed journal articles that were included. References of the 2011 Lancet systematic review of stillbirth risk factors in high-income countries were hand searched and included in this review.

Table 2-1 Criteria for types of studies including risk factors and causes associated with stillbirth

Study outcome	Study design
Stillbirth risk	Population-based cohort, case-control or cross sectional studies
Risk factors for stillbirth	Population-based and institutional based cohort, cross sectional and case-control studies.
Causes of stillbirth	Population-based and institutional based cohort or case-control studies
Prediction of stillbirth	Population-based and institutional based cohort studies

Duplicate publications of studies were identified, and the most recent publication used in this review. If duplication was unclear, we contacted or attempted to contact authors for clarification.

Exclusion Criteria

The following publications were excluded:

- Publications of preliminary or redundant reports from the same study; partially overlapping datasets; where more than one report of the same dataset was present the largest and most comprehensive version was chosen.
- Non-English language publications: and reports produced before 1998.
- Studies where stillbirth data could not be separated from composite information of fetal loss and/or perinatal deaths.
- Studies encompassing cohorts sourced from low- or middle-income countries
- Studies using smaller datasets that were identified as being encompassed by larger included studies using the same dataset, where both studies are examining the same risk factor – so as to avoid double counting births.

Definitions

Lifestyle risk factors: Lifestyle risk factors for the purpose of this review are modifiable behaviours that can be changed to improve a person's health[82]. They are part of a person's individual lifestyle, including social determinants or conditions in which people are born, grow, live, work and age that can strengthen or undermine the health and welfare of the individual or community.

Sociodemographic risk factors: Sociodemographic risk encompasses socioeconomic status (SES) factors such as income, educational attainment, and factors relevant to social

ranking. This includes factors such as income, poverty, and also race, ethnicity, marital status along with broader factors that although independent, have been shown to accumulate to undermine health and wellbeing[83].

Environmental risk factors: Environmental risk factors incorporate *"the probability of adverse effects resulting from exposure to an environmental agent or mixture of agents..." found in the families"*[84] homes, workplaces, social activities and surroundings (including air and water).

Stillbirth: for the purpose of this review stillbirth is defined as any death of a fetus after 20 weeks gestational age (GA) or weighing ≥400 grams at birth. It is acknowledged that countries and organisations may use definitions that differ to this. To eradicate potential bias, any definitions of stillbirth using limits ≥20 weeks GA, or ≥400 grams weight at birth were accepted for inclusion in this review. Studies detailing fetal deaths termed as "stillbirths" in the absence of GA or birthweight parameters were also included.

Selection of studies

Two researchers screened each title and abstract of search results and based inclusion on the inclusion/exclusion criteria outlined. A web-based platform, Covidence (https://www.covidence.org/), was used to screening titles and abstracts, as well as full texts. Each conflict was resolved by the entire review team in weekly meetings. Full text publications of short-listed studies were obtained, and the inclusion criteria applied independently by two reviewers. Where disagreement could not be resolved between the reviewers, another researcher (working team member) arbitrated to reach agreement. Full texts were collated for data extraction by the review team. Data extraction was undertaken by two researchers who resolved disagreements by discussion. Where agreement was not reached, a third person (a member of the review team) was consulted.

Quality assessment of selected studies

All relevant studies selected for this review were assessed independently by two reviewers for methodological quality, using a quality and bias assessment scale specifically designed by the RTI-University of North Carolina Evidence Based Practice Centre; the RTI item bank (RTI-IB)[85]. The scale includes 29 questions with multiple choice answers and additional space for free-text. The item-bank focuses on believability incorporating risk and precision of the results. Overall quality assessment is assigned qualitatively as: High, Medium or Low based on the RTI-IB criteria [85].

Data extraction and management.

Data extraction was undertaken by two independent researchers using standardised study extraction forms (Appendix E). Ten percent of extractions were undertaken in duplicate between reviewers and then compared for disagreements. The remaining 90% were undertaken completely by the first author (A Bowman), and then checked independently by a second reviewer. Disagreements were resolved through discussion between reviewers. Where agreement could not be reached, a third person (a member of the review team) was consulted.

Study characteristics and data extracted: design and methods employed in the study; population characteristics for which the sample was drawn (e.g. Geographic region and socioeconomic status); definition of stillbirth used; confounding variables controlled for, exclusion criteria and inclusion of terminations of pregnancy or congenital anomalies.

Numerical data extraction for combination of study results, where relevant, were managed in Excel and exported for analysis.

Data analysis and presentation

Results are summarised according to the following subgroups where possible:

- Gestational age: All stillbirths (GA20+), second trimester stillbirth (20-28 weeks GA), third trimester stillbirth (28+ weeks GA) and term stillbirth (37+ weeks GA).

- Risk factor severity where possible: pollution, hypertension, maternal BMI, smoking, drug use, alcohol use, socioeconomic status, remoteness categories.

- Populations: where relevant and possible, risk factors are presented by populations to form appropriate risk associations between stillbirth and populations at risk.

Where two or more studies presented adjusted odds ratios for association with stillbirth odds, meta-analysis was performed in STATA IC (version 16.1). Random effects meta-analysis was performed to produce pooled adjusted odds ratios and associated 95% CIs. This method was used due to the anticipated differences between study populations encompassed within study results, as well as the inclusion of case-control and cohort studies.

Sensitivity analysis was undertaken to explore the effect of study quality and heterogeneity on the results by excluding those studies considered to be of poor methodological quality, with high bias and poor adjustment for confounders according to the RTI-item bank used to assess bias and quality. All meta-analysis and sensitivity analysis were conducted by first author, A Bowman, and final check of coding framework was performed by SAHMRI Women and Kids Theme Lead Biostatistician, Dr T Sullivan.

Where results of a study were not included for meta-analysis, or where a risk factor was only investigated by one study, results are presented in text. Heterogeneity was firstly assessed by individual study population characteristics and demographics as described by the authors, then through meta-analysis using I^2 statistics.

Results

Literature searches yielded 74,707 publications. After review of titles and abstracts, 2,429 full text publications were reviewed against study criteria for potential inclusion. Following full text review, 390 studies (from 405 full text publications) were identified for inclusion (figure 1). Risk factors identified were grouped within 32 overarching risk factor categories.

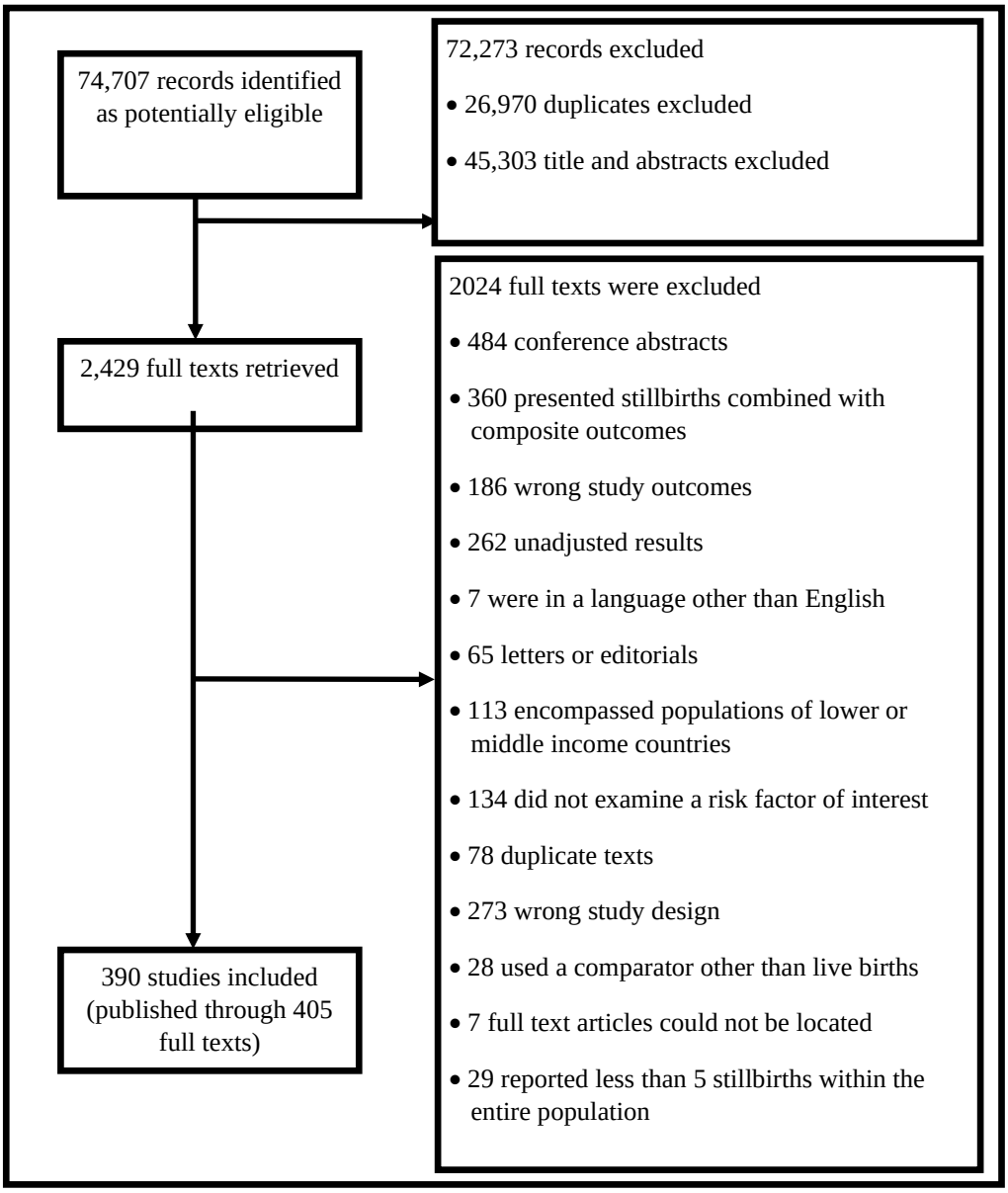


Figure 2-1 PRISMA flow diagram.

The definition of stillbirth varied between studies: 94 studies reported use of a stillbirth definition including both birthweight and gestational age criteria. Twenty studies incorporated only birthweight within their definition, 240 studies applied a gestational age criterion only, and 36 did not use either gestational age or birthweight criteria, and instead used the term 'stillbirth' within their study definitions (Appendix C). Of the studies that incorporated a definition using gestational age, 152 studies included stillbirths ≥20 weeks GA, and 61 included stillbirths with a definition of stillbirth that has a minimum GA between 20+1 and 27+6 weeks. Sixty-one studies included stillbirths only occurring during the third trimester of pregnancy. Of the included studies, 161 excluded multiple pregnancies, 71 excluded congenital anomalies, and 53 excluded terminations of pregnancy within their cohorts. Datasets encompassing populations from 30 high-income countries were included for review, detailed study characteristics are contained in Appendix C.

Quality assessment of each study using the RTI-item bank revealed varying quality of the included studies (Appendix D). Seventy-eight of the included studies were deemed to

have a high risk of bias, the predominantly due to poor detection of exposure status to the risk factor of interest. The second main cause for concern in studies with high bias and poor quality was due to attrition bias and poor identification of stillbirths within their cohorts. One hundred and thirty-eight studies were assessed to have an unclear risk of bias - reviewers implicated poor exposure measurements as the main cause of unclear bias. One-hundred and seventy-three studies demonstrated low bias through the RTI-item bank. Individual study quality scores are presented in (Appendix D)

Of the factors examined by studies screened, 32 addressed modifiable lifestyle, environmental, or sociodemographic factors. Factors were grouped according to their potential for modification or monitoring within the preconception/planning pregnancy period, and/or the antenatal period. Further factors were grouped into populations identified as at risk of stillbirth, and environmental pollutants associated with stillbirth risk in high-income countries.

Table 2-2 Overview of factors identified by this systematic review

Lifestyle, Environmental and Sociodemographic factors assessed for association with stillbirth odds.			
Preconception factors *(Chapter 3)*	***Antenatal factors*** *(Chapter 4)*	***Environmental pollutants*** *Chapter 5)*	***Populations at risk*** *(Chapter 6)*
Education level	Illicit drug use	Air pollution	Ethnicity
Marital status	Alcohol consumption	Water pollution	Indigenous status
Socioeconomic status	Smoking status	Noise pollution	Country of birth
Parental age	Family violence		Rural/remote living
Maternal BMI	Vaccination		Insurance status
Pre-existing hypertension	Parental occupation		Within community segregation
Pre-existing diabetes	Physical activity		Refugee/asylum status
Vaccination status	Place of birth		
Parity	Sleep characteristics		
Inter-pregnancy interval	Antenatal care adequacy		
Mode of conception	Gestational weight change		
Sexual orientation	Distance to care		
Blood donation			
Consanguinity			

The following summarises individual results of meta-analysis resulting from extraction of results pertaining to the above risk factors identified. Detailed analysis is encompassed within chapters 3-6 of this thesis.

Adequacy of Antenatal care (Chapter 4)

Inadequate or no antenatal care during pregnancy was revealed to have the highest association with stillbirth odds through meta-analysis. Fourteen studies incorporating populations from 14 high-income countries investigated the effect of antenatal care adequacy and associated stillbirth odds. Eleven different antenatal care regimens were described across the studies, and the association between care regimens and stillbirth odds differed considerably. The adequate number of antenatal care visits recommended during

pregnancy differed across countries from 7 (Australia) to 14 (Germany). Number of antenatal care visits was shown to have a stronger association with increased stillbirth odds than timing of care initiation during the antenatal period. Meta-analysis revealed that attendance of 50-99% and <50% of antenatal care visits was associated with a 21% and 94% increase in stillbirth odds respectively ((aOR 1.21 (95% CI 1.18, 1.25) – fig 4-5) and aOR 1.94 (1.89, 1.99) – fig-4-6) respectively), when compared with women who attended more than the recommended antenatal care visits. Analysis of studies reviewing antenatal care initiation did not show an association with stillbirth odds when care was initiated in either the second trimester, or after 20 weeks GA, compared with first trimester care initiation (aOR 0.93 (95% CI 0.70, 1.25) – fig4-3) and aOR 1.23 (0.89, 1.70) – fig4-4 respectively). Inadequate antenatal care and no antenatal care demonstrated a more than threefold increase in the odds of stillbirth compared with adequate antenatal care (aOR 3.24 (95% CI 3.12, 3.36) – fig 4-1, and aOR 3.51 (95% CI 1.79, 6.89) – fig4 4-2, respectively). One study conducted by Reime et al[86] stratified the impact of inadequate care by ethnicity and demonstrated a threefold increase in stillbirth odds for women of Mediterranean ethnicity compared with German women (aOR 3.00 (95% CI 1.71, 5.25)).

Two studies incorporating data from the USA and Canada, investigated the correlation of excessive antenatal care on stillbirth odds[87, 88]. Each study demonstrated differences in findings, although there were noted differences between the studies' definitions of adequate care (initiation and number of visits), and large differences in adjustments for confounders through analysis presented by the studies. Heaman et al[87] found no increased association between excessive antenatal care visits and stillbirth odds (aOR 1.01 (95% CI 0.19, 5.35)), yet Partridge et al[88] demonstrated a more than 2-fold increase in stillbirth odds associated with excessive antenatal care. The latter results were not adjusted for maternal health conditions and pregnancy complications, leaving residual confounders influencing the results.

This review did not identify any studies examining the relationship between preconception care and stillbirth odds.

Maternal sleep characteristics

The relationship between maternal sleep characteristics and position during late pregnancy was assessed by six case-control studies[32, 89-93] using cohorts from four high-income countries. Supine sleep position was found to have the highest association with stillbirth odds, increasing the odds of stillbirth threefold compared with that of non-supine sleeping women (aOR 3.00 (95% CI 1.92, 4.70) – fig 4-42). Meta-analysis of studies revealed 83% increased odds of stillbirth for women who slept less than 6 hours per night compared with 6-8.5 hrs (aOR 1.83 (95% CI 1.40, 2.40) – fig 4-36). Analysis of studies reporting aOR for women who woke up less than once during the night revealed more than twofold increased odds of stillbirth compared with women who woke more than once per night (aOR 2.24 (95% CI 1.58, 3.17) – fig 4-38), and women who reported excessive day time naps prior to stillbirth experienced an 84% increase in odds of stillbirth (aOR 1.84 (95% CI 1.34, 2.52) – fig 4-41). Right-sided sleep position, propped, and variable sleep position did not increase the odds of stillbirth. All studies that included analysis of mothers reporting variable/other sleep position through the night demonstrated decreased

odds of stillbirth, but results failed to reach statistical significance (aOR 0.64 (95% CI 0.35, 1.15) – fig 4-45).

Assault during pregnancy

Five studies of Australian, New Zealander, and USA populations analysed the impact of assault on stillbirth odds; four cohort studies[67, 94-96], and one case control study[97]. Results of three studies were combined through meta-analysis and results demonstrated a more than threefold increase in stillbirth odds when women were physically assaulted and required hospital admission during pregnancy compared with women who were not assaulted during pregnancy (aOR 3.16 (95% CI 2.31, 4.32) – fig 4-8). One study[95] stratified results by ethnicity within a New Zealand cohort of women revealed that compared with women who were not admitted for assault during pregnancy, both Māori and non-Māori women were at higher risk of stillbirth when assault required a hospital admission (aOR 3.10 (95% CI 1.50, 6.40) and aOR 2.70 (95% 1.50, 6.40) respectively). One study[94] encompassing a cohort of USA births revealed an 8-fold increase in odds of stillbirth comparing women who were admitted due to assault and who subsequently gave birth during the same admission with women who did not sustain an assault during pregnancy (aOR 8.13 (95% CI 4.61, 14.33))[94]. All studies used hospital admission for assault as a measure for exposure, no studies were identified that reported associations between assault without admission to hospital and stillbirth outcomes.

Maternal age (Chapter 3)

Cohorts from twenty high-income countries were included in analysis of maternal age and stillbirth, results were collated from 99 studies [32, 35, 40, 73, 87, 91, 92, 98-189]. Meta-analysis revealed that young maternal age (<16 years), compared with women >19 years, showed a 33% increase in stillbirth odds (aOR 1.33 (95% CI 1.19, 1.48) – fig 3-23), but no increased odds of stillbirth were seen for maternal age groups between 15 and 20 years (aOR 1.02 (95% CI 0.94, 1.11) – fig 3-24). Analysis of five studies assessing women aged between 30-34 years revealed an increase in stillbirth odds compared with women <29 years at time of birth (aOR 1.46 (95% CI 1.26, 1.69) – fig 3-28), and this risk then increased as maternal age increased. Births to women aged 35-40 years demonstrated a 40% increase (aOR 1.39 (95% CI 1.28, 1.50) – fig 3-31), 35-40 a 42% increase through subgroup analysis of third trimester stillbirths (aOR 1.42 (95% CI 1.19, 1.70) – fig 3-36), births to women aged 40-45 years demonstrated an 89% increase (aOR 1.89 (95% CI 1.47, 2.43) – fig 3-32) and women over 45 at the time of birth had more than 2-fold increase in stillbirth odds (aOR 2.65 (95% CI 2.06, 3.39) – fig 3-33). Stratification revealed additional burden for older women from areas of low socioeconomic status (fig 3-22), and also higher odds for older multiparous women (fig 3-33. Stratification by trimester of birth also revealed that within age groups, odds were increased further when analysis was restricted to third trimester stillbirths.

Maternal Body Mass Index (BMI) (Chapter 3)

The association between maternal BMI and stillbirth odds was assessed by 71 studies that recorded maternal BMI prior to pregnancy or at the first antenatal visit[43, 44, 67, 70, 71, 73, 92, 102, 103, 106, 118, 120, 121, 124, 127, 129, 134, 143, 164, 179, 181, 182, 184, 190-237]. Maternal BMI measuring techniques describes differed between studies; some recorded actual measurements and others reported maternally self-reported height and/or weight. Meta-analysis of studies examining underweight women and stillbirth odds revealed no clear association

compared with women with a healthy BMI (aOR 0.99 (95% CI 0.87, 1.12) – fig 3-47), and this finding was replicated in further analysis of underweight mothers, stratified by trimester of birth. Any maternal BMI over 25 was shown to be associated with 18% increased stillbirth odds, and by performing meta-analysis of overweight and obese BMI subcategories, results indicate that stillbirth odds increased in association with higher maternal BMI (25-30; (aOR 1.31 (95% CI 1.20, 1.43) – fig 3-51), 30-35; (aOR 1.41 (95% CI 1.25, 1.59) – fig 3-54), 35-40; (aOR 1.73 (95% CI 1.33, 2.25) – fig 3-55). Maternal morbid obesity was assessed by eight studies as BMI ≥40, two studies were excluded from meta-analysis as one reported use of the same dataset as another larger included study. The other reported second trimester BMI measurement, therefore results were deemed non-comparable to other included studies. Results of meta-analysis indicate a nearly two-fold increase in stillbirth odds (aOR 1.99 (95% CI 1.65, 2.39) – fig 3-57) association with maternal BMI ≥40, and an almost three-fold increase of stillbirth associated with maternal BMI ≥50 (aOR 2.65 (95% CI 0.92, 7.65) -fig 3-59). Subgroup analysis restricted to third trimester stillbirths, demonstrated slightly higher odds of stillbirth compared with healthy weight women than analysis of 2nd and 3rd trimester stillbirths.

Maternal pre-existing diabetes (Chapter 3)

Although the pathogenesis of pre-existing type 1 diabetes mellitus renders it a non-modifiable risk factor, management of diabetes can be considered modifiable and monitorable at an individual level. Studies included assessed either type 1 diabetes, type 2 diabetes, or pre-existing diabetes (type 1 and 2 diabetes combined) and the associated stillbirth odds. Studies including gestational diabetes within exposure groups were not included. Final meta-analysis of pre-existing diabetes (any type) and the association with stillbirth odds included 12 studies from Australia, Norway, Canada, the USA, Saudi Arabia, Finland, the UK, and Latvia[157, 158, 165, 238-240] [130, 157, 241-244]. Included studies all demonstrated an increased association between pre-existing diabetes and stillbirth odds except for one study of a Finnish population. The authors noted that in Finland all diabetic women considering pregnancy are enrolled into pre-conception care for diabetic monitoring[165]. Final analysis revealed a more than two-fold increased odds of stillbirth associated with pre-existing diabetes (aOR 2.59 (95% CI 2.02, 3.30) – fig 3-62). Through subgroup meta-analysis of five studies examining type 1 diabetes, analysis showed a more than three-fold increase odds of stillbirth (aOR 3.45 (2.79, 4.27) – fig 3-63)[39, 245-248]. Two studies examined the association between maternal pre-existing type 2 diabetes and stillbirth and results of both did not demonstrate increased odds of stillbirth[39, 248]. Much like the Finnish cohort, in Canada women with pre-existing diabetes enter into free health care and therefore may enter pregnancy with better glycaemic control than populations without access to this care[248].

Remoteness (Chapter 6)

Across high-income countries, access, reach and availability of appropriate antenatal care differs by geographic regions of remoteness. Inequity in healthcare between rural areas and major cities has caused concern as poorer pregnancy outcomes have been associated with antenatal services remotely. Eleven studies, using populations from five high-income countries, examined the association between remote living and stillbirth odds[62-64, 87, 146, 168, 177, 249-252]. Meta-analysis revealed no clear association between rural residence and stillbirth odds compared with women residing in major cities (aOR 1.09 (95% CI

0.96, 1.22) – fig 6-36). Studies were grouped by country where possible to examine country-specific remoteness. Within Australian cohorts[62, 168, 252], three studies examined the impact of accessibility and remoteness using two indexes. Two studies used the ARIA classification to measure accessibility by geographical area[168, 252], and the remaining study separated areas of Western Australia into three subgroups of remoteness[62]. Residence in very remote areas was associated with a more than two-fold increase in stillbirth odds compared with very accessible areas (aOR 2.66 (95% CI 1.35, 5.22) – fig 6-40). Meta-analysis of the three other less remote regions of Australia was not associated with increased odds. One study[168] of teenage mothers (≤19 years), examined the association between remote living and stillbirth odds and demonstrated comparable results to that of other Australian studies across all maternal ages[252]. Another study[62] examining the impact of remote residence on stillbirth odds within an Australian Aboriginal birth cohort, but used incompatible remoteness classification measures, and therefore was not included in meta-analysis[62]. Analysis of Aboriginal births in regional and rural regions of Australia did not reveal an association with stillbirth odds (aOR 0.97 (95% CI 0.76, 1.26) and aOR 1.16 (0.89, 1.51) respectively)[62]. Five studies assessed the impact of remoteness in Canada in comparison to urban areas[63, 64, 87, 146, 250]. After exclusion of studies reporting use of the same dataset to exclude double counting of births, meta-analysis incorporated three cohort studies and results demonstrated increased odds of stillbirth associated with births to mothers reporting rural living (aOR 1.27 (95% CI 1.04, 1.55) – fig 6-41). One included study[63] examined the impact of rural living and stillbirth risk exclusively for Canadian First Nations women and demonstrated no increased odds compared with urban living (OR 0.89 (95% CI 0.51, 1.53)).

Parental educational level of achievement (Chapter 3)

Review of 28 studies[40, 53, 54, 91, 92, 105, 109, 122, 127, 132, 150-153, 166, 177, 192, 253-263] revealed that births to women who completed short/medium further education courses, or university level education have lower odds of stillbirth (aOR 0.90 (95% CI 0.83, 0.99) – fig 3-8, and aOR 0.66 (95% CI 0.60, 0.74) – fig 3-7 respectively) than women who have completed high-school, or less. These findings were mirrored by two studies examining paternal education, whereby stillbirth odds were shown to increase in association with less than high-school education compared with further education completion[54, 257].

Maternal vaccination (Chapter 3 and 4)

Maternal vaccination status was explored following stratification by timing of vaccine. Pre-pregnancy HPV vaccination and associated stillbirth risk was assessed by three studies [264-266]. After exclusion of a smaller study[266], reportedly using the same dataset as a larger included study[264], meta-analysis of the remaining studies revealed no clear association between pre-pregnancy HPV vaccination and stillbirth odds (aOR 0.99 (95% CI 0.87, 1.13) – fig 3-73). Analysis of studies reporting the association between antenatal vaccinations and stillbirth odds demonstrated a protective association of H1N1 vaccination (aOR 0.79 (95% CI 0.68, 0.94) – fig 4-23) through meta-analysis of eight studies[52, 267-274]. Associations were similar when stratified by timing of vaccine delivery (first trimester (aOR 0.89 (95% CI 0.77, 1.03) – fig 4-21) [268, 271, 273], second trimester (aOR 0.83 (95% CI 0.59, 1.18) – fig 4-25)[268, 273] and third trimester (aOR 0.78 (95% CI 0.65, 0.93) – fig 4-26)[268, 273]).

Within community segregation (Chapter 6)

Segregation between linguistically and culturally diverse communities within high-income countries has been shown to affect perinatal outcomes. Two studies encompassing cohorts from the USA assessed the association between residential segregation and stillbirth odds[111, 275]. Residential segregation was assessed through use of the dissimilarity index and results varied by maternal race. White women residing in areas of high dissimilarity demonstrated a protective effect for odds of stillbirth (aOR 0.81 (95% CI 0.71, 0.93)), whereas a 60% increase of stillbirth odds was shown for black women residing in areas of high dissimilarity.

Through analysis of all included studies included in this review, aOR were calculated through random-effects model meta-analysis, and associations with stillbirth odds were revealed for:

- Marital status
- Household income
- Paternal age
- Parity
- Interpregnancy interval
- Drug, alcohol, caffeine or cigarette use
- Place of birth care
- Parental occupation
- Maternal ethnicity
- Maternal country of birth
- Tap water pollution
- Insurance status

Full results and discussion of these risk factors is provided in Chapters 3 to 6 of this thesis.

Discussion

This review provides a strong evidence synthesis of stillbirth risk associated with lifestyle, environmental and sociodemographic risk factors in high-income countries. The disparities in stillbirth rates across high-income countries indicate that there is opportunity for further reduction through prevention, and this review serves to identify the factors that need increased focus of strategies to aid stillbirth prevention. Within high-income countries, inadequate antenatal care and assault during pregnancy were associated with the strongest odds of stillbirth. Further efforts are needed to increase antenatal care engagement and to identify potential for assault prevention during pregnancy. Analysis of maternal BMI and sleep position revealed moderate associations with stillbirth odds. We confirmed the importance of maternal BMI as a risk factor for stillbirth. Maternal obesity before conception and maternal sleep position during pregnancy are identified as important key areas for risk modification to aid stillbirth prevention across high-income countries. Increasing maternal age also demonstrated associations with increased stillbirth odds after maternal age of 30 years compared with women aged less than 30 years.

Important timepoints for risk identification and modification are during the antenatal period, and also during preconception. To enable healthcare teams and support programs to effectively engage with women and families to prevent stillbirth, attending an adequate

number of antenatal care visits remains pivotal to effectively introduce risk modification strategies prior to birth.

The definition of adequate care varied across eleven identified care regimens described within studies. Findings suggest that optimally, women need to initiate care prior to 20 weeks GA and to engage in a minimum of 11 antenatal care visits to minimise stillbirth risk. Due to data limitations, it was not possible to undertake more detailed analyses to clearly determine an optimal number of antenatal care visits. One study revealed that the lowest rate of stillbirth occurred at 14 attended antenatal care visits[276], and our results are in line with this finding suggesting that any less than 11 attended visits increase stillbirth odds. Identification of barriers to antenatal care access at an individual, care provider and national policy are needed to form the basis to adequate timing and engagement with families. Despite increasing interest in preconception care as an important intervention in stillbirth prevention, this review did not identify any studies examining the association between preconception care and stillbirth.

Assault during pregnancy is not uncommon - 22% of women in high-income countries experience domestic violence[277] during their lives, and a quarter of women experiencing assault report that violence first occurred during pregnancy[278]. Results of this review reveal that women assaulted during pregnancy have between a three to eight-fold increased odds of stillbirth. These findings add to that of other studies demonstrating a strong association between physical assault and other composite adverse perinatal outcomes[96, 279]. National campaigns across high-income countries seek to offer support and help for people experiencing domestic violence, and during antenatal care, women are routinely asked to identify their risk of domestic violence[280]. It has been identified that ongoing repeat family violence screening is the main facilitator assisting women to disclose risk[281, 282], yet studies also identify the spouse as a barrier to family violence screening. Time available to offer adequate support and discussions concerning violence[282] was also identified as a barrier. The additional societal cost due to assault during pregnancy is $3.78 to $8.82 billion dollars per annum in the US alone [96, 283], an amount considered an underestimation due to evidence of poor screening, and poor disclosure of assault. Findings of this review are limited by exposure measures used by all included studies. Hospital admission due to assault was the only measure described to identify assault during pregnancy. Results that rely solely on hospital admission datasets fail to assess the impact to women assaulted during pregnancy who are not admitted to hospital. This review indicates that despite increased knowledge of the variability in assault that can occur, and the influence of stress and assault on pregnancy outcomes, there is a gap in evidence examining the association between assault in the absence of hospital admission, and stillbirth odds. Despite the findings indicating that severe physical assault during pregnancy has strong implications for increased stillbirth risk, limitations in detection of assault in the absence of a hospital admission renders these findings not generalisable to all forms of abuse.

Pre-existing medical conditions during the antenatal period[5, 244] such as diabetes and hypertension require additional monitoring to ensure effective maintenance and control of conditions during the preconception period. Findings of this review show that pre-existing diabetes carries a 2.5-fold increase in stillbirth odds. The association between type 2 diabetes and stillbirth diminished through study findings, and the association with

type 1 diabetes increased. The lack of association between type 2 diabetes and stillbirth odds is attributed, by authors[248], to robust preconception programs establishing good diabetes control prior to conception. However, previous literature has implicated type 2 diabetes as a risk factor associated with perinatal mortality[48, 284]. Integration of preconception planning into mainstream diabetic and hypertension care, often absent, needs higher priority[285].

Maternal age at first birth and maternal BMI at conception both continue to increase annually in high-income countries[76, 77, 286], despite previous findings emphasising their role in stillbirth risk. Within the 2011 systematic review of risk factors of stillbirth in high-income countries, both factors were identified as leadings factors contributing to adverse pregnancy outcomes[5]. Associations with increased maternal age and increased maternal BMI remain unchanged from the 2011 meta-analysis, indicating that this population of women that remain at more than double the risk of delivering a stillborn child over a decade later. Both BMI and maternal age are modifiable only through pregnancy planning, these findings highlight the importance of preconception care. The impact of both factors on chronic condition prevalence can not be overlooked either, as these factors are implicated in hypertension, cardiovascular disease, and diabetes. These findings highlight the need for preconception family planning, and education regarding the implications of delayed childbearing, and maintaining a healthy BMI prior to conception.

Through identification of risk factors with impacts on stillbirth odds in high-income countries and the subsequent potential for modification, prevention is required through a continuum of health care from pre-conception to the antenatal period. The identification of antenatal care adequacy as a major risk factor adds complexity to enacting preventative strategies and assisting families to decrease stillbirth risk. Addressing the inadequacy of antenatal care must start with evidence based global consensus on the definition of adequate antenatal care, alongside removal of barriers of access to antenatal care, particularly for disadvantaged women (barriers including culturally inappropriate care, lack of at home provision of care, universal free health care, lack of appropriate translation services). Many of the risk factors revealed to increase odds of stillbirth disproportionately affect socioeconomically disadvantaged women within high-income countries. The increased risk and prevalence of stillbirth within disadvantaged populations serves to perpetuate the cycle of inequality between socioeconomic classes. By identifying and providing sound evidence of risk factors associated with stillbirth, this review lays the foundation for focusing strategies to prevent and decrease risk, as well as providing the evidence base for preconception and antenatal care to interrupt intergenerational inequality and perpetuate improved health of populations within high-income countries. Given the large scope of modifiable risk factors identified in this review, continuity, and consistency of healthcare is important for high-income countries to decrease stillbirth rates.

Chapter 3 Sociodemographic Status and Preconception Health and Stillbirth Risk in High-Income Countries

Abstract

Background

Several sociodemographic factors and preconception health indicators have been shown to have associations with stillbirth risk. This systematic review and meta-analysis identifies preconception and sociodemographic factors contributing to stillbirth risks in high-income countries.

Methods

Published cohort and case-control studies (1998-2020) addressing sociodemographic status and preconception health, and associated stillbirth odds, were identified through database searches. Adjusted odds ratios per factor identified were calculated through random effects meta-analysis of individual factors.

Results

Two-hundred and ten studies examined the impact of sociodemographic and prenatal risk factors associated with stillbirth. Significant associations were shown for maternal bisexual or lesbian sexual orientation (aOR 2.85 (95% CI 1.40, 5.83)), maternal BMI ≥ 40kg/m^2 (aOR 2.80 (95% CI 1.59, 4.97)), advanced maternal age ≥45 years (aOR 2.65 (95% CI 2.06, 3.39)), pre-existing diabetes (aOR 2.58 (95% CI 2.08, 3.21) and chronic hypertension (aOR 1.86 (95% CI 1.77, 1.96)). Other associations with aOR ranging from 1.23 to 2.83 were: low parental education, unmarried status, low household income, advanced parental age (>40 years) and parity (4+ previous births). Conversely, high levels of maternal education, parity of three, vaccination, and maternal age <20 years were associated with decreased stillbirth odds.

Discussion and conclusion

This review confirms the importance of strategies to assist in risk mitigation associated with prenatal and sociodemographic risk factors, such as high maternal BMI, advanced maternal and paternal age, maternal sexual orientation, parental education and pre-existing medical conditions, as well as emerging research including maternal sexual orientation. Conversely maternal education, parity, vaccination status and age can be used to inform families planning pregnancy of strategies to reduce the odds of stillbirth.

Introduction

Stillbirth rates vary greatly across high-income countries for stillbirths ≥28 weeks gestational age (GA). Rates range from 13.12/1000 births to 1.42/1000 births (Appendix A) and around one third of all stillbirths in high-income countries are classified as unexplained[287]. Large variation in stillbirth rates between high-income countries alongside a high proportion of unexplained stillbirths indicate that some stillbirths are preventable through addressing particular risk factors. Optimal pre-pregnancy parental health has been shown to minimise poor pregnancy outcomes, including stillbirth[288], and optimisation prior to conception is particularly crucial, but poorly implemented across high-income countries. Particular focus of preconception programs should regard; education, interpregnancy interval, parity, body mass index (BMI)[2, 286, 289] and preconception vaccination status, as these factors are non-modifiable once a woman has

entered the antenatal period. High maternal BMI has been identified as a major risk factor for stillbirth in several high-income countries including Australia, USA, the UK[2, 286, 289]. Among overweight women (BMI 25-30) and obese women (BMI ≥30) the risk of stillbirth has been shown to increase by 23% and 60% respectively[177, 196, 205, 213], and risk then doubles for women with a morbidly obese BMI prior to pregnancy compared with women who have a healthy BMI[205, 229, 231]. Maternal age has also been implicated multiple times as a contributor to stillbirth rates, in 2020, nearly quarter of women having a baby in Australia were >35 years of age[76], and nearly 20% of women in the USA were >35 years of age at birth[290], while the global average maternal age continues to increase, the risk of stillbirth nearly doubles after age 35[128, 140]. Over 4000 stillbirths could be prevented across high-income countries by decreasing the maternal age at birth to <35 years[5, 38, 39].

Several factors influencing stillbirth risk can be modified through preconception health programs, and health literacy education prior to pregnancy[291, 292]. Preconception programs require a current evidence base so that focus of preventative strategies for stillbirth are effective. Multiple studies conducted throughout high-income and middle-income countries have highlighted individual sociodemographic and antenatal risk factors, such as BMI, maternal age and chronic disease as major contributors to stillbirth rates[288, 293, 294]. Although there is good translation of well-known risk factors to preventative campaigns for stillbirth[295-297], there has been an upward trend in studies examining lesser known risk factors such as paternal education, paternal age and consanguinity. To date, an up-to-date synthesis of evidence examining all sociodemographic, and lifestyle preconception risk factors for stillbirth in tandem, has been lacking. A cohesive, robust analysis of all available evidence is needed to better inform practice going forward.

Aims

To identify stillbirth risk factors that are potentially modifiable through the preconception period, as well as parental sociodemographic factors.

Methods

Literature Search Strategy

Systematic searches of the following major electronic databases were conducted: PubMed, MEDLINE, Ovid, the Cochrane Library and CINAHL. Literature searches were conducted for the period 1998-2017, with a language restriction to the English literature only. Top-up searches were conducted in July 2020 to supplement the original search with recent literature using the same inclusion/exclusion criteria. Search strategies are included in Appendix B.

Quality assessment of studies

Selected studies were assessed independently by two reviewers for methodological quality and bias, using a quality and bias assessment scale specifically designed by the RTI-University of North Carolina Evidence Based Practice Centre; the RTI item bank (RTI-IB)[85] (Appendix D). The scale includes 29 questions with multiple choice answers and additional space for free-text. The item-bank focuses on believability incorporating risk and precision of the results. Overall quality, and bias assessment was assigned qualitatively as: High, Medium or Low based on the RTI-IB criteria (results of RTI-IB

assessment per study located in Appendix D). Detailed methodology is contained within chapter 2 of this thesis.

Inclusion/exclusion criteria and screening of studies

Studies included in this review adhered to the inclusion/exclusion criteria outlined in Chapter 2. To minimise reviewer bias, each study was assessed independently by at least two study team researchers. Where disagreement was not resolved by discussion of the researchers, review from a third researcher was sought to arbitrate and reach consensus. Screening of studies was conducted using covidence (https://www.covidence.org/), an online systematic review platform.

Data extraction and management

Data extraction was undertaken by two independent research team reviewers and managed using the Microsoft office suite of applications (excel v2203 and word v2203). Ten percent of extractions were undertaken in duplicate between reviewers and then compared for disagreements. The remaining 90% were undertaken completely by the first author (A Bowman), and then checked independently by a second reviewer. Disagreements were resolved through discussion between reviewers. Where agreement could not be reached, a third person (a member of the review team) was consulted.

Adjusted results were extracted per study and combined through meta-analysis where possible. Random-effects meta-analysis was performed to construct forest plots to account for probable differences in exposure effect between studies as well as variability between cohorts used. Complete analyses were performed using STATA IC v16.1, by first author (A Bowman) and coding framework was checked by SAHMRI Women and Kids Theme Lead Biostatistician (Dr T Sullivan).

Results

Search results

Of the studies screened, 210 studies reported adjusted odds ratios of preconception period or sociodemographic factors that were associate with stillbirth odds[32, 35, 39, 40, 43, 44, 47, 48, 53, 54, 67, 70, 71, 73, 87, 91, 92, 98-185, 187-248, 253-270, 273, 284, 298-332]. Factors identified were parental education, marital status, sexual orientation, income, socioeconomic status (SES), parental age, maternal body mass index (BMI), blood donation, chronic hypertension, pre-existing diabetes and parity, vaccination, assisted reproductive therapy (ART) and interpregnancy interval. Stillbirths definitions included any definer encompassed within GA and birthweight parameters ≥20 weeks GA or ≥400g birthweight. Where a study did not include stillbirth GA or weight parameters, inclusion was based on inclusion of the term “stillbirth” used to describe pregnancy loss.

Scope, characteristics and quality of studies

Study populations are sourced from 22 high-income countries including Australia, Belgium, Canada, Denmark, UK, Finland, Norway, Sweden, France, Germany, Greece, Italy, Japan, Latvia, the Netherlands, New Zealand, Oman, Saudi Arabia, Slovenia, Spain, Uruguay and the USA. The study designs varied with 181 cohort studies, 28 case-control

studies, and one cross sectional study. The quality of each study was assessed as low, medium or high bias and is detailed in Appendix D.

Meta-analysis of findings

Parental education

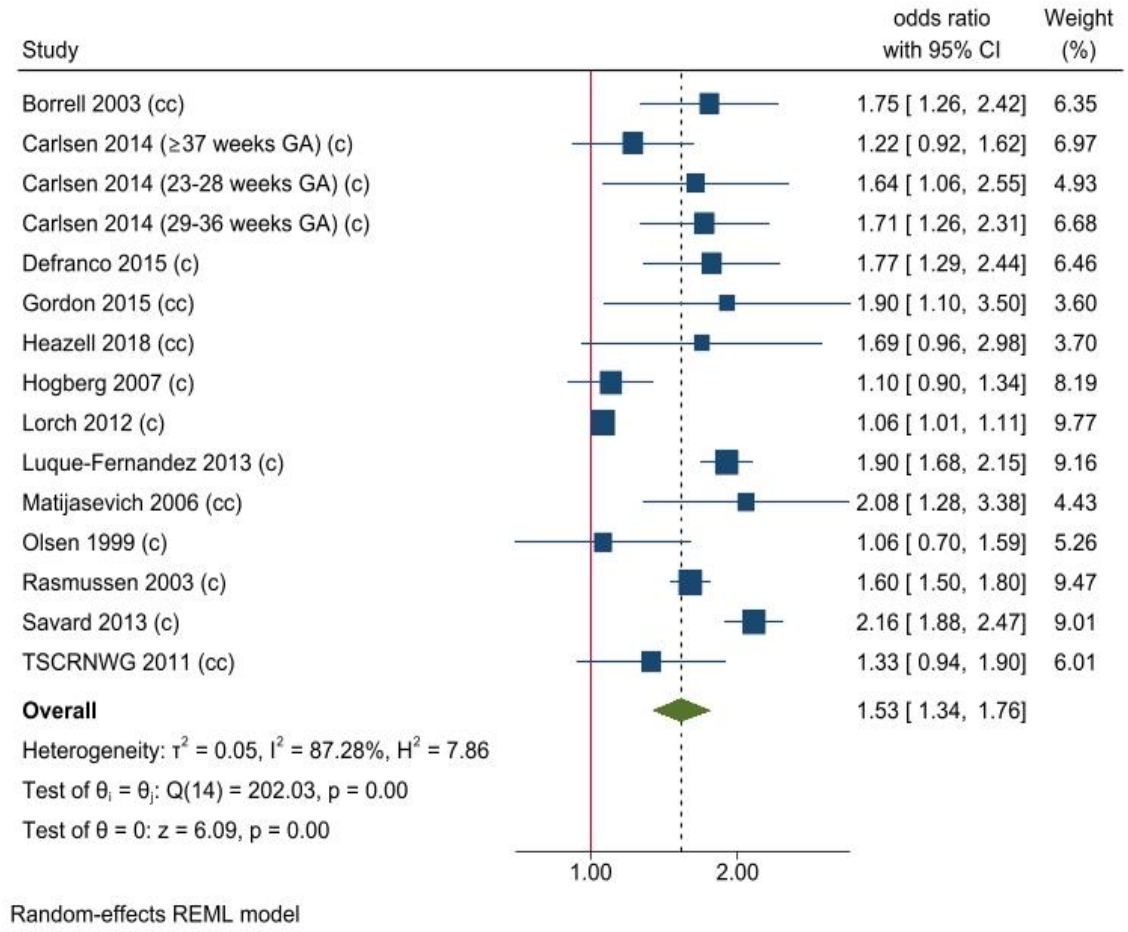
Twenty-eight studies examined the impact of parental education associated with stillbirth odds[40, 53, 54, 91, 92, 105, 109, 122, 127, 132, 150-153, 166, 177, 192, 253-263]. Twenty-six of the studies examined the impact of maternal education[40, 53, 91, 92, 105, 109, 122, 127, 132, 150-153, 166, 177, 192, 253-256, 258-263], one study[54] examined the impact of paternal education on stillbirth odds, and the remaining study examined the impact of both maternal and paternal education [257]. Included studies used data from 10 high-income countries including the USA[40, 105, 122, 127, 150, 192, 258], Australia[92], Denmark[53, 254], Sweden[132], Uruguay[257], Canada [54, 253, 256, 257, 259, 260, 262, 263], Greece[177], Spain[109, 151-153], Norway[166, 255, 261] and the UK[91].

Of the 28 studies included, 15 were assessed by reviewers as having a low risk of bias and high quality[40, 53, 54, 91, 109, 127, 132, 150, 153, 166, 177, 259-261, 263]; 12 were judged to have an unclear risk of bias[92, 109, 122, 151, 152, 253-258, 262], and the remaining two studies, Balayla et al[105] and Carmichael et al[192], demonstrated a high risk of bias[105, 192]. Carmichael et al[192] was assessed as having a high risk of bias due to differences in GA parameters used for cases (stillbirths) compared with controls used within analysis. Balayla et al[105] was considered at high risk of bias due to lack of methodological detail concerning the exposure groups, and method of data collection. Due to limited data availability, the results were subsequently only able to be adjusted for a small number of factors, likely causing residual bias within this study[105].

Maternal education

High-school (or less)

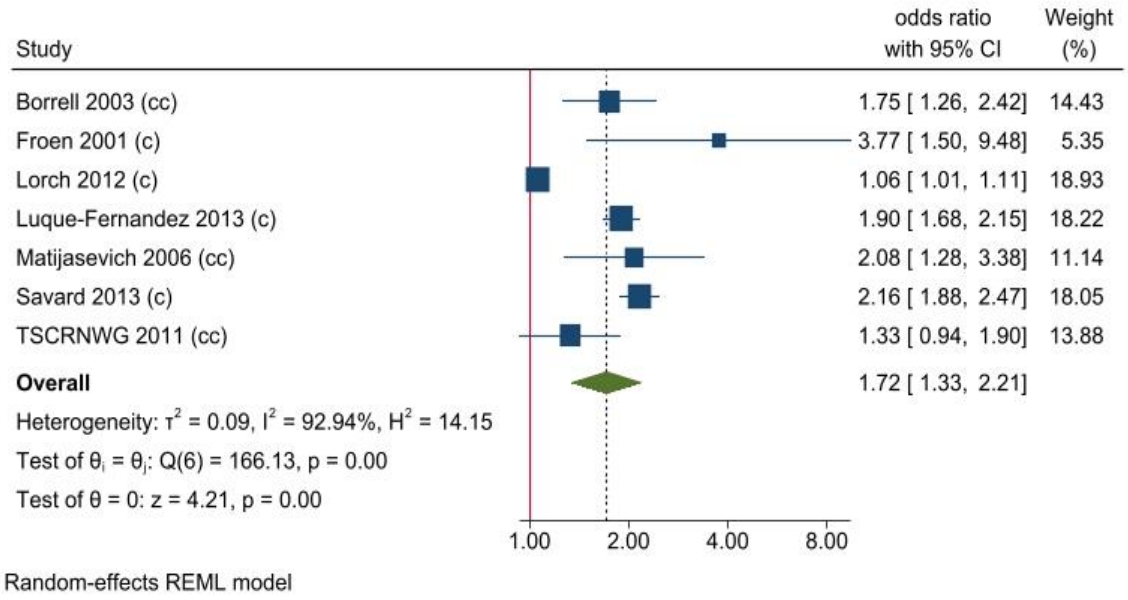
Twenty studies examined the impact of women who had completed high-school or lower educational levels of education, and stillbirth odds versus higher levels of education[54, 91, 92, 109, 122, 127, 132, 150-152, 166, 253-261, 333]. One study provided no study dates for the population and thus was excluded from analysis[258]. Seven of the remaining studies utilised the same data set, so to avoid double counting of births, the smaller studies were excluded[54, 122, 152, 253, 255, 256, 259] and the larger studies included in analysis[151, 166, 260]. One study examined the impact of maternal education through three subgroups of GA at birth[261], each subgroup was included in meta-analysis. Results demonstrated considerable heterogeneity between the study populations (I^2 = 87.28%). Therefore sensitivity analysis was performed and two studies were identified as contributors to heterogeneity[150, 260]. Lorch et al[150] assessed a study population with a disproportionately high number of African-American women within the exposure group owing to selection bias [150], and on review of Savard et al[260] no differences were identified contributing to the heterogeneity. Therefore both were included in the final meta-analysis. Overall results demonstrated an increased odds of stillbirth for maternal education level of high-school or less (aOR 1.53 (95% CI 1.34, 1.76) – fig 3-1) compared with higher education levels.



(c) = cohort studies
(cc) = case-control study
Figure 3-1 Meta-analysis of the association between high-school level of education and second and/or third trimester stillbirths compared with lower levels of education.

High-school (or less) (second and third trimester stillbirth)

Eleven studies examined the association between high-school maternal education or less completion, versus higher levels of education and stillbirth[109, 122, 127, 150, 151, 253, 255-258, 260]. Five studies reported use of the same dataset for analysis[122, 150, 253, 256, 260]. So as to avoid double counting of births, three smaller studies[122, 253, 256] were excluded and larger studies of the same dataset were included[150, 260]. Meta-analysis of the remaining seven studies demonstrated considerable heterogeneity, and thus, sensitivity analysis was performed. Lorch et al[150] was identified as the main contributor to high heterogeneity, yet no reason for heterogeneity could be identified and therefore Lorch et al remained in analysis. Final meta-analysis results demonstrated an almost 2-fold increase in the odds of stillbirth associated with maternal high-school or less level of education compared with women with higher than high-school levels of educational achievement (aOR 1.72 (95% CI 1.33, 2.21) – fig 3-2).

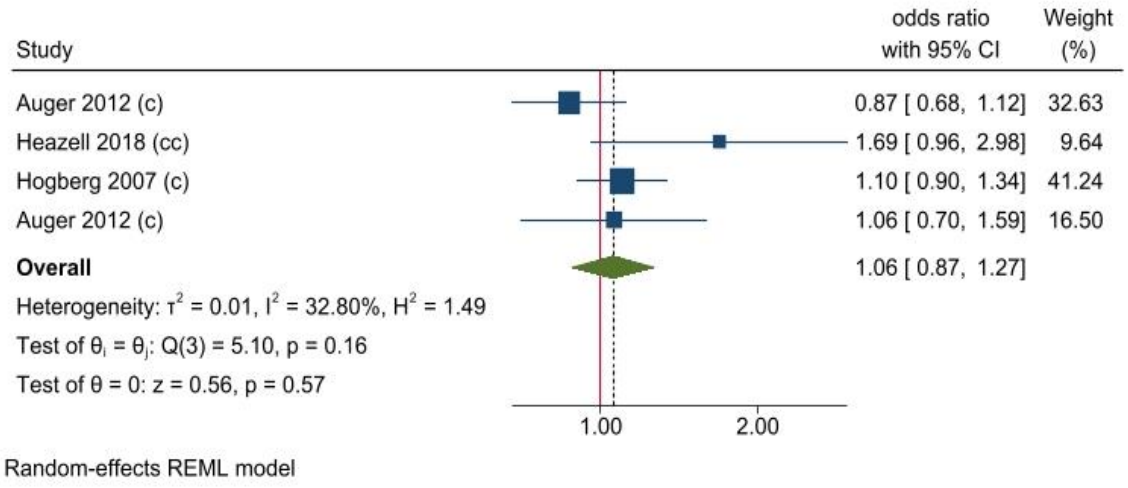


(c) = cohort studies
(cc) = case-control study

Figure 3-2 Meta-analysis of the association between high-school level of education and second and third trimester stillbirths compared with lower levels of education.

<u>High-school (or less) (third trimester stillbirth)</u>

Four studies reported odds of third trimester stillbirth associated with a maternal education level of high-school or less[91, 132, 254, 259] compared with births to women with higher levels of education. All 4 studies were included in meta-analysis and the results demonstrated no clear association between lower level of education and third trimester stillbirth compared with higher levels of education (aOR 1.06 (95% CI 0.87, 1.27) – fig 3-3).

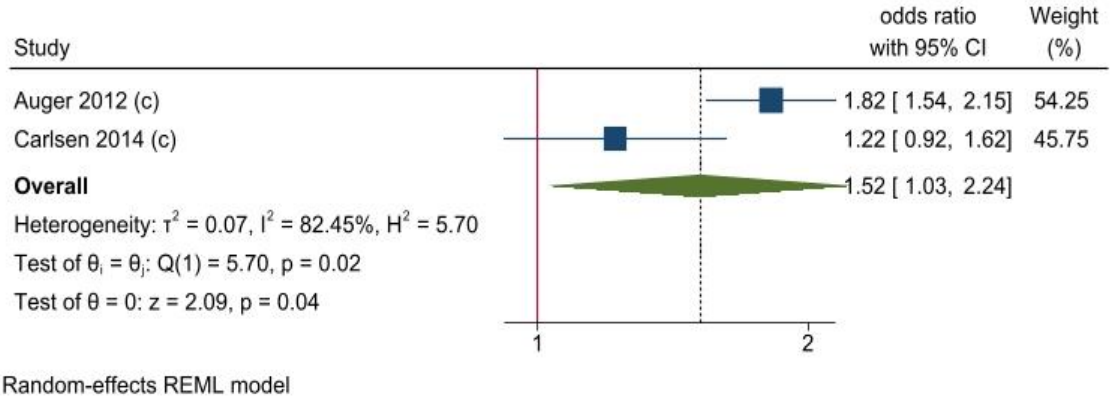


(c) = cohort studies
(cc) = case-control study

Figure 3-3 Meta-analysis of the association between maternal high-school (or less) education and third trimester stillbirth compared with women with higher levels of education.

High-school (or less) (term stillbirth)

Two studies examined the association between maternal high-school education level or less, and higher levels of education, with term stillbirths (≥ 37 weeks GA)[259, 261]. Both studies were included in meta-analysis, and results demonstrated an increased association with term stillbirth (aOR 1.52 (95% CI 1.03, 2.24) – fig 3-4). Analysis demonstrated considerable heterogeneity (I^2 = 82.4%), likely due to the differences between reference groups used. Auger et al[259] included mothers with ≥12 years of education, and Carlsen et al[261] included university educated mothers.

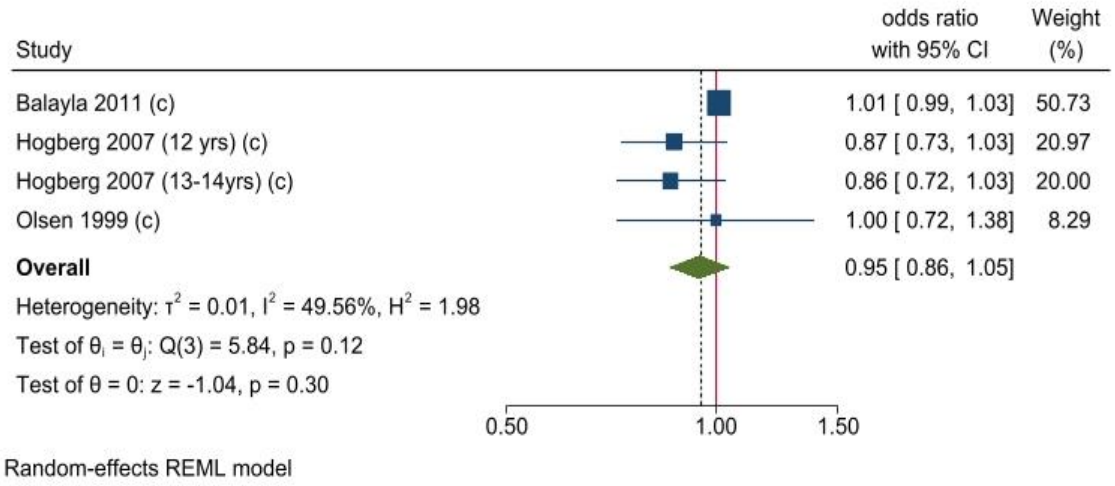


(c) = cohort studies
(cc) = case-control study

Figure 3-4 Meta-analysis studies examining the association between maternal level of education of high-school or less and term stillbirths.

Senior school (12-14 years of education) versus lower education levels

Three studies examined the association between completion of senior school education (12-14 years of education) compared with lower levels of education[40, 105, 132, 254]. Two of the studies compared senior high-school completion to 10-11 years of high-school[132, 254], and one compared senior high-school to 'some school completed'[40, 105]. The final meta-analysis demonstrated no clear association between completion of upper high-school and stillbirth odds compared with completion of lower levels of education (aOR 0.95 (95% CI 0.86, 1.05) – fig 3-5).

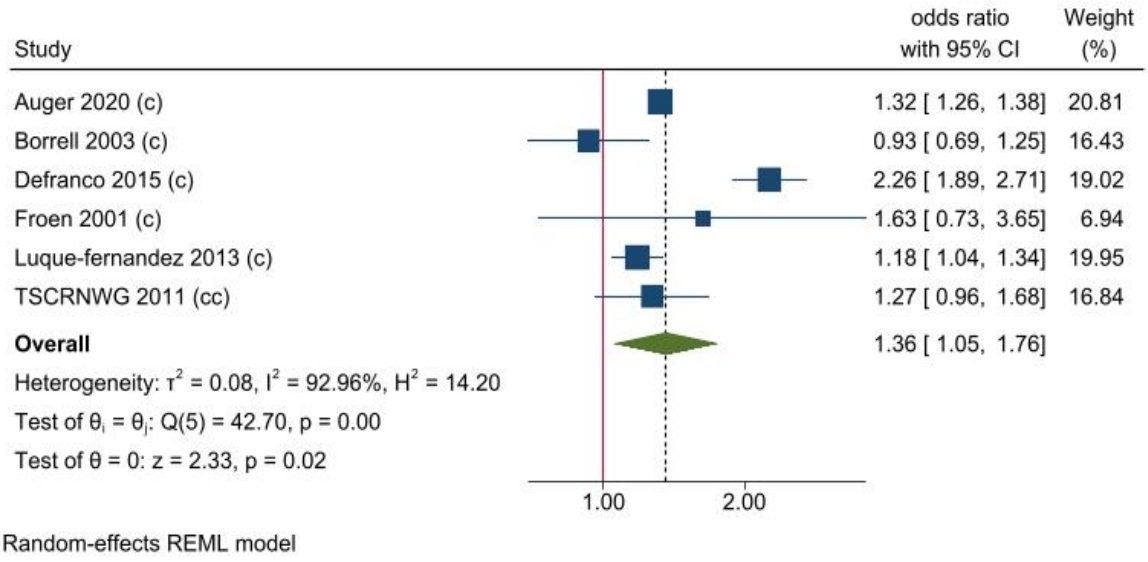


(c) = cohort studies
(cc) = case-control study

Figure 3-5 Meta-analysis of studies reporting the associations between senior high-school (12-14 years of education) versus lower levels of education and the associated odds of stillbirth.

Senior school (12-14 years of education) versus higher education levels

Nine studies reported the odds of stillbirth associated with maternal completion of senior school compared with higher levels of educational attainment[109, 127, 151, 152, 253, 255, 260, 263, 333]. Three of the studies[152, 253, 260] utilised the same data set as two other studies[151, 263]. To avoid double-counting births, these smaller studies were excluded[152, 253, 260]. Analysis demonstrated an increased association between senior school level of education attainment and stillbirth odds compared with higher levels of education (aOR 1.23 (95% CI 1.10, 1.37) – fig 3-6).

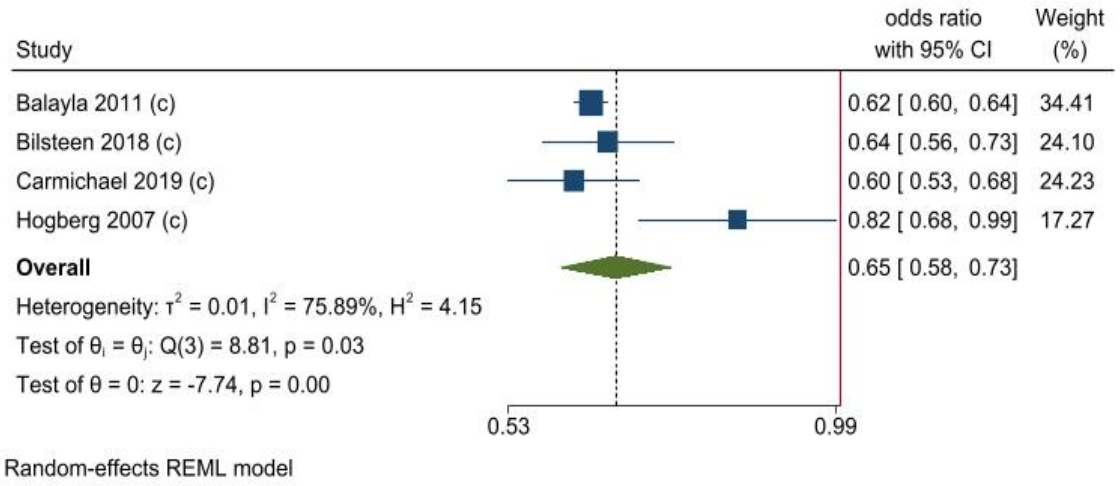


(c) = cohort studies
(cc) = case-control study

Figure 3-6 Meta-analysis of studies reporting the association between senior school (12-14 years of education) compared with higher levels of education and the odds of stillbirth.

University education level

Six studies examined the association between maternal completion of university (or beyond) education and stillbirth odds, compared with lower levels of education (including some or all high-school completion)[40, 53, 105, 132, 192, 254]. Initially all six studies were included in meta-analysis, but heterogeneity between studies was considerable. Therefore sensitivity analysis was performed, with exclusion of a study reporting births prior to 1990[254]. Generational differences in women participating in education were thought to contribute to this heterogeneity. Overall results demonstrated a protective effect of maternal university level of education that lowered the stillbirth odds - aOR 0.65 (95% CI 0.58, 0.73) – fig 3-7. Substantial heterogeneity (I^2=75.89%) is likely due to the differing definitions of stillbirths between the studies (second and third trimester stillbirths). Hogberg et al[132] was noted as an outlier through analysis and further examination of cohort characteristics and exposure measures used did not account for differences between study results.



(c) = cohort studies
(cc) = case-control study
Figure 3-7 Meta-analysis of the studies reporting the association between maternal university education level and stillbirth odds compared with ≤high-school education.

College education

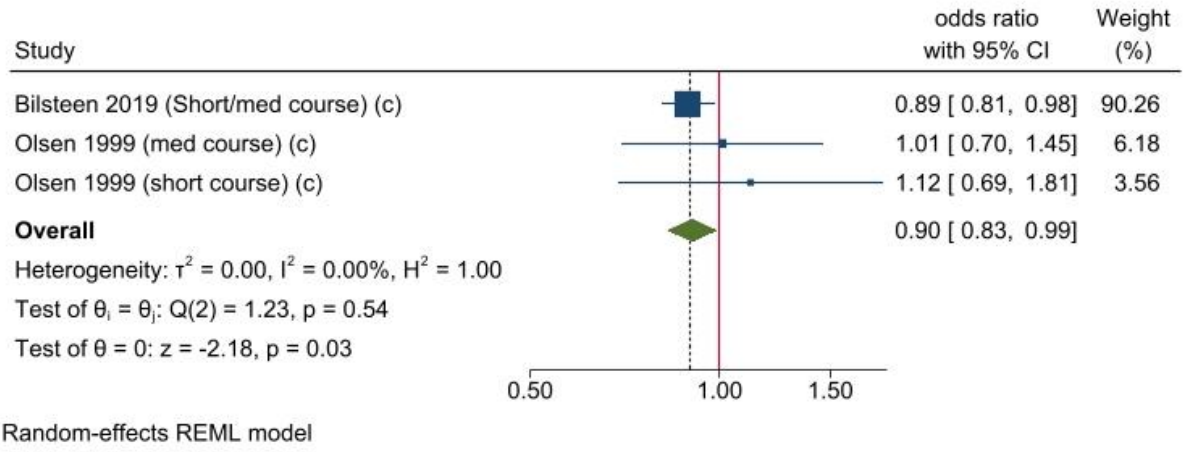
Four studies examined the association between college level of maternal education completion and stillbirth odds in high-income countries[40, 105, 192, 258]. Two studies used the same dataset[40, 105] and therefore the smaller of the two was excluded from analysis to avoid potential double-counting of births[40]. Two of the studies demonstrated a protective association between college graduation and stillbirth odds;

- Carmichael et al[192] aOR 0.60 (95% CI 0.53, 0.68)
- Balayla et al[105] aOR 0.77 (95% CI 0.75, 0.79)

Studies were not combined for meta-analysis due to high risk of selection bias between the livebirth and stillbirth groups identified through the RTI-IB tool of assessment concerning Carmichael et al[192]. The final study, Gallicchio et al[258], compared some college completion to college graduation and demonstrated no clear association with stillbirth odds (aOR 1.63 (95% CI 0.60, 4.38))[258].

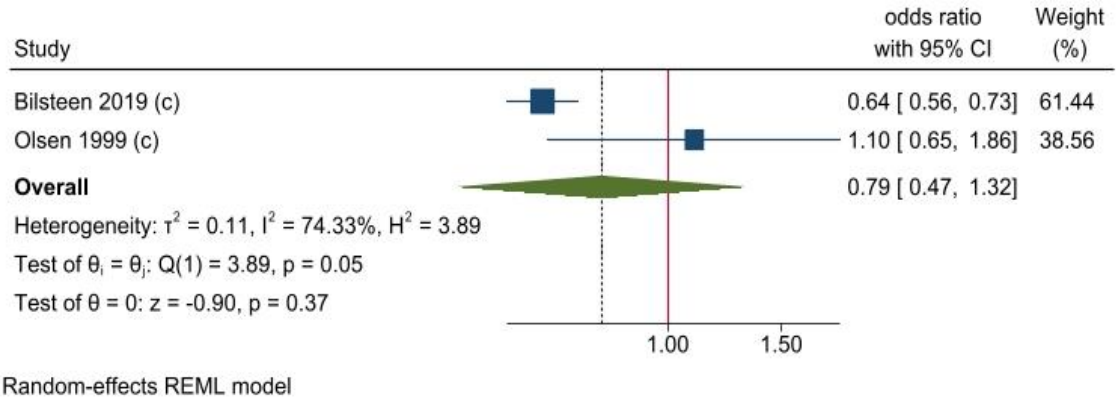
Further education by the length of courses

Two studies reported the odds of stillbirth associated with maternal completion of short/medium further education courses in comparison to completion of high-school education[53, 254]. Both studies encompassed Danish cohorts; Olsen et al[254] separated short and medium length courses[254], and Bilsteen et al[53] included these within the same exposure group[53]. Meta-analysis demonstrated that completion of a short or medium length course was protective of stillbirth in these populations compared with mothers who reported compulsory schooling completion alone (10-11 years) (aOR 0.90 (95% CI 0.83, 0.99) – fig 3-8).



(c) = cohort studies
(cc) = case-control study
Figure 3-8 meta-analysis of studies examining the association between short/medium further education courses and stillbirth odds versus high school completion alone.

The same two studies examined the association between stillbirth and long courses of education completion[53, 254]. Meta-analysis demonstrated no clear association between long course completion and stillbirth odds in comparison to completion of compulsory high-school education (10-11 years) as the highest level reached (aOR 0.79 (95% CI 0.47, 1.32) – fig 3-9). Heterogeneity was considerable between studies (I^2 = 74.3%) owing to a combination of differences in adjustment for confounders made by individual studies, as well as definitions of "long courses" used.



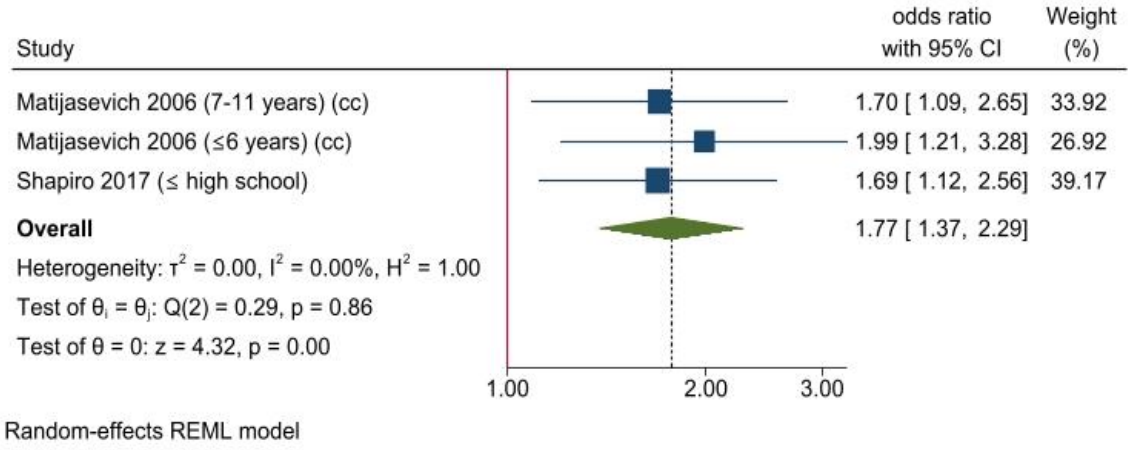
(c) = cohort studies
(cc) = case-control study
Figure 3-9 Meta-analysis of studies examining the association between long further education courses and stillbirth odds versus high school completion alone

Paternal education

Two studies examined the impact of paternal level of education reached on stillbirths odds compared with higher levels of education[54, 257]. One study examined the association in a Canadian population[54], and the other used data from a population of Uruguayan women[257]. Matijasevich et al[257] limited results to paternal attainment of high-school graduation or less compared with high-school level or more. Shapiro et al[54] examined

the risk in three exposure groups, less than high-school education, high-school education and post-secondary education compared with university level of education.

Results of less than high-school education level from both studies were able to be combined for meta-analysis and results demonstrated an almost two-fold increased odds of stillbirth if paternal level of education attainment was lower than high-school, compared with higher levels of education (aOR 1.77 (95% CI 1.37, 2.29) – fig 3-10).



(c) = cohort studies
(cc) = case-control study
Figure 3-10 Meta-analysis of studies examining the impact of paternal less than high-school education level with stillbirth odds compared with high levels of education.

Shapiro et al[54] reported that there was no clear association between paternal high-school (aOR 1.29 (95% CI 0.92 1.80)) or post-high-school (aOR 1.11 (95% CI 0.83, 1.48)) level of education and stillbirth odds in Canada.

Marital Status

Unmarried status

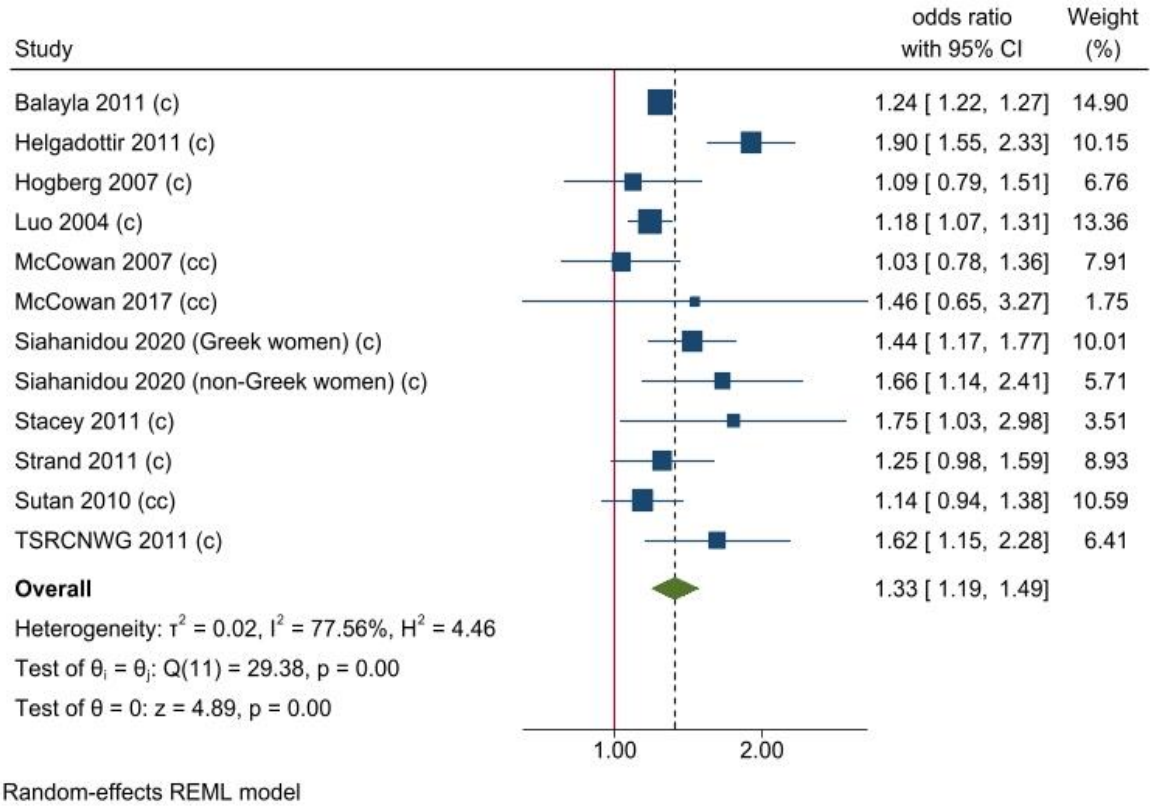
Sixteen studies examine the association between maternal marital status and stillbirth odds compared with non-married status[32, 40, 105, 111, 127, 130, 132, 151, 156, 166, 177, 180, 313, 323, 324, 327]. Risk of bias using the RTI tool of assessment showed that no studies had a low risk of bias, three studies were assessed to have high potential for bias[154, 313, 327], owing predominantly due to detection bias due to poor exposure measure definition and detection. The remaining studies showed an unclear potential for risk of bias.

Of the studies included, 11 compared married women to unmarried women in analysis of stillbirth odds. Across the included studies, unmarried women reported that they were either;

- Divorced/separated
- Single
- Unmarried
- Not cohabiting
- Not cohabiting with the baby's father

Meta-analysis of the studies to assess the impact of married status versus unmarried status mothers demonstrated an increased association with stillbirth (aOR1.33 (95% CI 1.19 to

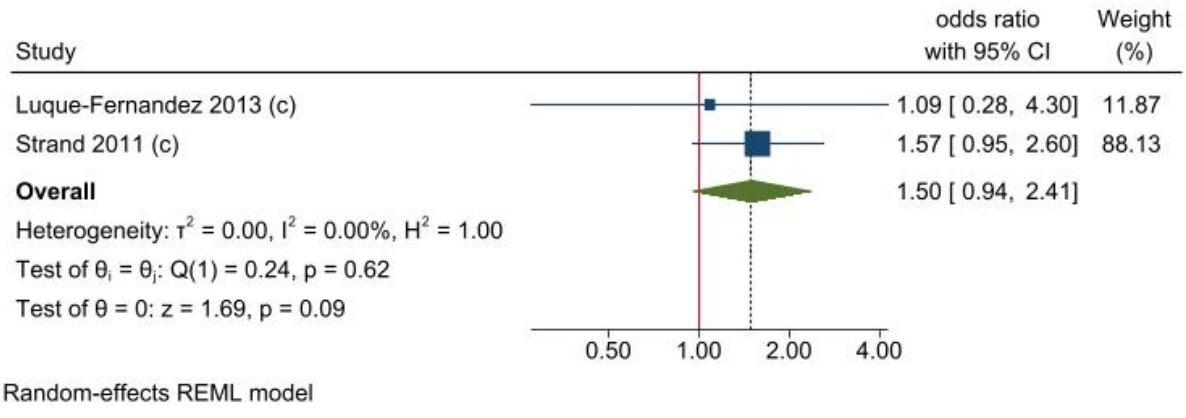
1.49) – fig 3-11). Considerable heterogeneity between studies (I^2 = 77.56%) was likely due to the different unmarried status definitions reported.



(c) = cohort studies
(cc) = case-control study
Figure 3-11Meta-analysis of studies examining the impact of unmarried status on stillbirth odds compared with married status

Divorced status

Marginally higher odds of stillbirth were shown through meta-analysis of two studies of women who reported being 'divorced' compared with 'married' (aOR 1.50 (95% CI 0.94, 2.41)- fig 3-12)[151, 327].

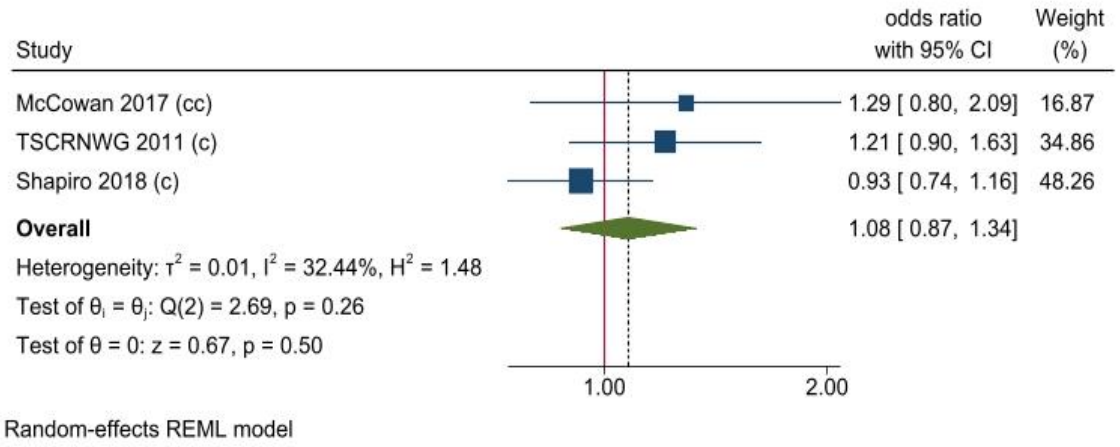


(c) = cohort studies
(cc) = case-control study

Figure 3-12 Meta-analysis of studies examining the impact of maternal divorced status and stillbirth odds compared with married status

Cohabiting status

Three studies examined the association between 'cohabiting' and stillbirth odds compared with 'married status'. Meta-analysis demonstrated no increased association with stillbirth for women who are co-habiting versus married (aOR 1.08 (95% CI 0.87 to 1.34) – fig 3-13)[32, 127, 323].



(c) = cohort studies
(cc) = case-control study

Figure 3-13 Meta-analysis demonstrating the association between cohabiting status and stillbirth odds compared with married status

Sexual orientation

One study[307] examined the association of maternal sexuality with odds of stillbirth within a cohort from the USA[307]. The study reference group included women who reported heterosexual orientation, and relationships with only with male partners. The exposure groups investigated were heterosexual women who have had both male and female partners, and secondly, women who reported their sexuality as bisexual/lesbian. Compared with heterosexual women (male partners only), odds of stillbirth were higher for heterosexual women who have had both male and female partners, aOR 1.71 (95% CI 0.80, 3.66). For women who reported their sexual orientation as bisexual/lesbian, the odds of stillbirth were almost three-fold that of heterosexual women with only male partners (aOR 2.85 (95% CI 1.40, 5.83)). In each of the exposure groups the number of stillbirths was less than 40, with large confidence intervals indicating that the study was underpowered for analysis, but the risk of bias assessment suggested that this study had a low risk of bias.

Consanguinity

One study[334] examined the association between biologically related parents and stillbirth odds compared with non-biologically related parents within a single institutional cohort from Sydney, Australia. Risk of bias assessment suggested that this study had unclear bias due to poor detection within the exposure cohort. Self-reported biological relation,

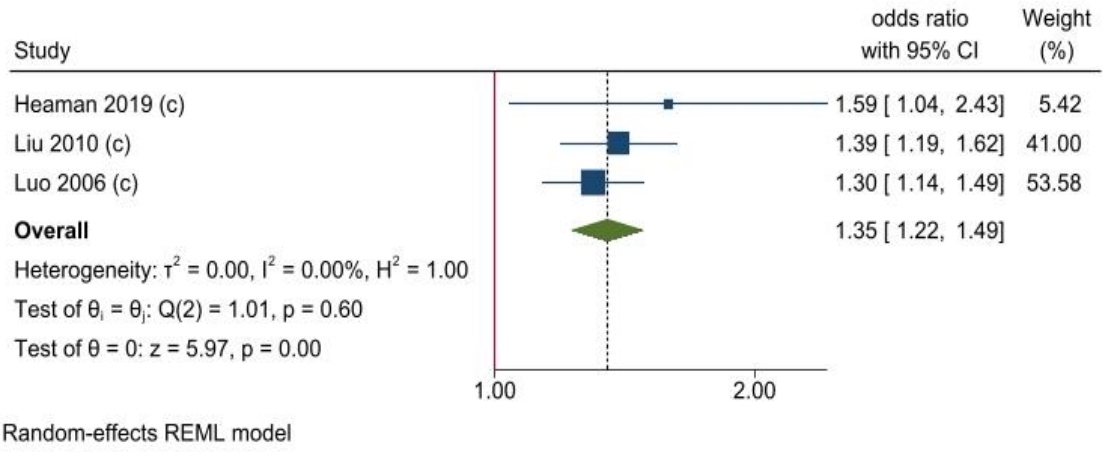
and no genetic analysis was used to confirm biological relations. Results of this study suggest an almost three-fold increased odds of stillbirth when parents report that they are biologically related (aOR 2.88 (95% CI 1.98, 4.28)).

Income

Eleven studies examined the association between income and stillbirth in high-income countries[35, 87, 113, 126, 127, 167, 303, 305, 312, 314, 317]. The studies sourced populations from four countries (USA, Netherlands, Canada, and Lithuania). Studies used differing measures of income; three studies examined income quintiles[87, 312, 314], and the remainder used high compared with low income according to the nation's average income, (three tiers of income). One study[317] was found to demonstrate a high risk of bias due to minimal adjustment for confounder in analysis, and also the selection of stillbirths from only low SES areas. Five studies demonstrated an unclear risk of bias[35, 126, 303, 305, 314], and five studies demonstrated a low risk of bias[87, 113, 127, 167, 312].

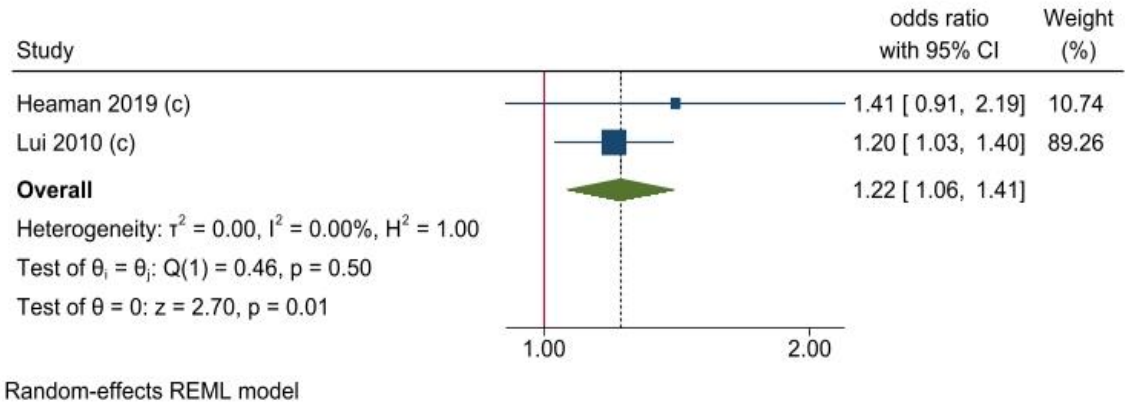
Maternal quintiles of income

Three studies examined the impact of income in Canada using quintiles of annual income[87, 312, 314]. One study reported the analysis of stillbirth odds for the lowest quintile compared with that of the highest income quintile[314], then further stratified results by rural or urban living. The resultant meta-analysis demonstrated an association between income and increased stillbirth odds in the three lowest quintiles of income in Canada. All studies used the highest income quintile as the reference population (fig 3-14). Similar results of increased stillbirth odds were also seen for second lowest quintile (fig 3-15); and middle quintile (fig 3-16) and second highest quintile (fig 3-17) - all compared with the highest income quintile.

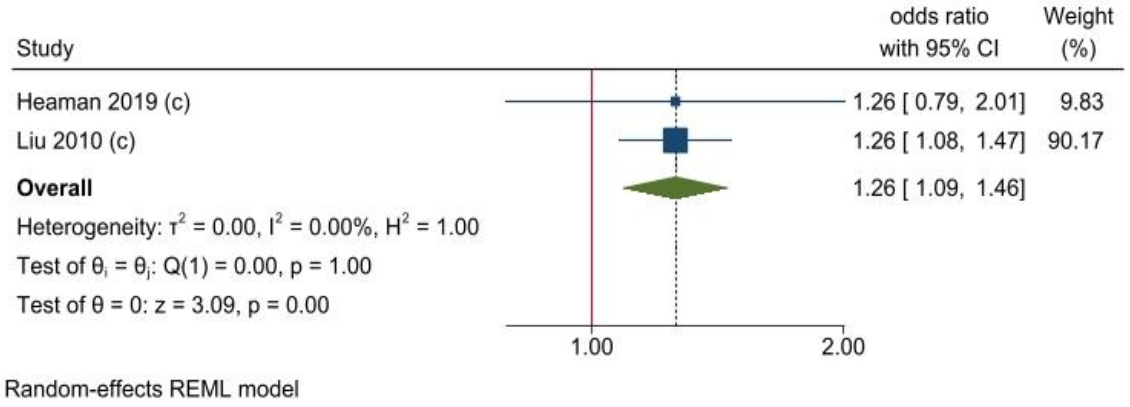


(c) = cohort studies
(cc) = case-control study

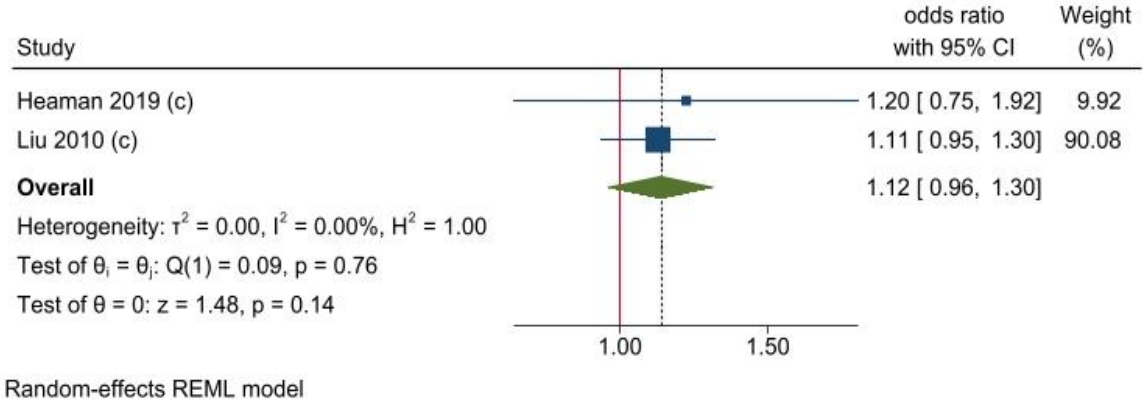
Figure 3-14: Meta-analysis of studies reporting the effect of maternal income in the lowest quintile on the odds of stillbirth compared with the highest income quintile



(c) = cohort studies
(cc) = case-control study
Figure 3-15 Meta-analysis of studies reporting the effect of maternal income in the second lowest quintile on the odds of stillbirth compared with the highest income quintile.



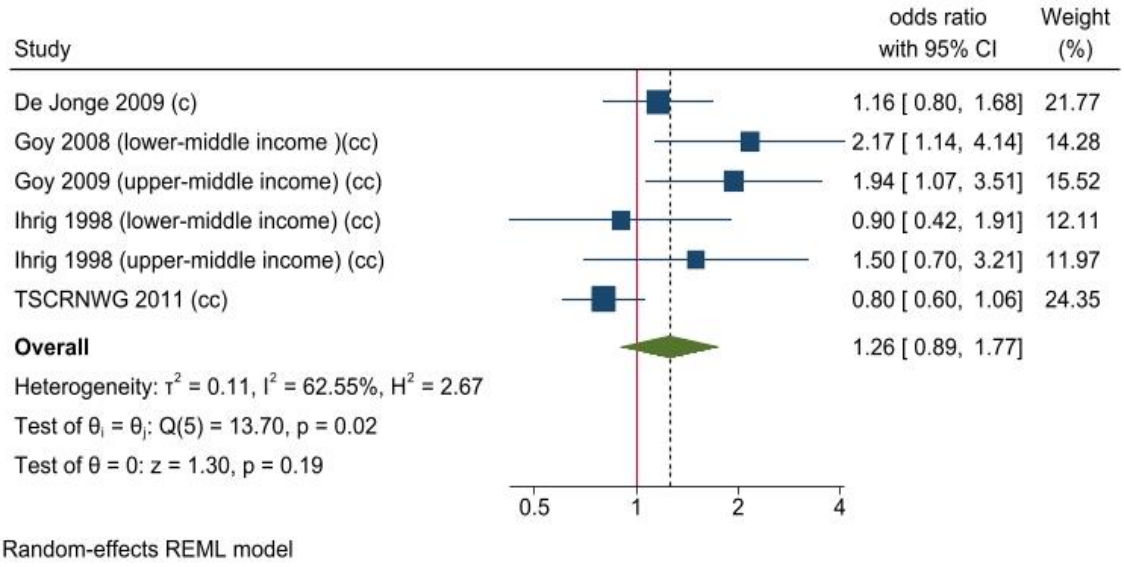
(c) = cohort studies
(cc) = case-control study
Figure 3-16 Meta-analysis of studies reporting the effect of maternal income in the middle quintile on the odds of stillbirth compared with the highest income quintile.



(c) = cohort studies
(cc) = case-control study
Figure 3-17 Meta-analysis of studies reporting the effect of maternal income in the second highest quintile on the odds of stillbirth compared with the highest income quintile.

Maternal middle income

Four studies examined the impact of middle level of maternal income compared with high maternal income on stillbirth odds[35, 113, 126, 127]. Two of the studies stratified data between two middle income groups (upper middle and lower middle income)[35, 126]. Final meta-analysis reported a possible association with stillbirth odds for middle income levels compared with the highest income category (aOR 1.26 (95% CI 0.89, 1.77) – fig 3-18).

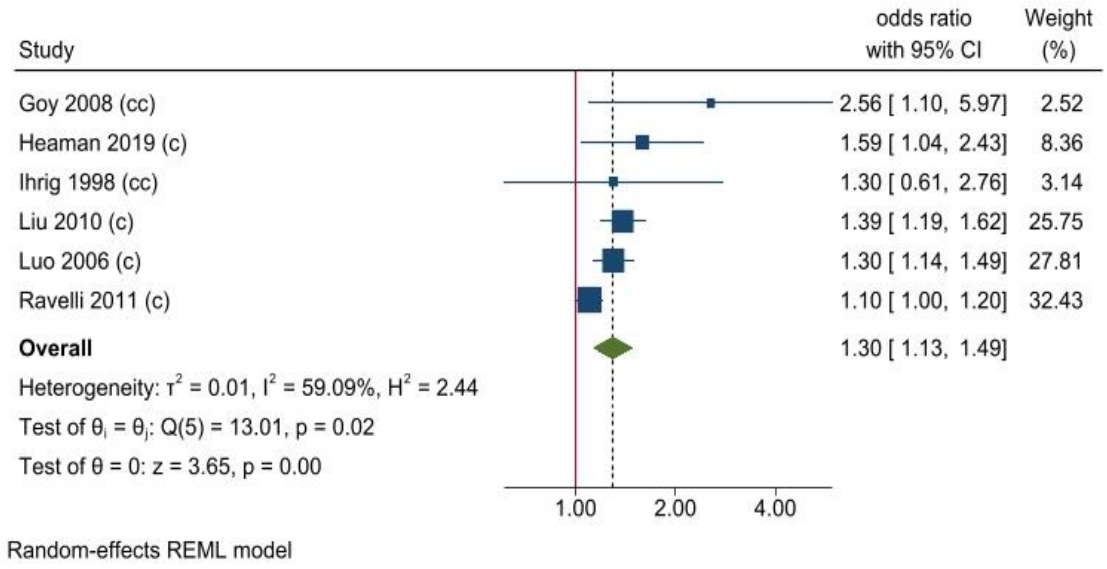


(c) = cohort studies
(cc) = case-control study

Figure 3-18 Meta-analysis of studies examining the impact of maternal income classified as middle income and associated stillbirth odds compared with women with income classified as high-income.

Maternal lowest income

Eleven studies examined the association of lower maternal income compared with higher income on stillbirth odds[35, 87, 113, 126, 127, 167, 303, 305, 312, 314, 317]. Three studies[113, 127, 305] were excluded from meta-analysis as they used datasets encompassed within larger cohort studies in this analysis[126, 167, 303]. Final meta-analysis demonstrated substantial heterogeneity, thus sensitivity analysis was performed. Sensitivity analysis identified that two studies that contributed substantially to heterogeneity. Maleckiene et al[317] was excluded due to its non-comparable population, (excluded stillbirths without intact fetal membranes). Brown et al[111] was excluded due to methodological differences in how income was classified that rendered results non-comparable. On exclusion, heterogeneity decreased to 59.09%. A 30% increase in odds of stillbirth associated with births to women from low-income households was shown compared with high-income households (aOR 1.30 (95% CI 1.13, 1.49) – fig 3-19).



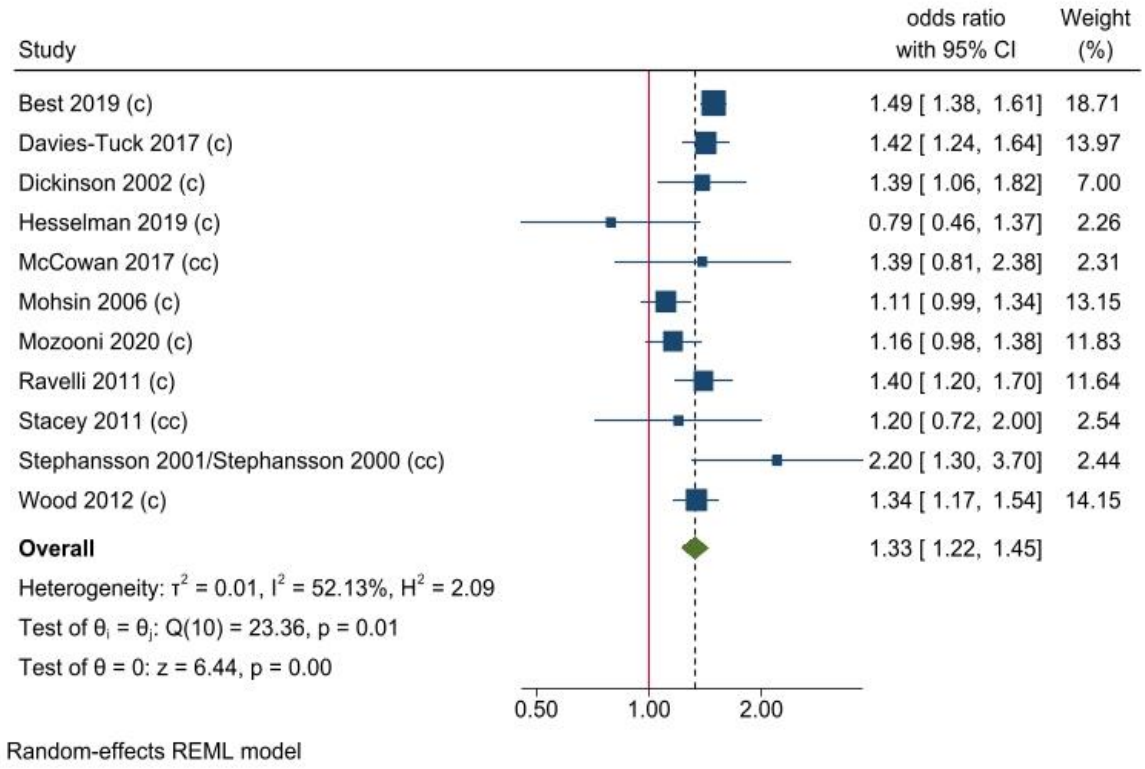
(c) = cohort studies
(cc) = case-control study
Figure 3-19 Meta-analysis of studies reporting the impact of maternal income classified as low household income and stillbirth odds, compared with women with high household income.

Socioeconomic status

Nineteen studies examined the association of socioeconomic status with stillbirth odds, studies encompassed populations from eight high-income countries[32, 73, 134, 151, 153, 157, 158, 167, 178, 179, 185, 249, 335-342]. Many studies included a scale of SES measure appropriate for their populations[73, 151, 178, 335, 338, 342], and analysis reported the impact of lowest SES group versus and high SES group on stillbirth odds within their populations[32, 73, 151, 157, 158, 167, 178, 185, 249, 335, 338-342]. A smaller number of studies reported middle level SES associations with stillbirth odds[157, 167, 249, 341]. One study examining the impact of SES on stillbirth odds was assessed as having high risk of bias as the study used a population from a single institution and a single doctor assessing fetal death[134], therefore selection bias was noted in this study. Nine studies were assessed as having an unclear risk of bias[32, 151, 157, 179, 249, 335-338, 340] and the remaining nine studies exhibited a low risk of bias[73, 153, 158, 167, 178, 185, 339, 341, 342].

Low socioeconomic status

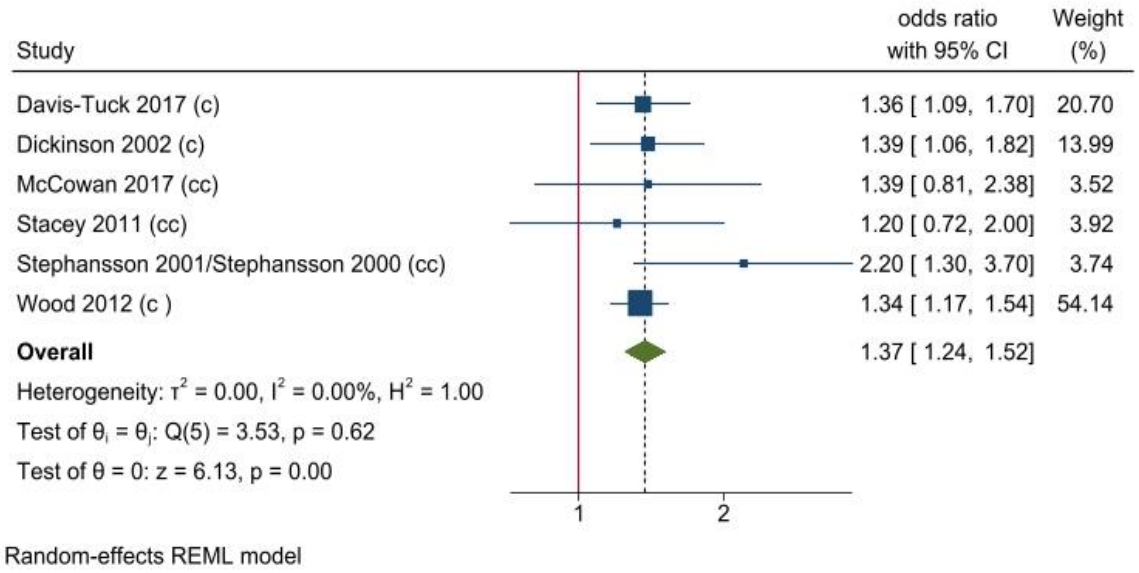
Of the studies included, 17 reported the odds of stillbirth associated with births to women in the lowest SES level [32, 73, 134, 157, 158, 167, 178, 179, 185, 249, 335-342]. Four studies [178, 185, 335, 338] reported the use of datasets that were encompassed in larger included studies[339, 340]. The smaller sub- studies were excluded to avoid double counting of results[178, 185, 335, 338]. Initial meta-analysis demonstrated considerable heterogeneity, and thus sensitivity analysis were performed. One study[134] was identified as the main contributor to heterogeneity and its exclusion decreased heterogeneity to a moderate level (I^2 = 52.13%). Risk of bias assessment suggested that this study has a high risk of bias due misclassification bias and poor exposure measures reported. Final analysis demonstrated an increased association between low socioeconomic status and stillbirth odds (aOR 1.33 (95% CI 1.22, 1.45) – fig 3-20).



(c) = cohort studies
(cc) = case-control study
Figure 3-20 Meta-analysis of studies reporting the association between low socioeconomic status and stillbirth odds compared to high socioeconomic status

Low socioeconomic status (third trimester stillbirth)

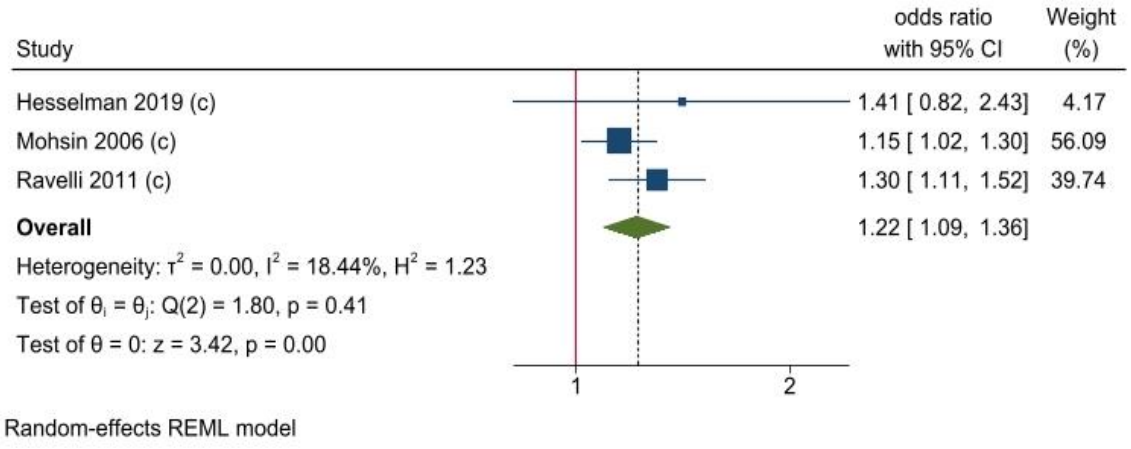
Six included studies examined the impact of low maternal socioeconomic status were noted to limit their analysis to third trimester stillbirths [32, 73, 179, 249, 336, 337, 339]. All studies were included in the final meta-analysis that demonstrated an increased association between low socioeconomic status and third trimester stillbirths (aOR 1.37 (95% CI 1.24, 1.52) – fig 3-21).



(c) = cohort studies
(cc) = case-control study
Figure 3-21Meta-analysis of studies reporting the association between low socioeconomic status and third trimester stillbirth odds compared with high socioeconomic status

Middle level socioeconomic status

Three studies reported the odds of stillbirth associated with middle level socioeconomic status[157, 167, 341]. All three studies were combined in meta-analysis and results demonstrated an increased association between middle socioeconomic status and stillbirth odds compared with high level socioeconomic status (aOR 1.22 (95% CI 1.09, 1.36) – fig 3-22).



(c) = cohort studies
(cc) = case-control study
Figure 3-22 Meta-analysis of studies reporting the association between middle level socioeconomic status and stillbirth odds compared with high socioeconomic status

Maternal age

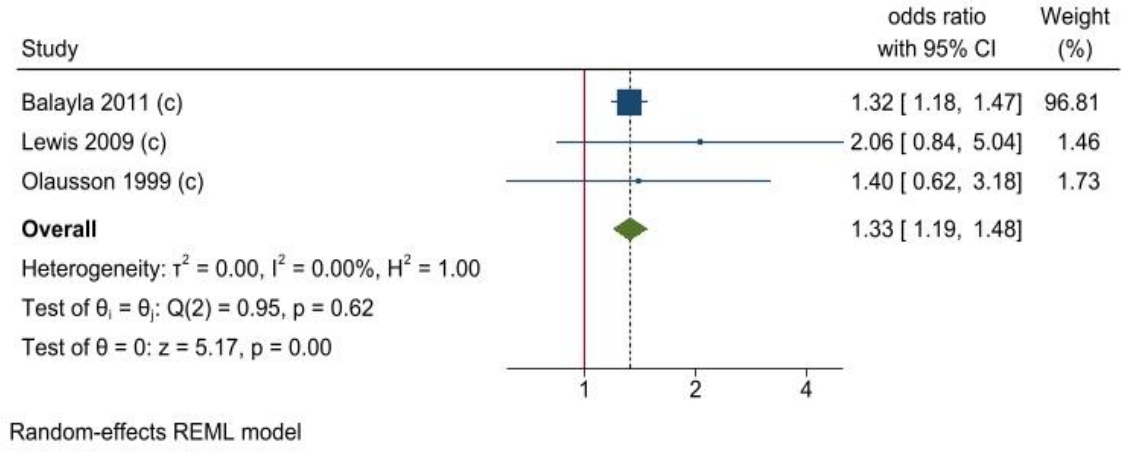
Ninety-nine studies examined the association between maternal age and stillbirth odds[32, 35, 40, 73, 87, 91, 92, 98-189] within cohorts sourced from twenty high-income countries globally.

Maternal age <16 years

Seven studies examined the association between maternal age <16 years and stillbirth odds[40, 105, 145, 154, 163, 174, 187] and study populations were drawn from three high-income countries globally. Four studies[100, 154, 174, 187] were identified as using the same data set as one larger study[105], thus to avoid double-counting of births, the four smaller studies were excluded from analysis. The final meta-analysis included three definitions of teen mothers including;

- Maternal age <15 years compared with 25-29 years [105],
- Maternal age 13-15 years compared with 20-24 years [163],
- and maternal age 12-16 years compared with >19 years [145].

Using the RTI tool of bias assessment, two studies were deemed to have a low risk of bias[40, 145], and the final study had an unclear risk of bias due to minimal adjustment of the study results[163]. The final meta-analysis demonstrated 30% increased odds of stillbirth associated with a maternal age <16 years (aOR 1.33 (95% CI 1.19, 1.48) – fig 3-23).



(c) = cohort studies
(cc) = case-control study

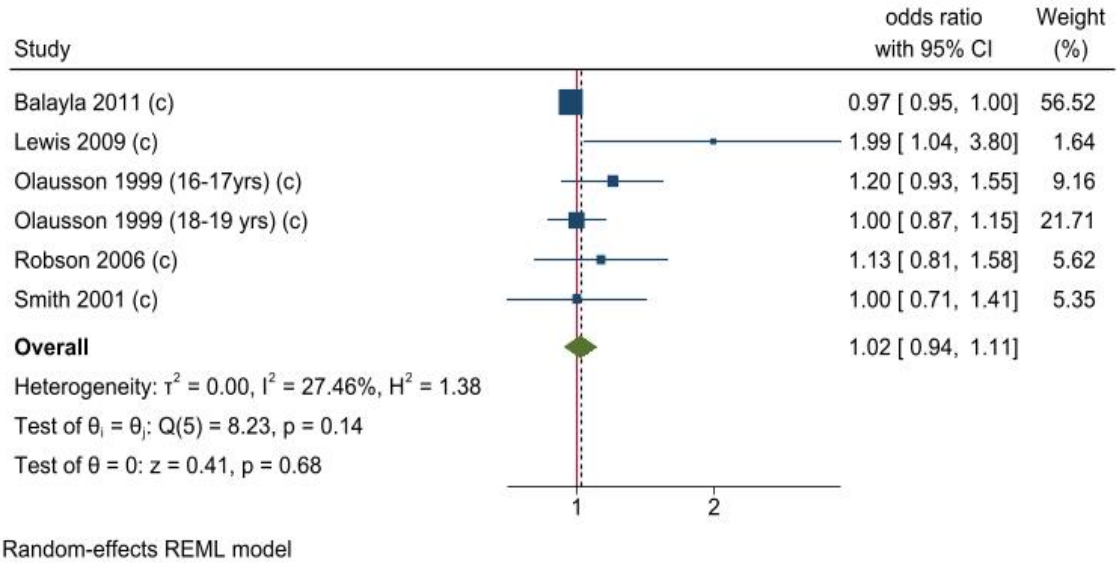
Figure 3-23 Meta-analysis of studies reporting the stillbirth odds associated with young maternal age (<16 years) to that of older mothers (>19 years)

Two studies stratified the results for women under the age of 15 years by the timing of stillbirth (antepartum and intrapartum)[100, 187], but meta-analysis was not possible due to the studies using the same datasets. The odds of antepartum stillbirth were doubled for women <15 years of age (aOR 2.3 (95% CI 1.7, 3.0))[187] and four-fold for intrapartum stillbirths (aOR 4.4 (95% CI 1.0, 4.7)) in a population of American women from Missouri[187] compared with a maternal age of >19 years. Aliyu et al[100] demonstrated similar findings for smoking mothers < 15 years at birth compared with women who were 20-24 years old at birth (intrapartum stillbirth odds; aOR 4.0 (95% CI 0.60, 28.7),

antepartum stillbirth odds; aOR 3.1 (95% CI 1.2, 8.3)), but due to a small sample size, analysis was underpowered.

Maternal age 15-19 years

Thirteen studies examined the correlation between maternal age of 15-19 years and the risk of stillbirth[40, 99, 100, 105, 111, 112, 145, 149, 163, 168, 174, 178, 187] compared with a maternal age of >19 years. Eight of the studies used the same datasets as larger cohort studies included, therefore to avoid double-counting births, the eight studies were excluded from analysis[40, 99, 100, 111, 112, 149, 174, 187]. The final meta-analysis included five studies from four high-income countries[40, 145, 163, 168, 178]. One study stratified births between maternal age groups 16-17 years and 18-19 years [163]. Analysis showed that there was no clear association between maternal age of 15-19 years and stillbirth risk in comparison to maternal age of >19 years (aOR 1.02 (95% CI 0.94, 1.11) – fig 3-24). Reference group differences were minimal; four studies reportedly using a reference group of between 20 and 29 years, and one using a reference group of 19 years[145].



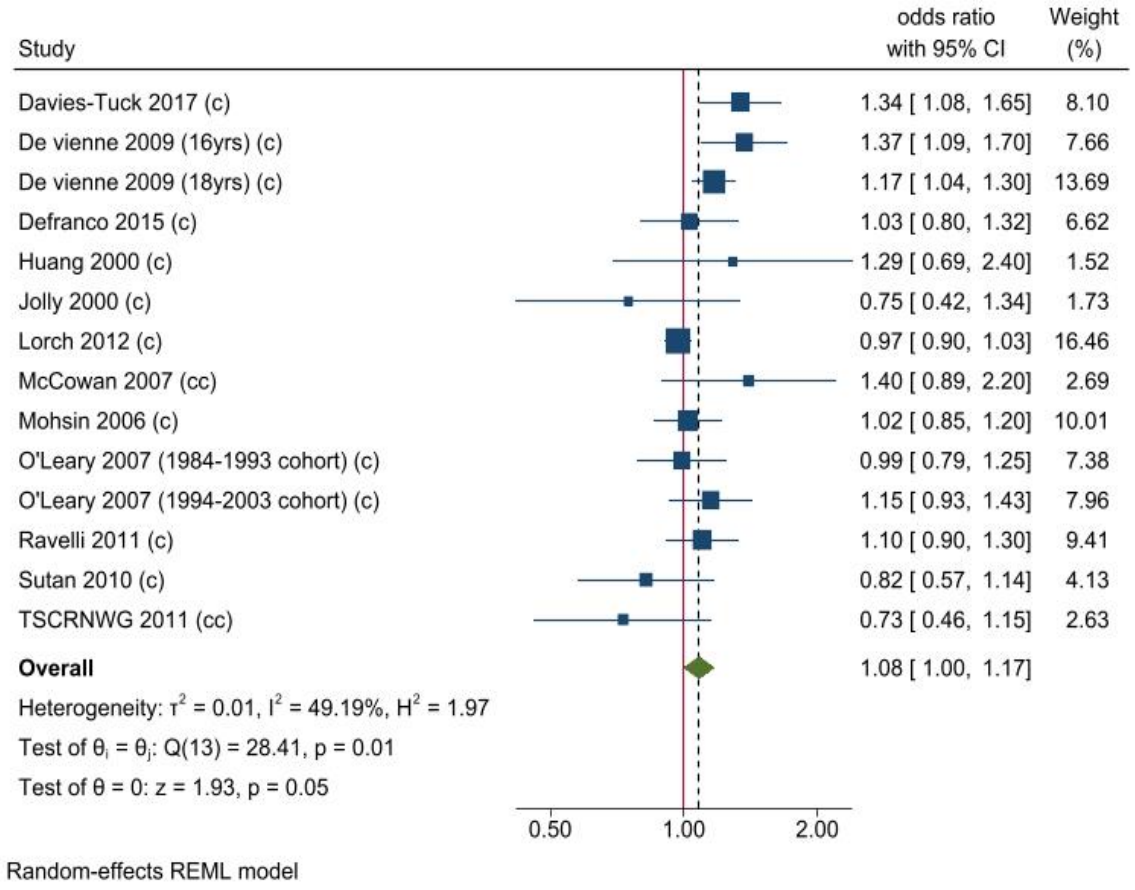
(c) = cohort studies
(cc) = case-control study

Figure 3-24 Meta-analysis of studies reporting stillbirth odds associated with maternal age 15-19 years compared with maternal age >19 years.

Maternal age <20 years

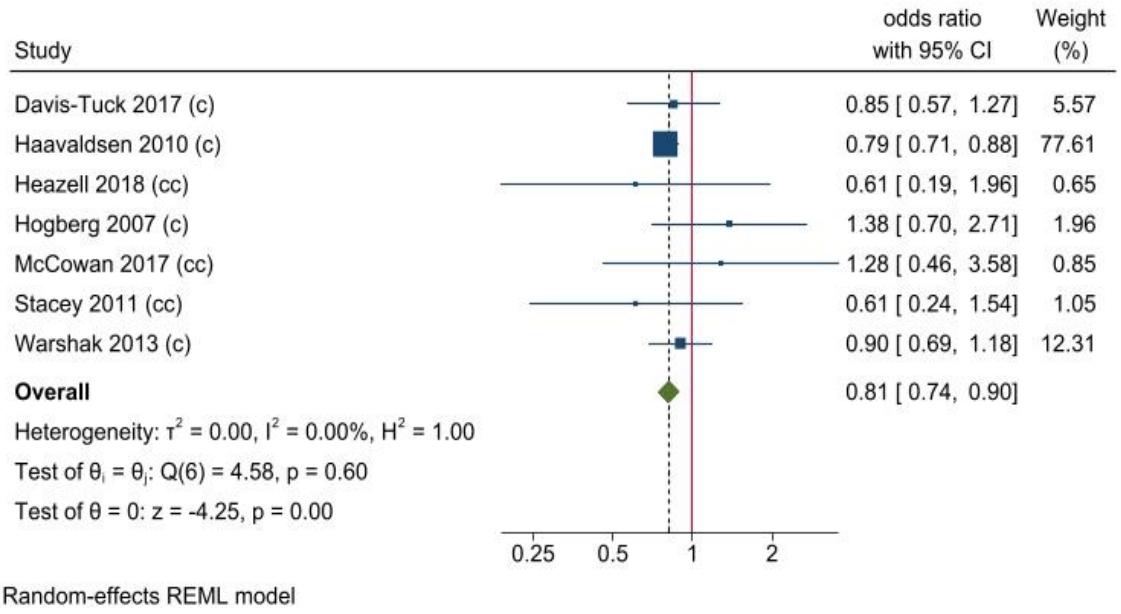
Twenty-four studies investigated the association between maternal age of <20 years and stillbirth odds compared with older women (20-34 years). Studies used differing reference groups with a range of ages from 20 to 39 years[32, 35, 73, 91, 107, 114, 125, 127, 128, 132, 134, 139, 150, 156, 157, 161, 167, 178-181, 184, 188, 333]. Populations included in the studies spanned eight high-income countries. Six of the studies examined stillbirth risk in datasets used within larger studies included in this meta-analysis. Therefore, to avoid double counting, smaller studies were excluded from analysis[35, 107, 125, 178, 181, 188]. The remaining studies were separated according to the timing of the stillbirth definitions used (second and third

trimester, or third trimester), the first analysis included fourteen studies that included stillbirths across second and third trimesters of pregnancy[73, 114, 127, 134, 138, 139, 150, 156, 157, 161, 167, 180, 333], showing a small increase in stillbirth odds for maternal age <20 years (aOR 1.08 (95% CI 1.00, 1.17) – fig 3-25).



(c) = cohort studies
(cc) = case-control study
Figure 3-25 Meta-analysis of studies reporting the stillbirth odds of maternal age <20 years compared with maternal age 20-34 years.

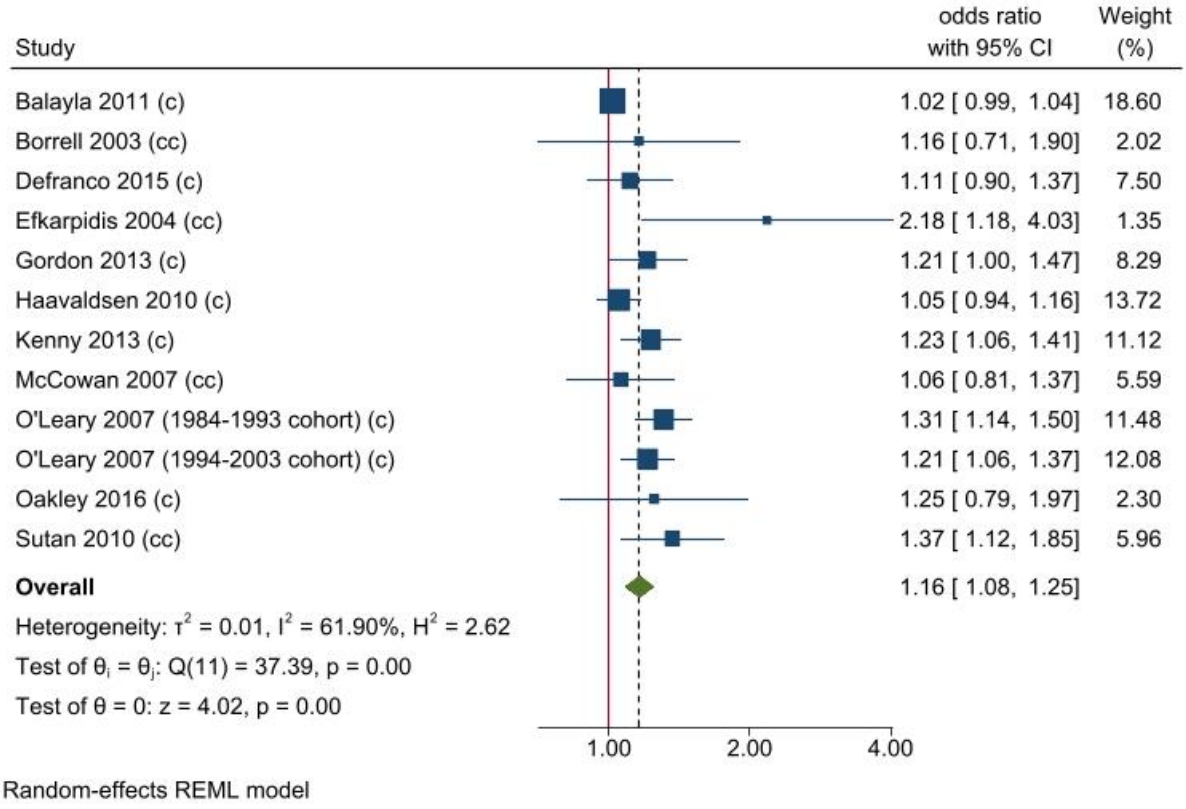
Seven studies examined the association between maternal age of <20 years and third trimester stillbirth (≥28 weeks GA – definitions encompassed within this definition was also included)[32, 73, 91, 128, 132, 179, 184] compared with mothers aged 20-34 years. Meta-analysis demonstrated a protective association with a maternal age <20 and third trimester stillbirth odds (0.81 (95% CI 0.74, 0.90) – fig 3-26).



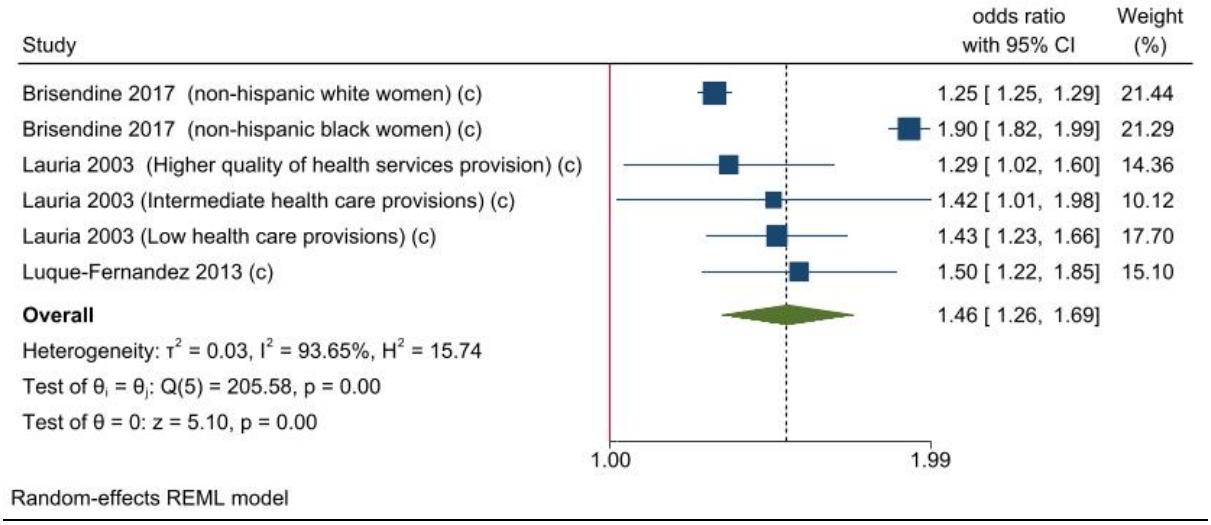
(c) = cohort studies
(cc) = case-control study
Figure 3-26 Meta-analysis of studies reporting the odds of third trimester stillbirth associated with a maternal age of <20 years in comparison to a maternal age of 20-34 years.

Maternal Age 30-34 years

Twenty-four studies document maternal age of 30-34 years and associated odds of stillbirth[40, 105, 107, 109, 110, 112, 114, 120, 121, 124, 125, 128, 140, 144, 149, 151, 156, 159, 161, 162, 176, 178, 180, 182, 333]. Twelve studies used the same dataset as larger included studies[40, 107, 112, 114, 121, 124, 125, 149, 159, 176, 178, 182, 333], and thus the smaller studies were excluded from analysis. Three studies examined the odds of stillbirth associated with a maternal age of 30-34 years compared with ≤19 years[110, 144, 151], and the remainder used a reference cohort of women with an age at birth between 20 and 29 years[105, 109, 120, 125, 128, 140, 156, 161, 162, 180], analysis was subgrouped by the reference groups described. Results of meta-analysis demonstrated an increase in association between women aged between 30-34 years and stillbirth odds compared with women aged between 20 and 29 at birth (aOR 1.16 (95% CI 1.08, 1.25) – fig 3-27) (Heterogeneity, I^2=61.9%). The impact on stillbirth of the same exposure group (30-34 years) when compared with a younger cohort of women (≤ 19 years) was further increased (aOR 1.46 (95% CI 1.26, 1.69)) but with considerable heterogeneity (I^2=94%). Within the second analysis comparing women aged 30-34 years to women aged ≤ 19 years, two studies stratified their results; one by ethnicity, and one by healthcare provisions available to women. All subgroups were included in analysis and results demonstrated a 46% increase in stillbirth odds (aOR 1.46 (95% CI 1.26, 1.69) - fig 3-28).



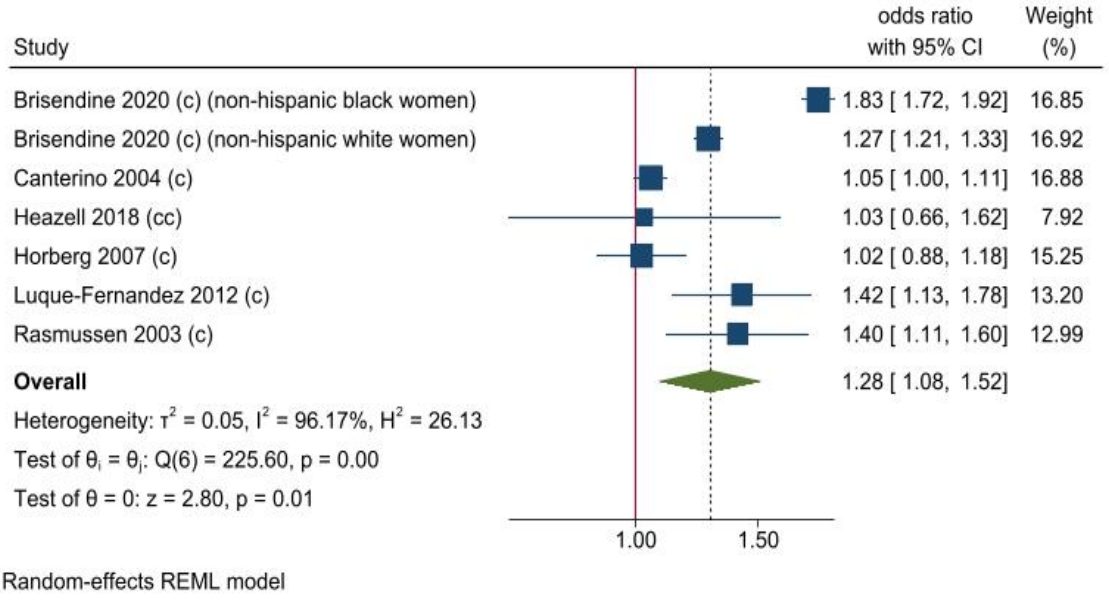
(c) = cohort studies
(cc) = case-control study
Figure 3-27 Meta-analysis of studies reporting the association of maternal age at birth of 30-34 years and stillbirth odds compared with women ages 20-29 years



(c) = cohort studies
(cc) = case-control study
Figure 3-28 Meta-analysis of studies reporting the association of maternal age at birth of 30-34 years and stillbirth odds compared with women who are ≤19 years at the time of birth.

Maternal Age 30-34 years (third trimester stillbirth)

Nine studies examined the association of maternal age of 30-34 years at birth with third trimester stillbirth odds compared with women <30 years of age at birth[91, 99, 110, 112, 128, 132, 152, 166, 183]. Two studies were excluded from analysis due to their use of the same dataset used in larger studies[99, 128]. One study stratified by parity, education level, and smoking level[183] and could not be included in meta-analysis due to double counting of births between results. Final meta-analysis included six studies and demonstrated considerable heterogeneity (I^2 = 97%). Through sensitivity analysis, Brisendine et al[110] was identified as the main contributor to heterogeneity. Although the study cohort only included non-Hispanic Black and White women, no further reason to justify exclusion could be found. Final analysis demonstrated an increase in stillbirth odds associated with maternal age of 30-34 and third trimester stillbirth compared with women <29 years at birth (aOR 1.28 (95% CI 1.08, 1.52) – fig 3-29).



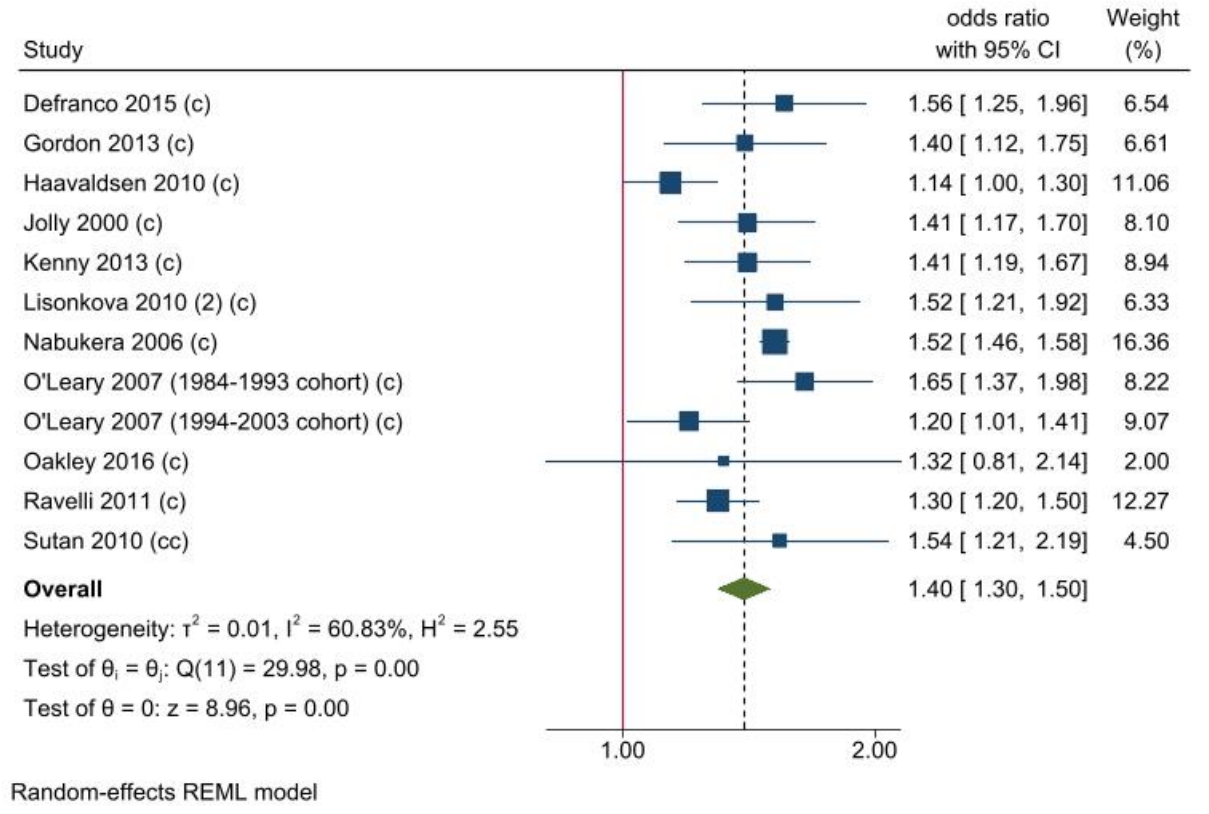
(c) = cohort studies
(cc) = case-control study

Figure 3-29 Meta-analysis of studies reporting stillbirth odds associated with maternal age of 30-34 and third trimester stillbirth compared with women who are <29 years at birth.

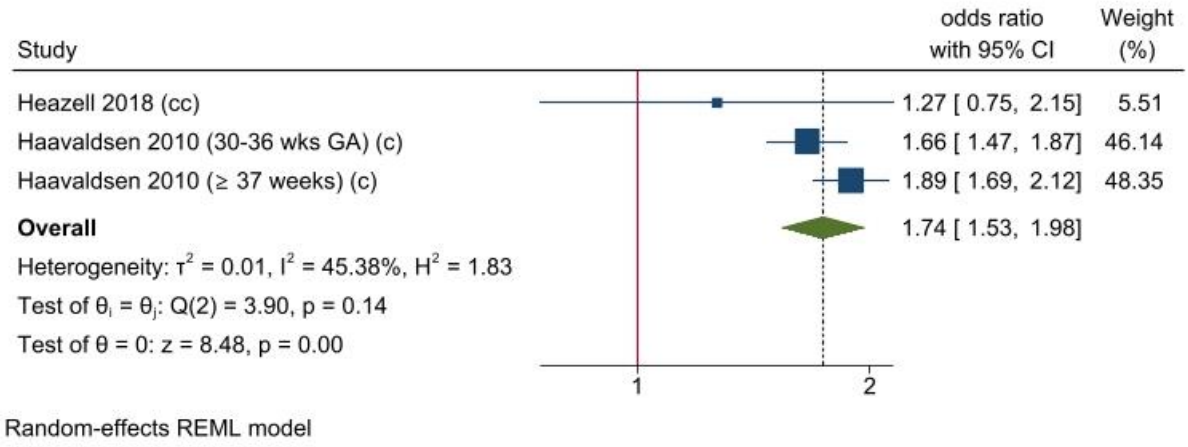
Maternal age 35-40 years

Twenty-eight studies examined the association between maternal age of 35-40 years with stillbirth odds, in comparison with women aged <30 years[40, 91, 99, 105, 107, 110, 112, 125, 127, 128, 130, 131, 134, 138, 140, 144, 146, 149, 159, 161, 162, 166, 167, 176, 178, 180, 181, 183, 333]. Several studies were identified as using the same datasets for analysis. The larger studies included were retained for analysis, and smaller studies using the same datasets were excluded in an effort to avoid double counting of births[40, 92, 99, 105, 107, 112, 127, 130, 131, 134, 149, 166, 176, 178, 181, 182]. Studies included populations from ten high-income countries, and results were able to be stratified by stillbirth definitions (stillbirth from 20 weeks onwards, and third trimester stillbirths), maternal socioeconomic status (SES) (high/low) and parity (nulliparous, and multiparous). Meta-analysis of all studies examining the impact of a maternal age of 35-40 years and stillbirth odds in comparison to women <30 years of age

demonstrated an increase in stillbirth odds (aOR 1.40 (95% CI 1.30, 1.50) – fig 3-30). Odds increased to aOR 1.74 (95% CI 1.53, 1.98) – fig 3-31 for women who experienced third trimester stillbirth within this exposure category. Women aged 35-40 years with high SES had increased odds of stillbirth in high-income countries compared with women <35 years (aOR 1.42 (95% CI 1.19, 1.70) – fig 3-32). However, women with low SES (aOR 1.63 (95% CI 1.37, 1.95) – fig 3-33) had even higher odds of stillbirth compared with women < 35 years. Subgroup analysis examining the effect of maternal age of 35-40 years in nulliparous and multiparous women demonstrated increased odds of stillbirth for older maternal age for both subgroups of parity, but marginally higher association for older nulliparous women (aOR 1.46 (95% CI 1.18, 1.82) – fig 3-34) than older multiparous women (aOR 1.37 (95% CI 1.15, 1.63) – fig 3-35) through analysis of maternal age.

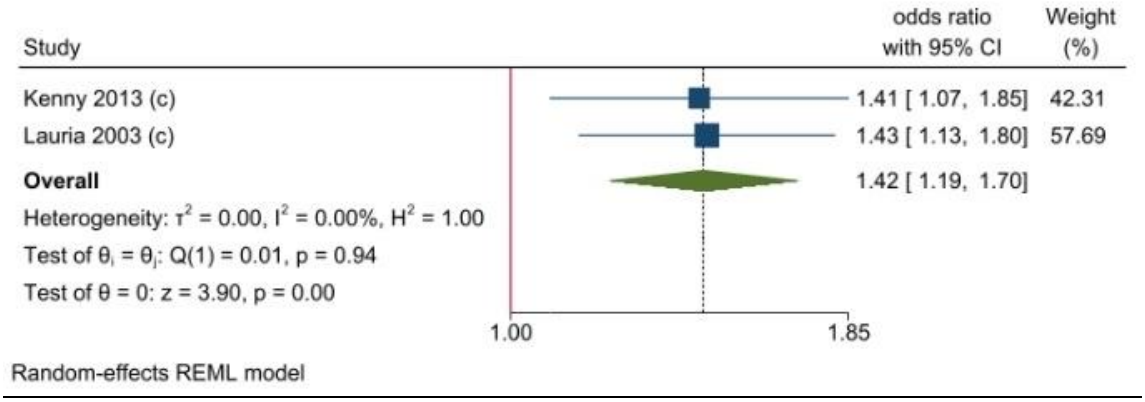


(c) = cohort studies
(cc) = case-control study
Figure 3-30 Meta-analysis of studies reporting the association between maternal age of 35-40 years and stillbirth odds compared with a maternal age of <30 years.



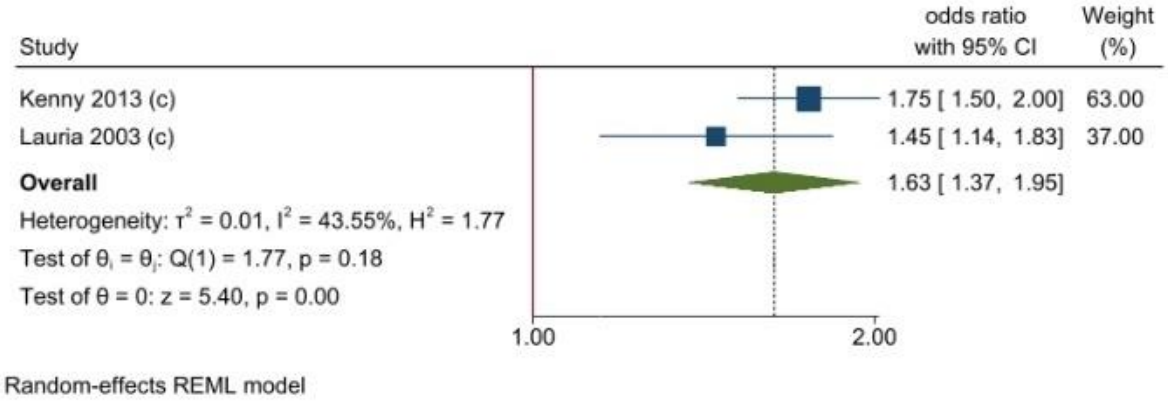
(c) = cohort studies
(cc) = case-control study

Figure 3-31 Meta-analysis of studies reporting the association between maternal age of 35-40 years and third trimester stillbirth odds compared with a maternal age of <35 years.



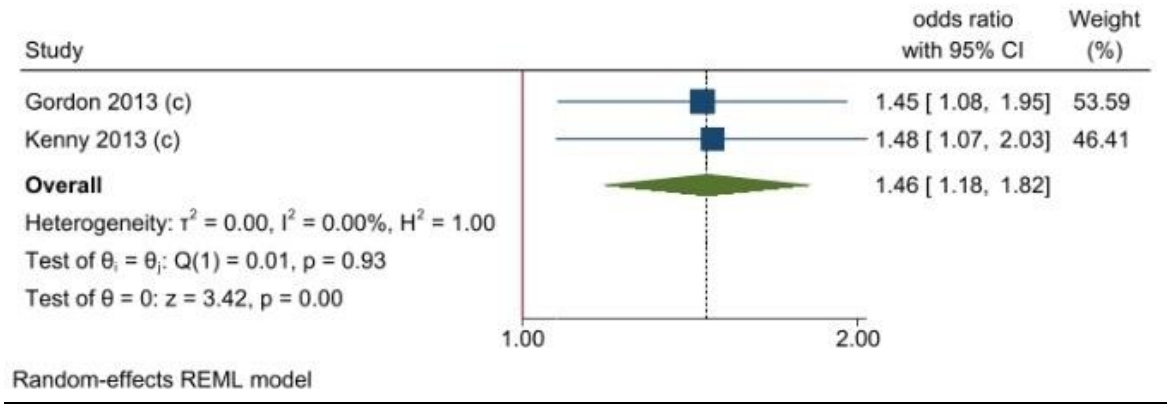
(c) = cohort studies
(cc) = case-control study

Figure 3-32 Meta-analysis of studies reporting the association between maternal age of 35-40 years and stillbirth odds compared with a maternal age of <30 years (High SES)

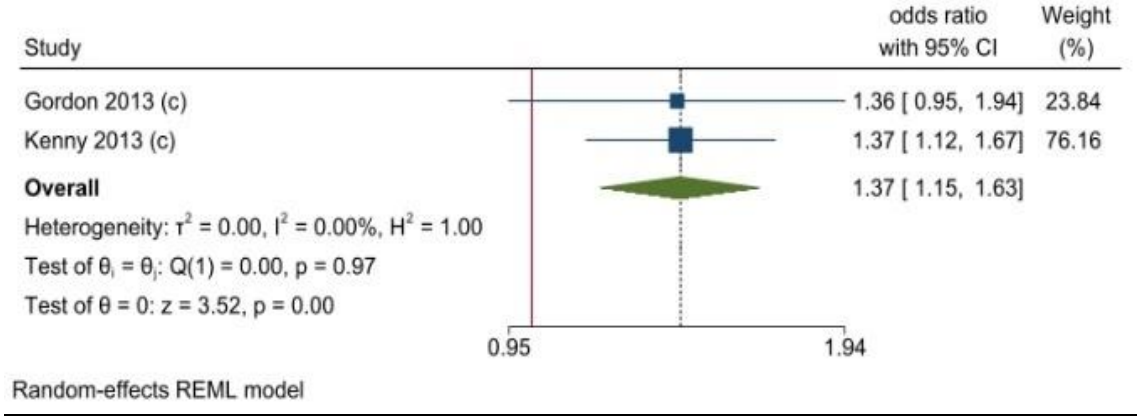


(c) = cohort studies
(cc) = case-control study

Figure 3-33 Meta-analysis of studies reporting the association between maternal age of 35-40 years and stillbirth odds compared with a maternal age of <30 years (Low SES)



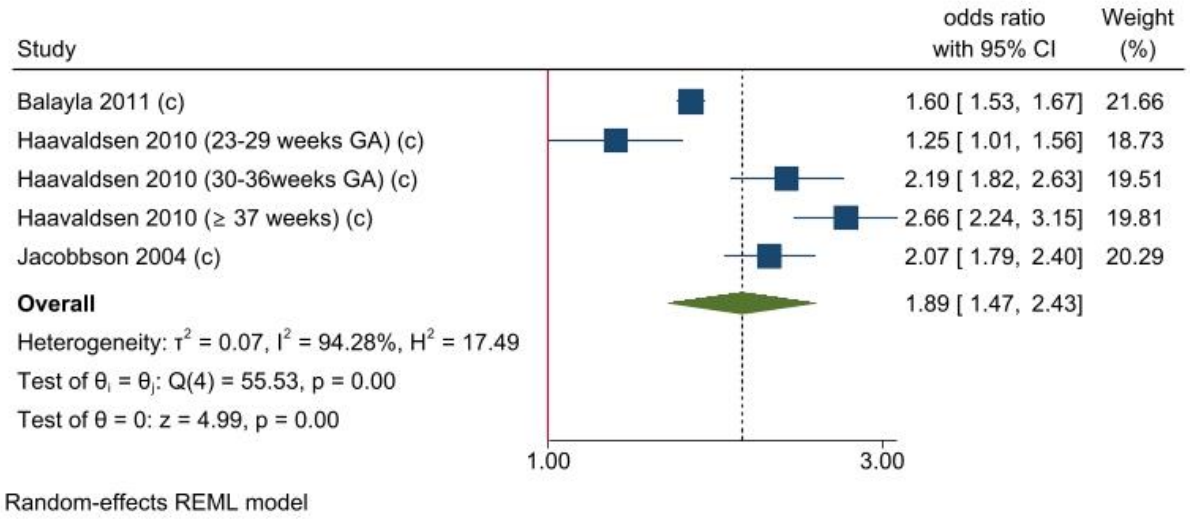
(c) = cohort studies
(cc) = case-control study
Figure 3-34 Meta-analysis of the association between maternal age of 35-40 years and stillbirth odds compared with a maternal age of <30 years (nulliparous)



(c) = cohort studies
(cc) = case-control study
Figure 3-35 Meta-analysis of the Association between maternal age of 35-40 years and stillbirth odds compared with a maternal age of <30 years (multiparous)

Maternal age 40-45

Eight studies reported the odds of stillbirth associated with maternal age of 40-45 years in comparison to a maternal age of 20-29 years[40, 99, 105, 112, 128, 137, 149, 166]. There was some overlap between the cohorts used within the studies, smaller studies using the same datasets as larger included studies were excluded from meta-analysis to avoid double counting of births[40, 99, 112, 149, 166]. Heterogeneity between studies was considerable through final meta-analysis (I^2 = 94.28%) but sensitivity analysis did not identify any main contributors. There was an almost two-fold increase in stillbirth odds associated with maternal age of between 40-45 years compared with women between 20 and 29 years at birth (aOR 1.89 (95% CI 1.47, 2.43) – fig 3-36), but due to increase heterogeneity, results should be interpreted with caution. Through analysis it was noted that one included study[128] stratified by GA at birth, and demonstrated an increase in stillbirth odds as gestation approached term, indicating a possible association with placental pathology.

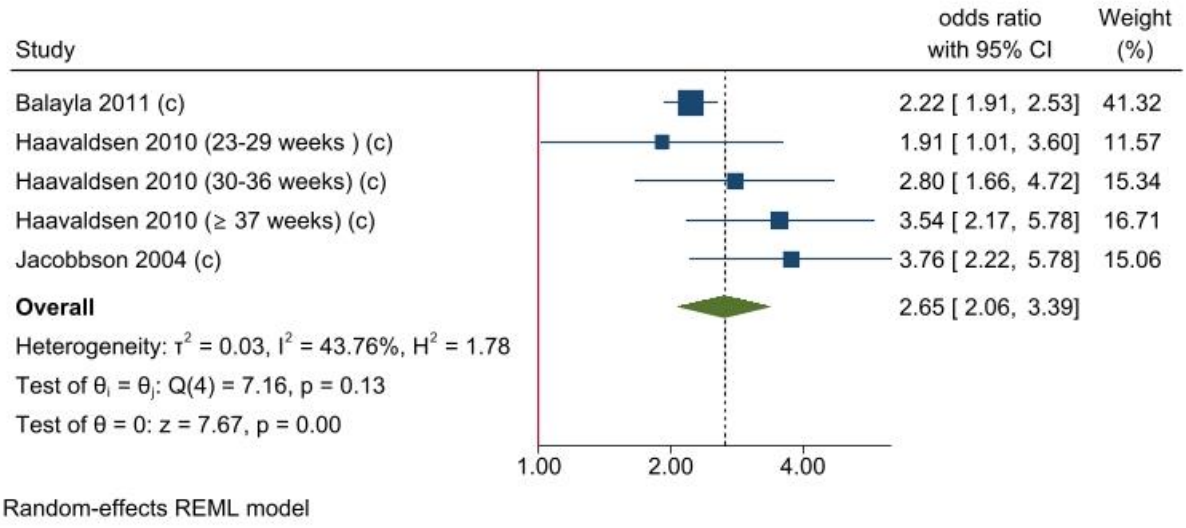


(c) = cohort studies
(cc) = case-control study

Figure 3-36 Meta-analysis of the studies reporting stillbirth odds for the association between a maternal age of 40-45 years and stillbirth odds compared with a maternal age of 20-29 years.

Maternal age >45 years

Four studies examined the association between a maternal age of >45 years and stillbirth odds compared with women aged 20-29 years [40, 105, 128, 137]. One study[40] was excluded from meta-analysis to avoid double counting of births, as it reported use of a dataset contained within a larger included study. Final meta-analysis included three studies, including one study that stratified results by GA at birth[128]; all subgroups were included within the meta-analysis. Results indicate that maternal age over 45 was associated with a 2.5-fold increase in stillbirth odds (aOR 2.65 (95% CI 2.06, 3.39) – fig 3-37) compared with a younger maternal age.



(c) = cohort studies
(cc) = case-control study
Figure 3-37 Meta-analysis of studies reporting the association between a maternal age of >45 years and stillbirth odds compared with a maternal age of 20-29 years.

Maternal age >50 years

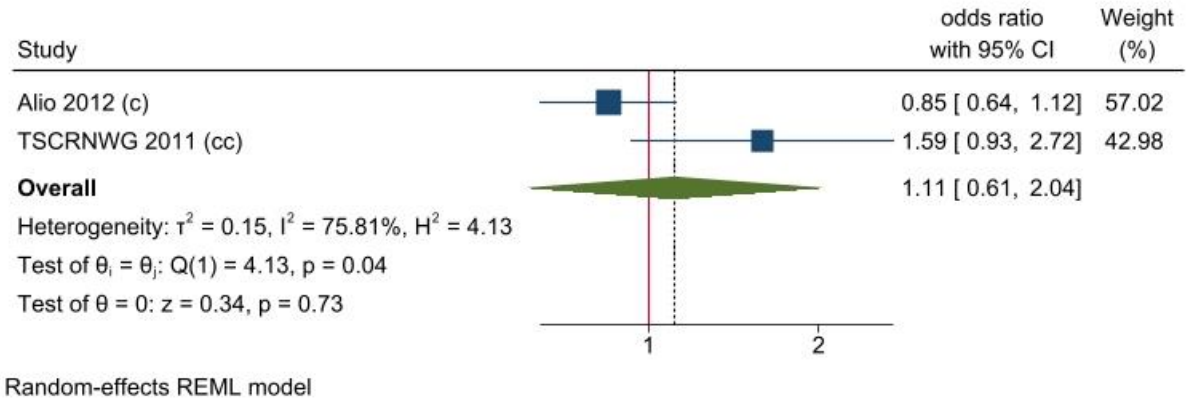
One study examined the association between a maternal age of >50 years at birth and stillbirth odds, compared to a women aged 20-29 years[172]. Results indicate a more than two-fold increase in stillbirth odds for women aged over 50 at birth compared with women aged 20-29 years (aOR 2.20 (95% CI 1.01, 4.75)). Large confidence intervals associated with these findings reflect the small sample size within this exposure group (n=349), highlighting that these results should be interpreted with caution.

Paternal age

Eight studies reported the association between paternal age and stillbirth odds[103, 127, 141, 155, 177, 298, 301, 329]. Study populations were sourced from four high-income countries - USA, Denmark, Greece and Italy. Two of the studies reported the effect of the calculated difference between maternal and paternal age[141, 177], stratified by ethnicity. The remaining six studies investigated the effect of paternal age on stillbirth odds categorically[103, 127, 155, 298, 301, 329]. All studies were assessed using the RTI tool of assessment and one study was assessed to have a high risk of bias [103]. This was predominantly caused by lack of adjustment in analysis leaving residual bias, and the exclusion of large for gestational age babies indicated selection bias.

Paternal age <20 years

Two studies examined the effect of a paternal age <20 years on stillbirth odds in high-income countries[127, 298] compared with fathers aged 20-34 years. Both studies used populations within the USA. Meta-analysis demonstrated no clear association between paternal age <20 years and stillbirth odds (aOR 1.11 (95% CI 0.61, 2.04) – fig 3-38). Heterogeneity was substantial and could be attributed to the difference in study design, one case-control study and the other a cohort study.



(c) = cohort studies
(cc) = case-control study
Figure 3-38 Meta-analysis of the studies reporting the association between paternal age <20 years and stillbirth odds compared with paternal age of 20-34 years.

Paternal age <25 years

Two studies examined the association between paternal age of <25 years and stillbirth odds, compared with cohorts of fathers aged between 25 and 34 years[301, 329]. Both studies used the same dataset, and therefore to avoid double-counting, meta-analysis was not performed. The studies stratified analysis by gestational age (GA) at birth, and demonstrated no clear increase in stillbirth odds for any GA strata (table 3-1)[329].

Table 3-1Summary of aOR reported by Urhoj et al[329] through analysis of paternal age <25 and stillbirth odds compared with a paternal age of 30-34 years

Gestational age parameters	***Results***
≥ 22 weeks GA	aOR 1.10 (95% CI 0.94, 1.27)
22-37 weeks GA	aOR 1.15 (95% CI 0.96, 1.39)
22-28 weeks GA	aOR 1.02 (95% CI 0.77, 1.36)
≥ 28 weeks GA	aOR 1.13 (95% CI 0.95, 1.34)
≥ 37 weeks GA	aOR 1.01 (95% CI 0.79, 1.29)

Paternal age 20-24 years

One study examined the association between paternal age 20-24 years on the odds of stillbirth[298] compared with a paternal age of 25-29 years. Results demonstrated no clear increase in odds of stillbirth when all stillbirths ≥ 20 weeks GA were included, however, through stratification by the trimester of stillbirth, Alio et al[298] showed an increased odds of second trimester stillbirth (20-28 weeks GA aOR 1.22 (95% CI 1.01, 1.48)), with a less clear result for third trimester stillbirth, aOR 0.99 (95% CI 0.85, 1.16).

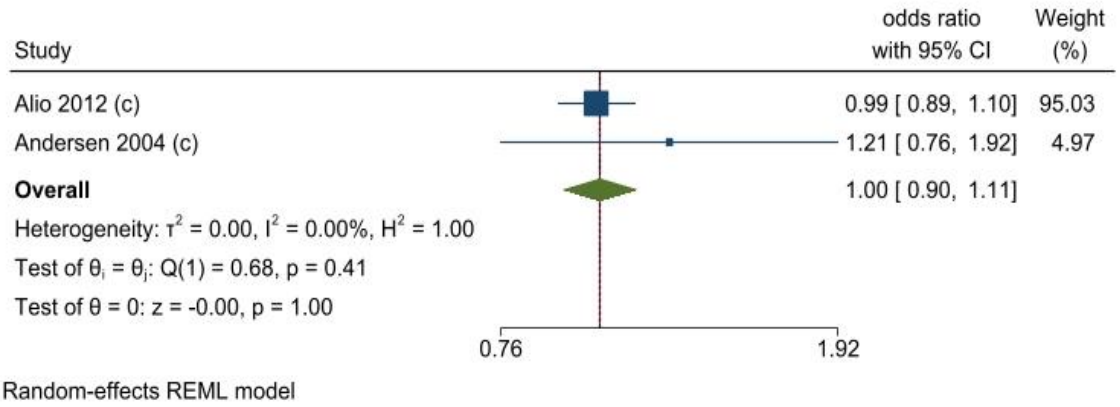
Paternal age 25-30 years

Two studies reported the odds associated with paternal age of 25-30 years[177, 329]. One of the studies examined paternal age in conjunction with maternal age, and therefore is reviewed alongside studies investigating the impact of parental age gap[177]. The second study[329] stratified results by GA and reported possibly increased odds for stillbirths ≥ 22 weeks GA (aOR 1.03 (95% CI 0.95, 1.13))[329] and 22-37 weeks GA (aOR 1.06 (95% CI

0.95, 1.18), 22-28 weeks (aOR 0.96 (95% CI 0.82, 1.13)), ≥28 weeks (aOR 1.06 (95% CI 0.96, 117)) or ≥37 weeks (aOR 1.00 (95% CI 0.87, 1.14)).

Paternal age 30-40 years

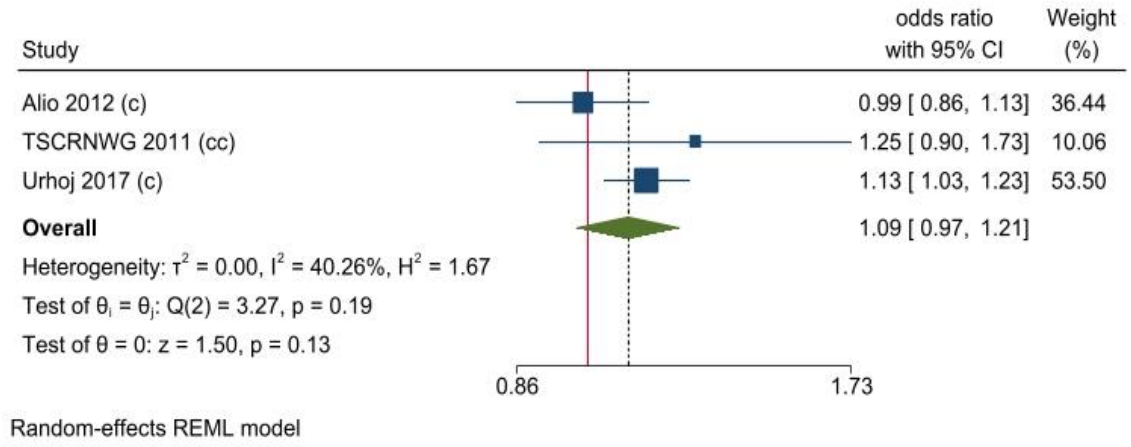
Five studies examined the impact of a paternal age of 30-40 years on stillbirth odds across the USA, Denmark, and Italy[103, 127, 298, 301, 329]. Two studies examined the age category; 30-34 years compared with paternal age between 20 and 29 years[298, 301], four studies examined the age category; 35-39 years compared with three different reference groups encompassing paternal ages between 20 and 34 years. The final study compared 30-39 years to 20-29 years [103]. The studies examining paternal age 30-39 years were combined in meta-analysis and demonstrated no association compared to a paternal age of 20-34 years (aOR 1.00 (95% CI 0.90, 1.11) – fig 3-39). Results should be interpreted with cautions, as it should be noted that results contained reference groups that spanning into the exposure group category of ages.



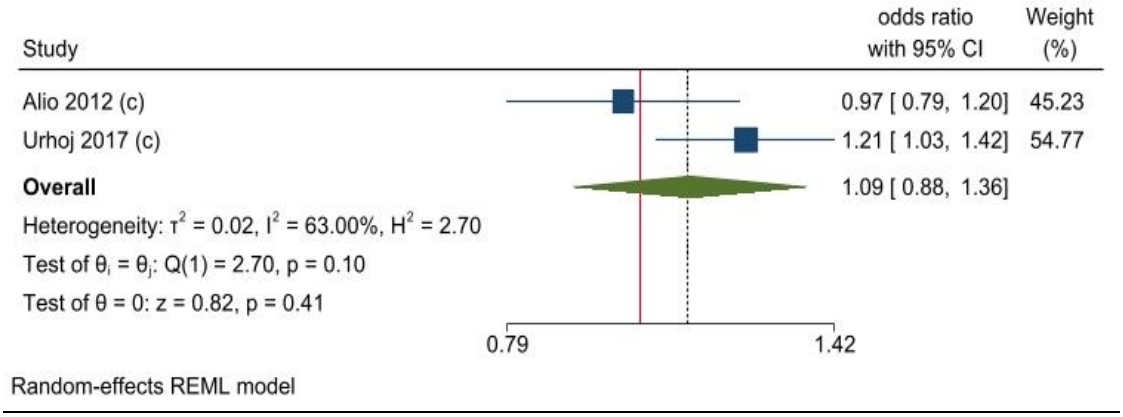
(c) = cohort studies
(cc) = case-control study

Figure 3-39 Meta-analysis of studies reporting the odds of stillbirth associated with a paternal age of 30-39 years compared with 20-34 years.

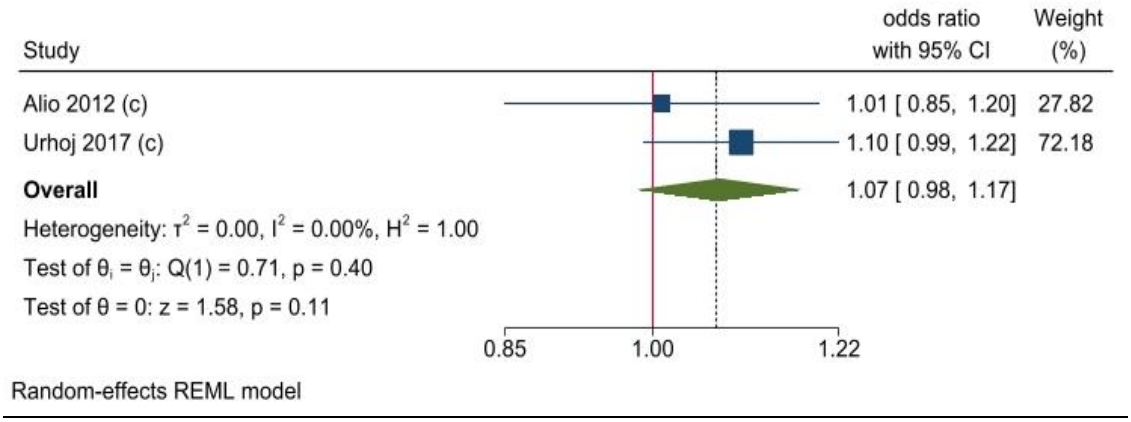
Two of the studies stratified by GA and were combined through meta-analysis of second and third trimester stillbirths. Andersen et al used a Danish cohort that was encompassed within another study included in this analysis[329], and therefore Andersen et al was excluded. Results indicate a possible association between paternal age of 35-39 years and stillbirth, aOR 1.09 (95% CI 0.97, 1.21) – fig 3-40. Analysis of second and third trimester stillbirths each included two studies, with a possible association between paternal age of 35-39 and second (aOR 1.09 (95% CI 0.88, 1.36) – fig 3-41) or third trimester stillbirths (aOR 1.07 (95% CI 0.98, 1.17) – fig 3-42) compared with reference groups of fathers aged between 25 and 34 years.



(c) = cohort studies
(cc) = case-control study
Figure 3-40 Meta-analysis of studies reporting the association between a paternal age of 35-39 years and stillbirth odds compared with a paternal age of 20-34 years.



(c) = cohort studies
(cc) = case-control study
Figure 3-41 Meta-analysis of studies reporting the association between a paternal age of 35-39 years and second trimester stillbirth odds compared with a paternal age of 20-34 years.

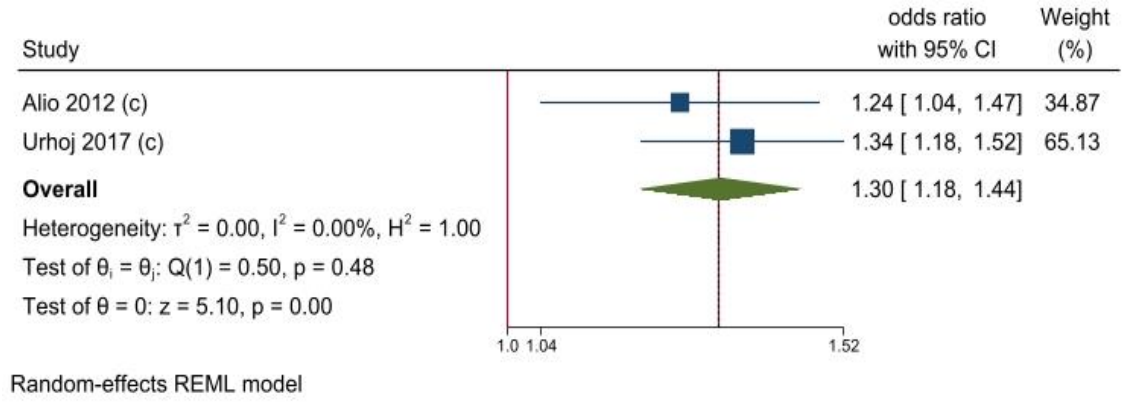


(c) = cohort studies
(cc) = case-control study

Figure 3-42 Meta-analysis of studies reporting the association between a paternal age of 35-39 years and third trimester stillbirth odds compared with a paternal age of 20-34 years.

Paternal age of 40-45

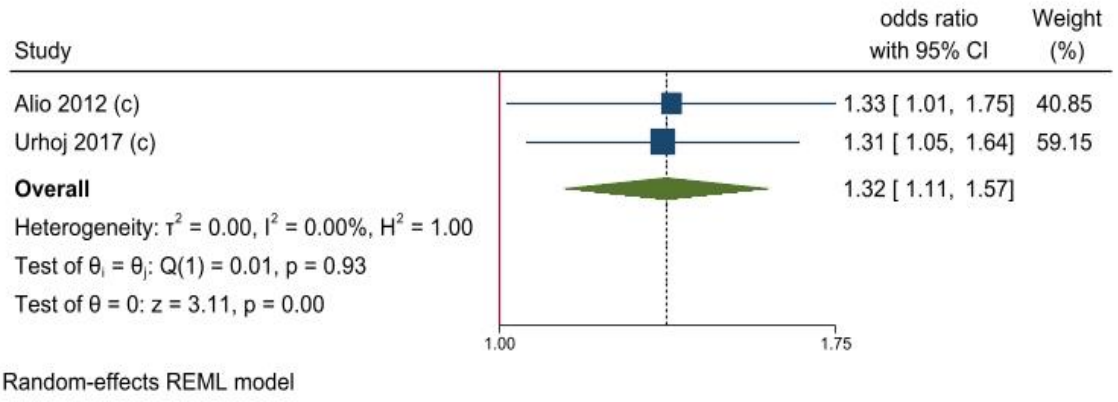
Three studies reported the odds of stillbirth associated with paternal age of 40-45 years[298, 301, 329] compared with reference groups of fathers aged between 25 and 34 years. Andersen et al used a dataset also used within Urhoj et al[329], and therefore the smaller cohort was excluded from meta-analysis. Final analysis included two studies[298, 329] and demonstrated an increased association between paternal age and stillbirth odds (aOR 1.30 (95% CI 1.18, 1.44) – fig 3-43).



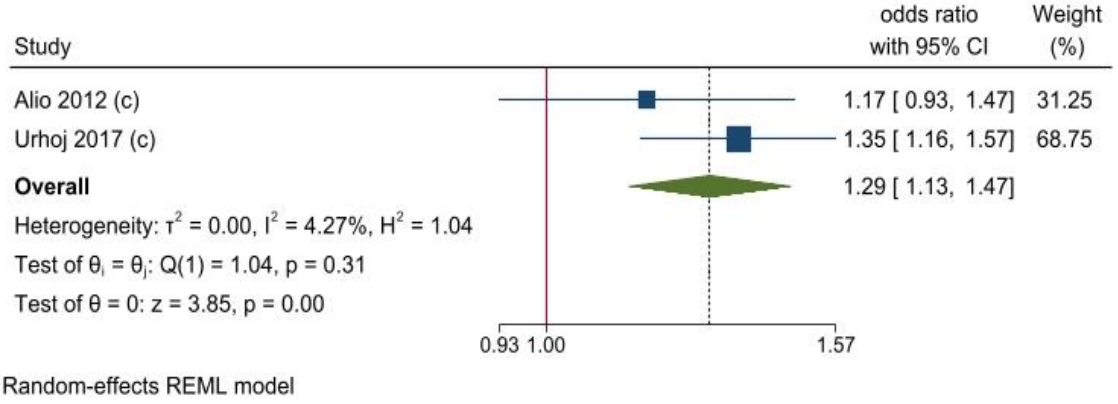
(c) = cohort studies
(cc) = case-control study

Figure 3-43 Meta-analysis of studies reporting the odds of stillbirth for a paternal age of 40-45 years compared with paternal age cohorts encompassing 25-34 years

Two studies stratified their analysis by GA, both reporting stillbirth association stratified by trimester of stillbirth; second and third trimesters. Results of analysis demonstrate an increased association between paternal age of 40-45 years compared with 25-34 years for both second and third trimester stillbirth odds (aOR 1.32 (95% CI 1.11, 1.57) – fig 3-44, and aOR 1.29 (95% CI 1.13, 1.47) – fig 3-45, respectively).



(c) = cohort studies
(cc) = case-control study
Figure 3-44 Meta-analysis of studies examining the association between paternal age of 40-45 years and second trimester stillbirth odds compared with a paternal age of 25-34 years.



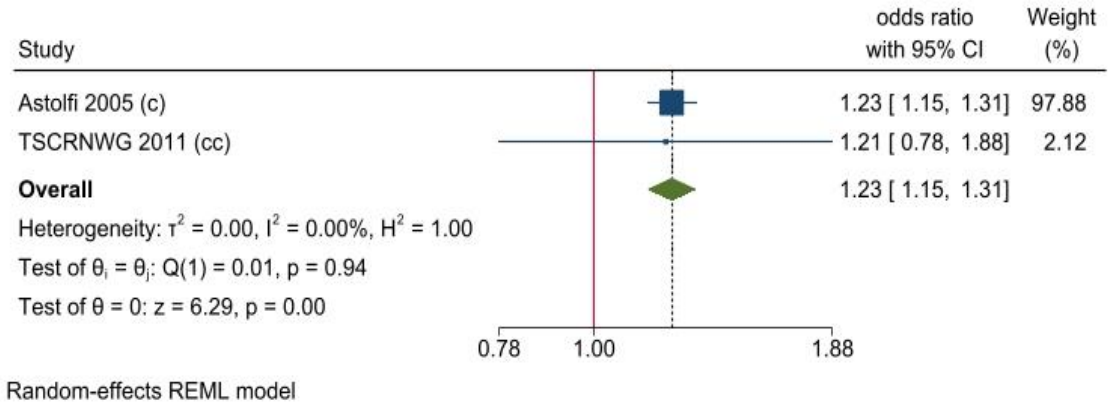
(c) = cohort studies
(cc) = case-control study
Figure 3-45 Meta-analysis of studies examining the association between paternal age of 40-45 years and second trimester stillbirth odds compared with a paternal age of 25-34 years.

Paternal age 45-50 years

Two studies examined the association between fathers aged 45-50 years and stillbirth odds[301, 329] compared with different reference groups. One study included a paternal age of 30-34 years[301], and the other used a paternal age of 25-29 years within the reference group[301]. Meta-analysis was unable to be performed due to the risk of double-counting births, as both studies reported use of the same dataset. Urhoj et al[329] reported odds ratios stratified by gestational age and demonstrated an increased association between paternal age 45-50 years and second trimester stillbirths (22-28 weeks GA aOR 1.31 (95% CI 0.88, 1.94) and also increased association when analysis was restricted to preterm births (22-37 weeks GA aOR 1.29 (95% CI 0.98, 1.70)). No clear association was demonstrated for third trimester (≥ 28 weeks GA) (aOR 1.02 (95% CI 0.77, 1.35)) or term (≥ 37 weeks GA) stillbirths (aOR 0.82 (95% CI 0.54, 1.24)). Andersen et al[301] also reported no clear association between paternal age of 45-50 years and stillbirth odds (aOR 1.40 (95% CI 0.40, 4.85))[301].

Paternal age ≥40 years

Two studies reported the association between paternal age of ≥40 years and stillbirth odds[103, 127] compared with a paternal age of 20-34 years. Astolfi et al[103] stratified analysis by parity, and reported that although paternal age of ≥40 years was associated with increased odds of stillbirth (aOR 1.23 (95% CI 1.15, 1.31)), this risk was mitigated for multiparous women (aOR 1.05 (95% CI 0.87, 1.27)). Within a nulliparous cohort, paternal age of ≥40 years demonstrated increased odds of stillbirth (aOR 1.34 (95% CI 1.15, 1.55)). When the two studies were combined there was an increased odds of stillbirth when the paternal age was ≥40 years (aOR 1.23 (95% CI 1.15, 1.31) – fig 3-46).



(c) = cohort studies
(cc) = case-control study

Figure 3-46 Meta-analysis of studies reporting the association between a paternal age ≥40 years on stillbirth odds compared with paternal age of 20-34 years.

Paternal age ≥ 50 years

Two studies examined the association of paternal age of ≥50 years with stillbirth odds[301, 329] compared to 20-25 years. Both studies used the same dataset and therefore were unable to be combined through meta-analysis[301, 329]. Urhoj et al[329] demonstrated a possible increase in odds of stillbirth with advanced paternal age, but analysis demonstrated wide confidence intervals owing to a small sample size (aOR 1.33 (95% CI 0.96, 1.85)). Andersen et al[301] reported a nearly four-fold increase in stillbirth odds for paternal age ≥50 years compared with a paternal age of 25-29 years (aOR 3.94 (95% CI 1.12, 13.80)). Results should be interpreted with caution due to a small sample size and wide confidence intervals.

Parental age gap

Two studies examined the impact of parental age gap on stillbirth odds[141, 177] defined as the difference in age between the mother and father. Each study categorised which parent was older in their analysis. Both studies stratified by ethnicity, Kinzler et al[141] examined the impact of parental age gap on stillbirth odds between black and white women in the USA, and Siahanidou et al[177] examined the impact for Greek and non-Greek parents in Greece.

Kinzler et al[141] demonstrated that the parental age gap (maternal age – paternal age) did not increase stillbirth association for black women, but that any age gap increased stillbirth odds for white women (if either maternal or paternal age was greater). The

largest age gaps (maternal age ≥10 years greater than paternal age), odds were shown to increased by 20-40% through analysis. Greatest increases were seen when paternal age was ≥10 years more than maternal age (aOR 1.4 (95% CI 1.1, 1.7))[141].

Siahanidou et al[177] examined combinations of maternal and paternal age categories and found that paternal age ≥35 years in combination with maternal age ≥25 years (categories stratified into groups: 25-34 years and ≥35 years), increased the odds of stillbirth for non-Greek women (aOR 1.54 (95% CI 1.23, 1.92) and aOR 1.77 (95% CI 1.07, 2.94) respectively). Within the cohort of Greek women, odds of stillbirth were increased for the following combinations of age categories; maternal age 25-34 and paternal age <25 years (aOR 1.39 (95% CI 1.08, 1.80)), maternal age 25-34 and paternal age ≥35 years (aOR 1.38 (95% CI 1.25, 1.52)), maternal age ≥35 years and paternal age <25 years (aOR 2.00 (95% CI 1.47, 2.73)), maternal age ≥35 years and paternal age 25-34 years (aOR 1.48 (95% CI 1.21, 1.82))[177].

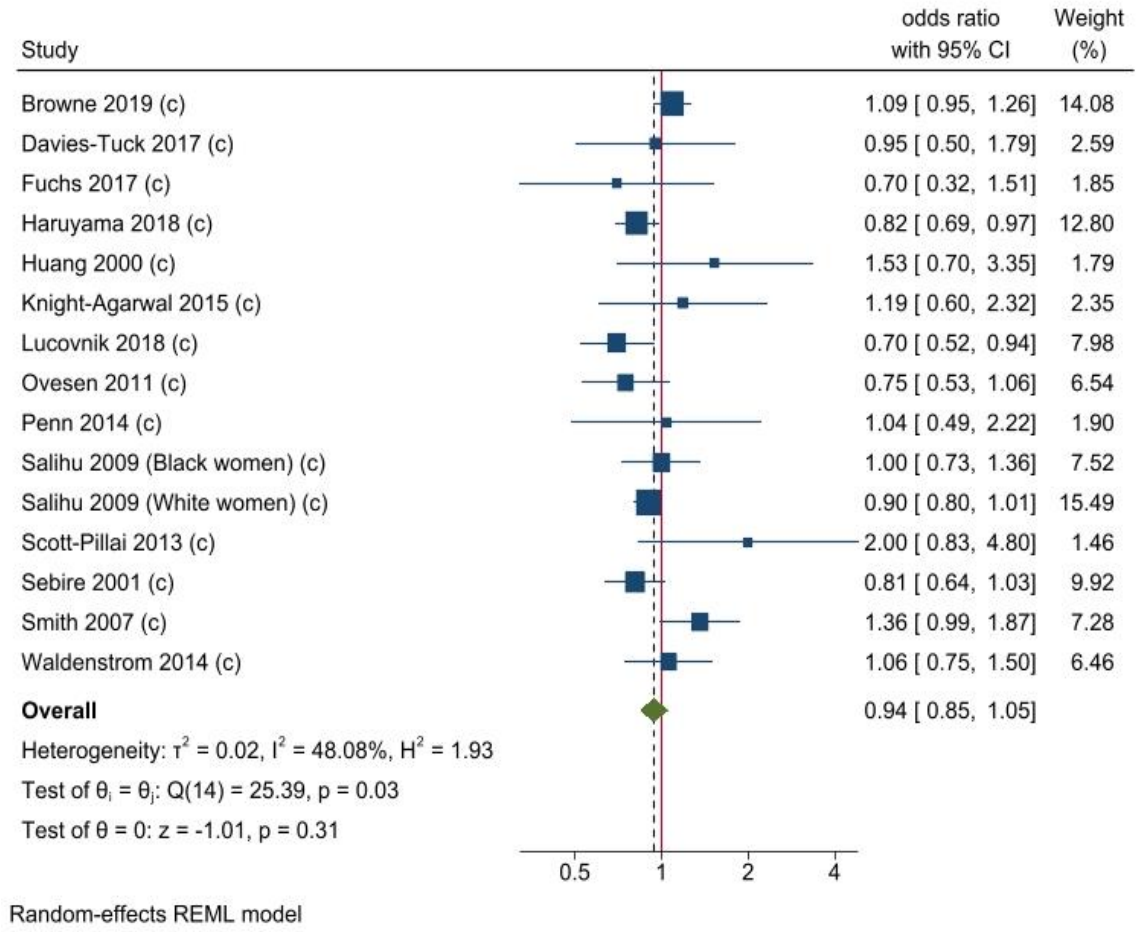
Maternal body mass index (BMI)

Seventy-one studies of the studies included, examined the association between maternal BMI and stillbirth odds[43, 44, 67, 70, 71, 73, 92, 102, 103, 106, 118, 120, 121, 124, 127, 129, 134, 143, 164, 179, 181, 182, 184, 190-237]. Sixteen of the studies were deemed as having a high risk of bias[44, 70, 103, 129, 134, 184, 192, 194, 196, 198, 205, 208, 209, 212, 213, 223, 225, 229], and for a majority of these, bias was due to exposure group detection bias. Many of these studies had inadequately described BMI measurements or were self-reported measurements. Twenty-three studies were reported to have an unclear risk of bias[43, 67, 71, 92, 102, 106, 120, 121, 124, 143, 164, 179, 195, 197, 200-202, 210, 214, 219, 228, 230, 234]. Twenty-seven[73, 118, 127, 181, 182, 190, 191, 193, 199, 204, 206, 207, 211, 215, 218, 221, 222, 224, 226, 227, 230-233, 235, 236] studies were considered to have a low risk of bias, and these results were based on high quality studies and data collection. The studies grouped maternal BMI into a variety of subgroups and, in some instances, were also separated into second and third trimester stillbirths.

Maternal underweight status (BMI ≤20)

An underweight BMI is classified as ≤ 18.5, (in some studies ≤ 20). Twenty-seven studies examined the impact of low maternal BMI and the association with stillbirth[70, 71, 73, 106, 127, 129, 134, 164, 182, 191, 192, 199, 201, 202, 204, 208-211, 214, 215, 219, 221, 224-226, 343]. Twenty-three studies incorporated a definition of stillbirth that spanned from 20 weeks GA onwards[70, 71, 73, 106, 129, 134, 164, 182, 191, 199, 201, 202, 204, 208, 211, 215, 219, 221, 224-226, 229], two studies limited their analysis to second trimester stillbirths[70, 192], and five restricted analysis to third trimester stillbirths[70, 191, 209, 210, 214].

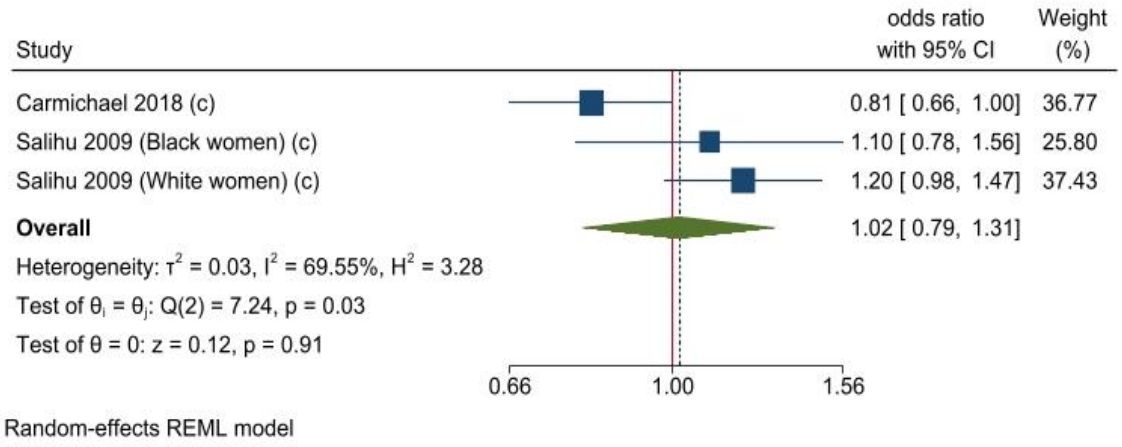
Of the studies examining maternal underweight status associated with stillbirths from 20 weeks GA onwards, six were excluded from meta-analysis to avoid double-counting births as they reported using the same datasets as larger studies within the analysis[71, 106, 127, 201, 202, 204, 219]. One study was excluded as the cohort was restricted to triplet births[221]. Final meta-analysis included fourteen studies and found the overall effect size demonstrated no increase or decrease associated with maternal underweight status, and second and third trimester stillbirths combined (aOR 0.94 (95% CI (0.85, 1.05) – fig 3-47)[70, 73, 129, 134, 164, 182, 191, 199, 208, 211, 215, 224-226, 229].



(c) = cohort study
(cc) = case-control study
Figure 3-47 Meta-analysis of studies reporting the association between maternal underweight status (BMI <20) and stillbirth odds compared with women with a healthy BMI (20-25).

Maternal BMI (<20) (second trimester stillbirth)

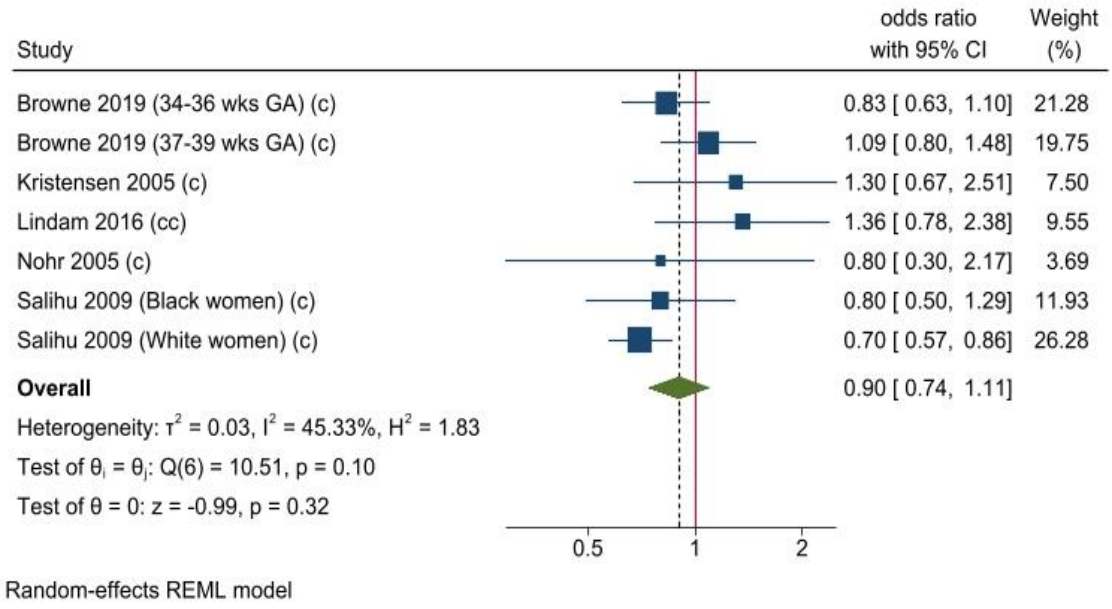
The two studies examined the association between maternal underweight status and second trimester stillbirths, were both included within meta-analysis[70, 192]. Overall analysis demonstrated no association between maternal underweight status and second trimester stillbirths in comparison to women who were of healthy weight (BMI 20-25) (aOR 1.02 (0.79, 1.31) – fig 3-48). Analysis demonstrated substantial heterogeneity which may be, in part, due to stratification of results by Salihu et al[70], but a major contributor is Carmichael et al's[192] differing gestational age inclusions between livebirths (37-41+6 weeks GA) and stillbirths (20-25+6 weeks gestation) within their study.



(c) = cohort study
(cc) = case-control study
Figure 3-48 Meta-analysis of studies reporting the association between maternal underweight status (BMI <20) and second trimester stillbirth odds compared with women with a healthy BMI (20-25).

Maternal BMI (< 20) (third trimester stillbirth

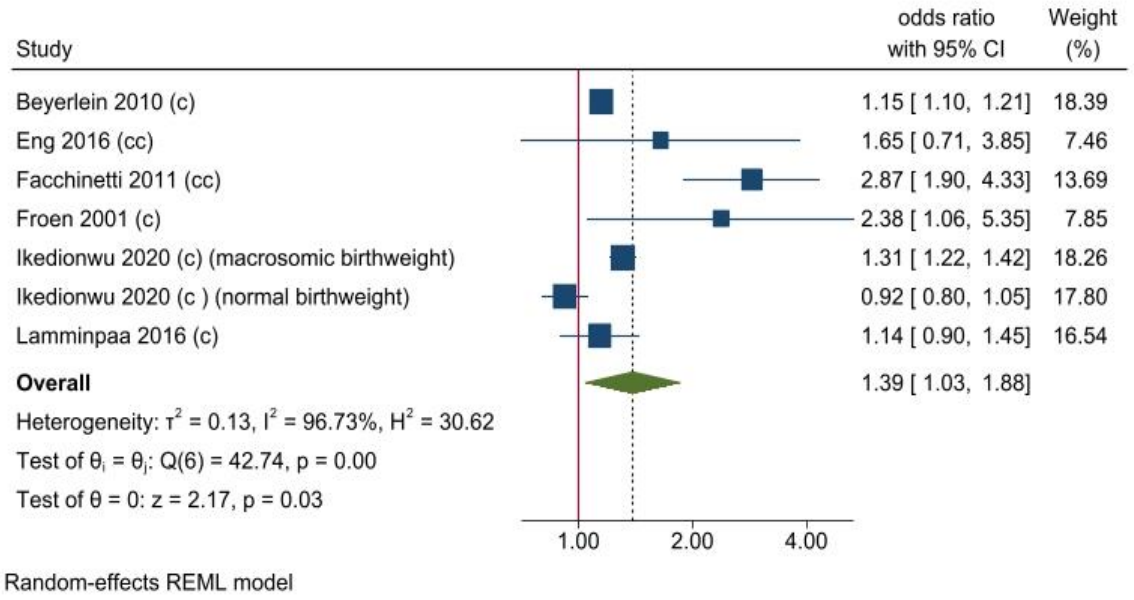
Five studies examined third trimester stillbirths and the association with maternal underweight status in comparison with healthy maternal weight. All were included in meta-analysis as none of the study cohorts overlapped[70, 191, 209, 210, 214]. Heterogeneity was moderate (I^2=45.33%) and was accepted as the populations included were diverse. Resultant effect size did not demonstrate increased risk of third trimester stillbirth for underweight mothers (aOR 0.90 (95C% CI 0.74, 1.11) – fig 3-49)



(c) = cohort study
(cc) = case-control study
Figure 3-49 Meta-analysis of studies examining the association between maternal BMI <20 and stillbirth odds compared with maternal BMI 20-25

Overweight/obese maternal BMI (≥25)

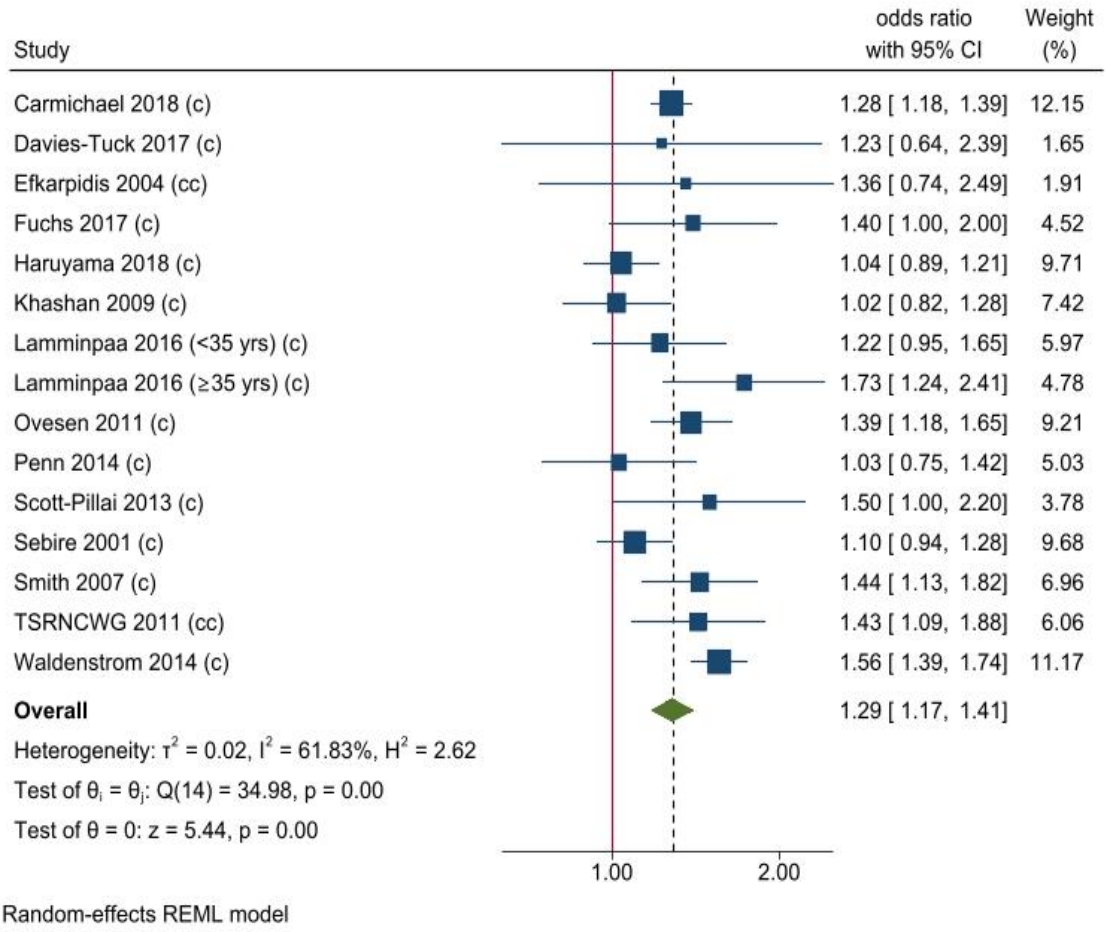
Six studies reported the correlation between any maternal BMI ≥25 and stillbirth odds[43, 124, 143, 190, 198, 205]. Initial meta-analysis of the studies demonstrated considerable heterogeneity (I^2 = 86.0%). Two of the included studies were deemed to have a high risk of bias using the RTI-IB tool of assessment - this was attributed to the collection method and timepoints for maternal BMI (~20 weeks GA). One study subgrouped analysis by birthweight, both groups were included in meta-analysis. On exclusion of these studies from meta-analysis, heterogeneity decreased to 0%, but exclusion could not be justified, so they remained in analysis. Overweight maternal BMI was associated with an increase in stillbirth odds. (aOR 1.39 (95% CI 1.03, 1.88) – fig 3-50) compared with a healthy maternal BMI (20-25).



(c) = cohort study
(cc) = case-control study
Figure 3-50 Meta-analysis of the association between overweight/obese maternal BMI (≥25) and stillbirth odds in comparison to a healthy maternal BMI (20-25).

Overweight maternal BMI (25-30)

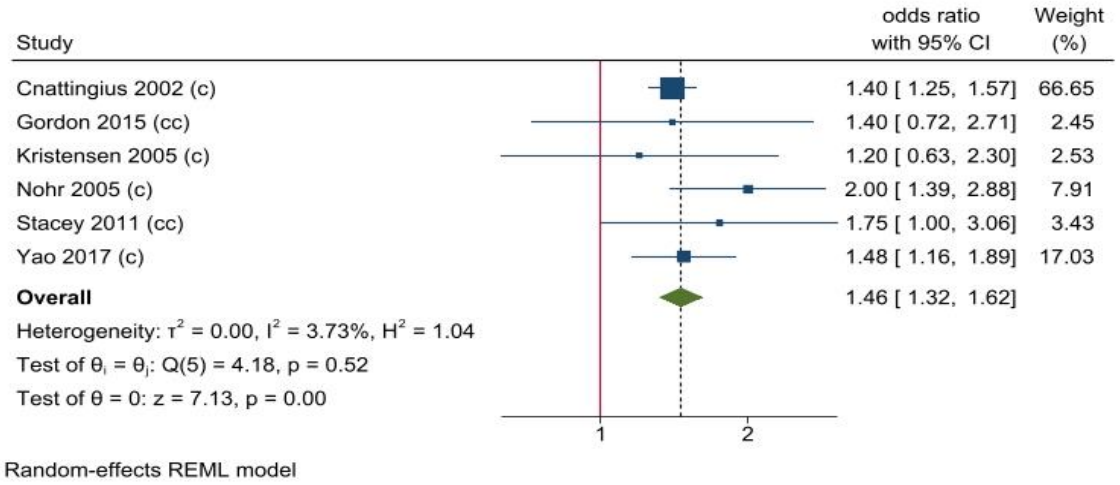
Twenty-three studies investigated the impact of maternal overweight status during pregnancy and its impact on stillbirth odds[73, 120, 121, 127, 129, 143, 164, 182, 192, 199, 201-203, 206, 208, 215, 219, 221, 224-227, 343]. The populations included within the studies span nine high-income countries. For the analysis, any definition of overweight that was inclusive of a lower limit of BMI = 25, and an upper limit of BMI = 30 was used. One study was excluded from meta-analysis due to not providing a study time period[227], six of the studies used populations that were encompassed within larger studies examining the same risk factor and therefore the smaller studies were excluded to avoid double counting births[121, 201-203, 206, 208, 219]. One study only included triplet pregnancies and was excluded due to population differences[221]. Heterogeneity of the studies included was substantial (I^2 = 61.83%, on exclusion of Waldenstrom et al[182] heterogeneity decreased to 36%, but no reason for the heterogeneity was apparent.. Therefore Waldenstrom et al[182] was included in meta-analysis and heterogeneity was accepted. The resultant effect size from meta-analysis demonstrated an increase in stillbirth associated with maternal overweight status (aOR 1.29 (95% CI 1.17, 1.41) – fig 3-51).



(c) = cohort study
(cc) = case-control study
Figure 3-51 Meta-analysis of the association between overweight maternal BMI (25-30) and stillbirth odds in comparison to a healthy maternal BMI (20-25).

<u>Overweight maternal BMI (25-30) (third trimester stillbirth)</u>

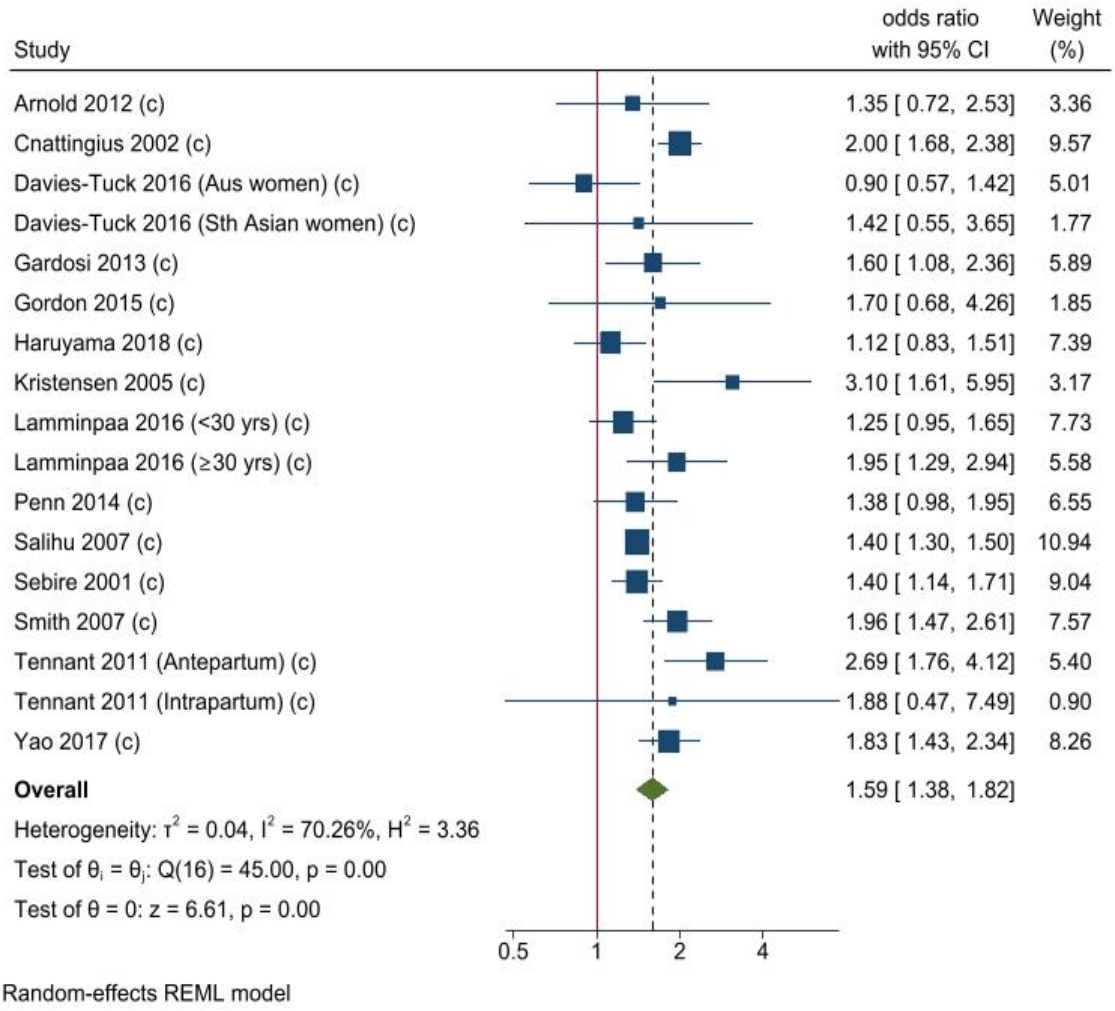
Nine studies from five high-income countries reported the impact of maternal overweight status (maternal BMI 25-30) on third trimester stillbirth odds[92, 179, 181, 194, 195, 209, 210, 214, 236]. Three studies [194, 195, 210] reported that they used the same data, so to avoid double-counting births, the smaller studies were excluded from analysis[194, 210]. A further study was excluded from meta-analysis as the results provided did not include 95% confidence intervals[181]. Results of meta-analysis demonstrated a 46% increase in the odds of third trimester stillbirth for overweight women compared with women with a healthy maternal BMI (20-25) (aOR 1.46 (95% CI 1.32, 1.62) – fig 3-52).



(c) = cohort study
(cc) = case-control study
Figure 3-52 Meta-analysis of studies reporting the association between overweight maternal BMI (25-30) and third trimester stillbirth odds in comparison to a healthy maternal BMI (20-25).

Obese maternal BMI (≥ 30)

Twenty-two studies reported the effect of any maternal obesity (BMI ≥30), on stillbirth odds[92, 102, 106, 129, 143, 164, 184, 194, 195, 197, 200, 203, 209, 210, 219, 222, 223, 225, 226, 228, 236, 237]. Several included studies reported use of the same datasets, therefore to avoid double-counting births, smaller studies were excluded[106, 184, 194, 203, 210, 219, 222, 237], and the larger studies retained for analysis[92, 102, 129, 143, 164, 195, 197, 200, 209, 223, 225, 226, 228, 236]. Three studies stratified results by ethnicity[197], maternal age (<30 and ≥30 years)[143], and timing of stillbirth (intrapartum and antepartum)[228]. Meta-analysis of results demonstrated substantial heterogeneity of 70.26%, thus sensitivity analysis was performed, but did not alter heterogeneity. Final meta-analysis demonstrated that women with obesity are at 59% increased odds of stillbirth than women with healthy weight (aOR 1.59 (95% CI 1.38, 1.82) – fig 3-53).



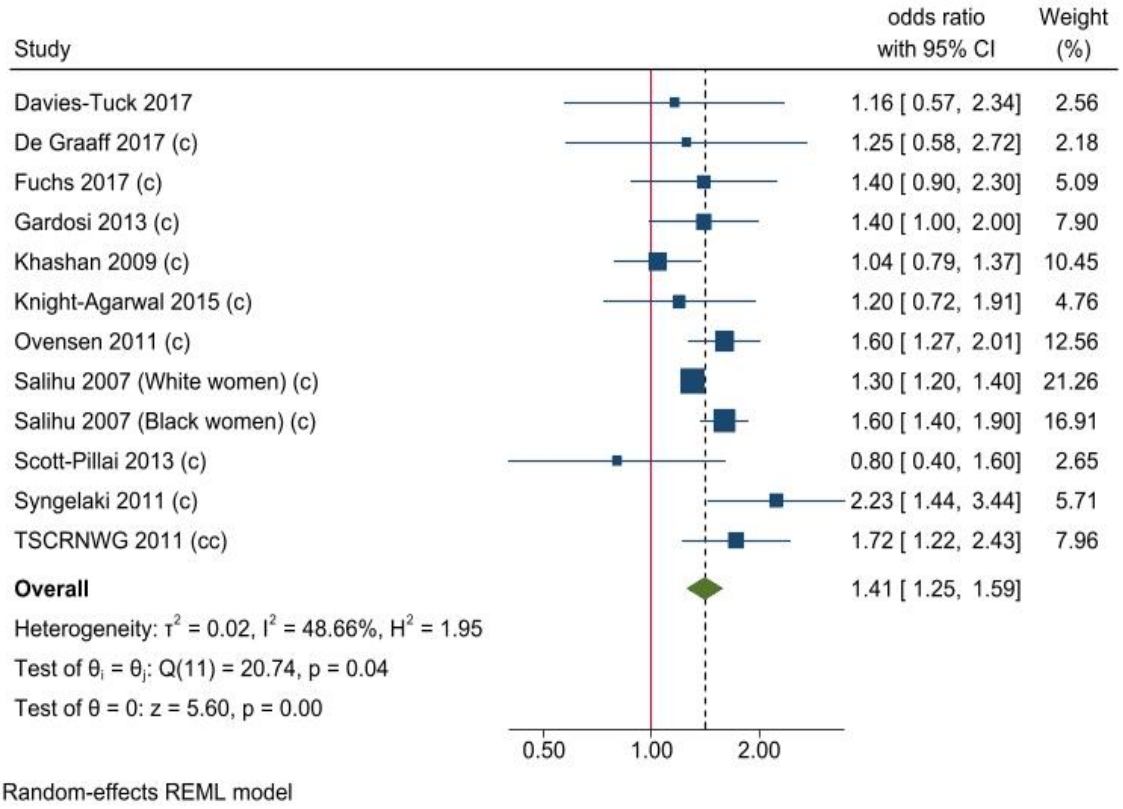
(c) = cohort study
(cc) = case-control study

Figure 3-53 Meta-analysis of studies reporting the association between obese maternal BMI (≥30) and third trimester stillbirth odds compared with a healthy maternal BMI (20-25).

Maternal class I obesity (BMI 30-35)

Sixteen studies reported the odds of stillbirth associated with maternal class 1 obesity (BMI 30-35) compared with healthy maternal BMI (20-25)[67, 73, 127, 192, 199-202, 204, 205, 208, 215, 219, 223, 224, 227]. Several studies report use of the same dataset for analysis, therefore, in an effort to avoid double counting births, three smaller studies were excluded[127, 192, 201, 202, 219, 343] and the larger studies retained for analysis[204, 223, 230]. Two studies were excluded due to methodological differences, one used different gestational age parameters between cases and controls and therefore was not comparable for our analysis[192] and the other presented stratified results that are non-comparable for our analysis[205]. Twelve studies were combined through meta-analysis and due to considerable heterogeneity (I^2=93.1%), sensitivity analysis was performed. One study[204] contributed considerably to the high heterogeneity, and exclusion decreased heterogeneity to 48.66% (considered not important). Hilden 2019[204] excluded all women who had pre-existing diabetes - as there is a direct relationship between obesity and class 2 diabetes mellitus, exclusion of these women alters the exposure group characteristics considerably. Final meta-analysis included 10 studies, one of which stratified women by

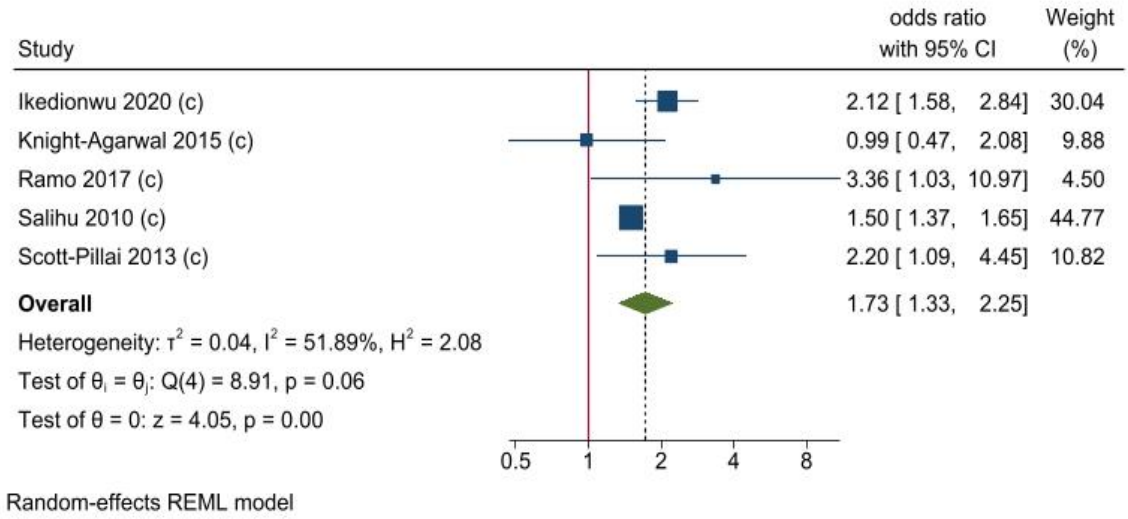
ethnicity, and both groups were included in the meta-analysis[70]. The association between class 1 obesity (BMI 30-35) and stillbirth is increased in comparison to women with a healthy maternal BMI (aOR 1.41 (95% CI 1.25-1.59) – fig 3-45).



(c) = cohort study
(cc) = case-control study
Figure 3-54 Meta-analysis of the association between maternal class I obesity (BMI 30-35) and stillbirth odds in comparison with a healthy maternal BMI (20-25).

Maternal class II obesity (BMI 35-40)

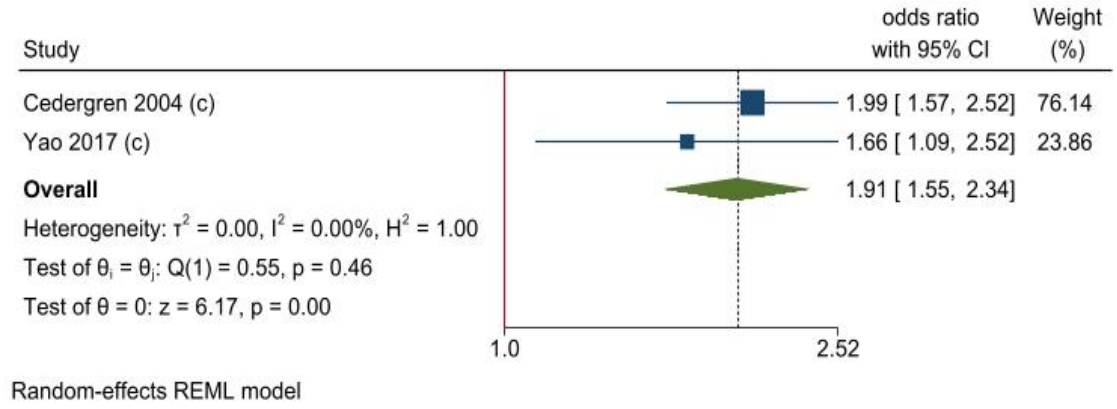
Seven studies reported the association between maternal class 2 obesity (BMI 35-40) and stillbirth odds[67, 205, 208, 219, 222-224]. Four studies reported using the same dataset, therefore to avoid double-counting births, two smaller studies using the datasets were excluded[67, 223] and the larger studies were retained for analysis[208, 223]. Final meta-analysis demonstrated moderate heterogeneity at I^2 = 55.1% and this was accepted. The results demonstrated almost double the odds of stillbirth in women with a BMI defined as class 2 obesity (aOR 1.73 (95% CI 1.33, 2.25) – fig 3-55).



(c) = cohort study
(cc) = case-control study
Figure 3-55 Meta-analysis of the association between maternal class II obesity (BMI 35-40) and stillbirth odds in comparison with a healthy maternal BMI (20-25).

Maternal class II obesity (BMI 35-40) (third trimester stillbirth)

Three studies examined the association between class 2 obesity and third trimester stillbirths[181, 193, 230]. One was excluded from meta-analysis due to no confidence intervals reported for the aOR[181], two studies are therefore included in the meta-analysis[193, 230]. Results demonstrated a two-fold increase in third trimester stillbirth odds for women with class II obesity (aOR 1.91 (95% CI 1.55, 2.34) – fig 3-56).

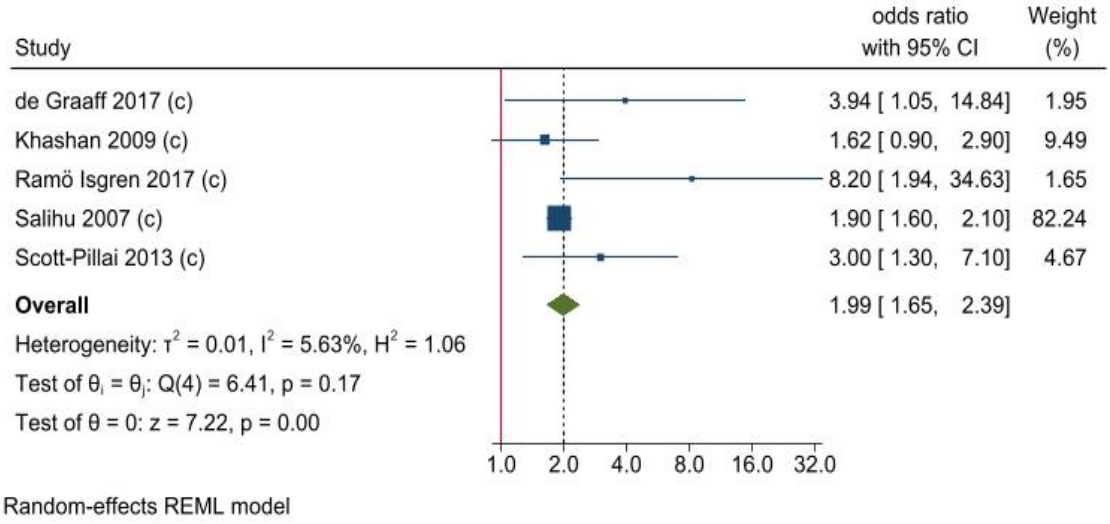


(c) = cohort study
(cc) = case-control study
Figure 3-56 Meta-analysis of studies reporting the association between maternal class II obesity (BMI 35-40) and third trimester stillbirth odds in comparison to a healthy maternal BMI (20-25).

Maternal class III obesity (BMI ≥ 40)

Eight studies examined the association between maternal class 3 obesity and stillbirth odds compared to women with a healthy maternal BMI (20-25)[67, 205, 208, 219, 222-224, 333]. Two studies reported using the same dataset, therefore to avoid double-counting of births, the smaller of the two studies was excluded, and the larger included in analysis[223]. The resultant six studies were included in meta-analysis, demonstrating high heterogeneity at

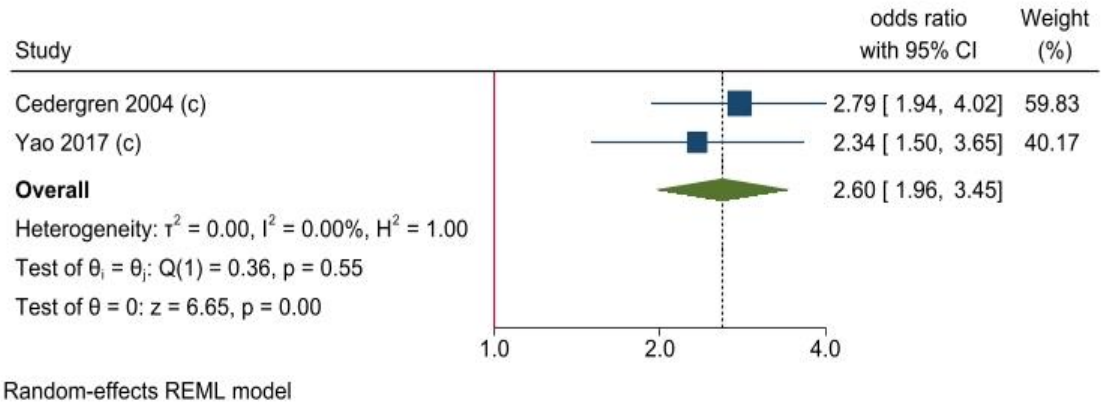
90.2%. Through sensitivity analysis it was identified that two studies contributed substantially to heterogeneity[205, 208]. One of the studies reported that BMI was collected predominantly in the second trimester of pregnancy[208] and on review there were multiple concerns with the second study regarding; data collection, confounder adjustment and non-comparability of stratified groups for this analysis[205]. Both were excluded due to methodological differences decreasing heterogeneity to 5.63%. The overall aOR for maternal class 3 obesity (BMI >40) compared with women with a healthy BMI (20-25) was 1.99 (95% CI 1.65, 2.39) – fig 3-57.



(c) = cohort study
(cc) = case-control study
Figure 3-57 Meta-analysis of studies reporting the association between maternal class III obesity (BMI ≥40) and stillbirth odds in comparison to a healthy maternal BMI (20-25).

<u>Maternal class III obesity (BMI ≥ 40) (third trimester stillbirth)</u>

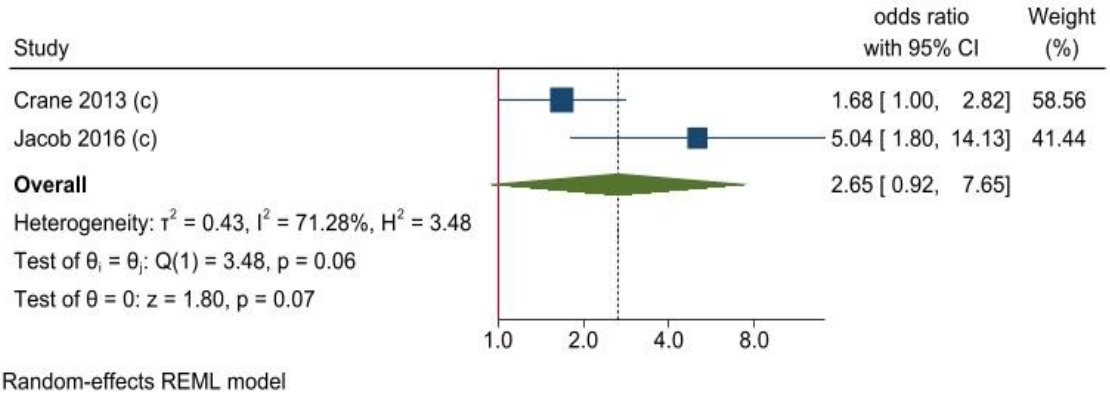
Three studies examined the association between maternal class III obesity (BMI ≥40) and third trimester stillbirth odds[181, 193, 230, 236]. One study failed to provide confidence intervals for the aOR and therefore could not be included in meta-analysis[181]. Final meta-analysis demonstrated an increased aOR of 2.60 (95% CI 1.96, 3.45) (– fig 3-58) associated with third trimester stillbirth.



(c) = cohort study
(cc) = case-control study
Figure 3-58 Meta-analysis of studies reporting the association between maternal class III obesity (BMI ≥40) and third trimester stillbirth odds in comparison to a healthy maternal BMI (20-25).

Maternal class IV obesity (BMI ≥ 50)

Two studies examined the relationship between class IV maternal obesity (BMI ≥ 50) and stillbirth[196, 206]. Studies reported very small numbers of stillbirths (1 and 4 stillbirths in the exposure groups of the two studies), rendering the meta-analysis underpowered. The aOR of 2.65 (95% CI 0.92, 7.65) (fig 3-59) exhibits a wide confidence interval indicating that the results should be interpreted with caution and requires further research of stillbirth odd associations for women with a maternal BMI ≥ 50.



(c) = cohort study
(cc) = case-control study
Figure 3-59 Meta-analysis of studies reporting the association between maternal class IV obesity (BMI ≥50) and stillbirth odds in comparison to a healthy maternal BMI (20-25).

Maternal BMI (stratified by ethnicity)

Four studies stratified the association of maternal BMI with stillbirth by maternal ethnicity using populations from two high-income countries: the USA and Australia[44, 70, 197, 223]. One study examines the association of maternal obesity (≥ 30) within a South Asian-born cohort[197]. The resultant aOR of 1.42 (95% CI 0.55 to 3.63) shows increased odds of stillbirth for South Asian-born women with obesity compared with healthy weight (BMI 20-25) South Asian born women, though confidence intervals are wide. In a cohort of Australian born women, obesity did not show increased odds of stillbirth for obese

women (aOR 0.90 (95% CI 0.57, 1.42))[197]. Three studies examined the association of maternal obesity between black and white women in the USA[44, 70, 223]. One study[223] compared black women with white women of healthy BMI and found that as BMI increased for black women, the odds of stillbirth were consistently higher than for white women of the same BMI exposure group (table 3-2).

Table 3-2 Shows results of aOR comparing maternal BMI, stratified by ethnicity, to that of white women with a healthy BMI (18.5-24.9). Results are adjusted by maternal age, educational achievement, marital status, smoking habits during pregnancy, adequacy of pregnancy adequacy of prenatal care, fetal gender, year of birth[223].

Maternal body mass index (BMI)	White women in exposure group (aOR (95% CI))	Black women in exposure group (aOR (95% CI))
30+	1.4 (1.3, 1.5)	1.9 (1.7, 2.1)
30-34.9	1.3 (1.2, 1.4)	1.6 (1.4, 1.9)
35-39.9	1.4 (1.2, 1.6)	1.9 (1.5, 2.3)
40+	1.8 (1.6, 2.2)	2.3 (1.8, 2.9)

One study examined the impact of maternal underweight status stratified by ethnicities (black and white)[70] and further subgrouped by GA (≥20 weeks GA, and 20-28 weeks GA). Furthermore, results of this study demonstrated marginally higher odds of stillbirth for underweight white women delivering between 20-28 weeks GA (aOR 1.2 (95% CI (1.0, 1.5)) compared with black women at the same GA[70]. The final study that reported risk of maternal BMI by ethnicity further stratified results by parity and gestational age (in three week blocks through pregnancy from 20 weeks GA)[44]. This study concluded that the odds of stillbirth increase over all gestational ages with higher maternal obesity across all ethnicities.

Maternal BMI (stratified by diabetic status)

Two studies examined the association between BMI and stillbirth for women who had been diagnosed with pre-gestational diabetes mellitus (type I or II)[190, 191]. One study demonstrated an increased association for diabetic women as BMI increased[191]. This study further demonstrated an increase in stillbirth odds in all categories of maternal BMI in comparison to women who have a healthy BMI and no diagnosis of pregestational diabetes. Beyerlein et al[108] found no increased odds of stillbirth for overweight (BMI ≥25) diabetic women compared with healthy weight (BMI <25) diabetic women (aOR 0.76 (95% CI 0.49, 1.18))[190], in contrast to odds of stillbirth shown for non-diabetic overweight women (aOR 1.15 (95% CI 1.10, 1.21)) compared with healthy weight non-diabetic women[190].

Maternal BMI (stratified by maternal age)

Two studies examined the combined impact of maternal age and BMI on stillbirth odds[143, 184]. One study cohort excluded women >18 years of age and stratified birth to women <18 years of age by gestational age at birth[184]. Women <18 years old, with a maternal BMI >30 demonstrated an increased association for odds of stillbirth at all gestational ages (aOR 1.7 (95% CI 1.02-2.9)), but due to small sample size, confidence intervals were wide, and results should be interpreted with caution.

The second study[143] examined the impact of maternal age (< or ≥35 years) on the relationship between maternal BMI and stillbirth. Women who were <35 years and overweight had lower odds (aOR 1.22 (95% CI 0.95, 1.65)) than women ≥35 years and overweight (aOR 2.23 (95% CI 1.52-3.26)) compared to women of the same age with a healthy BMI. Overweight women ≥35 years old had an odds ratio of 1.98 (95% CI 1.48, 2.64) showing nearly a two-fold increase in odds of stillbirth than overweight women <35 years. Obese women (BMI ≥ 30) had increased odds of stillbirth associated with maternal age ≥ 35 years compared with < 35 years (aOR 1.25 (95% CI 0.95, 1.65)). The study results examining the impact of maternal age for women with a BMI <25 reported 2-fold increased odds of stillbirth (aOR 2.23 (95% CI 1.52, 3.29)) for women ≥35 years of age compared with women <35 years of age. These findings suggest that older women who were overweight or obese are at higher risk of stillbirth than younger overweight or obese women.

Maternal BMI and parity

Two studies included subgroups of maternal BMI analysis stratified by parity[44, 194]. The studies were not able to be included in meta-analysis due to the stratification of non-comparable exposure groups. Cnattingius et al[194] grouped women by parity (nulliparous or multiparous), and included women with BMI ≤19.9 in the reference groups[194]. The association with stillbirth was increased for nulliparous women with a BMI of 20.0-24.9 (aOR 2.2 (95% CI 1.2, 4.1)), BMI 25.0 – 29.9 (aOR 3.2 (95% CI 1.6, 6.2)) and BMI ≥ 30 (aOR 4.3 (95% CI 2.0, 9.3)). Although stillbirth odds for multiparous women still showed a linear relationship with BMI, odds were consistently lower than shown for nulliparous women (BMI 20.0-24.9 (aOR (95% CI 0.9 (95% CI 0.6, 1.3)), BMI 25.0 – 29.9 (aOR 1.1 (95% CI 0.7, 1.8)) and BMI ≥30 (aOR 2.0 (95% CI 1.2, 3.3)). Carmichael et al[44] stratified results investigating the impact of maternal BMI on stillbirth odds by maternal race and parity[44]. The result shown concurred with Cnattingius et al[194] demonstrating that risk of stillbirth was increased for nulliparous women of all ethnicities and across all gestational age subgroups reinforcing the previous findings that nulliparity appears to confound the impact of maternal BMI.

Maternal history of gastric bypass surgery

One study[344] examined the association between maternal previous gastric bypass surgery to aid weight loss and the associated stillbirth odds. Although a large cohort, results demonstrated large confidence intervals owing to the small number of stillbirths within the exposure group (n=14). Risk of bias assessment suggested an unclear risk of bias owing to the lack of adjustment for confounders within analysis. Results were inconclusive in demonstrating an association between maternal history of gastric bypass and stillbirth odds (aOR 0.83 (95% CI 0.13, 5.36)).

Blood donation

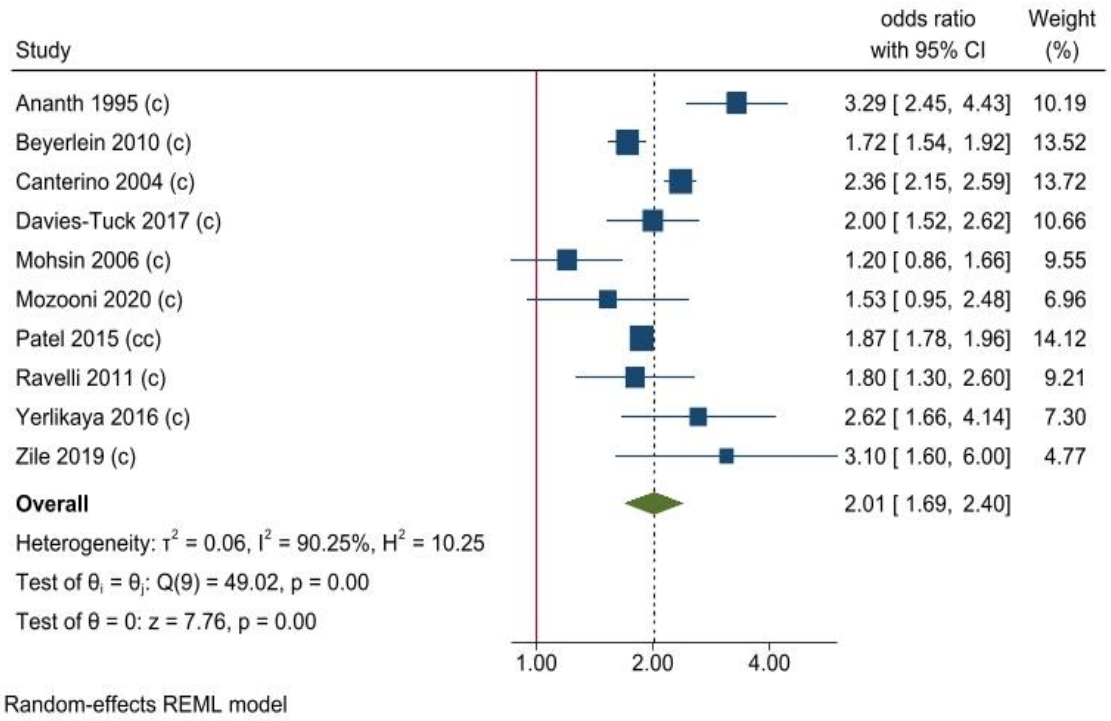
One study conducted in Québec, Canada, examined the effect of blood donation on the odds of stillbirth (within the six months prior to conception)[308]. Bias assessment using the RTI tool of assessment found a high risk of bias owing to failure to incorporate "non-donor" controls within the reference group. The study did not demonstrate an association between two or more whole blood or apheresis red blood cell (RBC) donation within the six months prior to conception versus no donations (aOR 0.97 (95% CI 0.23, 4.07)). When one whole blood or apheresis RBC donation within the two years prior to conception

versus none, the unadjusted RR was 1.98 (95% CI 1.09, 3.62), yet when adjusted for confounders, this association diminished (aRR 0.97 (95% CI 0.23-4.07)).

Chronic hypertension

Chronic hypertension (all stillbirth)

Twenty-two included studies examined the impact of maternal chronic hypertension (pre-existing hypertension) and its impact on second or third trimester stillbirth risk[47, 73, 108, 112, 118, 122, 125, 150, 157, 158, 167, 192, 238, 240, 244, 300, 304, 309, 319, 320, 330, 332, 345] compared with women without chronic hypertension. Where studies had sourced data from the same dataset, we selected the study with the largest cohort, resulting in eight studies being excluded from meta-analysis[122, 150, 192, 238, 304, 309, 319, 320]. One further study was excluded as no study time period was reported [345]. The final meta-analysis examining the association between maternal diagnosis of chronic hypertension and odds of stillbirth included 10 studies[73, 108, 112, 125, 157, 158, 167, 240, 244, 300, 320] and demonstrated considerable heterogeneity (I^2 = 90.25%). Through sensitivity analysis two studies were identified that contributed greatly to heterogeneity[112, 157]. No reason could be attributed to this heterogeneity, and therefore all studies were included in the final meta-analysis. Chronic hypertension was shown to be associated with a two-fold increase in odds of stillbirth (aOR 2.01 (95% CI 1.69, 2.40) – fig 3-60).

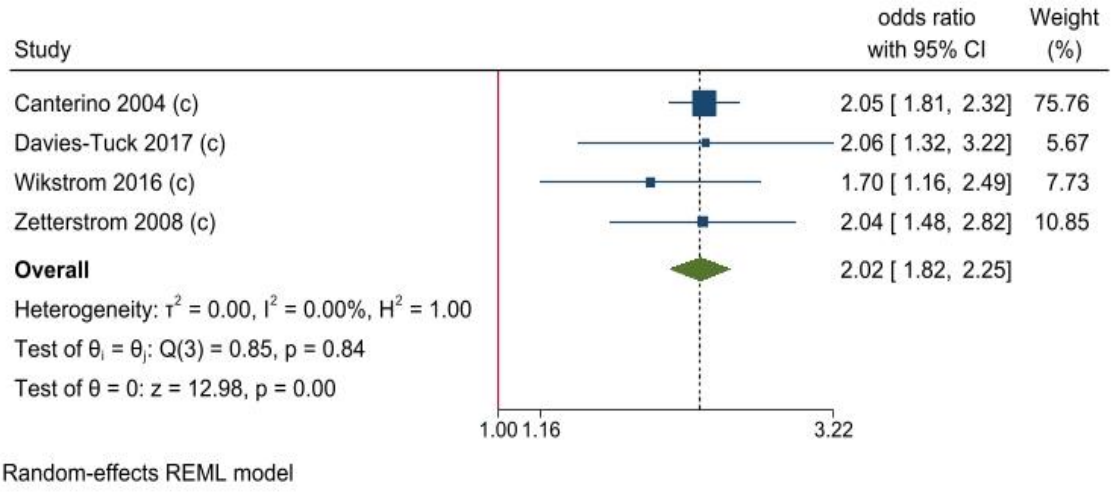


(c) = cohort study
(cc) = case-control study
Figure 3-60 Meta-analysis of stillbirth odds association between maternal chronic hypertension and second and/or third trimester stillbirth in comparison with no chronic hypertension.

Chronic hypertension (third trimester stillbirth)

Four studies examined the relationship between chronic hypertension and third trimester stillbirth. Meta-analysis demonstrated an increase in third trimester stillbirths associated

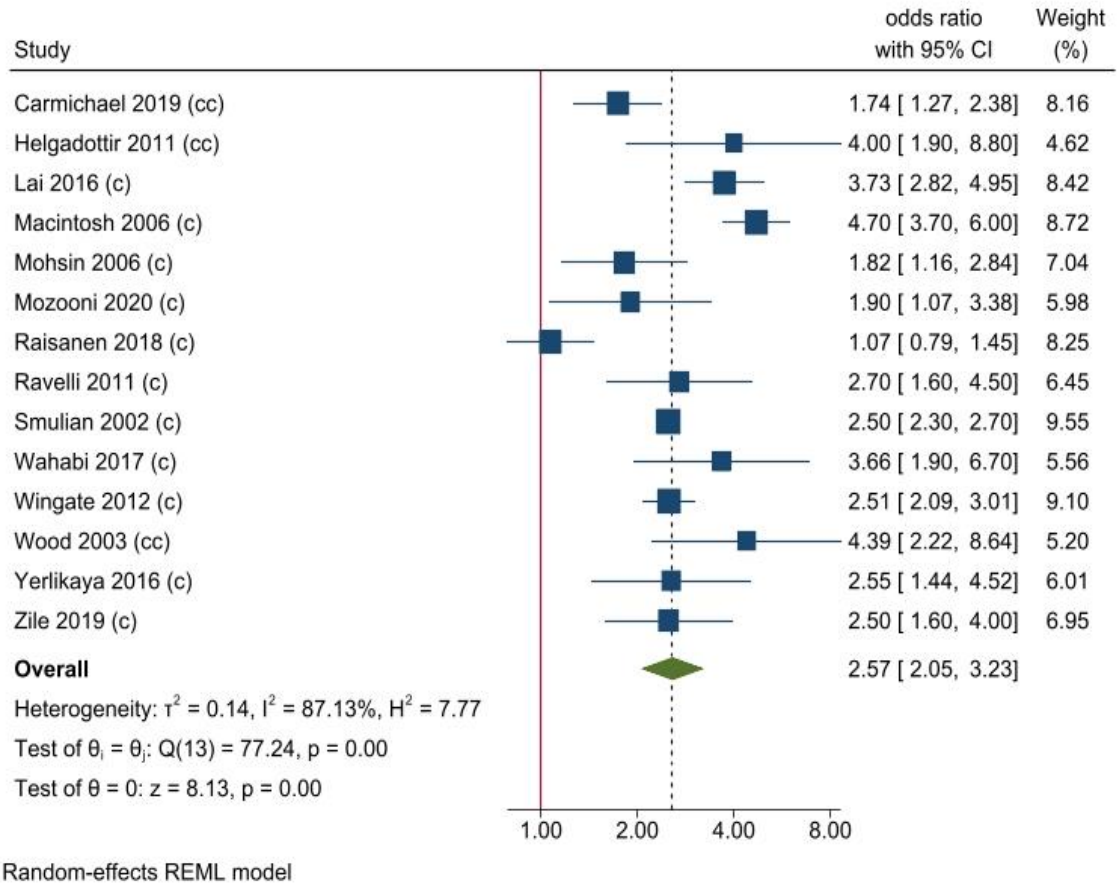
with chronic hypertension versus no chronic hypertension (aOR 2.02 (95% CI 1.82, 2.25) – fig 3-61).



(c) = cohort study
(cc) = case-control study
Figure 3-61 Meta-analysis of third trimester stillbirth odds association between maternal chronic hypertension and second and/or third trimester stillbirth in comparison to no chronic hypertension.

Pre-existing diabetes

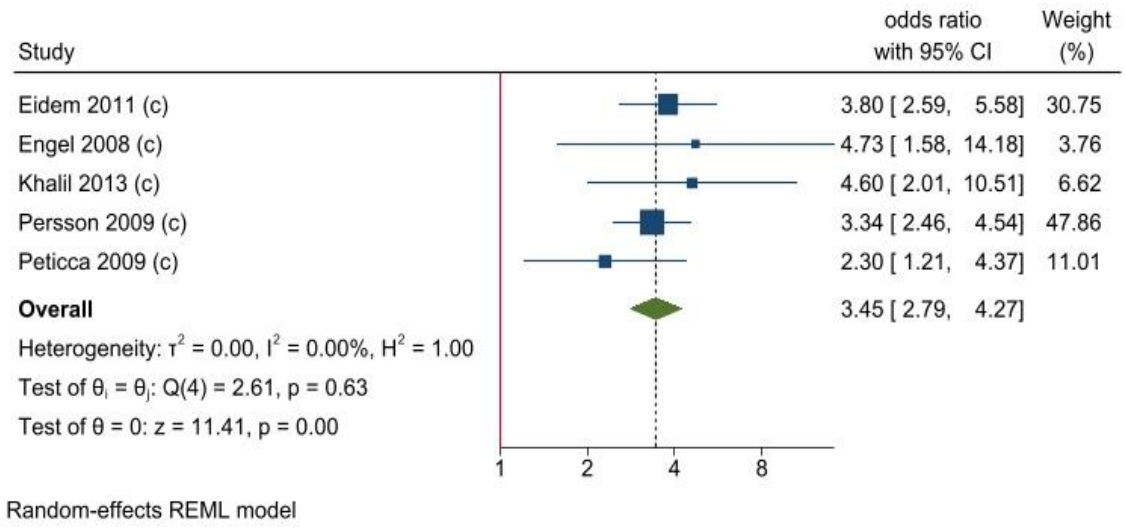
Twenty-four studies examined the association between maternal pre-existing diabetes and stillbirth odds[39, 122, 125, 130, 157, 158, 165, 167, 181, 192, 238-248, 309, 315, 331]. Of the studies, nineteen grouped type 1 and type 2 diabetes together to examine the associated stillbirth odds[122, 125, 130, 157, 158, 165, 167, 181, 192, 238-244, 309, 315, 331]. Two studies were excluded from analysis due to differences in their cohort characteristics. One study exclusively included twin pregnancies [315], and the other study stratified analysis by intra/antepartum stillbirths[309]. Two studies reported use of the same dataset for analysis and therefore to avoid double counting of births, the smaller study[125] was excluded and the larger study retained for analysis[157]. The final study that was excluded did not provide confidence intervals for its analysis and therefore could not be used for meta-analysis of results[181]. Following initial analysis, two studies were identified as contributors to high heterogeneity[192, 331]. One study minimally adjusted findings for confounders[331], and the other compared only previable stillbirths with term livebirths within its cohort (mismatched GA)[192], neither was deemed a reason for exclusion. Fourteen studies were included in meta-analysis, through reviewer assessment; six were assessed to have a low risk of bias[157, 158, 165, 238-240], four had unclear risk of bias[130, 157, 243, 244] and two were judged as having a high risk of bias[241, 242]. The final odds from meta-analysis of studies demonstrated more than double the odds of stillbirth associated with maternal pre-existing diabetes (aOR 2.57 (95% CI 2.05 to 3.23) – fig 3-62). Heterogeneity remained considerable (I^2 = 87.13%). Heterogeneity was likely due to the inclusion of type 1 and type 2 diabetes combined within the exposure groups included, and the differing populations of women who experienced diabetes prior to pregnancy.



(c) = cohort study
(cc) = case-control study
Figure 3-62 Meta-analysis of pre-existing diabetes (type 1 and 2) and the association with stillbirth odds compared with mothers without pre-existing diabetes.

Maternal type I diabetes

Five studies analysed stillbirth odds for women who had been diagnosed with type 1 diabetes prior to pregnancy[39, 245-248]. The result of meta-analysis demonstrated more than three-fold increased association between type 1 diabetes and stillbirth odds (aOR 3.45 (95% CI 2.79, 4.27) – fig 3-63).



(c) = cohort study
(cc) = case-control study
Figure 3-63 Meta-analysis of pre-existing type 1 diabetes and the association with stillbirth odds compared with mothers without pre-existing diabetes.

Maternal type 2 diabetes

Two studies grouped women with type 2 diabetes and investigated the association with stillbirth odds compared with women with no history of diabetes[39, 248]. One study was excluded from analysis due to no study period dates provided [39]. The second study did not indicate increased risk associated with maternally pre-existing type 2 diabetes (aOR 0.42 (95% CI 0.02, 1.88))[248], contrary to other literature that indicates an increased rate of perinatal mortality in women with type 2 diabetes diagnosed prior to pregnancy[48, 284]. One explanation that the authors offer for this finding is that previous studies consistently correlate poorer outcomes to mothers with type 2 diabetes due to late antenatal care presentation. The women included in their Canadian cohort who had type 2 diabetes entered antenatal care early, had access to free health care, and therefore may have entered pregnancy with better glycaemic control than other populations[248].

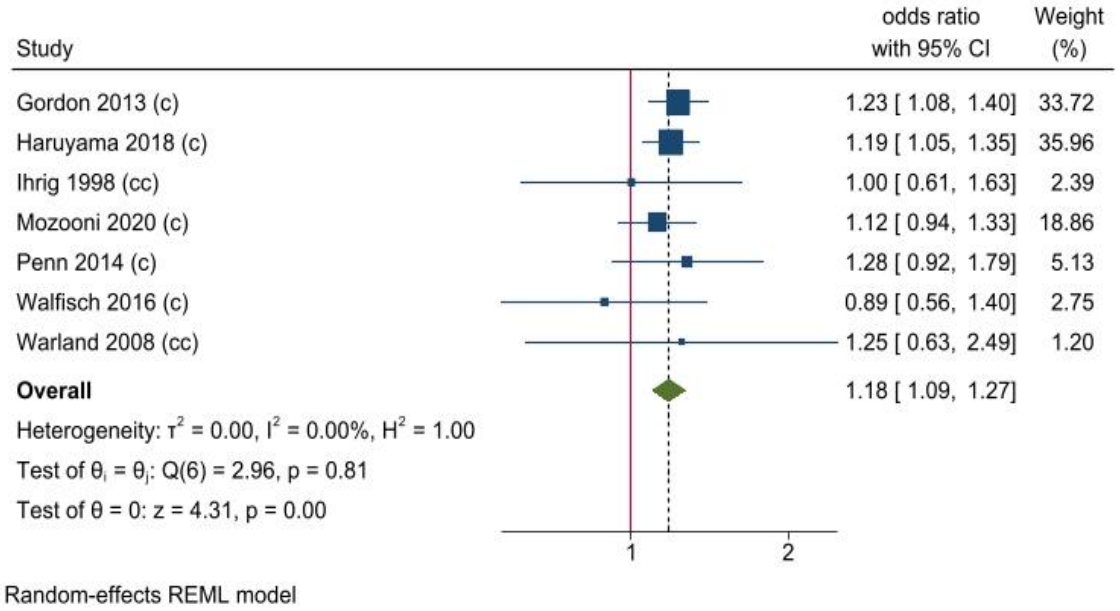
Parity

Thirty-one studies reported on odds of stillbirth associated with parity in high-income countries[32, 35, 87, 91, 99, 104, 113, 119-121, 125, 129, 134, 144, 151-154, 157, 158, 164, 168, 177, 180, 181, 185, 200, 262, 299, 325, 330]. All studies were reviewed using the RTI tool of assessment for bias, and five were deemed to have a high level of bias[99, 129, 134, 144, 168], 11 had a low risk of bias[87, 91, 104, 113, 125, 153, 154, 158, 177, 181, 185], and 15 were assessed as having an unclear risk or bias[32, 35, 119-121, 151, 152, 157, 164, 180, 200, 262, 299, 325, 330]. High risk of bias was attributed predominantly to study cohort sourced from one study centre as well as lack of detail of confounders in adjustment of results, alongside a lack of adjustment for potential confounders.

Nulliparity

Fourteen studies examined the association between nulliparous women, versus multiparous women[35, 113, 125, 129, 151-153, 158, 164, 168, 181, 185, 262, 330]. Ten studies examined stillbirth within the second and third trimester [35, 125, 129, 151, 158, 164, 168, 185, 262, 330] One study was excluded from analysis as the study results did not provide confidence intervals and

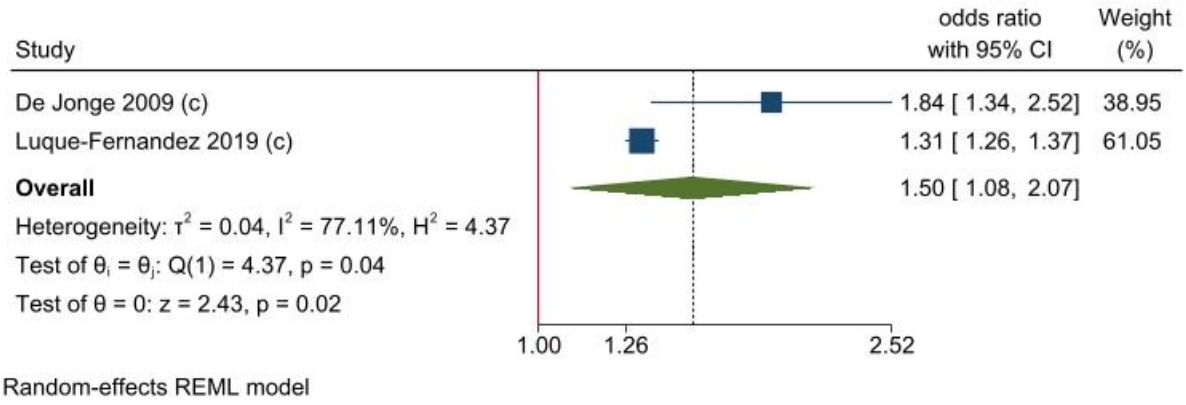
therefore could not be included for meta-analysis[181]. Of the studies examining nulliparity, two were excluded[168, 185] as they used the same datasets as larger studies included in analysis of this factor[125, 164]. The smaller studies were excluded. One further study was excluded from meta-analysis as the parity included in the reference group was not comparable to other included studies[151]. Final meta-analysis included seven studies. Odds of stillbirth associated with nulliparity were shown to increase compared with multiparous women (aOR 1.18 (95% CI 1.09, 1.27) – fig 3-64).



(c) = cohort study
(cc) = case-control study
Figure 3-64 Meta-analysis of the association between nulliparity on odds of stillbirth compared with multiparous women (≥1 previous birth)

Nulliparity (third trimester stillbirth)

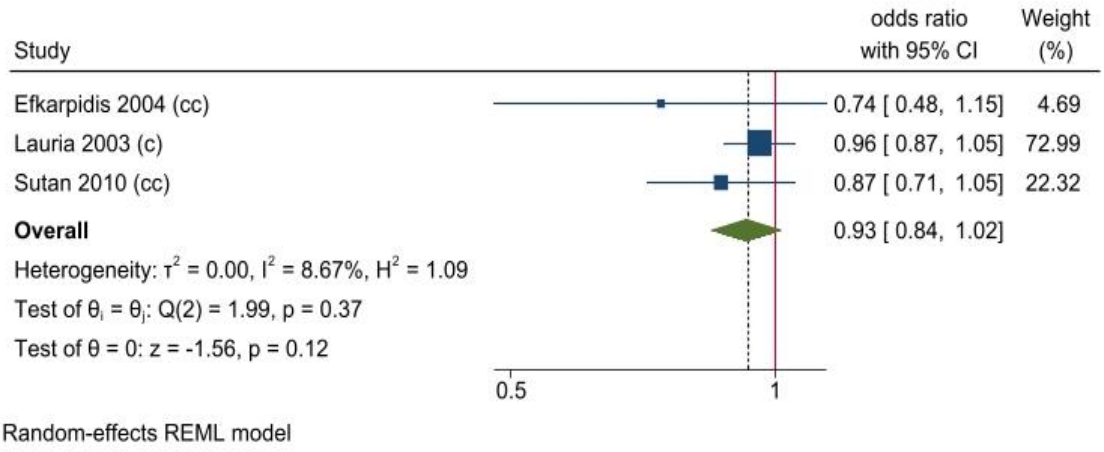
Three studies examined stillbirth odds exclusively in the third trimester of pregnancy[113, 152, 153]. Two studies reported use of the same dataset for analysis, and therefore the smaller of the two studies was excluded[152] and the larger retained for analysis[153] to avoid double-counting births. Meta-analysis showed an increased association with nulliparity and third trimester stillbirth (aOR 1.50 (95% CI 1.08, 2.07) – fig 3-65) compared with multiparous women.



(c) = cohort study
(cc) = case-control study
Figure 3-65 Meta-analysis of the association between nulliparity on odds of third trimester stillbirth compared with multiparous women (≥1 previous birth).

<u>One previous birth (parity = 1)</u>

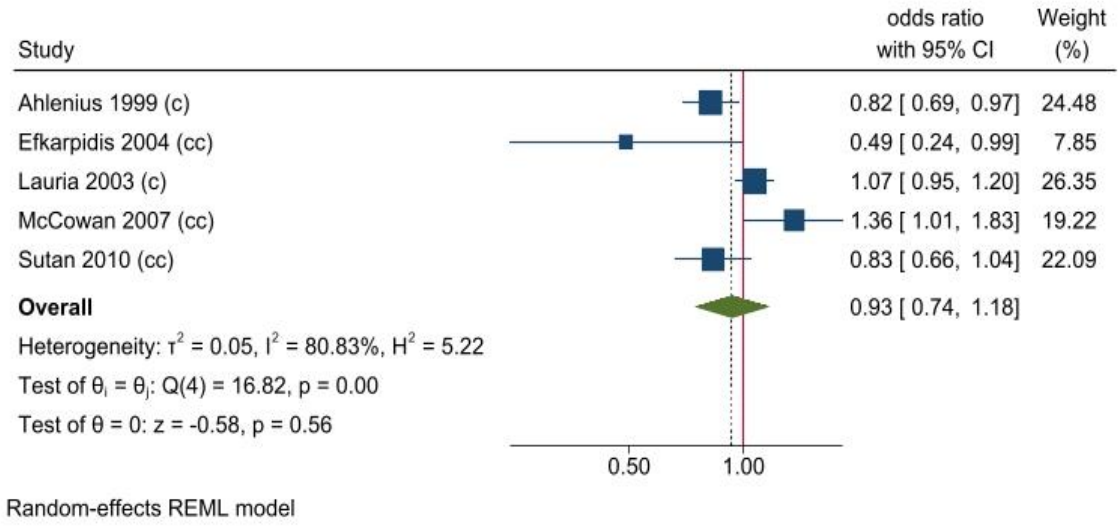
Six studies reported analyses for women with one prior birth and their associated stillbirth odds[120, 121, 144, 154, 177, 180]. The studies described differently defined reference groups. Five of the studies compared one previous birth for women who had no previously recorded births, and one study used a comparison group of women who had 2-3 recorded previous births, this study was therefore excluded from meta-analysis[177]. It was noted that one study restricted analysis to women <15 years old and demonstrated increased odds of stillbirth associated with parity = 1 compared with nulliparity (aOR 2.37 (95% CI 2.05, 2.74))[154]. Through meta-analysis and subsequent sensitivity analysis, this study was noted increased heterogeneity to unacceptably high levels and was therefore excluded as it used a restricted cohort of young women that was not comparable to other included study cohorts. Another study[121] was excluded due to use of the same dataset as a larger study included in the analysis[120]. Final analysis demonstrated a non-significant protective association between one previous birth compared with no previous births (aOR 0.93 (95% CI 0.84, 1.02) – fig 3-66).



(c) = cohort study
(cc) = case-control study
Figure 3-66 Meta-analysis of one previous birth on stillbirth odds in the current pregnancy in comparison to no previous births.

Two previous births (parity = 2)

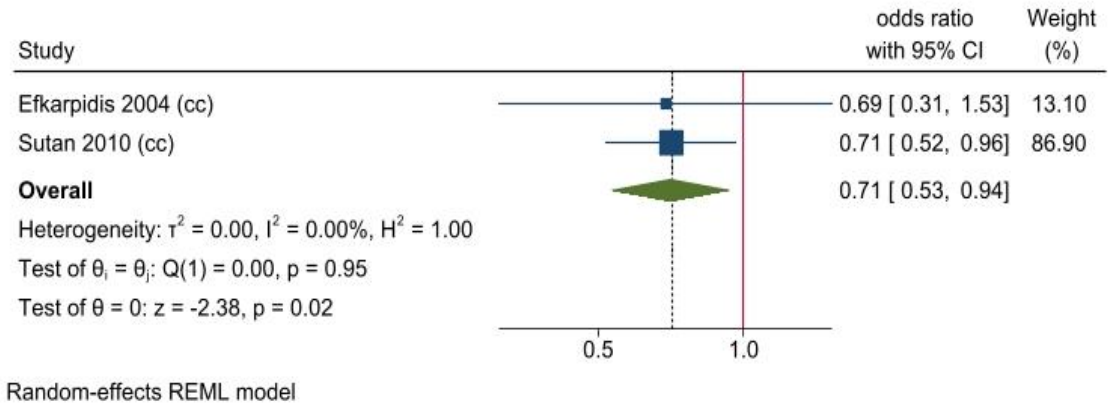
Seven studies reported the association of two previous births on stillbirth odds[32, 99, 120, 121, 144, 154, 180]. Two studies reported using the same dataset for analysis, therefore to avoid double counting of births, the smaller of the two studies[121] was excluded and the study using a larger cohort from the dataset was retained for analysis[120]. One study restricted analysis to a subgroup of women who were < 15 years old[154]. This study demonstrated very high association between two previous births and stillbirth odds (aOR 5.03 (95% CI 3.61, 7.00). Due to the difference in characteristics of study populations, this study was excluded from analysis. The final meta-analysis included five studies[32, 99, 120, 144, 180] comparing women with 2 previous births to women with ≤1 previous birth demonstrated considerable heterogeneity that could not be explained by sensitivity analysis (I^2 = 81%) and was therefore accepted. The analysis did not show a clear association between two previous births and stillbirth odds (aOR 0.93 (95% CI 0.74, 1.18) – fig 3-67).



(c) = cohort study
(cc) = case-control study
Figure 3-67 Meta-analysis of studies reporting the effect of 2 previous births on stillbirth odds compared with ≤1 previous birth.

Three previous births (parity = 3)

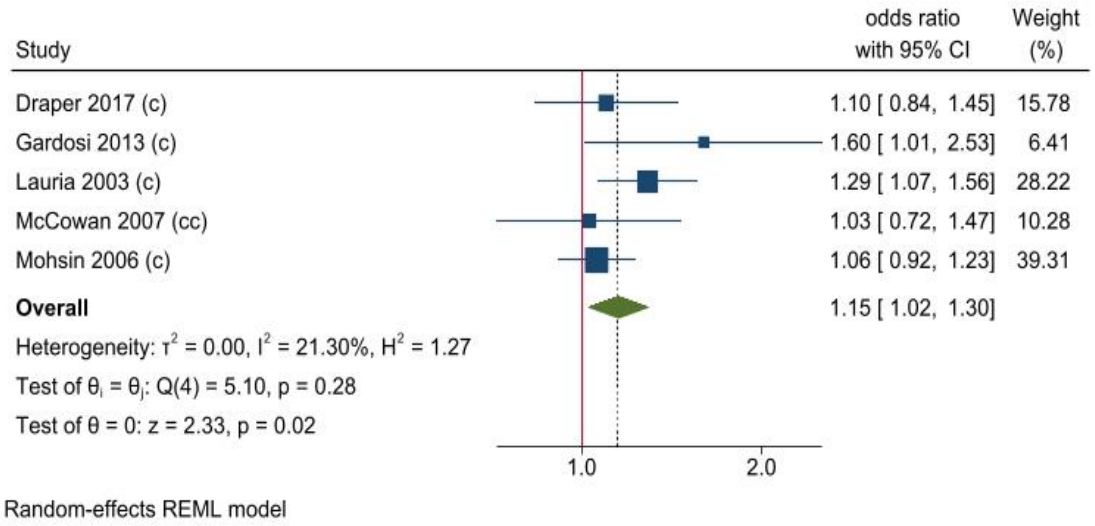
Four studies investigated the association between parity = 3 and stillbirth odds[99, 120, 121, 180]. Two studies reported using the same dataset for analysis of this risk factors, therefore to avoid double counting births, the smaller of the two studies[121] was excluded and the study using a larger cohort from the dataset was retained for analysis[120]. The resultant meta-analysis showed moderate-substantial heterogeneity (I^2=53%) between studies that was attenuated through sensitivity analysis excluding Ahlenius et al [99]. Ahlenius et al[99] reported use of a comparison group of women with one previous birth, differing from the other studies (no previous births). On exclusion of Ahlenius et al[99], heterogeneity decreased (I^2=0%). Results indicate a protective effect of three previous pregnancies in comparison to none (aOR 0.71 (95% CI 0.53, 0.94) – fig 3-68).



(c) = cohort study
(cc) = case-control study
Figure 3-68 Meta-analysis of studies reporting the association of 3 previous births on stillbirth odds compared with ≤1 previous birth.

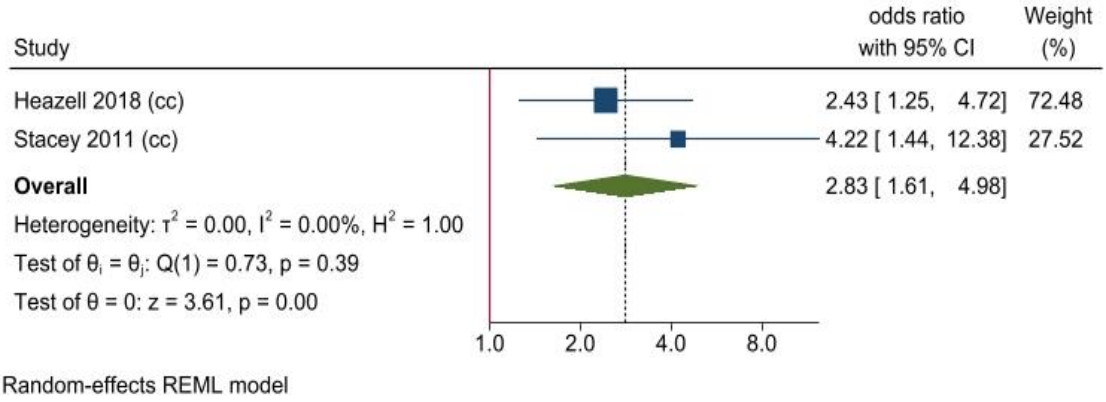
≥3, ≥4 and ≥5 previous births

Seven studies explored the relationship between women who had three or more previous births and odds of stillbirth[32, 91, 119, 144, 157, 200, 325]. Of these studies, two restricted analysis to third trimester stillbirths and subgroup meta-analysis was performed[91, 325]. Meta-analysis of studies reporting the associated effect of three or more previous births on stillbirth odds, demonstrated increased odds for all GAs; aOR 1.15 (95% CI 1.02, 1.30) – fig 3-69, and further increased odds of stillbirth for third trimester stillbirths (aOR 2.83 (95% CI 1.61, 4.98) – fig 3-70). Four studies examined the impact of four or more previous births[32, 87, 120, 121], and two studies examined the impact of five or more previous births[99, 180] on stillbirth odds compared to 0-3 previous births. Following the exclusion of one study[121] that reported use of the same dataset as a larger included study[120], three studies were included in meta-analysis. Heterogeneity was deemed acceptable in all analyses except for the analysis of five or more previous births (I^2 = 62.34%). This is owing to differences in stillbirth definition between the studies included in analysis (Ahlenius et al[99] included stillbirths ≥ 28 weeks GA and Sutan et al[180] included all unexplained stillbirths ≥ 20 weeks GA). Meta-analysis of studies indicates that four or more previous births increases odds of stillbirth (aOR 1.53 (95% CI 1.10, 2.13) – fig 3-71). Conversely, five or more previous births did not demonstrate a clear difference in risk of stillbirth (aOR 0.77 (95% CI 0.48, 1.22) – fig 3-72). High heterogeneity and wide confidence intervals of these analysis reinforce uncertainty, and findings should be interpreted with caution.

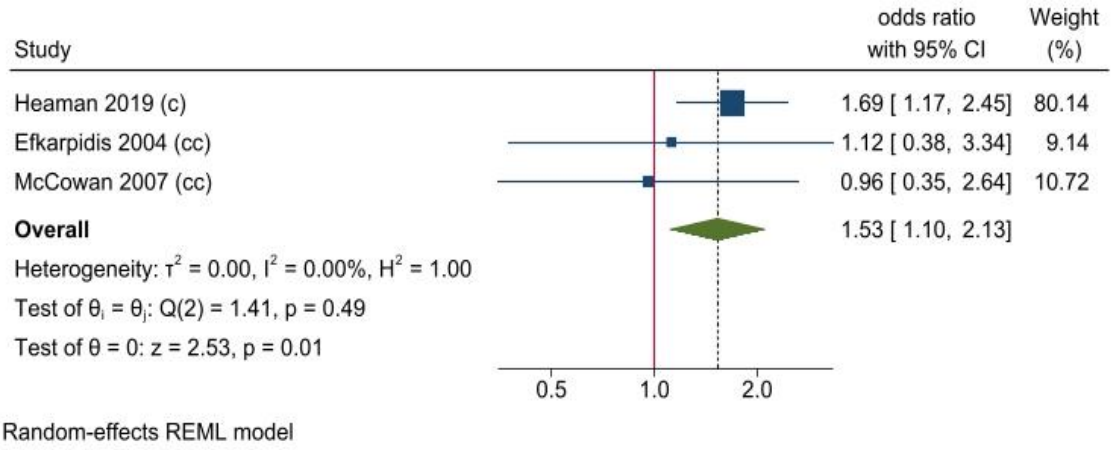


(c) = cohort study
(cc) = case-control study

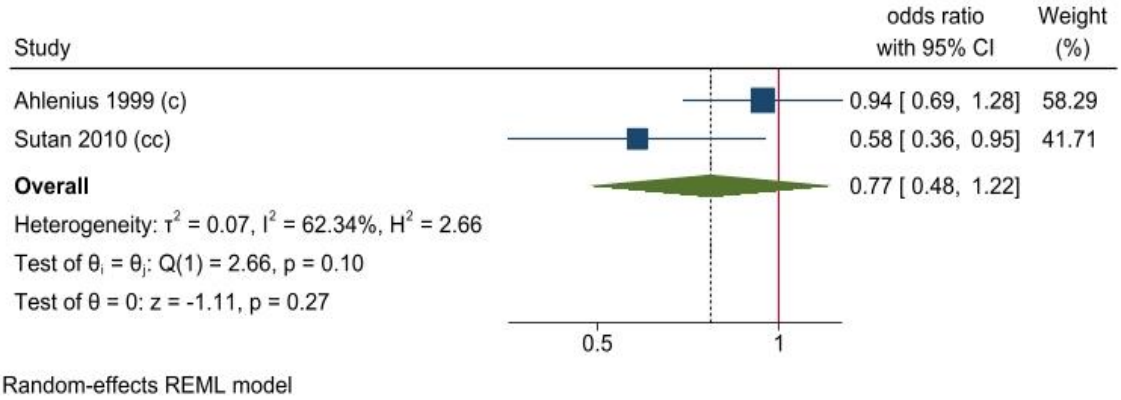
Figure 3-69 Meta-analysis of studies reporting the association between ≥3 previous births and stillbirth odds compared with 0-2 previous births.



(c) = cohort study
(cc) = case-control study
Figure 3-70 Meta-analysis of studies reporting the association between ≥3 previous births and third trimester stillbirth odds compared with 0-2 previous births.



(c) = cohort study
(cc) = case-control study
Figure 3-71 Meta-analysis of studies reporting the association between ≥4 previous births and stillbirth odds compared with 0-2 previous births.



(c) = cohort study
(cc) = case-control study
Figure 3-72 Meta-analysis of studies reporting the association between ≥5 previous births and stillbirth odds compared with 0-2 previous births.

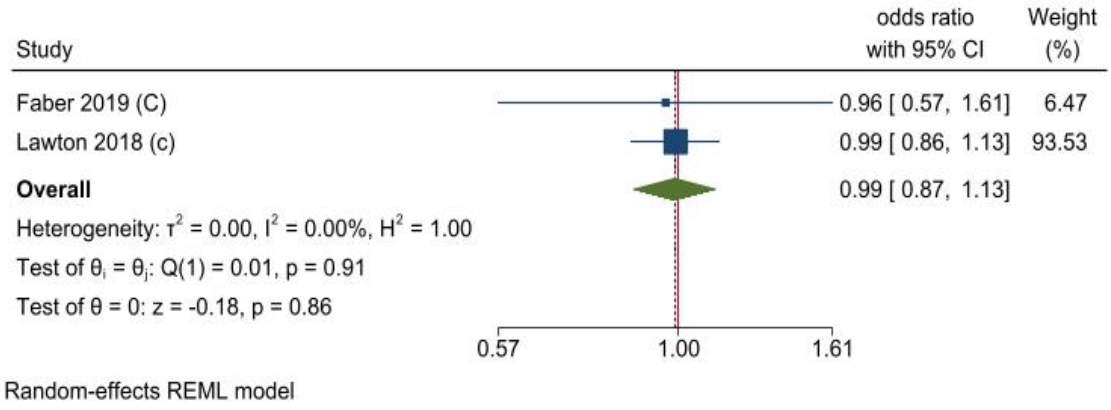
Grand-multiparity (parity ≥10)

Only one study population sourced from the USA had sufficient numbers to examine the impact of grand multiparity on stillbirth odds[299]. Aliyu et al[299] examined births to women who recorded 10 or more previous births and found the association with stillbirth odds increased in direct association with increasing parity from 10-14 previous births (aOR 1.96 (95% CI 1.79, 2.14)) to ≥18 previous births (aOR16.17 (95% CI 8.77, 29.82)).

Vaccination

Preconception HPV vaccination

Three studies investigated the effect of maternal HPV vaccination prior to conception on the risk of stillbirth odds[264-266]. Of the three studies, two used the same dataset[264, 266] and therefore the smaller study was excluded from meta-analysis to avoid double-counting of births[266]. One study controlled for the length of time between vaccination and pregnancy but only included women who had their most recent dose of HPV vaccination within the 4 weeks prior to conception[264]. The remaining study included women who had ever had the HPV vaccination prior to conception[265]. The results of meta-analysis demonstrate no clear association between history of HPV vaccination and stillbirth odds compared with no recorded HPV vaccination (aOR 0.99 (95% CI 0.87, 1.13) – fig 3-73).



(c) = cohort study
(cc) = case-control study

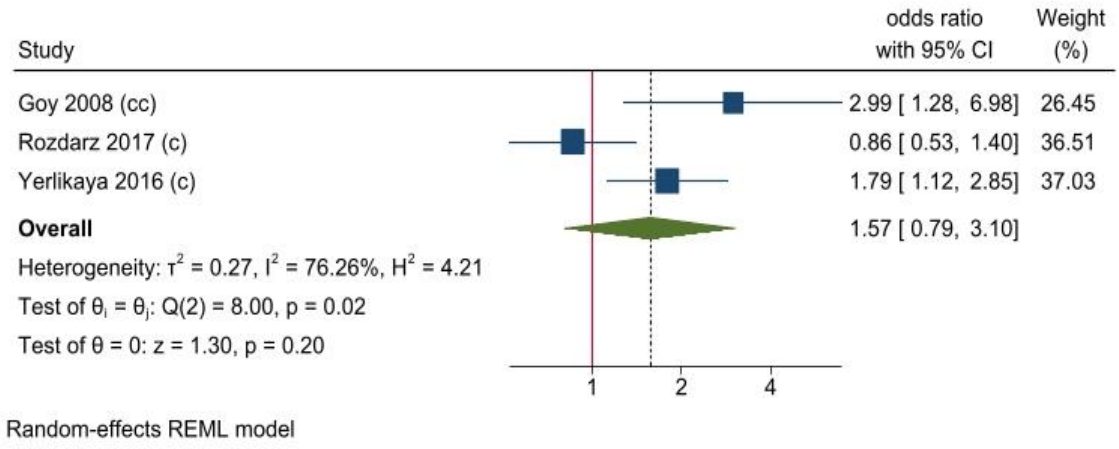
Figure 3-73 Meta-analysis of the association between HPV vaccination prior to pregnancy and stillbirth odds compared with women who have not received the HPV vaccination prior to the indexed pregnancy.

Assisted reproductive technology (ART).

Ten studies examined the use of assisted reproductive technology (ART) and odds associated with stillbirth across five high-income countries[67, 117, 126, 131, 165, 240, 302, 311, 322, 345]. Exposure groups were categorised into any ART, use of ovulation drugs, in-vitro fertilisation (IVF), and intra-uterine insemination (IUI). All studies were assessed by two independent reviewers using the RTI tool of assessment for bias/quality. One of the studies demonstrated a high risk of bias[311] as data collection regarding ART medication used was not corroborated with medical records, and data related to "ever used ART", instead of in relation to the current pregnancy. Four studies were deemed to demonstrate an unclear risk of bias[67, 117, 126, 345], and five have a low risk of bias[131, 165, 240, 302, 322].

Assisted reproductive technology – any modality

Four studies reported the association of any fertility treatment and stillbirth odds[117, 126, 240, 322]. Two studies reported use of the same dataset for analysis, therefore the smaller study [117] was excluded from analysis and the larger study retained[126]. Final meta-analysis demonstrated considerable heterogeneity (I^2 = 76.26%). Rozdarz et al[322] was identified as the main contributor to heterogeneity, and reported that study data was sourced from a single institution. Meta-analysis demonstrated a possible increased association between ART and stillbirth (aOR 1.56 (95% CI 0.79, 3.10) – fig 3-74), but alongside high heterogeneity and large confidence intervals, results should be interpreted with caution.

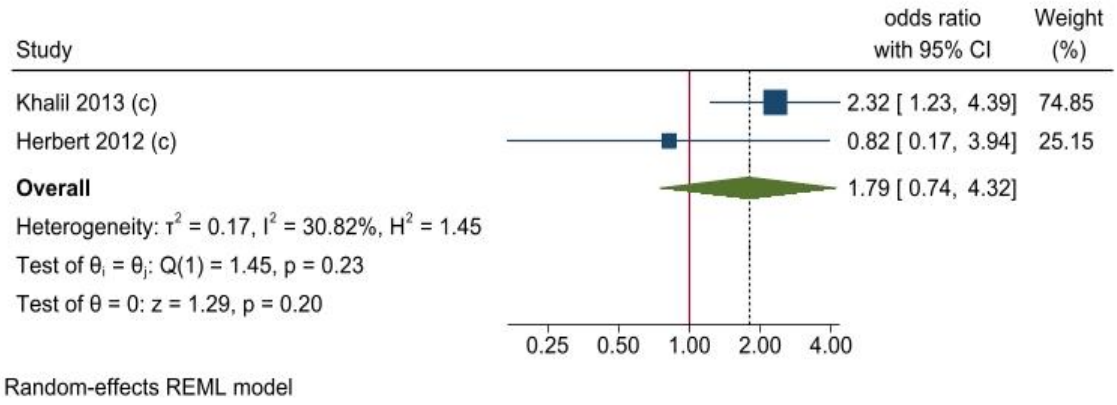


(c) = cohort study
(cc) = case-control study

Figure 3-74 Meta-analysis of studies reporting the association between any assisted reproductive technology use on stillbirth odds compared with spontaneous conception.

Ovulation induction

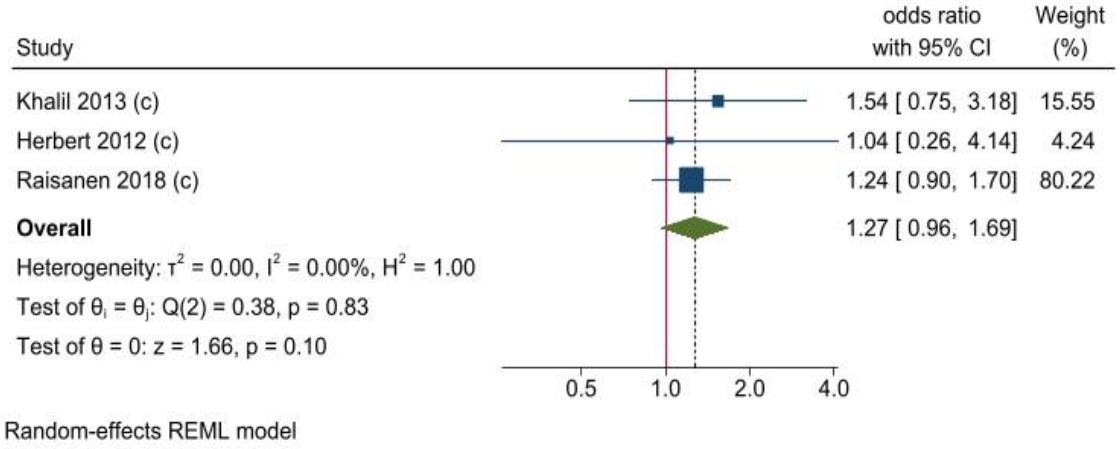
Three studies examined the use of ovulation induction therapy association with stillbirth odds[67, 311, 345] compared with spontaneous conception. One study[67] used a population that overlapped with a another study[311] also included in this analysis, and therefore the smaller study was excluded[67]. Final meta-analysis included two studies, the results of the meta-analysis demonstrated an increase in stillbirth odds associated with ovulation induction (aOR 1.74 (95% CI 0.74, 4.32) – fig 3-75). Large confidence intervals likely reflect the small cohort sizes of the included studies.



(c) = cohort study
(cc) = case-control study
Figure 3-75 Meta-analysis of studies reporting the association between ovulation induction on stillbirth odds compared with spontaneous conception.

In vitro fertilisation (IVF)

Four studies reported the association between the use of IVF and stillbirth odds[67, 165, 311, 345] compared with spontaneous conception. Two studies reported using the same dataset for analysis and therefore, to avoid double-counting births, the smaller study[67] was excluded from meta-analysis and the larger study retained[311]. Final meta-analysis included the remaining three studies and demonstrated a possible association with stillbirth (aOR 1.27 (95% CI 0.96, 1.69) – fig 3-76).



(c) = cohort study
(cc) = case-control study
Figure 3-76 Meta-analysis of studies reporting the association between IVF use and stillbirth odds compared with spontaneous conception.

Two further studies analysed the association between IVF and stillbirth odds stratified by GA [131, 302]. Henningsen et al[131] demonstrated the greatest increased odds of stillbirth associated with IVF at 22+0 to 27+6 weeks GA (aOR 2.08 (95% CI 1.55, 2.78)), but the association was not replicated for any other GA categories. Bay et al[302] stratified results to term births and demonstrated a two to three-fold increased association with all categories of term stillbirths and IVF or intracytoplasmic sperm injection (ICSI) versus spontaneous conception (table 3-3).

Table 3-3 Bay et al[302] results of analysis of stillbirth odds associated with IVF/ICSI pregnancy compared with spontaneous conception.

GA parameter (weeks + days)	Reference cohort	Exposure	aOR (95% CI)
≥37+0	Spontaneous conception	IVF/ICSI	2.40 (1.60, 360)
≥38+0	Spontaneous conception	IVF/ICSI	2.30 (1.50, 3.60)
≥39+0	Spontaneous conception	IVF/ICSI	2.50 (1.50, 4.10)
≥40+0	Spontaneous conception	IVF/ICSI	3.00 (1.70, 5.20)
≥41+0	Spontaneous conception	IVF/ICSI	2.40 (0.90, 5.90)
≥42+0	Spontaneous conception	IVF/ICSI	6.80 (1.30, 36.60)

Intra-uterine insemination (IUI)

One study, Bay et al, examined the association between IUI and different GA categories of term stillbirths (≥37, ≥38, ≥39, ≥40, ≥41 weeks GA)[302] compared with pregnancies conceived spontaneously. Results showed that odds of stillbirth were increased for ≥37 weeks GA (aOR 1.90 (95% CI 1.00, 3.60)), and then again for ≥41 weeks GA (aOR 3.70 (95% CI 1.20, 11.60)). The sample size for analysis of the separate categories of GA, in most instances, contained <10 stillbirths decreasing the power of analysis and subsequent confidence in findings.

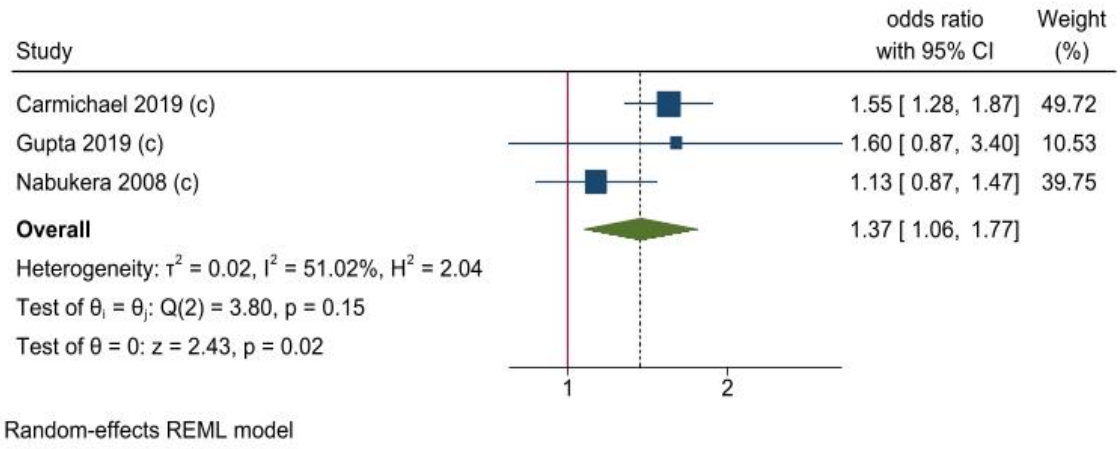
Interpregnancy interval

Seven studies examined the association between interpregnancy interval with stillbirth odds[132, 160, 192, 310, 318, 321, 326]. Two studies reported use of the same dataset to for analysis and therefore the smaller of the two studies was excluded from meta-analysis to avoid double-counting births[318]. One study examined risk of subsequent stillbirth following a previous stillbirth, and was therefore reviewed separately[321]. The remaining five studies described comparable exposure groups. Four studies were assessed to have a low risk of bias[132, 318, 321, 326], one an unclear risk of bias[160], and two a high risk of bias due to methodological differences in the selection of cases and controls[192], and lack of study method description[310].

Short interpregnancy interval (≤ 6 months)

Four studies included analysis of women who's calculated date of conception was ≤6 months after their last birth[160, 192, 310, 318]. Two studies reported use of the same dataset to for analysis and therefore the smaller of the two studies was excluded from meta-analysis to avoid double-counting births[318]. Two of the remaining studies demonstrated a high risk of bias[192, 310], and the remaining study demonstrated an unclear risk of bias[160]. High risk of bias was attributed to the comparison of non-viable stillbirths (20-25 weeks GA) to viable livebirths (26-42 weeks GA)[192], and the other study assessed as having a high risk of bias did not adequately describe the study methodology in relation to maternal interview and data collection[310]. Odds of stillbirth associated with a short interpregnancy

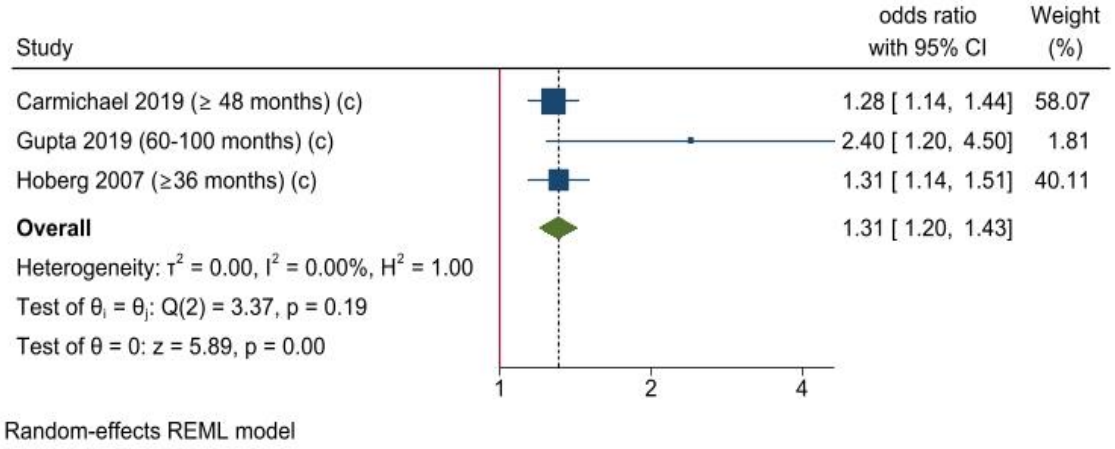
interval of ≤ six months was shown to be increased (aOR 1.37 (95% CI 1.06, 1.77) – fig 3-77). Analysis demonstrated substantial heterogeneity (I^2 = 51.02%).



(c) = cohort study
(cc) = case-control study
Figure 3-77 Meta-analysis of the association between a short interpregnancy interval (≤6 months) in comparison to 6-23 months interpregnancy interval.

Long interpregnancy interval (≥ 36 months)

Four of the studies included in the examination of long interpregnancy interval included a subgroup of women who had very large interpregnancy intervals (over 3 years between pregnancies) compared with 12-36 months interpregnancy interval[132, 192, 310, 326]. One study[326] reported use of the same dataset as a larger study included[132]. To avoid the potential to double-count births, the smaller study was excluded from meta-analysis. Results demonstrate an increased risk of stillbirth associated with long interpregnancy interval of aOR 1.33 (95% CI 1.16, 1.52) (– fig 3-78) compared with a 12–36-month pregnancy interval.



(c) = cohort study
(cc) = case-control study
Figure 3-78 Meta-analysis of studies reporting the association between a long interpregnancy interval (≥ 36 months) and stillbirth odds in comparison to 12-36 months interpregnancy interval.

One study[326] subgrouped analysis to non-comparable interpregnancy intervals with other studies and therefore was not be included in meta-analysis[326]. This study examined interpregnancy intervals of 0-3, 4-7, 8-11, 36-71, ≥72 months, and found an increased odds of stillbirth associated with 36-71 and ≥72 months between pregnancies (aOR 1.2 (95% CI 1.0, 1.4) and aOR 1.5 (95% CI 1.1, 2.1) respectively)[326].

Interpregnancy interval following a previous stillbirth

One study examined the association between interpregnancy interval on subsequent stillbirth rates[321]. This study included births from three high-income countries, Finland, Norway and Australia, and stratified interpregnancy interval to <6 months, 6-11 months and 12-23 months compared with women who had an interpregnancy interval of 24-59 months. No increase in odds of stillbirth were demonstrated for pregnancy intervals less than 24 months compared to 24-59 months following stillbirth.

Table 3-4 Chapter 3 summary of meta-analysis findings

Risk factor category	Reference group	Exposure group	All stillbirths (aOR (95% CI))	Second trimester stillbirths (20-27 weeks GA) (aOR (95% CI))	Third trimester stillbirths (≥28 weeks GA) (aOR (95% CI))	Term Stillbirths (≥37 weeks GA) (aOR (95% CI))
Maternal Education	Higher levels of education	*High-school or less*	**1.53 (1.34, 1.76)**	-	1.06 (0.87, 1.27)	**1.52 (1.03, 2.24)**
	≤ high-school education (12 years)	*Senior high-school (12-14 years)*	0.95 (0.86, 1.05)	-	-	-
	≥ 12years of education	*Senior high-school (12-14 years)*	**1.36 (1.05, 1.76)**	-	-	-
	≤ high-school education (12 years)	*Completion of short/medium further education courses*	**0.90 (0.83, 0.99)**	-	-	-
	≤ high-school education (12 years)	*Completion of long further education courses*	0.79 (0.47, 1.32)	-	-	-
	≤ high-school education (12 years)	*University level of education*	**0.66 (0.58, 0.73)**	-	-	-
Paternal education	≥ 12 years of education	*High-school or less*	**1.77 (1.37, 2.29)**	-	-	-
Marital status	Married	*Unmarried*	**1.33 (1.19, 1.49)**	-	-	-
	Married	*Divorced*	1.50 (0.94, 2.41)	-	-	-
	Married	*Co-habiting*	1.08 (0.87, 1.34)	-	-	-
	Q1 richest	*Q2*	1.12 (0.96, 1.30)	-	-	-

Household income	Q1 richest	*Q3*	**1.26 (1.09, 1.46)**	-	-	-
	Q1 richest	*Q4*	**1.22 (1.06, 1.41)**	-	-	-
	Q1 richest	*Q5 (poorest)*	**1.35 (1.22, 1.49)**	-	-	-
	Highest income	*Middle income*	1.26 (0.89, 1.77)	-	-	-
	Highest income	*Lowest income*	**1.30 (1.13, 1.49)**	-	-	-
Socioeconomic status	Highest SES	*Lowest SES*	**1.33 (1.22, 1.45)**	-	**1.37 (1.24, 1.52)**	-
	Highest SES	*Middle SES*	**1.22 (1.09, 1.36)**	-	-	-
Maternal age	>19 years	<16 years	**1.33 (1.19, 1.48)**	-	-	-
	>19 years	*15-19 years*	1.02 (0.94, 1.11)	-	-	-
	20-34 years	*<20 years*	**1.08 (1.00, 1.17)**	-	**0.81 (0.74, 0.90)**	-
	≤19 years	*30-34 years*	**1.46 (1.26, 1.69)**	-	-	-
	20-29 years	*30-34 years*	**1.16 (1.08, 1.25)**	-	**1.28 (1.08, 1.52)**	-
	<30 years	*35-40 years*	**1.40 (1.30, 1.50)**	-	**1.74 (1.53, 1.98)**	-
	<35 years (high SES)	*35-40 years (high SES)*	**1.42 (1.19, 1.70)**	-	-	-
	<35 years (low SES)	*35-40 years (low SES)*	**1.63 (1.37, 1.95)**	-	-	-
	<35 years (nulliparous)	*35-40 years (nulliparous)*	**1.46 (1.18, 1.82)**	-	-	-
	<35 years (multiparous)	*35-40 years (multiparous)*	**1.37 (1.15, 1.63)**	-	-	-
	20-29 years	*40-45 years*	**1.89 (1.47, 2.43)**	-	-	-
	20-29 years	*>45 years*	**2.65 (2.06, 3.39)**	-	-	-
Paternal age	20-34 years	*<20 years*	1.11 (0.61, 2.04)	-	-	-
	20-30 years	*30-40 years*	1.00 (0.90, 1.11)	-	-	-

	25-35 years	*35-39 years*	1.09 (0.97, 1.21)	1.09 (0.88, 1.36)	1.07 (0.98, 1.17)	-
	25-35 years	*40-45 years*	**1.30 (1.18, 1.44)**	**1.32 (1.11, 1.57)**	**1.29 (1.13, 1.47)**	-
	20-34 years	*≥40*	**1.23 (1.15, 1.31)**	-	-	-
Maternal BMI	20-25	≤20	0.94 (0.85, 1.05)	1.02 (0.78, 1.33)	0.90 (0.74, 1.10)	-
	20-25	≥ 25	**1.39 (1.03, 1.88)**	-	-	-
	20-25	25-30	**1.29 (1.17, 1.41)**	-	**1.46 (1.32, 1.62)**	-
	20-25	≥ 30	**1.59 (1.38, 1.82)**	-	-	-
	20-25	30-35	**1.41 (1.25, 1.59)**	-	-	-
	20-25	35-40	**1.73 (1.33, 2.25)**	-	**1.91 (1.55, 2.34)**	-
	20-25	≥ 40	**1.99 (1.65, 2.39)**	-	**2.60 (1.96, 3.45)**	-
	20-25	≥ 50	2.65 (0.92, 7.65)	-	-	-
Chronic hypertension	No chronic hypertension	*Chronic hypertension*	**2.01 (1.69, 2.40)**	-	**2.02 (1.82, 2.25)**	-
Pre-existing diabetes	No pre-existing diabetes	*Pre-existing diabetes (type 1 or 2)*	**2.57 (2.05, 3.23)**	-	-	-
	No pre-existing diabetes	*Type 1 diabetes*	**3.45 (2.79, 4.27)**	-	-	-
	Multiparity	*Nulliparity*	**1.18 (1.09, 1.27)**	-	**1.50 (1.08, 2.07)**	-
	Nulliparity	*1 previous birth*	0.93 (0.84, 1.02)	-	-	-
	Nulliparity	*2 previous births*	0.93 (0.74, 1.18)	-	-	-
	Nulliparity	*3 previous births*	**0.71 (0.53, 0.94)**	-	-	-
	Nulliparity	*3+ previous births*	**1.15 (1.02, 1.30)**	-	**2.83 (1.61, 4.98)**	-
	Nulliparity	*4+ previous births*	**1.53 (1.10, 2.13)**	-	-	-
	Nulliparity	*5+ previous births*	0.77 (0.48, 1.22)	-	-	-

Vaccination	No HPV prior to pregnancy	*HPV vaccination prior to pregnancy*	0.99 (0.87, 1.13)	-	-	-
ART	No ART	*Any ART*	1.56 (0.79, 3.10)	-	-	-
	No ART	*Ovulation induction*	1.79 (0.74, 4.32)	-	-	-
	No ART	*IVF*	1.27 (0.96, 1.69)	-	-	-
Interpregnancy interval	6-23 months	*≤6 months*	**1.37 (1.06, 1.77)**	-	-	-
	12-36 months	*≥36 months*	**1.31 (1.20, 1.43)**	-	-	-

Discussion and conclusions

Results of this systematic review and meta-analysis provide the most comprehensive evidence base for synthesis of preconception and sociodemographic risk factors of stillbirth in high-income countries to date. Through review, maternal obesity, sexual orientation, chronic hypertension and pre-existing diabetes are shown to have the strongest impact in increasing stillbirth odds, followed by low parental education, unmarried marital status, low income, medium and low SES, high parental age, high parity and long and short interpregnancy interval.

Chronic hypertension has been identified previously in reviews as a major risk factor for poor pregnancy outcomes including stillbirth[346, 347]. Our results support these findings and demonstrate that the aOR for chronic hypertension (aOR 2.01 (95% CI 1.69, 1.40)) warrants focus for prevention and management to minimise the risk of associated stillbirth. The observed 2-fold increased odds of stillbirth associated with chronic hypertension did not change through subgroup analysis of studies examining third trimester stillbirths (aOR 2.02 (95% CI 1.82, 2.25)) highlighting the need to address this chronic disease early. Results indicated that pre-existing type 1 diabetes has the greatest impact on stillbirth odds (aOR 3.45 (95% CI 2.79, 4.27)). A Finnish cohort study included in our review did not find an increased association between diabetes and stillbirth odds, the authors attributed this to strict policy and procedure in Finland regarding preconception planning and a detailed surveillance program for women with diabetes prior to pregnancy[165]. The impact that BMI and increased maternal age have on the pathogenesis of chronic hypertension and type 2 diabetes cannot be overlooked, and through this review, both BMI and increased maternal age are also identified as preconception risk factors of stillbirth, and the multifactorial risk cascade that ensues needs to be a priority in preconception care.

High maternal BMI has been identified as a major public health problem in recent national health surveys from the UK, USA and Australia[286, 291, 348]. Among women of reproductive age, 50% and 70% of women in the UK and USA were classified as overweight or obese respectively[291, 348]. In Australia, nearly 50% of all births in 2019 were to overweight or obese mothers[286]. Our results show that women entering pregnancy with a BMI >25 demonstrate increased odds of stillbirth compared with healthy weight women (aOR 1.18 (95% CI 1.04, 1.34)). When overweight women lost weight during pregnancy, the association is exacerbated (as shown by results outlined in chapter 4) to increase more than three-fold (aHR 3.44 (95% CI 2.34, 5.05) (chapter 4))[237]. This signals the importance of promoting maternal weight loss prior to conception to prevent the detrimental impact of weight management during pregnancy. Decreasing maternal BMI prior to pregnancy to a lower category is shown to partially mitigate the odds of stillbirth (Table 3-4).

Socioeconomic demands in high-income countries have contributed to delayed childbearing and resultant increase infertility. The demands for higher income and higher standards of living have resulted in women delaying child-bearing, and it has been show that older maternal age contributes to infertility rates within high-income countries[349, 350]. Our results indicate that maternal age of >30 years was associated with an increase in stillbirth odds (aORs ranging from 1.17-2.65), peaking for women >45 years at birth (aOR 2.65 (95% CI 2.06, 3.39)). Alongside maternal age, increasing paternal age of >40 years was shown to

increase stillbirth odds by 23% (aOR 1.23 (95% CI 1.15, 1.31)). This evidence supports the overall implications of our review findings that the preconception care incorporating pregnancy planning (including age of childbearing) is fundamental in management and mitigation of preconception risk factors in high-income countries.

Women within sexual-orientation minority groups were also shown to have increased odds of stillbirth (bisexual/lesbian women - aOR 2.85 (95% CI 1.40, 5.83))[307]. Previous research suggests that women from sexual minority groups experience heterosexism, alongside perceived rejection from the LGBTQ community, resulting in a lack of crucial support networks during pregnancy that are fundamental to assist families transitioning to parenthood[351-353]. Results from this emerging area of research indicate the need to further investigate pregnancy and birth outcomes for women in sexual minority groups.

Maternal SES, income and education all demonstrated inverse relationships with stillbirth odds in high-income countries. The highest odds were associated with low maternal education level (aOR 1.92 (95% CI 1.67, 2.20)) and low paternal education level (aOR 1.77 (95% CI 1.37, 2.29)), followed by low income (aOR 1.35 (95% CI 1.22, 1.49)) and SES (aOR 1.33 (95% CI 1.22, 1.45)). These factors are intricately entwined with one another as education level facilitates employment opportunities, and in turn, predicts the income and SES of a family's household. While these risks are unable to be altered by the health care system in high-income nations, it is important to be aware of the driving force behind inequity in health status. Disadvantage in high-income countries is firmly entrenched and for families that are already marginalised, the inequities are exacerbated feeding into intergenerational poverty. Universal free healthcare is still not available for all families in high-income countries, and cost, travel, childcare, cultural appropriateness, and non-flexible work commitments further deter engagement with low- SES families.

It has been acknowledged that there is a gap in the continuum of care from childhood to the antenatal period[349] and although the preconception period has been previously defined as the three months prior to conception[294, 354], the risks identified in this systematic review span the entirety of adulthood. Intervention during the preconception period (three months prior to conception) would likely have very little effect on maternal BMI and is unable to alter parental age, parity or interpregnancy interval. The risk associated with previously diagnosed diabetes or hypertension have the potential to be decreased with appropriate management but achieving this within the three-month period preceding conception is unachievable. Pre-conception care has been identified as a challenge for healthcare systems globally[350, 355]. Although multiple health initiatives are implemented during the antenatal period such as supplementation, improved diet quality and smoking cessation aids[291], many interventions can do little to mitigate the impact of pre-existing risk, such as obesity or related conditions, during the antenatal period. Although lifelong health is promoted in many high-income countries to aid in decreasing the burden of chronic health conditions, the role of lifelong health is not widely promoted as a tool available to adolescents and young adults to improve pregnancy outcomes [355, 356]. Closing the gap within the continuum of care from childhood to the antenatal period is the cornerstone for management and prevention of chronic health conditions such as obesity, hypertension and diabetes[357], and to aid planning associated with interpregnancy interval, parental age, and parity[349, 355, 356]. Previous studies examining the impact of community preconception care programs

concluded that programs were effective and reduced neonatal mortality by nearly 20%[349]. The same may be also true for stillbirth.

While this review was comprehensive, there are several limitations that could not be avoided. A lack of paternal risk factors examined across studies reflects that collection of paternal risk factors within datasets is lacking among all high-income countries. This gap in research limits holistic analysis of parental preconception health on stillbirth odds. Where paternal factors are examined, consistent lack of adjustment in analysis lead to large confounder bias, resulting in poor confidence in findings. The decision to include all cohort studies resulted in high heterogeneity between studies through several analysis. Had we limited analysis to national cohort studies, heterogeneity may have been decreased along with the impact of institutional bias. A further limitation identified concerns longitudinal data use through analysis. The cohorts included data that spanned four decades, and the impact of this is most noticeable in analysis of maternal education where participation rates differ between generations. Generational differences between the cohorts used within each study impact heterogeneity and fail to account for changes in practice within antenatal care. The results may also reflect differences between women delivering in the early 1990s in comparison to women delivering in the 2000s.

All factors identified as contributors to increased stillbirth odds within high-income countries; maternal BMI, parental age, interpregnancy interval planning, maternal chronic hypertension and pre-existing diabetes, have potential for management to ensure that parental health is optimal prior to conception. Ideally, families would choose to engage in preconception care, but in high-income countries rates of unplanned pregnancy are still high. Indeed, 1 in 3 births in Britain is unplanned or ambivalent[291], and nearly a third of pregnancies in Australia[358] . Unplanned pregnancy leaves little room for advanced engagement in pre-conception care, which is why life-long optimal health and emotional wellbeing strategies are needed. Previous studies have emphasised strategies to address the gap that exists in high-income countries to engage adults in health improvement programs, but many focus on communicable disease, smoking and supplementation and not BMI and pregnancy planning[292].

In conclusion, the findings form a much-needed cohesive evidence base and provide focus for high-income countries to engage families in primary prevention strategies to optimise health and wellbeing before pregnancy. Maternal BMI, chronic hypertension and pre-existing diabetes were all shown to double the odds of stillbirth, and a similar increase in stillbirth odds associated with increased parental age highlights the need for nation-wide programs aimed at combining life-long health promotion, with pregnancy planning.

Implications of findings and future research needed

Findings highlight the needs for research to investigate strategies that would ensure the best health and wellbeing prior to the antenatal period. The identification of parental age, maternal BMI, SES, income and parental education indicate that disadvantage and inequity continues to drive the relationship between sociodemographic status and stillbirth odds. Future research should seek to trial strategies that have been seen to work in Canada and Europe to close disparity in stillbirth risk.

Although multiple risk factors were identified assessing maternal health, there is a gap in research examining paternal risk factors associated with stillbirth odds. To enable a holistic analysis of parental risk factors and the association with stillbirth odds, registry datasets should seek to encompass paternal risk where available.

Although pre-conception care has been a focus of recent reviews, the impact of parental age and chronic conditions on stillbirth odds cannot be negated through brief pre-conception care. Lifelong health planning and ongoing primary prevention programs form fundamental groundwork that can address risks of stillbirth such as chronic hypertension, diabetes, and maternal BMI. Research has highlighted potential strategies to improve life-long health, but without uptake from key stakeholder within communities and policy makers, the suggested solutions are useless to the communities that need them most. From here, research should be designed to address the gap in continuity of care, with policymakers, healthcare workers and consumer engagement.

Implications of findings for policy

Findings indicate that there exists opportunity to reduce stillbirth rates within high-income countries by reducing the incidence of obesity, diabetes, hypertension and promotion of health education. The culmination of risk factors prior to pregnancy due to increased parental age, maternal BMI, and pregnancy planning factors (interpregnancy interval alongside parity) highlight opportunity for policy makes and stakeholders to implement primary prevention strategies targeting these identified risks to decrease the burden of stillbirth on communities.

As parental age increases, so do the odds of stillbirth. Policy makers should examine the reasons for later childbearing within high-income countries alongside the burden caused by increased stillbirth rates. Implementation of policy to incentivise younger childbearing, and ongoing health improvement targeting diabetes and hypertension risk factors may result in a decrease of stillbirth rates.

Chapter 4 Modifiable Risk Factors During the Antenatal Period and Stillbirth Risk in High-Income Countries.

Abstract

Background

The antenatal period provides opportunity to assess modifiable risk factors for stillbirth and possibilities for stillbirth prevention. This systematic review and meta-analysis aimed to identify potentially modifiable risk factors contributing to stillbirth risk in high-income countries.

Methods

Cohort and case-control studies published between 1998-2020 examining modifiable antenatal period factors and their association with stillbirth odds were included. Adjusted odds ratios were calculated through meta-analysis for individual risk factors (adequacy of care, distance to care, maternal weight change, assault during pregnancy, illicit drug use, alcohol use, smoking status, vaccination status, parental occupation, maternal sleep characteristics, maternal nutrition, physical activity and place of birth).

Results

Across 140 studies, there were adjusted odds ratios (aOR) for 14 factors that were deemed modifiable during the antenatal period. Stillbirth was associated with inadequate (aOR 3.24 (95% CI 3.12, 3.36)) or no antenatal care (aOR 3.51 (95% CI 1.79, 6.89)), assault during pregnancy (aOR 3.16 (95% CI 2.31, 4.32)) and supine sleep position (aOR 3.00 (95% CI 1.92, 4.70)). Other important associations with aOR ranging from 1.21 to 2.24 were: maternal awakening during the night, excessive daytime naps, <6 hrs sleep, ≥3 cups of caffeine intake/day, maternal smoking, maternal unemployment, paternal exposure to ionising radiation, cannabis use, and alcohol consumption during pregnancy. Antenatal H1N1 vaccination was found to decrease the odds of stillbirth (aOR 0.79 (95% CI 0.68, 0.94))

Discussion and conclusion

This review confirms the importance of addressing modifiable risk factors for stillbirth during the antenatal period such as sleep position, family violence, caffeine intake, smoking status, and drug and alcohol use. These findings bring a new focus on the need to address and provide support for families with modifiable risk factors during the antenatal period in high-income country settings.

Introduction

Globally, there is increasing recognition of the associated hidden burden of pregnancy loss[5, 6, 18, 21]. In 2019 the average stillbirth rate per 1000 births ≥28 weeks gestational age (GA) within high-income countries was 3.00[1]. In addition to this, recent analysis of national datasets estimate that the burden of early stillbirth is 1.5 times that of late stillbirth in high-income countries[1]. Stillbirth rates across high-income countries from 2000-2019 have decreased by 24.4%, and although promising, this decrease is largely seen for the first half of this period (2000-2010), with progress slowing between 2010 and 2019[1]. Compared with infant mortality rate reduction spanning the same period which, progress in stillbirth prevention is poor. The resounding message through recent literature concerns the opportunities to prevent stillbirth, and the need for increasing awareness and evidence-based knowledge of modifiable risk factors.

Modifiable risk factors through the antenatal period are ideally identified within the first trimester, with behaviour/treatment modification to prevent poor pregnancy outcomes. Although two thirds of respondents surveyed within a high-income population indicated that they know someone who has had a stillborn child, between 50-63% of those surveyed were unaware that stillbirth is preventable through addressing modifiable risk[5, 359]. Fatalistic comments such as "it was nature's way"[359] and "it's natural selection"[359] fuel this notion of inevitability. In order to address this deficit in knowledge we need to collate international research findings and provide an evidence base for awareness campaigns that identify all of the modifiable risk factors associated with stillbirth. This will enable antenatal carers to offer sounds advice based on recent and relevant research evidence.

Aims

This review aims to identify modifiable risk factors for stillbirth that are relevant to the antenatal period within high-income country settings. Where possible, risk factor analysis will be stratified by GA.

Methods

Literature Search Strategy

Systematic searches of the following major electronic databases were conducted: PubMed, MEDLINE, Ovid, the Cochrane Library and CINAHL. Literature searches were conducted for the period 1998-2017, with a language restriction to the English literature only. Top-up searches were conducted in July 2020 to supplement the original search with recent literature using the same inclusion/exclusion criteria. Search strategies are included in Appendix B.

Inclusion/exclusion criteria for studies

Studies included in this review adhered to the inclusion/exclusion criteria stipulated in Chapter 2 of this work. Case-control and cohort studies including aOR results for risk factor associations with fetal loss at ≥20 weeks GA or ≥400g birthweight were included, or where fetal loss was defined as 'stillbirth'.

Extraction and assessment of the studies

To minimise bias, each study was assessed independently by at least two researchers. Where disagreement was not resolved by discussion of the researchers, external review from an expert researcher was sought to arbitrate and reach consensus. All relevant studies selected for this review were assessed independently by two reviewers for their individual methodological quality. This was done by using a quality and bias assessment scale specifically designed by the RTI-University of North Carolina Evidence Based Practice Centre; the RTI item bank (RTI-IB) [85]. The scale includes 29 questions with multiple choice answers and additional space for free-text. The item-bank focuses on believability, incorporating risk and precision of the results. Overall quality and bias assessment was assigned qualitatively as: High, Medium or Low based on the RTI-IB criteria. Quality and bias assessment of studies are included in Appendix D.

Adjusted results were extracted per study and combined through meta-analysis where possible. Random-effects meta-analysis was performed to construct forest plots to account for probable differences in exposure effect between studies as well as variability between

cohorts used. Complete analyses were performed using STATA IC v16.1, by first author (A Bowman) and coding framework was checked by SAHMRI Women and Kids Theme Lead Biostatistician (Dr T Sullivan).

Results

Search results

Of the studies screened, 140 studies reported aORs of behaviour modification risk factors in the antenatal period[32, 51, 52, 55, 56, 58, 60, 67, 68, 73, 86-97, 99, 100, 102, 105, 108, 113, 118, 122, 124-127, 129, 130, 132, 150, 154, 156-158, 165, 167, 168, 175, 176, 178-182, 185, 188, 192, 195, 200, 202, 207, 208, 231, 232, 234-237, 240, 242, 257, 258, 262, 267-274, 276, 305, 306, 316, 320, 324, 325, 327, 335, 345, 360-431]. Modifiable factors associated with the antenatal period identified included: adequacy of antenatal care, distance to antenatal care, maternal weight change, assault during pregnancy, significant life events during pregnancy, illicit drug use, alcohol consumption, smoking status, antenatal vaccination status, maternal and paternal occupation, maternal sleep characteristics and position, maternal nutrition, physical activity and place of birth.

Scope, characteristics and quality of studies

The 140 studies included populations from 17 high-income countries including Australia, Canada, Denmark, Chile, the UK, Finland, France, Germany, Italy, Japan, New Zealand, Norway, Sweden, the Netherlands, Uruguay, and the USA. One of the studies used a web-based questionnaire of populations spanning multiple countries[432]. Studies varied in their design, with 20 case-control studies, 3 cross-sectional studies and 117 cohort studies included. Of the included studies, using the RTI-tool, 58 were deemed to be at a low risk of bias[52, 60, 73, 86, 87, 91, 94, 96, 97, 108, 113, 118, 125, 127, 132, 150, 154, 156, 158, 165, 167, 175, 178, 181, 182, 185, 207, 232, 235, 240, 267, 268, 270-272, 274, 276, 360, 366, 373, 374, 377, 384-387, 393, 399, 400, 402, 411, 412, 415, 417, 420, 431, 433], 56 at an unclear risk of bias[32, 56, 58, 67, 68, 88, 90, 92, 93, 105, 113, 122, 124, 126, 130, 157, 176, 179, 180, 195, 200, 202, 234, 237, 257, 258, 262, 269, 273, 305, 306, 324, 327, 335, 345, 361-364, 367, 369, 371, 372, 378, 379, 381, 382, 394, 396, 398, 404, 408, 413, 414, 421, 422, 424, 426, 429, 430, 434, 435], and 23 at a high risk of bias[51, 86, 95, 129, 168, 188, 208, 242, 320, 365, 370, 383, 388-390, 392, 403, 416, 419, 436-438]. Details of individual bias, as well as the reasons for high risk of bias assessments, are included per analysis (Appendix D). Study results were extracted per factor, and results were categorically reviewed through meta-analysis.

Meta-analysis of findings

Antenatal care adequacy

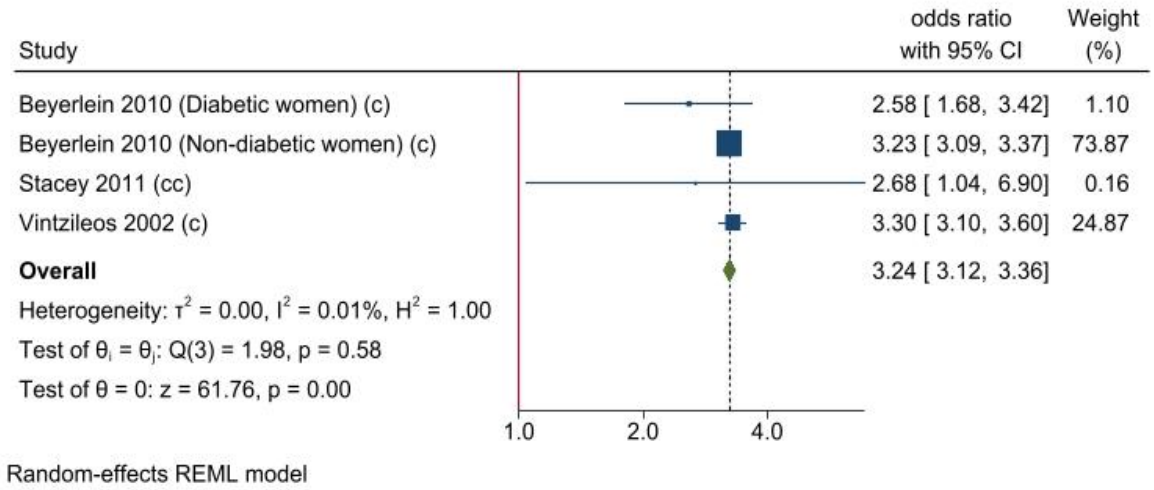
Fourteen studies reported the association between the adequacy of antenatal care and odds of stillbirth in high-income countries[86-88, 108, 122, 150, 154, 157, 167, 188, 257, 276, 324, 360, 362, 363]. Eight studies demonstrated a low risk of bias[86, 87, 108, 150, 154, 167, 276, 360] five studies were assessed as having an unclear risk of bias[88, 93, 122, 157, 257, 324, 362, 363] and one study was assessed as having a high risk of bias due to the collection method of exposure data combined with unclear data linkage methodology[188]. Populations included in the studies were collected from seven high-income countries, Australia, Canada, Germany, Netherlands, New Zealand, Uruguay and the USA. Antenatal care adequacy was assessed by all studies according to the number of visits attended during pregnancy compared with national recommendations during the study period, as well as the timing of antenatal care initiation (table 4-1).

Table 4-1 Summary of antenatal care adequacy characteristics per study

Study	Country of study population	Initiation of antenatal care	Number of antenatal care visits required by 40 weeks GA	Adequacy of antenatal care; Index used.
Beyerlein 2010[190]	Germany	Not described	10	German maternity guidelines of care[439] (established 1965)
Faiz 2012[122], Lorch 2012[150], Allen 2018[360].	USA	<12 wks GA	Not described	None
Heaman 2019[87]	Canada	<12 wks GA	13	GRINDEX-R index [440]
Malabarey 2012[154], Partridge 2012[88]	USA	<20 wks GA	11	APNCU index [441]
Matijasevich 2006[257]	Uruguay	Not described	≥1	None
Mohsin 2006[157]	Australia	<20 wks GA	≥1	None
Ravelli 2011[251]	The Netherlands	<12 wks GA	Not described	None
Reime 2009[86]	Germany	Not described	14	Not described
Stacey 2011[179, 362, 442]	New Zealand	<12 wks GA	10 (nulliparous) 7 (multiparous)	Australian pregnancy care guidelines
Vintzileos 2002[276]	USA	Not described	≥1	None
Wolfe 2005[188]	USA	Not described	Not described	None

Inadequate antenatal care

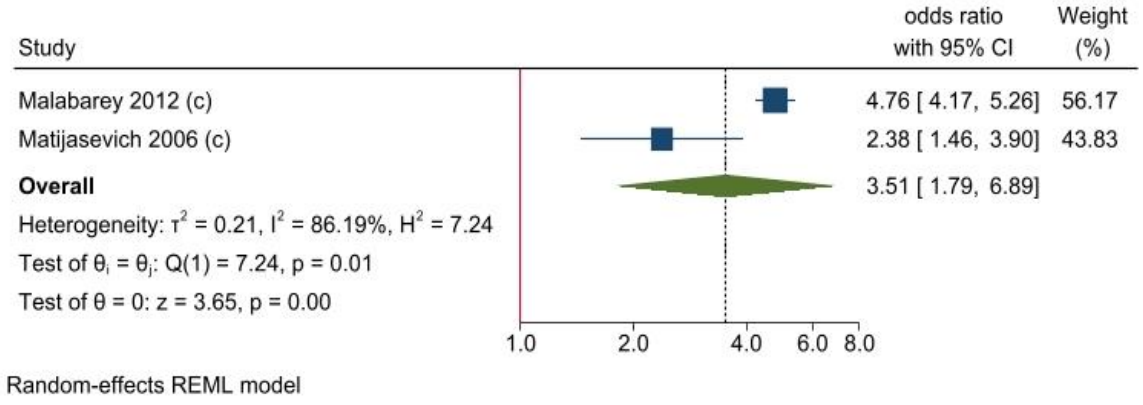
Five studies included in this review examined inadequate antenatal care in comparison to adequate antenatal care and its association with stillbirth odds[86, 87, 108, 276, 324, 362, 363, 442]. Inadequate antenatal care was defined as late initiation of care, combined with an inadequate number of antenatal care visits compared with national recommendations. Two studies reported use of the same dataset, therefore in an attempt to avoid double counting births, the smaller of the two studies was excluded from analysis[86] and the larger study retained[108]. Final meta-analysis of studies exhibited high homogeneity (I^2= 0.0%), and final odds demonstrated more than a threefold increase in stillbirth odds with inadequate versus adequate antenatal care (aOR 3.24 (95% CI 3.12, 3.36) – fig 4-1).



(c) = cohort study
(cc) = case-control study
Figure 4-1 Meta-analysis demonstrating the association between inadequate antenatal care and stillbirth odds compared with adequate antenatal care

No antenatal care

Five studies reported aORs of the association between no antenatal care versus adequate antenatal care and stillbirth[122, 154, 188, 257, 276]. Four studies reported use of the same dataset for analysis, therefore the smaller studies[122, 188, 276] were excluded to avoid double-counting of births. Two studies remained for analysis using populations from Uruguay and the USA. Differences between these populations and the type of antenatal care models were thought to account for the high heterogeneity of results (I^2 = 86.2%). The final meta-analysis demonstrated more than a three-fold increase in stillbirth odds with no antenatal care versus adequate antenatal care in pregnancy (aOR 3.51 (95% CI 1.79, 6.89) – fig 4-2).

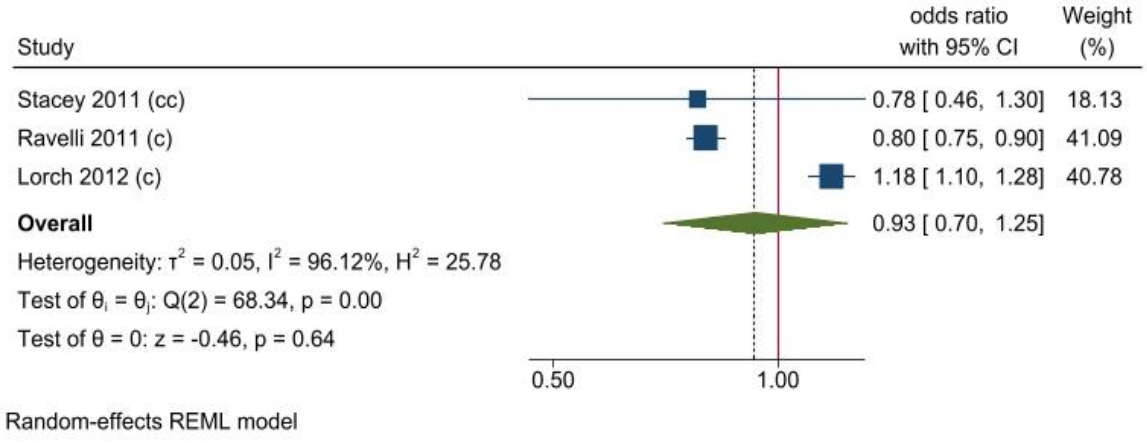


(c) = cohort study
(cc) = case-control study
Figure 4-2 Meta-analysis demonstrating the association between no antenatal care and stillbirth odds compared with adequate antenatal care during pregnancy

Timing of antenatal care initiation

Second trimester initiation

Three studies examined the impact of starting antenatal care visits during the second trimester of pregnancy compared with the first trimester, in populations sourced from three high-income countries; the Netherlands[167], New Zealand[324, 362, 363] and the USA[150]. All three studies were included for meta-analysis and demonstrated high heterogeneity (I^2 = 97.1%). Although Lorch et al[150] was identified as contributing significantly to heterogeneity, no reason could be identified for the differences between study populations. Lorch et al's study was reviewed for bias using the RTI tool and was determined to have a low risk of bias, and was thus not excluded from the analysis. Final meta-analysis demonstrated that no association between second trimester antenatal care initiation and stillbirth odds (aOR 0.93 (95% CI 0.70, 1.25) – fig 4-3).



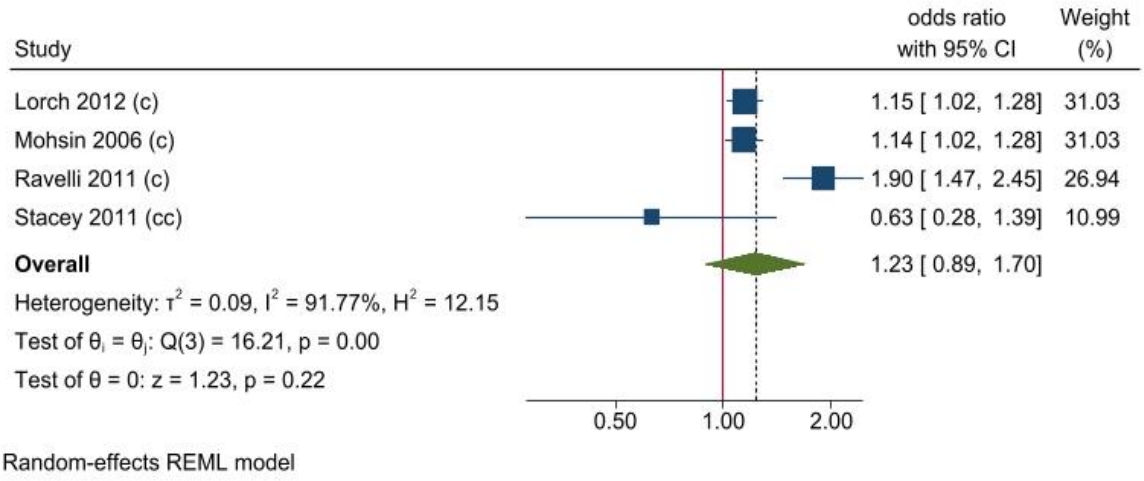
(c) = cohort study

(cc) = case-control study

Figure 4-3 Meta-analysis demonstrating the association between antenatal care initiated in the second trimester of pregnancy and stillbirth odds compared with care initiated in the first trimester of pregnancy

Antenatal care initiation >20 weeks GA

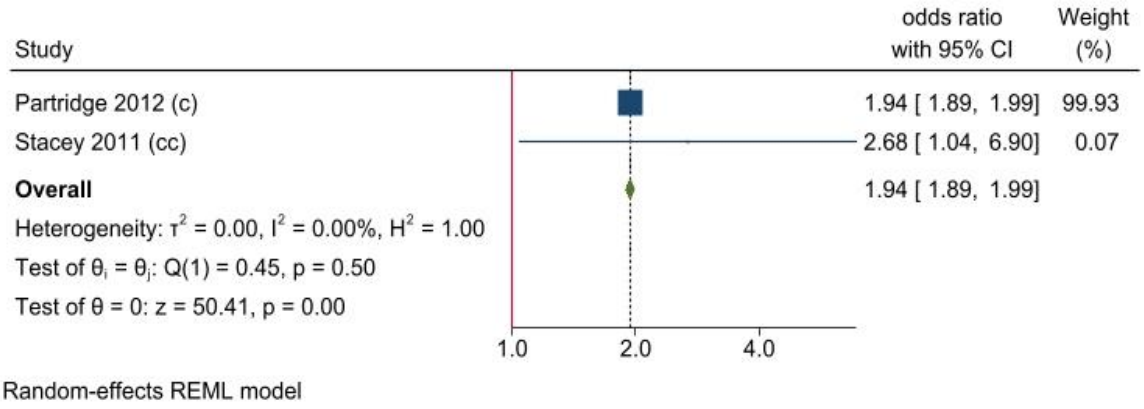
Five studies examined the impact of initiating antenatal care visits after 20 weeks GA on the odds of stillbirth[150, 157, 167, 179, 324, 360, 362, 363]. Two studies reported use of the same dataset[150, 360]; therefore to avoid double counting of births, the smaller of the studies was excluded from meta-analysis[360]. Analysis of the four remaining studies demonstrated considerable heterogeneity (I^2=91.77%) and sensitivity analysis could not identify any one study contributing greatly to this. Meta-analysis demonstrated a marginal association between initiation of antenatal care after 20 weeks GA and stillbirth odds but failed to reach statistical significance (aOR 1.23 (95% CI 0.89, 1.70) – fig 4-4).



(c) = cohort study
(cc) = case-control study
Figure 4-4 Meta-analysis demonstrating the association between antenatal care initiated after 20 weeks GA and stillbirth odds compared with women whose antenatal care was initiated prior to 20 weeks GA.

Attending ≤50% recommended antenatal care visits.

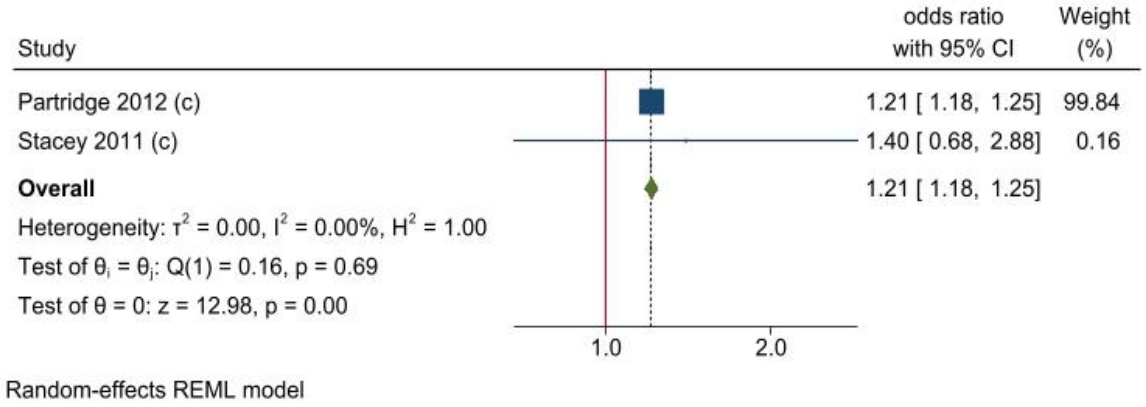
Two studies examined antenatal care adequacy by comparing the number of visits attended with the national guidelines and grouped women who attended 50% of appointments or less[88, 324, 325, 362, 363]. The odds of stillbirth for women attending ≤50% of recommended visits were compared with women who attended between 80-109% of nationally recommended antenatal appointments. Final meta-analysis demonstrated low heterogeneity (0.0%) and results showed nearly double the odds of stillbirth for women who attended 50% or less of the recommended antenatal care visits (aOR 1.94 (95% CI 1.89, 1.99) – fig 4-5).



(c) = cohort study
(cc) = case-control study
Figure 4-5 Meta-analysis demonstrating the association between attendance of ≤50% of recommended antenatal care appointments compared with 50-109% of recommended antenatal care appointments.

Attending 50-99% of recommended antenatal care visits

Two studies examined the impact of women attending 50-99% of their recommended antenatal care visits during pregnancy compared with ≥100% attendance of antenatal care visits[88, 93, 324, 362, 363]. High homogeneity was demonstrated between the studies through meta-analysis (I^2= 0.0%). Results of the meta-analysis demonstrate an increased odds of stillbirth associated with 50-99% antenatal care in comparison to ≥100% attendance of antenatal care visits (aOR 1.21 (95% CI 1.18, 1.25) – fig 4-6).



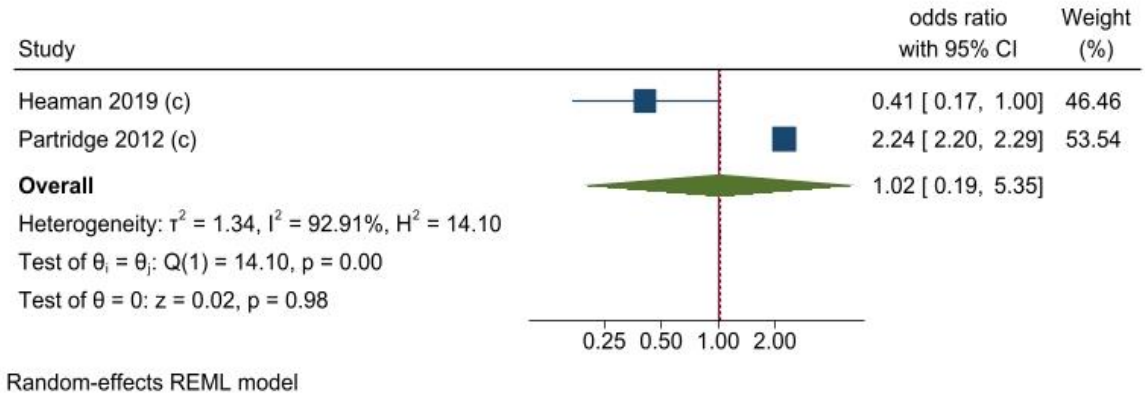
(c) = cohort study

(cc) = case-control study

Figure 4-6 Meta-analysis demonstrating the association between women attending 50-99% of recommended antenatal appointment and stillbirth odds compared with women attending ≥100% attendance

High levels of antenatal care

Two studies examined the impact of high levels of antenatal care and its association with stillbirth odds compared with adequate antenatal care. The definition of high levels of antenatal care differed per study[87, 88]; Partridge et al[88] defined intensive antenatal care as women who attended +1 standard deviation above the mean number of antenatal appointments. Heaman et al[87] defined intensive antenatal care as women who attended 110% or more visits during their pregnancy. Meta-analysis demonstrated high heterogeneity (I^2 = 92.9%) and the results indicate no association between high levels of antenatal care appointments and stillbirth odds (aOR 1.02 (95% CI 0.19, 5.35) – fig 4-7). A large confidence interval indicates that the studies used in meta-analysis were possibly underpowered and that further research is required to confirm these findings.



(c) = cohort study
(cc) = case-control study
Figure 4-7 Meta-analysis demonstrating the association between high levels of antenatal care and stillbirth odds compared with women with adequate antenatal care.

Distance to care

Two studies reported the association between distance of travel to antenatal care service providers, and the odds of stillbirth[383, 384]. Paranjothy et al[384] measured the distance between the maternal residence to the hospital by 15-minute increments of travel time. Through analysis, distance was stratified between the actual hospital delivering care, the nearest hospital offering care, and parity. This study was unable to demonstrate an association between maternal distance to hospital and stillbirth odds, with the exception of births >37 weeks GA, and time to travel to the hospital. Every 15-minute increase in travel time to the actual birth hospital for births over 37 weeks GA was associated with a 36% increase in odds of stillbirth (aOR 1.36 (95% CI 1.17, 1.59))[384]. Pilkington et al[383] demonstrated increased odds of stillbirth associated with 45+ km of travel to the birthing hospital (aOR 1.08). The odds increased marginally when analysis was restricted to unemployed mothers (aOR 1.15), single mothers (aOR 1.08) and foreign born residents (aOR 1.17)[383].

Maternal weight change

Seven studies examined the impact of weight gain or loss on pregnancy outcomes[118, 207, 208, 232, 234, 235, 237]. Four of the studies reported aORs of the association between inter-pregnancy weight change and stillbirth[208, 232, 234, 235], and the remaining three studies examined gestational weight change[118, 207, 237]. One study examined gestational weight loss and its impact on odds of stillbirth, results were further stratified by gestation at birth[237]. The remaining studies examining gestational weight gain used measured gain in kgs or pounds.

Gestational weight change

The three studies that examined gestational weight change during the antenatal period used different methodologies rendering results incompatible with meta-analysis. Yao et al stratified analysis by initial maternal body mass index (BMI), and GA at birth[237]. Johansson et al[207] stratified analysis by initial maternal BMI only, and Dongarwar et al[118] compared women collectively by weight gain over the entire pregnancy regardless of BMI status at conception. Odds of stillbirth associated with weight loss were reported in one included study, and due to stratification by initial maternal BMI and gestational age at birth, the

results were underpowered. A summary of results is shown in table 4-2 followed by a descriptive summary.

Table 4-2 Summary of study results for two studies examining maternal weight change stratified by initial maternal BMI, Yao et al (236) * and Johansson et al[206]**

Body mass index (BMI) classification at the start of pregnancy	**Weight loss during the antenatal period (*Study name/gestational age* (aOR (95% CI)))**	**Inadequate weight gain during the antenatal period (*Study name/gestational age* (aOR (95% CI)))**	**Excessive weight gain during the antenatal period (*Study name/gestational age* (aOR (95% CI)))**
Underweight women	*Yao et al (29-33 wks GA)* – 1.4 (0.66, 2.98)	*Yao et al (24-28 wks GA)* – 1.49 (0.67, 3.31) *Yao et al (29-33 wks GA)* – 1.40 (0.66, 2.98) *Yao et al (34-36 wks GA)* – 1.38 (0.55, 3.45) *Yao et al (37+ wks GA)* – 0.64 (0.27, 1.51)	*Yao et al (24-28 wks GA)* – 1.18 (0.50, 2.76) *Yao et al (29-33 wks GA)* – 1.66 (0.77, 3.56) *Yao et al (34-36 wks GA)* – 1.41 (0.55, 3.60) *Yao et al (37+ wks GA)* – 0.57 (0.23, 1.39)
Healthy weight women	*Yao et al (24-28 wks GA)* - **2.45 (1.52, 3.95)** *Yao et al (29-33 wks GA)* –***5.00 (2.66, 9.37)*** *Yao et al (34-36 wks GA)* – ***9.67 (5.00, 18.67)*** *Yao et al (37+ wks GA)* - **18.85 (8.25, 43.09)** *Johansson et al* – 0.58 (0.13, 2.63)	*Yao et al (24-28 wks GA)* **– *1.41 (1.11, 1.79)*** *Yao et al (29-33kws GA)* – ***1.72 (1.31, 2.26)*** *Yao et al (34-36 wks GA)* – **1.52 (1.12, 2.06)** *Yao et al (37+wks GA)* - **1.81 (1.37, 2.40)** *Johansson et al* – 0.85 (0.48, 1.49)	*Yao et al (24-28 wks GA)* – **0.57 (0.44, 0.72)** *Yao et al (29-33 wks GA)* – 0.88 (0.67, 1.14) *Yao et al (34-36 wks GA)* – 0.85 (0.65, 1.11) *Yao et al (37+ wks GA)* – ***1.48 (1.16, 1.88)*** *Johansson et al* – 1.63 (0.37, 1.77)
Overweight women	*Yao et al (24-28 wks GA)* – **2.68 (1.75, 4.11)** *Yao et al (29-33 wks GA)* – **3.55 (2.15, 5.87)** *Yao et al (34-36 wks GA)* – **6.82 (3.69, 12.60)** *Yao et al (37+ wks GA)* –**5.87 (2.99, 11.55)** *Johansson et al* – 1.97 (0.69, 5.62)	*Yao et al (24-28 wks GA)* – **2.47 (0.78, 3.42)** *Yao et al (29-33 wks GA)* – **2.14 (1.54, 2.98)** *Yao et al (34-36 wks GA)* – **2.78 (1.80, 4.29)** *Yao et al (37+ wks GA)* –**2.74 (1.94, 3.88)** *Johansson et al* – 0.82 (0.35, 1.94)	*Yao et al (24-28 wks GA)* – 0.77 (0.57, 1.04) *Yao et al (29-33 wks GA)* – **0.62 (0.45, 0.85)** *Yao et al (34-36 wks GA)* – 0.93 (0.63, 1.38) *Yao et al (37+ wks GA)* –0.88 (0.64, 1.20) *Johansson et al* – 0.51 (0.05, 4.70)
Obese women	*Yao et al (24-28 wks GA)* – 1.18 (0.86, 1.64) *Yao et al (29-33 wks GA)* – **2.15 (1.47, 3.13)** *Yao et al (34-36 wks GA)* – **1.84 (1.09, 3.11)** *Yao et al (37+ wks GA)* –**3.44 (2.34, 5.05)**	*Yao et al (24-28 wks GA)* – **1.52 (1.16, 1.99)** *Yao et al (29-33 wks GA)* – **2.04 (1.49, 2.79)** *Yao et al (34-36 wks GA)* – **2.58 (1.76, 3.79)** *Yao et al (37+ wks GA)* –**2.30 (1.71, 3.11)** *Johansson et al* – 0.71 (0.43, 2.90)	*Yao et al (24-28 wks GA)* – 1.06 (0.84, 1.34) *Yao et al (29-33 wks GA)* – 1.42 **(1.09, 1.85)** *Yao et al (34-36 wks GA)* – **1.73 (1.23, 2.43)** *Yao et al (37+ wks GA)* –**2.00 (1.55, 2.58)** *Johansson et al* – 0.28 (0.03, 2.59)

Morbidly obese women	*Yao et al (24-28 wks GA)* – **0.56 (0.34, 0.95)** *Yao et al (29-33 wks GA)* – 1.14 (0.61, 2.10) *Yao et al (34-36 wks GA)* – 0.98 (0.41, 2.33) *Yao et al (37+ wks GA)* – 0.88 (0.44, 1.76)	*Yao et al (24-28 wks GA)* – 1.04 (0.68, 1.57) *Yao et al (29-3 wks GA)* – 1.20 (0.72, 1.98) *Yao et al (34-36 wks GA)* – 1.58 (0.81, 3.07) *Yao et al (37+ wks GA)* – 1.26 (0.77, 2.04)	*Yao et al (24-28 wks GA)* – 1.14 (0.81, 1.59) *Yao et al (29-33 wks GA)* – **1.79 (1.21, 2.65)** *Yao et al (34-36 wks GA)* – **3.05 (1.76, 5.26)** *Yao et al (37+ wks GA)* – **3.16 (2.17, 4.62)**

**Yao et al[237]: confounders included in adjustment - maternal age, race, smoking, infant sex, hypertensive disorders.*

***Johansson et al[207]: confounders included in adjustment - maternal age, height, BMI, smoking, living with partner, pre-pregnancy hypertension and diabetes*.

Underweight women at the start of pregnancy

One study examined weight change over the antenatal period in underweight women[237], with neither excessive nor inadequate weight gain associated with an increase in stillbirth odds during any stage of gestation (≥20 weeks GA).

Healthy weight women at the start of pregnancy

Healthy weight women who lost weight during pregnancy were shown by Yao et al to have an increased odds of stillbirth from 24-28 weeks GA (aOR 2.45 (1.52, 3.95)) to term (≥37 weeks GA) (aOR 18.85 (8.25, 43.09))[237] compared with healthy weight women who gained the recommended amount of weight during pregnancy. This is at odds with findings of Johansson et al who found no association with stillbirth odds following weight loss or inadequate weight gain[207] compared with recommended weight gain.

Inadequate weight gain, for women with a healthy starting weight, was explored by both studies but only Yao et al demonstrated an association between inadequate weight gain and stillbirth odds. This was highest for term births (≥37 weeks GA), aOR 1.81 (1.37, 2.40), and slightly less association for second trimester stillbirth, aOR 1.41 (1.11, 1.79) and preterm births, aOR 1.72 (1.31, 2.26).

Both studies found that excessive weight gain was not associated with an increase in stillbirth odds, but due to large confidence intervals, and a small sample size in both the reference and exposure groups, these results need to be validated through further research.

Overweight women at the start of pregnancy

For all gestations, second trimester (24-28 weeks GA), early preterm (29-33 weeks GA), preterm (34-36 weeks GA) and term (≥37 weeks GA), Yao et al demonstrated an increased odds of stillbirth with weight loss. Although Johansson et al replicated these findings, results were non-significant probably owing to a small sample size and underpowered analysis. Women who were overweight at the start of pregnancy, and who gained inadequate weight (<1pound per week) were found to have an increased odds of stillbirth for second trimester (24-28 weeks GA) aOR 2.47 (0.78, 3.42), early preterm (29-33 weeks GA) aOR 2.14 (1.54, 2.98), preterm (34-36 weeks GA) aOR 2.78 (1.80, 4.29) and term (≥37 weeks GA) aOR 2.74 (1.94, 3.88)[237]. Johansson et al did not replicate these findings across all gestations and demonstrated no clear association between inadequate weight gain and stillbirth odds.

Neither study demonstrated an association between excessive weight gain for women who were initially overweight and stillbirth odds.

Obese women at the start of pregnancy

Yao et al investigated the impact of maternal weight loss during the antenatal period and stillbirth odds in obese women[237]. Results indicated an increasing trend in the association with stillbirth odds as the pregnancy progresses towards term. Johansson et al's sample size prevented them from investigating total pregnancy weight gain, but in examining the impact of weight loss between the start of the antenatal period and 22 weeks GA, no association was demonstrated with stillbirth odds[207].

Obese women who demonstrated inadequate weight gain during pregnancy (<1 pound/week) were shown by Yao et al to show incremental increases in the association with stillbirth odds as the pregnancy progressed towards term[237]. Johansson et al did not replicate these results, as sample sizes rendered the analysis underpowered. Findings are inconclusive.

Both Yao et al and Johansson et al examined the impact of excessive weight gain on odds of stillbirth in obese women, but due to very small sample sizes used by Johansson et al, the results of analysis are inconclusive[207, 237]. Yao et al demonstrated increases in stillbirth odds from 29 weeks GA onwards due to >1.3 pounds gain per week during pregnancy [237].

Morbidly obese women at the start of pregnancy

One study examined the impact of weight change during pregnancy on stillbirth odds within a cohort of morbidly obese women. Weight loss was shown to be protective for stillbirth odds for women who are morbidly obese at the start of pregnancy. Inadequate weight gain was shown to have no association with stillbirth odds for morbidly obese women for all gestational ages of stillbirth.

Excessive weight gain was shown by Yao et al to increase the odds of stillbirth incrementally as births approached term[237]. Births occurring between 29- and 33-weeks GA demonstrated almost double the odds of stillbirth in morbidly obese women with excessive weight gain (aOR 1.79 (1.21, 2.65)).

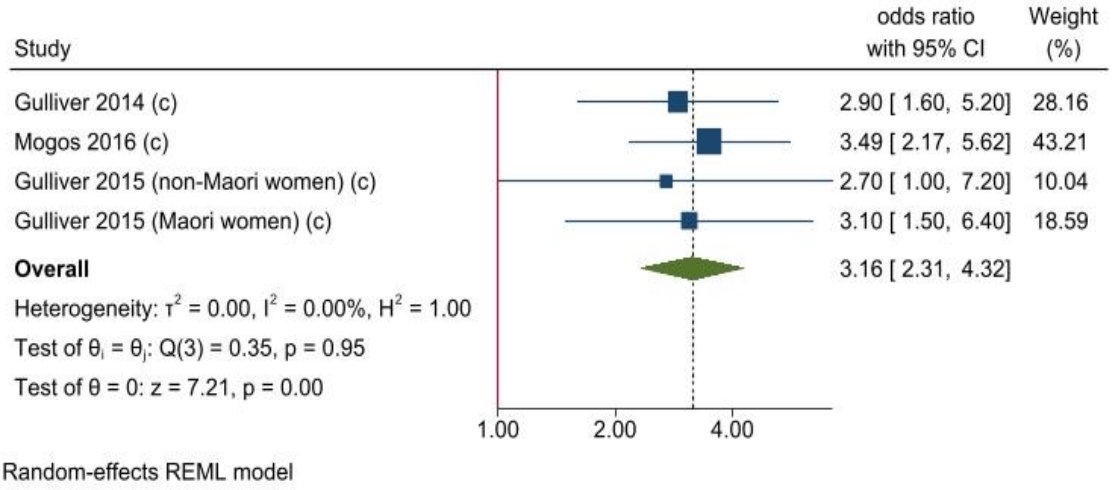
In summary, weight loss was only protective for early stillbirth in women whose starting BMI was classified as morbidly obese. Dongarwar et al[118] found that within an American cohort of women not stratified by initial BMI, weight loss and inadequate weight gain adversely affected stillbirth odds (aOR 4.15 (4.12, 4.18)). This finding was reinforced by Yao et al's findings that for women with a BMI under 40, weight loss increased the odds of stillbirth[237]. Johansson failed to replicate these results, but small cohort size leaves large margins of uncertainty in the results of this study[207]. Dongarwar et al examined the impact of <20 pounds gained per pregnancy, 31-40 pounds gained per pregnancy and also >40 pounds gained per pregnancy. In line with results from Yao, 31-40 pounds gained per pregnancy (1 pound/week) was protectively associated with stillbirth odds when examined through Dongarwar's cohort (aOR 0.79 (0.78, 0.81)); however Dongarwar also demonstrated a protective association between excessive weight gain (>40 pounds per pregnancy) and stillbirth odds (aOR 0.82 (0.80, 0.84)) which was only replicated within Yao et al's subgroup of underweight women giving birth at term.

Assault during pregnancy; and Significant Life Events (SLEs).

Five studies examined the impact of family abuse or trauma within cohorts from three high-income countries; Australia, New Zealand, and the USA[67, 94-97]. Four of the studies were retrospective cohorts[67, 94-96], and one; a case-control study[97]. All studies used hospital admission records of assault as exposure measures. All studies were assessed by two reviewers using the RTI tool of assessment for bias and quality, three were assessed as having a low risk of bias[94, 96, 97], one demonstrated an unclear risk of bias[67], and the last had a high risk of bias due to poor data collection of exposures[95].

Assault during pregnancy

Three studies examined physical assault during pregnancy, and its association with odds of stillbirth compared with pregnancies without maternal exposure to physical assault[94-96]. All three studies collected data from medical records relating to abuse during pregnancy and relied on admission coding of physical assault during pregnancy. The final meta-analysis included two studies and demonstrated high homogeneity ($I^2 = 0\%$)[95, 96].



(c) = cohort study

(cc) = case-control study

Figure 4-8 Meta-analysis demonstrating the odds of stillbirth for women who have an assault recorded during pregnancy compared with women who have no assault reporting during pregnancy.

Results of meta-analysis demonstrated more than 3-fold increased odds of stillbirth associated with hospital admission for assault during pregnancy (aOR 3.16 (96% CI 2.31, 4.32) – fig 4-8) compared with women with no evidence of assault during pregnancy. Gulliver et al[95] investigated the association between assaults related to birth within the same admission, compared with assaults not associated with birth within the same admission (ongoing pregnancy) and found no increase in odds of stillbirth (aOR 1.02 (0.56, 1.84)). This study further demonstrated that women who were admitted for assault and gave birth during the same admission compared with women with no antenatal admission related to assault had an eight fold increase in odds of stillbirth (aOR 8.13 (95% CI 4.62, 14.33))[94]. The results demonstrated large confidence intervals due to small sample numbers, however still indicate an alarming increase in stillbirth risk associated with physical assault.

Significant Life Events (SLEs)

Two studies examined the impact of significant life events experienced and stillbirth odds[67, 97]. SLEs were defined as suboptimal social support, financial issues or housing problems, notable relationship issues, being isolated without any support, major financial and housing issues, and violence, emotional life events, and traumatic life events. Combinations of all SLEs and their impact collectively on stillbirth was investigated by de Graaf et al[67] in an Australian low socioeconomic status (SES) population, and was found to be associated with a three-fold increase in the odds of stillbirth (aOR 3.08 (95%

CI 1.27, 7.47)). Hogue et al stratified results by type of life event experienced, as well as the number of life events experienced within the last 12 months prior to birth. The highest odds of stillbirth were demonstrated for women with experience of a financial life event (such as loss of job) within the 12 months prior to pregnancy. Analysis of the cumulative effect of SLEs experienced upon stillbirth found a direct relationship between the number of events, with four SLE experienced leading to an almost doubling in the odds of stillbirth (aOR 1.91 (95% CI 1.20, 3.04))[97] compared with no SLEs.

Illicit drug use

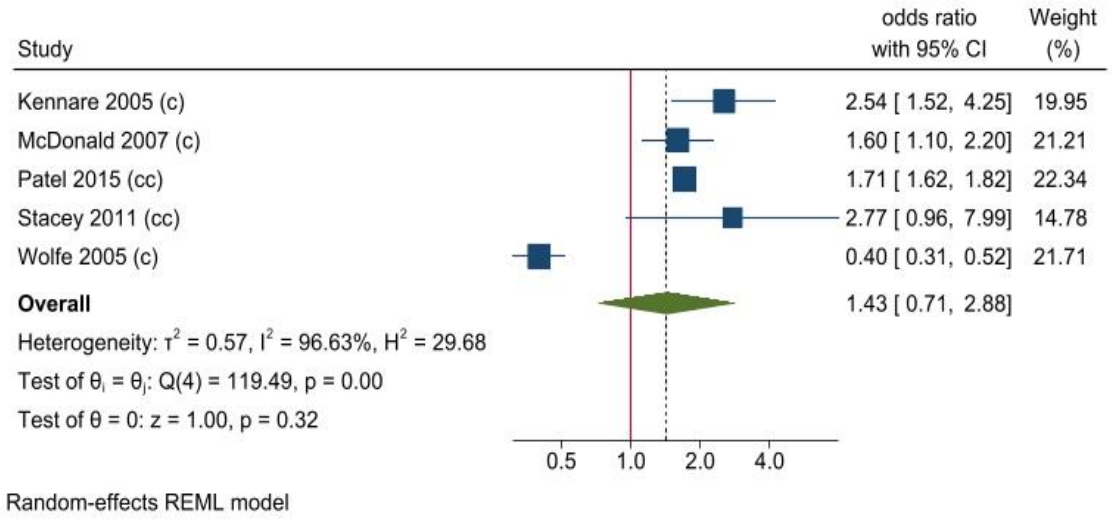
Eleven studies examined the odds of stillbirth associated with maternal illicit drug use compared with no maternal illicit drug use[127, 188, 320, 363, 385-391]. The studies included cohorts from four high-income countries and investigated several classes of maternal drug use compared with mothers with no illicit drug use. Details of exposure categories are provided in table 4-3 'Any illicit drug use' compared with no drug use was also investigated as a risk factor group, encompassing any illicit drug use, by six studies[127, 188, 320, 363, 390, 391]. One additional study examined opioid use disorder during pregnancy[385]. Risk of bias assessment suggested that four studies were assessed as having a low risk of bias[127, 385-387], three as having an unclear risk of bias[363, 391, 434] and five with a high risk of bias[188, 320, 388-390]. High risk of bias was reported as predominantly due to poor exposure data collection. A high risk of detection bias was identified for all studies due to lack of data regarding drug use timing, quality and method of consumption. One included cohort study had a very small sample size (n=6,468), and analysis was deemed underpowered through review[389].

Table 4-3 Exposure details of studies examining maternal drug use

Study ID	Drugs included in exposure group(s)	Alcohol exposure included (Y/N)
Alemu 2020[385]	Opioid use	Yes separate
Corsi 2019[388]	Cannabis, opioid, Other drugs(cocaine, methamphetamines)	Yes separate
Kennare 2005[391]	Substance use (alcohol, marijuana, amphetamines, heroin, methadone, narcotics/opiates, LSD, polydrug use)	Yes composite
Luke 2019[387]	Cannabis use	No
McDonald 2007[390]	Non-tobacco drug dependence (Illicit, components not specified)	Not described
Patel 2015[320]	Drug use (illicit, components not specified)	Yes separate
Petrangelo 2019[386]	Cannabis use	No
Stacey 2011[179, 362, 442]	Recreational drugs (predominantly marijuana use)	No
The Stillbirth Collaborative Research Network writing group 2011[127]	Lifetime illicit drug use	Yes separate
Warshak 2015[389]	Marijuana	No
Wolfe 2005[188]	Amphetamine, cocaine, polydrug (both), and others	Yes composite

Any illicit drug use

Six included studies examined the association between illicit drug use compared with no illicit drug use and stillbirth odds[127, 188, 320, 363, 390, 391]. Two of the studies grouped exposures in a composite measure including maternal alcohol use, and the remaining four restricted exposure to poly-drug use. Three of the included studies utilised the same dataset, so to avoid double counting of births, the smaller studies were excluded[127], and the larger studies were retained for meta-analysis[188, 320].



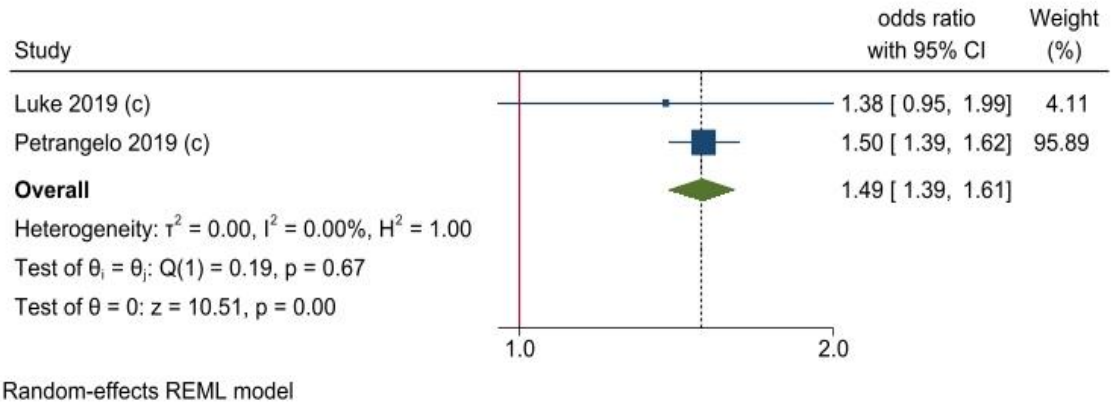
(c) = cohort study design
(cc) = case-control study design

Figure 4-9 Meta-analysis demonstrating the association between illicit drug use and stillbirth odds compared with no illicit drug use

The resultant meta-analysis demonstrates a non-significant increased association between maternal drug use and stillbirth odds compared with no maternal drug use (aOR 1.43 (95% CI 0.71, 2.88) – fig 4-9). Two studies were limited by cohort size[363, 391]. Two studies within the meta-analysis did not report case numbers for the exposure groups[188, 390]. Considerable heterogeneity is shown between included studies (I^2 = 96.63%). This is expected due to the number of drugs included between study analysis, as well as poor drug-exposure measurement methods, and lack of quantity or changes in exposure causing large differences in the populations included in each study exposure group. One of the included studies demonstrated a protective relationship between drug use and stillbirth[188], and through review, potential over-adjustment of the results was identified as the cause. This was also thought to contribute to high heterogeneity. Authors suggest that the protective results are due to increased monitoring and care given to women identified as drug users through the antenatal period. Variables used in adjustment models of this study include low birth weight and low educational level, both are considered intermediate variables and may indicate over-adjustment of the results.

Cannabis use

Four studies examined the relationship between maternal cannabis use and stillbirth[386-389]. Two of the included studies used the same dataset[386, 389], therefore to avoid double counting births, the smaller of the studies was excluded from meta-analysis and the larger study was included in meta-analysis[386].



(c) = cohort study design
(cc) = case-control study design
Figure 4-10 Meta-analysis demonstrating the association between maternal cannabis use and stillbirth compared with no maternal cannabis use during pregnancy.

Meta-analysis revealed an increased odds of stillbirth with cannabis use versus no use (aOR 1.49 (95% CI (1.39, 1.61) – fig 4-10).

Opioid use

One study examined the odds of stillbirth associated with hospital codes indicating maternal opioid use during pregnancy compared with no drug use. Analysis demonstrated a 48% increase in odds of stillbirth (aOR 1.48 (95% CI 1.30, 1.91))[385]. The study was assessed as having a low risk of bias using the RTI tool, but it was noted by the authors that hospital coding is inherently affected by misclassification bias within this cohort. This bias is due to data collection and coding for billing purposes only, and not intended for use in research/risk factor identification.

Amphetamine use

Wolfe et al stratified mothers by type of drug use and examined amphetamine use as one of the subgroups[188]. Women with documented amphetamine use had a possibly increased odds of stillbirth compared with women with no documented use (aOR 1.20 (95% CI 0.90, 1.46)). The confidence interval was not significant and therefore results should be interpreted with caution. The use of voluntary toxicology measures at birth from mother and infant implies that selection bias may impact results, and toxicology of all mothers and infants would be preferable to improve generalisability of results.

Maternal self-inflicted poisoning

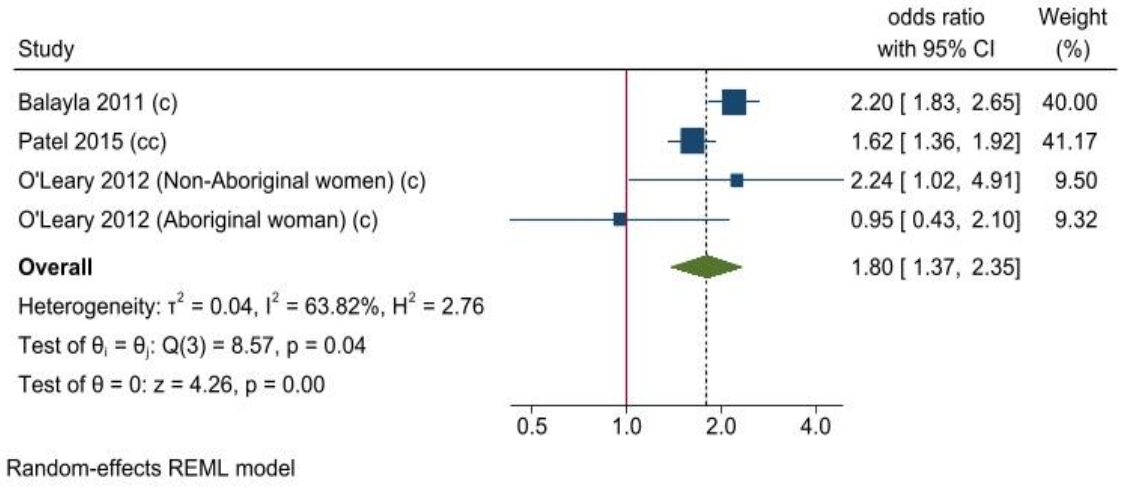
One study[434] examine the association between self-inflicted poisoning during pregnancy and stillbirth odds. Association was assessed through analysis of a Californian cohort of births, and self-inflicted poisoning was identified through hospital discharge records. Results demonstrate no association between self-inflicted poisoning and stillbirth odds (aOR 1.19 (95% CI 0.30, 4.77)), although it should be noted that sample size was underpowered for analysis, therefore results should be interpreted with caution.

Alcohol Use

Eleven studies examined the impact of alcohol consumption on stillbirth odds compared with no alcohol consumption across five high-income countries[105, 202, 262, 320, 364-371]. Through review using the RTI tool, three studies were deemed to have a high risk of bias[320, 365, 370] attributed to the methods of data collection of alcohol use. Alcohol use collected at birth was deemed to be highly unreliable, as were lifelong alcohol estimation measures (as opposed to during pregnancy). Seven of the studies included were assessed to have an unclear risk of bias[105, 202, 262, 364, 367-369, 371] and the remaining study had a low risk of bias[366]. A range of outcomes were assessed, including any alcohol use during pregnancy, quantity of alcohol use during pregnancy as well as preconception and post-pregnancy alcohol consumption.

Any alcohol consumption

Four studies categorised the use of alcohol during pregnancy dichotomously (y/n) and reported the association with stillbirth compared with women who did not report alcohol consumption[105, 320, 365, 368]. Two studies were deemed to have a high risk of bias[320, 365], and two had an unclear risk of bias[105, 368]. The studies used populations from the USA[105, 320, 368] and Australia[365], and as one of the studies from the USA did not provide study dates[368], it was not possible to ascertain whether its population was independent of the other studies. This study was therefore excluded from meta-analysis. All studies included second and third trimester stillbirths, but the timepoint of exposure data collection varied between the studies. Three studies were combined for meta-analysis and the result indicated substantial heterogeneity (I^2 = 63.82%) which was explored using exclusion though exclusion of individual studies did not decrease heterogeneity. Results of the final meta-analysis demonstrated that alcohol use during pregnancy was associated with increased odds of stillbirth compared with no alcohol exposure (aOR 1.80 (95% CI 1.37, 2.35) – fig 4-11).



(c) = cohort study design
(cc) = case-control study design

Figure 4-11Meta-analysis demonstrating the association between any alcohol use and stillbirth odds compared with no alcohol use during pregnancy

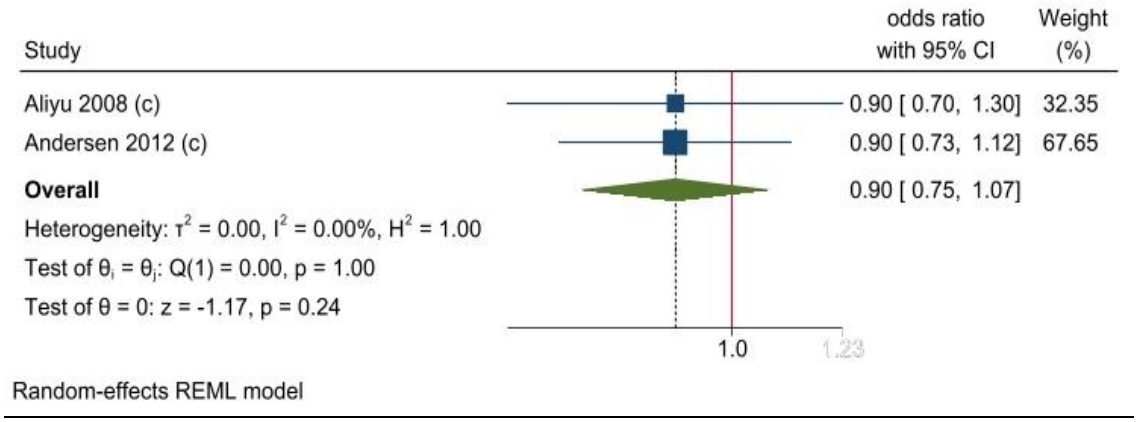
Binge drinking alcohol

Two studies examined the risk of binge drinking using different methods, and therefore could not be combined into meta-analysis. Strandberg-Larsen et al[369] examined the number of binge drinking episodes in the first trimester of pregnancy (≥60 mL of alcohol in one episode), and the timing (GA) of the binge drinking episodes within the first trimester of pregnancy. Increased odds of stillbirth were demonstrated when women engaged in 3+ binge drinking episodes during the first trimester of pregnancy (aOR 1.56 (95% CI 1.01, 2.4)), results were not replicated for 1 or 2 binge drinking episodes (aOR 0.82 (95% CI 0.62, 1.09)) and aOR 1.06 (95% CI 0.7, 1.59) respectively)[369]. Through stratification, it was demonstrated that the impact of GA (weeks) of binge drinking episodes had an association with stillbirth odds.

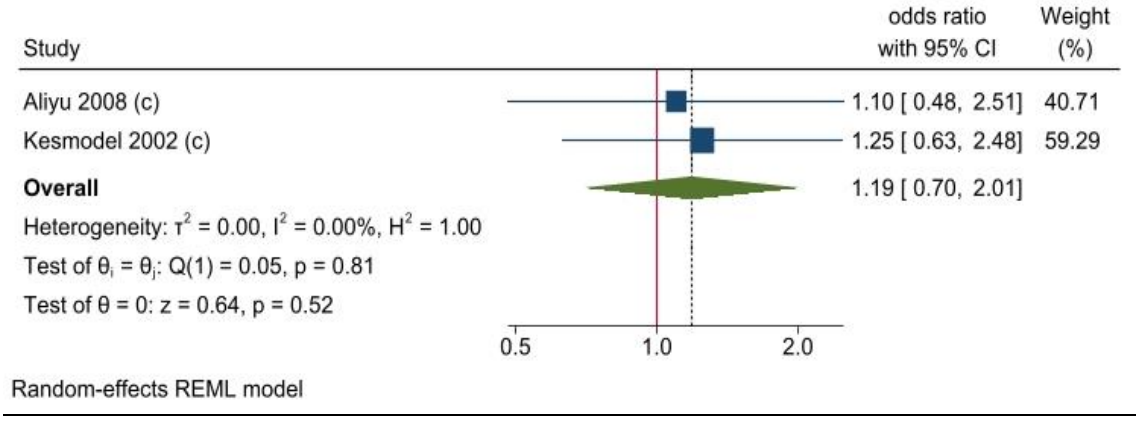
Cornman-Homonoff et al[366] also examined the association between stillbirth and binge drinking (>60 g alcohol/day) stratified by maternal awareness of pregnancy (before and after pregnancy awareness). This study demonstrated differences in odds of stillbirth when binge drinking occurred before and after maternal awareness of the pregnancy (aOR 2.08 (95% CI 0.66, 6.5)) and aOR 2.23 (95% CI 0.75, 6.61)) respectively) compared with no binge drinking. Limitations of the cohort size were acknowledged by authors and the resultant lack of power through analysis was demonstrated by large confidence intervals for aOR presented.

Alcoholic drinks consumed/week

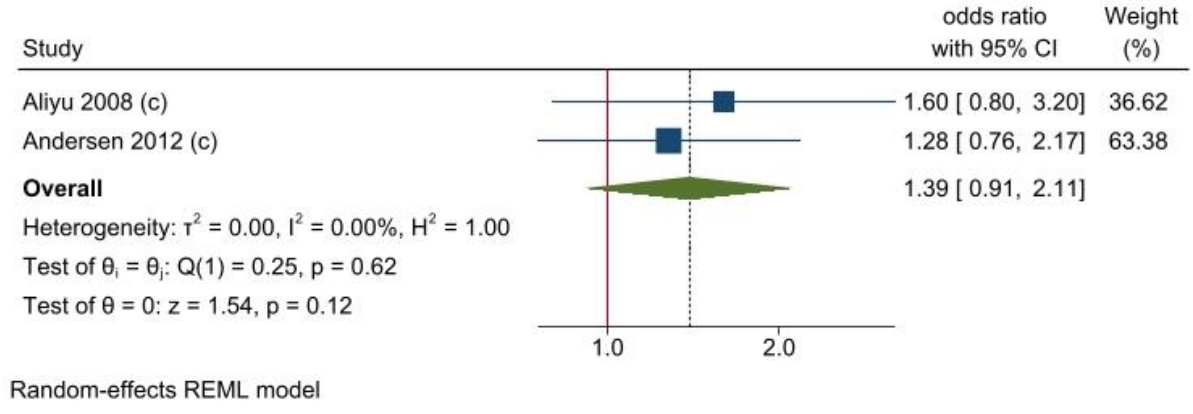
Four studies examined the quantity of alcohol, measured as maternal self-reported drinks consumed per week during pregnancy, and the association with stillbirth[202, 364, 367, 370, 371]. Only one study provided specific measures (mls) for the alcohol per drink consumed (12-15 ml/drink)[371], and the other studies counted number of drinks as reported by the mother[367, 370]. The studies were conducted across two high-income-countries, Denmark and the USA, and risk of bias was assessed to be high for one[370] due to collection of the exposure measure post birth, and unclear for the remaining studies[202, 364, 367, 371] as exposure data were collected at ~104 days GA, and applied to the entire pregnancy without accounting for change in alcohol consumption habits over the course of pregnancy. Four of the studies used the same datasets as other included studies[202, 364, 367, 370, 371], and therefore the smaller studies[202, 364, 371] were excluded to avoid double counting of births. Odds associated with drinking during pregnancy increased as alcohol consumption increased (fig 4-12, fig 4-31). Four or more alcoholic drinks per week compared with no alcohol consumption was associated with the highest odds of stillbirth (aOR 1.39 (95% CI 0.91, 2.11) – fig 4-14) but the resultant large confidence intervals were indicative of the studies using small cohorts. Meta-analysis results by quantity of alcohol are shown below:



(c) = cohort study design
(cc) = case-control study design
Figure 4-12 Meta-analysis demonstrating the association between maternal alcohol consumption between 1-2 alcoholic drinks/week and stillbirth odds, compared with no alcohol consumption during pregnancy.



(c) = cohort study design
(cc) = case-control study design
Figure 4-13 Meta-analysis demonstrating the association between maternal alcohol consumption between 3-4 alcoholic drinks/week and stillbirth odds, compared with no alcohol consumption during pregnancy.



(c) = cohort study design
(cc) = case-control study design
Figure 4-14 Meta-analysis demonstrating the association between maternal alcohol consumption of 4+ alcoholic drinks/week and stillbirth odds, compared with none during pregnancy.

Aliyu et al[370] further stratified birth outcomes per alcohol consumption category by gestational ages (≥20 weeks GA, 20-28 weeks GA, ≥28 weeks GA) and although the results of analysis showed consistently increased associations between stillbirth and 5+ alcoholic drinks/week, minimal variation was demonstrated between different gestational ages at birth of stillbirths (≥20 weeks GA (aOR 1.7 (95% CI 1.0, 3.0)), 20-28 weeks GA (aOR 2.0 (95% CI 0.9, 4.6)), ≥28 weeks GA (aOR 2.65 (95% CI 1.18, 5.97))).

Stratification by parity within analysis of one included study failed to demonstrate an increased association between alcohol consumption and stillbirth odds in primigravid women (aOR between 0.79-1.08)[367].

Pre-pregnancy alcohol consumption

Two studies examined the impact of pre-conception alcohol consumption and stillbirth[202, 364, 365] across two high-income countries, USA and Australia. Assessment of the risk of bias demonstrated a high risk for one study due to collection of alcohol exposure data through use of hospital admission records. As this method of measuring exposure status of women captures extreme exposure requiring admission, there is potential for misclassification of women with alcohol exposure without admission to the non-exposure cohort. The second study had an unclear risk of bias using the RTI tool of assessment[202, 364]. The studies were not combined through meta-analysis due to the differing time periods assessed pre-pregnancy, and different methods of measuring alcohol consumption. Results from both studies are displayed below (table 4-4):

Table 4-4 Study results of maternal alcohol consumption within the preconception period (aOR (95% CI)) compared with women who did not drink alcohol/have an alcohol related admission within the preconception period[202, 364, 365].

Gaskins 2016/ Gaskins 2014	**0.1-1.9g/day alcohol**	**2-4.9g/day alcohol**	**5-9.9g/day alcohol**	**≥10g/day alcohol**
1-6 years pre-pregnancy	1.11 (0.77, 1.59)	1.08 (0.71, 1.64)	0.99 (0.61, 1.61)	1.36 (0.84, 2.19)

O'Leary 2012	Australian Aboriginal women		Australian non-Aboriginal women	
Alcohol related hospital admissions	Admission ≤1 yr preconception	Admission >1 yr preconception	Admission ≤1 yr preconception	Admission >1 yr preconception
	1.18 (0.50, 2.77)	1.15 (0.69, 1.92)	1.46 (0.94, 2.27)	1.16 (0.46, 2.90)

These results demonstrated no clear increase in stillbirth odds with increased daily alcohol consumption 1-6 years prior to pregnancy, and no clear effect of preconception alcohol related admission in non-Aboriginal and Aboriginal women compared with women with no alcohol related discharge diagnosis.

Alcohol consumption post-pregnancy.

One study examined alcohol related admissions post pregnancy and their relationship to stillbirth outcome of the previous pregnancy[365]. Results demonstrated an increased odds of stillbirth associated with maternal admission ≤1 year post pregnancy compared with no admission post pregnancy in Aboriginal women (aOR 3.22 (1.67, 6.23))[365].

Smoking status

Sixty-four studies examined the impact of maternal smoking (passive or active) on the odds of stillbirth[32, 51, 68, 73, 92, 93, 99, 100, 102, 105, 108, 122, 124-127, 129, 130, 132, 156-158, 165, 167, 168, 175, 176, 178-182, 185, 188, 192, 195, 231, 240, 242, 262, 305, 320, 324, 327, 345, 362, 368, 372, 374, 414-431]. Study populations spanned across 12 countries and many incorporated different aspects of tobacco smoke exposure during pregnancy into their analysis. Multiple studies explored maternal smoking as a dichotomous risk factor categorised as 'smoking' or 'non-smoking' during pregnancy, while other studies examined the following exposure categories:

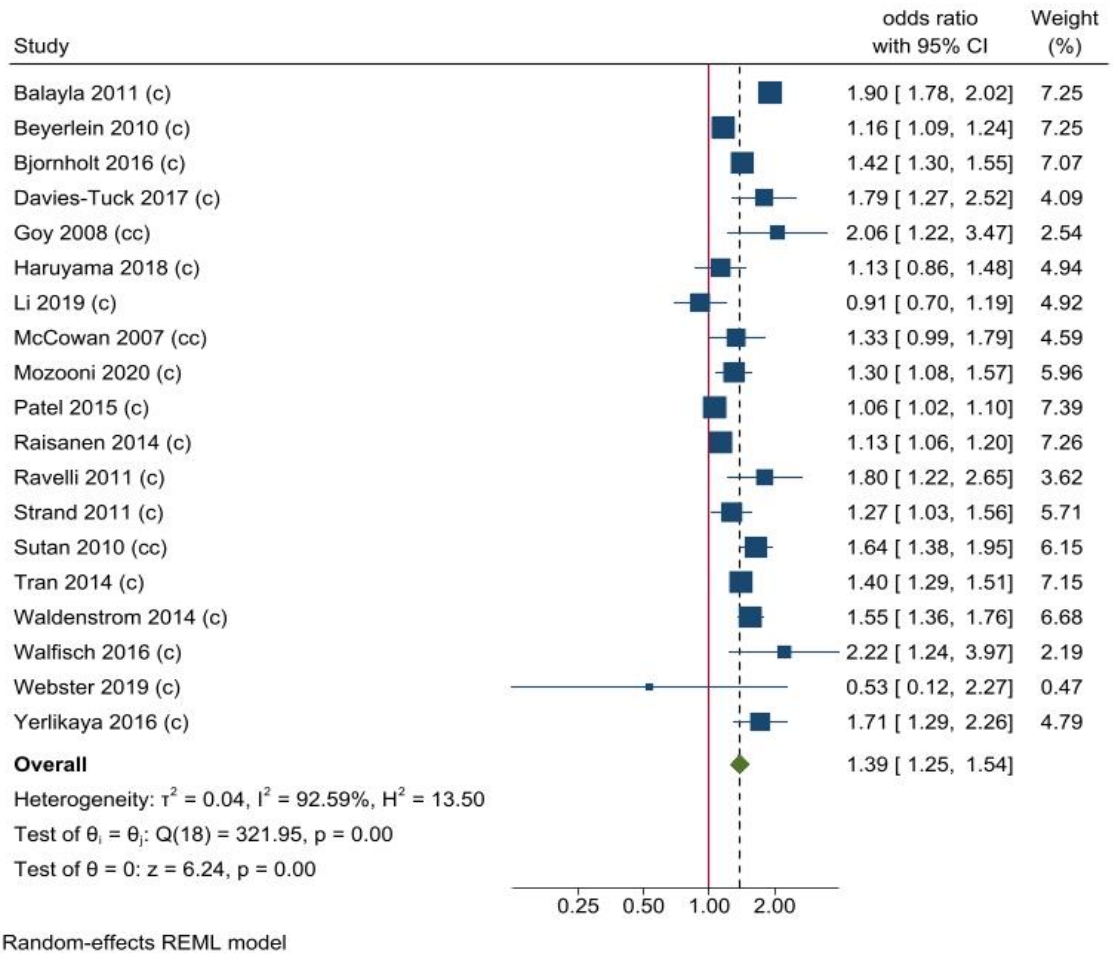
- smoking cessation
- smoking quantity
- snuff use
- smoking and ethnicity
- smoking and coffee consumption
- second-hand smoke exposure
- the use of nicotine replacement therapy
- and smoking with pre-gestational diagnosis of diabetes.

Risk of bias assessment by independent reviewers determined that thirteen of the studies had a high bias[51, 99, 100, 105, 129, 168, 188, 192, 242, 320, 416, 419, 428], predominantly due to data collection methods (commonly self-reported by the mother). Two studies used maternal serum cotinine measures to assess tobacco smoke exposure association with stillbirth. Although a reliable biomarker for tobacco smoke exposure, the two studies examined different forms of tobacco smoke exposure and so were unable to be combined for meta-analysis[420, 429].

Smoking (any)

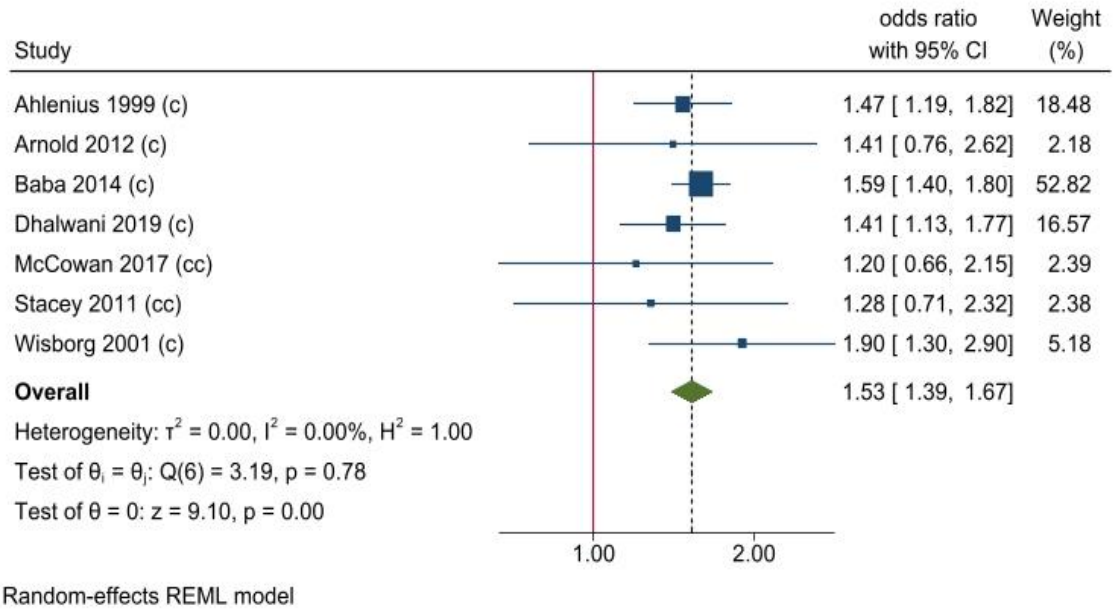
Fifty-one studies examined smoking as a dichotomous variable (Y/N) according to self-reports at one timepoint during pregnancy[32, 73, 92, 93, 99, 100, 102, 105, 108, 122, 125, 126, 129, 130, 132, 156-158, 165, 167, 176, 178-182, 185, 188, 192, 231, 240, 262, 305, 320, 324, 327, 345, 362, 368, 415-419, 421-425, 427, 428, 430].

One provided aOR without confidence intervals and so was excluded from meta-analysis[181], 17 studies used the same dataset as other studies within meta-analysis. To avoid double counting births, the smaller subset of studies were excluded from meta-analysis[100, 122, 125, 130, 157, 165, 176, 178, 188, 192, 305, 415, 419, 424, 425, 427, 428]. Two studies did not provide cohort dates and were therefore excluded from meta-analysis[345, 368]. Final meta-analysis of 19 studies demonstrated considerable heterogeneity between studies included (I^2 = 92.59%) and thus sensitivity analysis was performed using step-wise exclusion. As no single study decreased heterogeneity considerably, heterogeneity was accepted. This may reflect a number of inherent differences between studies, including; different demographics of women who smoke between countries, different timepoints of exposure data collection as well as differing study definitions of stillbirth. The overall odds of stillbirth were increased in smokers (aOR 1.39 (95% CI 1.25, 1.54) – fig 4-15) compared with non-smokers.



(c) = cohort study design
(cc) = case-control study design
Figure 4-15 Meta-analysis demonstrating the association between maternal smoking during pregnancy and stillbirth odds compared with maternal non-smokers during pregnancy.

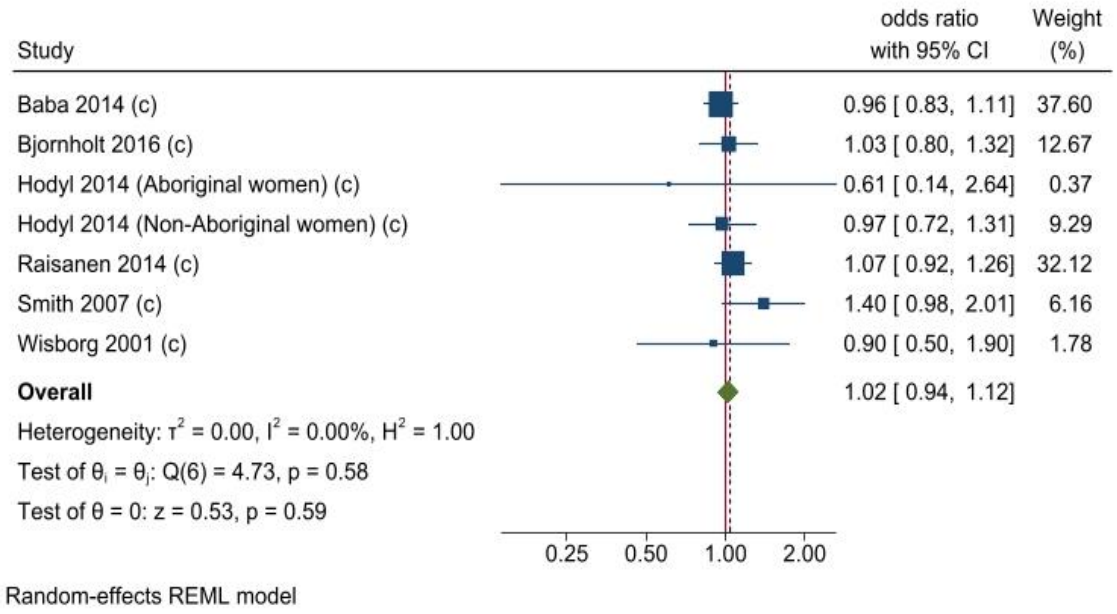
Ten studies in total examined the relationship between pregnancy smoking status and third trimester stillbirth (any definition encompassing ≥28 weeks GA was included)[32, 92, 93, 99, 102, 132, 179, 231, 324, 362, 417, 423, 430]. Three studies reported using the same datasets as larger studies within this meta-analysis, therefore to avoid double counting births, the smaller studies were excluded from analysis[92, 132, 231]. The odds of third trimester stillbirth with any maternal smoking were increased compared with non-smokers (aOR 1.53 (95% CI 1.39, 1.67) – fig 4-16). This result is slightly higher, but comparable to the risk associated with smoking and any GA of stillbirth (≥20 weeks) compared with non-smoking, as shown above.



(c) = cohort study design
(cc) = case-control study design
Figure 4-16 Meta-analysis demonstrating the association between maternal smoking during pregnancy and third trimester stillbirth compared with women who did not smoke during pregnancy.

Smoking cessation during pregnancy

Women may cease smoking when they find out they are pregnant or quit shortly thereafter. Seven studies included from this review captured data for women who had initially smoked during pregnancy, but reported that they had stopped smoking[68, 165, 178, 418, 422, 423, 430]. Three studies included women who reported smoking cessation prior to 15 weeks GA[418, 423, 430], one reported smoking cessation prior to 20 weeks GA[68], and the final two reported smoking cessation within the first trimester of pregnancy[178, 422]. Two studies reported use of the same dataset, therefore to avoid double counting of births, the smaller was excluded from meta-analysis[165]. Therefore six studies were included in the final meta-analysis examining the impact of smoking on stillbirth in women who stopped smoking during pregnancy. Results of final analysis (aOR 1.02 (95% CI 0.94, 1.12) – fig 4-17) demonstrate equivalent stillbirth odds between smoking cessation and non-smokers.

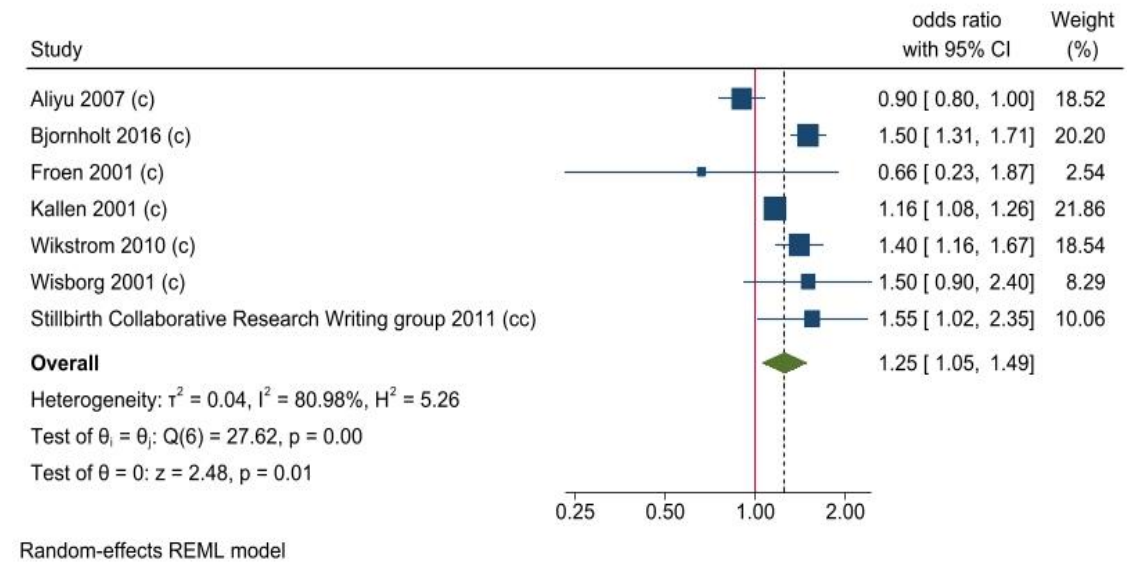


(c) = cohort study design
(cc) = case-control study design
Figure 4-17Meta-analysis demonstrating the association between maternal smoking cessation during pregnancy and stillbirth odds compared with maternal non-smokers.

Smoking Quantity

Sixteen studies stratified smoking mothers by quantity of cigarettes smoked per day[99, 124, 127, 132, 176, 195, 372, 374, 418, 420, 425, 426, 428-431] and reported the association with stillbirth odds compared with non-smokers. Two studies used maternal cotinine as an exposure measure[420, 429], and the remainder relied upon maternal self-reporting which has been shown to result in under-reporting of tobacco use.

Thirteen studies examined smoking ≤10 cigarettes/day during pregnancy and its association with stillbirth[99, 100, 124, 127, 132, 176, 195, 372, 418, 425, 428]. Six of the included studies reported using datasets that were also used by other studies within analysis. To avoid the potential for double counting births, the smaller six studies were excluded from meta-analysis[99, 132, 176, 195, 372, 425]. The resultant meta-analysis included seven studies[124, 127, 418, 426, 428, 430, 431] and demonstrated considerable heterogeneity (I^2 = 80.98%). Subsequently heterogeneity was explored through exclusion and one study was identified as the main contributor to heterogeneity[428]. On closer review, the study dataset included births from the 1970s through to the early 1990s, much older than the other included studies, and therefore cohort bias was through to contribute to the heterogeneity. Following exclusion of this study, heterogeneity decreased to 59.7%. The odds of stillbirth with smoking 1-10 cigarettes/day through pregnancy (compared with not smoking) was increased (aOR 1.25 (95% CI 1.05, 1.49) – fig 4-18).

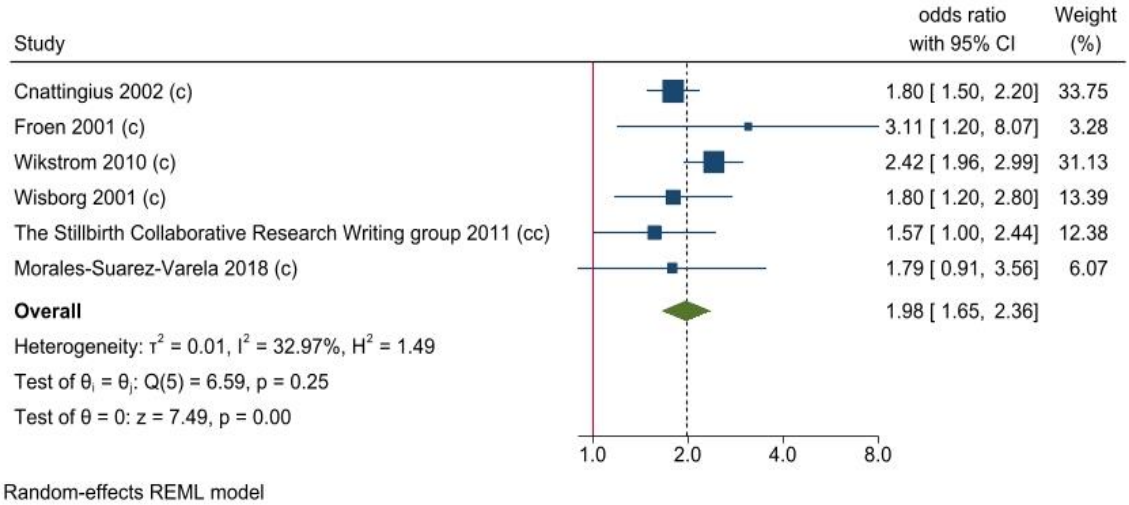


(c) = cohort study design
(cc) = case-control study design

Figure 4-18 Meta-analysis demonstrating the odds of stillbirth associated with 1-10 cigarettes smoked per day compared with maternal non-smokers

≥10 cigarettes/day

Eight studies examined the impact of maternal smoking ≥10 cigarettes per day on stillbirth odds compared with maternal non-smokers[124, 127, 132, 195, 372, 426, 430, 431]. Six studies were included in the final meta-analysis following the exclusion of duplicate/overlapping datasets and studies[124, 127, 195, 372, 426, 430]. Results indicate an almost two-fold increase in stillbirth odds for women who smoked >10 cigarettes/day compared with non-smokers (aOR 1.98 (95% CI 1.65, 2.36) – fig 4-19).



(c) = cohort study design
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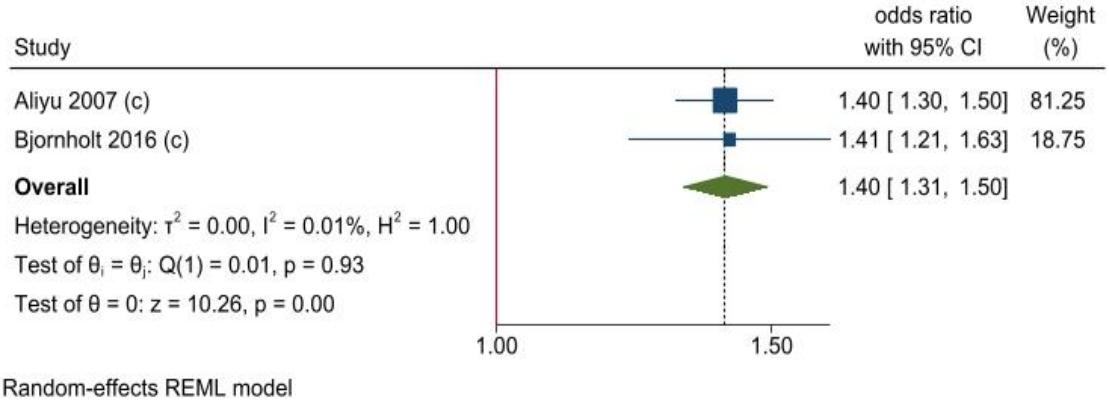
Figure 4-19 Meta-analysis demonstrating the association between maternal smoking of ≥10 cigarettes per day and stillbirth compared with non-smokers.

Between 10 and 20 cigarettes/day

Four studies examined the impact of smoking between ten and twenty cigarettes per day and stillbirth odds[176, 418, 425, 428]. Following the exclusion of duplicate/overlapping datasets/studies[176, 425], the meta-analysis included two studies. Resultant aOR from meta-

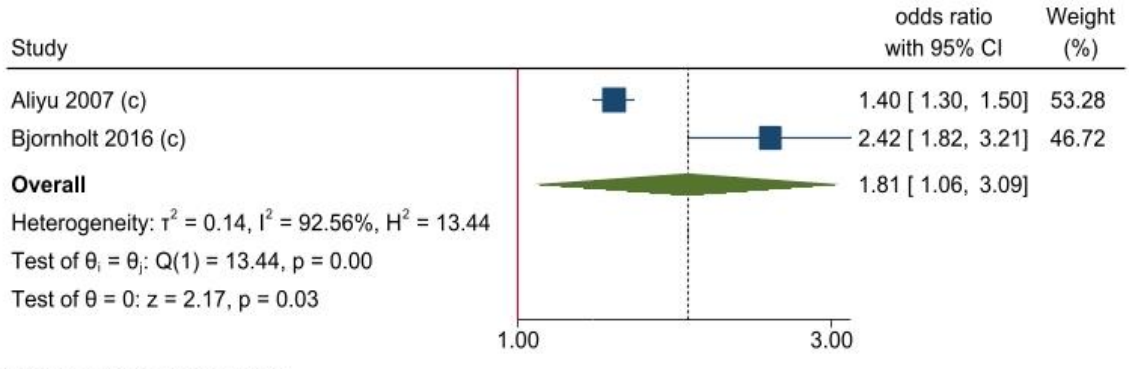
analysis indicated a increase in odds of stillbirth for women who smoke between 10 and 20 cigarettes/day compared with non-smokers (aOR 1.40 (95% CI 1.31, 1.50) – fig 4-20).



(c) = cohort study design
(cc) = case-control study design
Figure 4-20 Meta-analysis demonstrating the association between maternal smoking between 10 and 20 cigarettes/day and stillbirth odds compared with non-smokers.

≥20 cigarettes/day

Four studies examined the impact of maternal smoking ≥20 cigarettes/day during pregnancy on the odds of stillbirth[176, 418, 425, 428]. Following exclusion of duplicate/overlapping data and studies, the final meta-analysis included two studies[176, 425]. Results indicate an almost 2-fold increase in stillbirth odds associated with smoking ≥20 cigarettes/day compared with not smoking (aOR 1.81 (95% CI 1.06, 3.09) – fig 4-21). Overall, results demonstrate an increase in the association between the number of cigarettes smoked/day and the odds of stillbirth.



(c) = cohort study design
(cc) = case-control study design
Figure 4-21Meta-analysis demonstrating the association between maternal smoking >20 cigarettes/day and stillbirth odds compared with non-smokers.

Cotinine measures of smoking exposure during pregnancy

Cotinine is a primary metabolite of nicotine and is a biomarker of exposure to tobacco products. Of the studies examining tobacco use during pregnancy, only two used cotinine as a measure of exposure[420, 429]. Both studies were conducted in the USA, one case-control study investigated cotinine as a measure of active smoking during pregnancy[420], and the other, a cohort study, examined environmental smoke exposure that excluded

women who were active smokers (cotinine levels >10.0 ng/ml)[429]. The studies defined stillbirth as ≥20 weeks GA , but measured cotinine at different timepoints during pregnancy, one at 15-19 weeks GA[429] and the other at birth[420]. Any cotinine measure >10.0 ng/ml was used as an indication of maternal active smoking. Varner et al[420] found an almost three-fold increase in the odds of stillbirth for women who had serum samples at birth that indicated active smoking (aOR 2.70 (95% CI 1.72, 4.25)). Environmental tobacco smoke exposure (<10.0 ng/ml) in non-smokers, examined by Kharrazi et al, was also found to possibly increase the odds of stillbirth with each unit increase in log cotinine level (aOR 1.58 (95% CI 0.78, 3.21))[429].

Maternal exposure to cigarette smoke combined with coffee intake

One study[372] examined the effect of smoking quantity combined with coffee intake per day during pregnancy and found increased odds of stillbirth associated with ≤10 cigarettes per day combined with >3 cups of coffee per day (aHR 1.77 (95% CI 1.08, 2.90)). As demonstrated by the large confidence intervals, these results are based on a small sample size and should be interpreted with caution. It should be noted that results for this analysis are similar to that found in the above meta-analysis for women who smoke ≥10 cigarettes per day.

Maternal ethnicity and cigarette exposure

Two studies examined the impact of tobacco use on stillbirth risk for Aboriginal and Torres Strait Islander women[68, 415]. One study was conducted in New South Wales, Australia[415] and the other in South Australia[68]. The analysis of the New South Wales cohort examined the association by quantity of cigarettes smoked, and found that the odds of stillbirth decreased for maternal non-smoking status compared with smoking (aRR 0.60 (95% CI 0.43, 0.84)). Hodyl et al examined smoking as a risk factor of stillbirth in South Australia stratified by maternal ethnicities (non-Aboriginal or Torres Strait Islander, and Aboriginal or Torres Strait Islander), finding Aboriginal and Torres Strait Islander women had consistently higher odds of stillbirth than non-Aboriginal and Torres Strait Islander women (table 4-5).

Table 4-5 Results of Hodyl et al[68] of analysis of the association between smoking status and stillbirth odds compared with non-smokers stratified by ethnicity

	Non-smoker	**Quit smoking (aOR (95% CI)**	**1-10 cig/day (aOR (95% CI)**	**11+cig/day (aOR (95% CI)**
Aboriginal women	Referent	0.61 (0.14, 2.63)	0.92 (0.51, 1.65)	0.87 (0.43, 1.76)
Non-Aboriginal women	Referent	0.97 (0.73, 1.31)	**1.42 (1.17, 1.72)***	**1.48 (1.16, 1.88)***

**Bold results indicate significant results.*

One study examined smoking between maternal ethnicities in the USA, comparing stillbirth odds for smokers between black and white women[242]. The results demonstrated no increased association with stillbirth for women who were black and smoking versus women who were white and smoking (aOR 0.96 (95% CI 0.83, 1.10)).

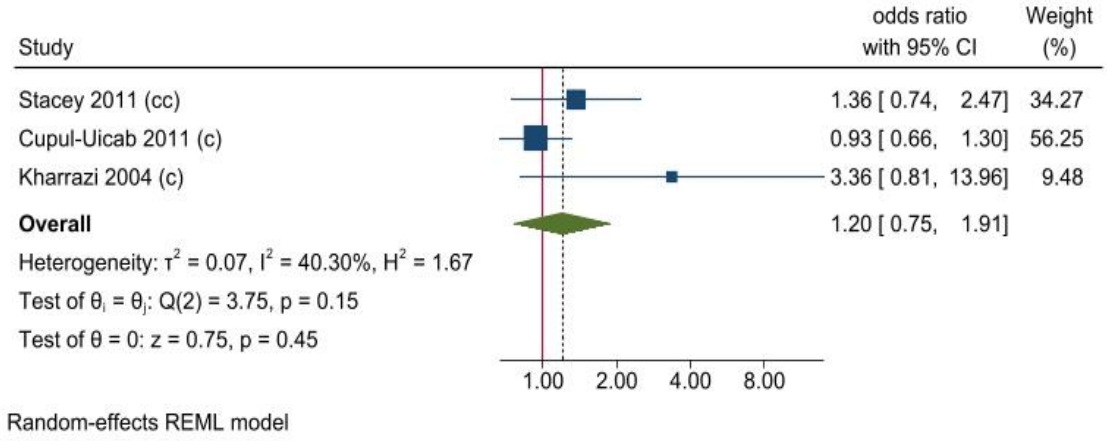
Maternal snuff use

Two studies examined the use of snuff during pregnancy and its association with stillbirth odds compared with no maternal snuff use[423, 426]. Both used a large Swedish cohort of

women and reported using the same dataset. The larger of the two studies demonstrated an increased odds of stillbirth associated with current use of snuff during pregnancy compared with non-snuff/tobacco users (aOR 1.43; 95% CI 1.02, 1.99)[423]. Wikstrom et al[426] conducted further analysis of snuff use, showing increased odds associated with snuff use and third trimester stillbirth (> 28 weeks GA) (aOR 2.1 (95% CI 1.3, 3.4)).

Second-hand smoke exposure

Three studies analysed passive smoking exposure during pregnancy[93, 179, 324, 362, 424, 429]. Passive smoking was defined as exposure to cigarette smoke in the home, but no report of the woman smoking cigarettes herself. Passive smoking was self-reported in two of the included studies, and in the final study, serum cotinine measures were used to identify women exposed to tobacco smoke who were non-smokers (serum cotinine levels between 0.235 and 10.00ng/ml). Cohorts were drawn from three high-income countries, one population of Norwegian women, another from New Zealand, and the final study was conducted in the USA. The studies described different definitions of stillbirth, one only included third trimester stillbirths and the others included all stillbirths ≥20 weeks GA. Meta-analysis demonstrated a possibly slightly increased odds of stillbirth with maternal exposure to passive smoking compared with no to exposure to passive smoke (aOR 1.20 (95% CI 0.75, 1.91) – fig 4-22).



(c) = cohort study design
(cc) = case-control study design

Figure 4-22 Meta-analysis demonstrating the association between second-hand smoke exposure during pregnancy and stillbirth odds compared with women not exposure to passive smoking.

One study examined lifetime exposure to smoke compared with no lifetime second-hand smoke exposure in the home or workplace and its association with stillbirth[51]. Findings demonstrate increased associations between the number of years of passive smoking exposure at home (as an adult and child) and within the workplace and stillbirth odds[51];

- Childhood ≥10 years + adult home <20 years + adult work <10 years aOR 1.16 (95% CI 0.94, 1.43)
- Childhood ≥10 years + adult home <20 years + adult work ≥10 years **aOR 1.61 (95% CI 1.27, 2.04)**
- Childhood ≥10 years + adult home ≥20 years + adult work <10 years aOR 1.18 (95% CI 0.93, 1.50)

- Childhood ≥10 years + adult home ≥20 years + adult work ≥10 years **aOR 1.55 (95% CI 1.21, 1.97)**[51]

This study was judged to be at high risk of bias as data were collected from post-menopausal women and exposure data was not restricted to the antenatal period (included postnatal exposure).

Maternal nicotine replacement therapy (NRT) use

One study examined the use of NRT compared with non-smokers not using NRT, and its association with stillbirth odds[427]. Maternal use of NRT showed no increase in stillbirth odds compared with non-smoking mothers (aOR 0.57 (95% CI 0.28, 1.16))[427]. Subgroup analysis of varying types of NRT (patches, chewing gum, inhaler, various combinations) compared with non-users, did not reveal increases in stillbirth odds for any type;

1. Patches compared with non-users aOR 0.94 (95% CI 0.30, 2.94)
2. Chewing gum compared with non-users aOR 0.30 (95% CI 0.08, 1.22)
3. Inhaler compared with non-users aOR 0.74 (95% CI 0.18, 3.00)
4. Various types compared with non-users aOR 0.68 (95% CI 0.10, 4.85)

The study also included a subgroup of women who were still smoking while using NRT and found that they also did not show increased odds of stillbirth in comparison to non-smoking women using NRT (aOR 0.83 (95% CI 0.34, 2.00)). It should be noted that these findings include large confidence intervals, and therefore may indicate a small study size.

Smoking and pre-gestational diabetes

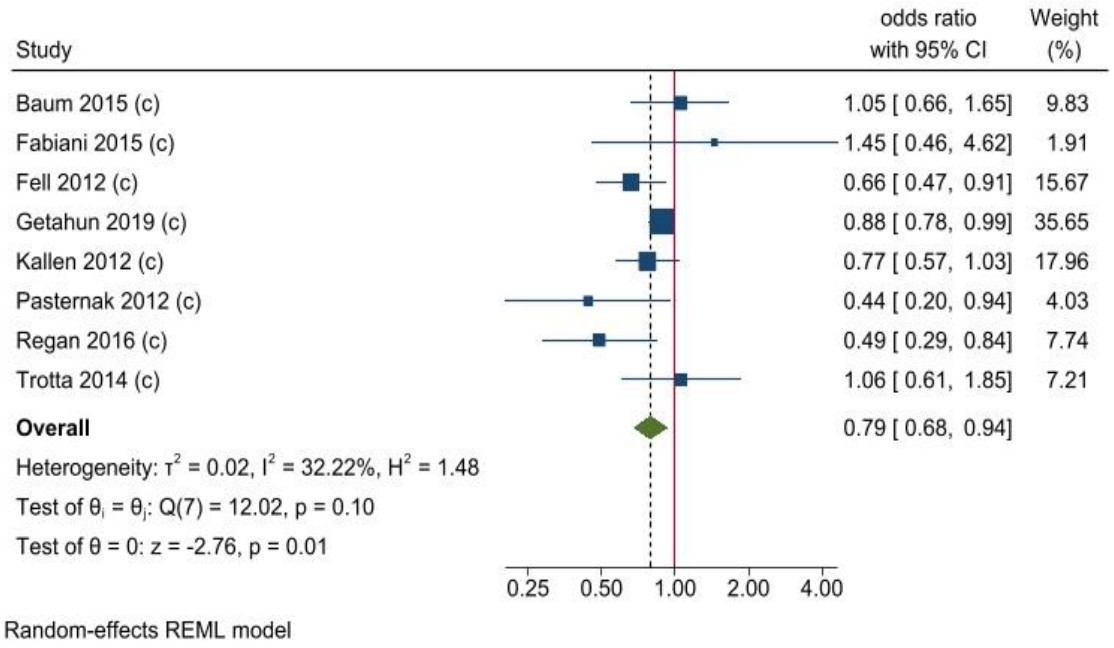
Beyerlein et al[108] examined the impact of maternal smoking in a cohort of women who had a pregestational diagnosis of diabetes. Findings demonstrated a three-fold increase in the odds of stillbirth for diabetic smokers compared with diabetic non-smokers (aOR 2.98 (1.82, 4.87)) [108].

Antenatal vaccination

Ten studies examined the impact of antenatally administered vaccinations and its association with stillbirth odds[52, 267-273, 306, 316]. Study populations included those from eight high-income countries (UK, Italy, Sweden, Australia, Canada, Finland, Denmark and the USA). The studies investigated the effect of two different vaccines; H1N1 which prevents maternal influenza infection, as well as neonatal influenza infection[52, 271, 272, 316, 443]; and the pertussis vaccine[306]. Results of assessment using the RTI tool of assessment for bias demonstrated that seven of the studies had a low risk of bias[52, 267, 268, 270-272, 274], and three had an unclear risk of bias[269, 273, 306].

Influenza H1N1 vaccination

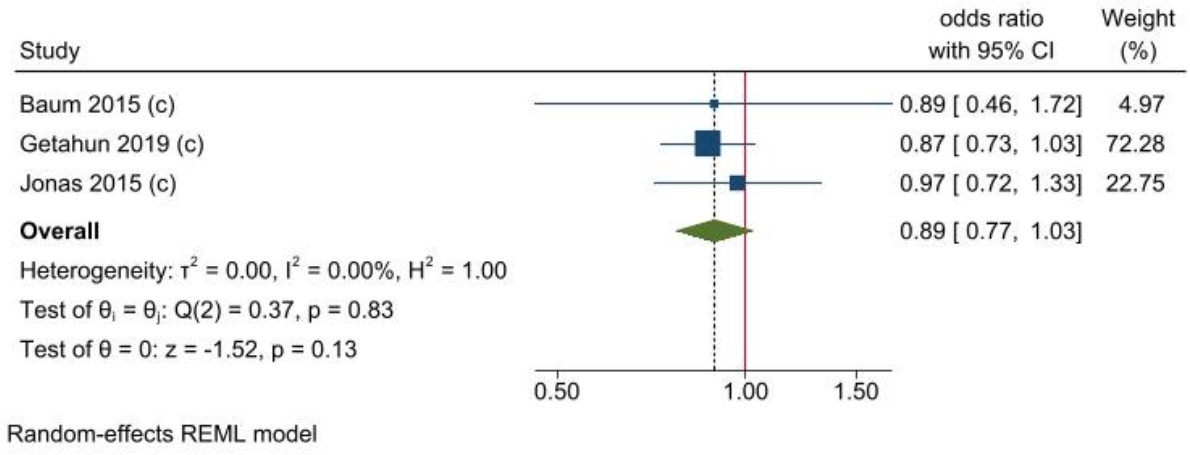
In total, nine studies examined the association between administration of the H1N1 vaccine at any stage during pregnancy and stillbirth risk[52, 267-274]. Of these studies, one cohort study[273] utilised a study population that was encompassed within another study[269]. The smaller study was thus excluded from meta-analysis to avoid double counting births[273]. The remaining eight studies were combined through meta-analysis and demonstrated an overall adjusted odds ratio of 0.79 (95% CI 0.68, 0.94) (– fig 4-24) confirming a protective effect of stillbirth with maternal H1N1 vaccination during pregnancy.



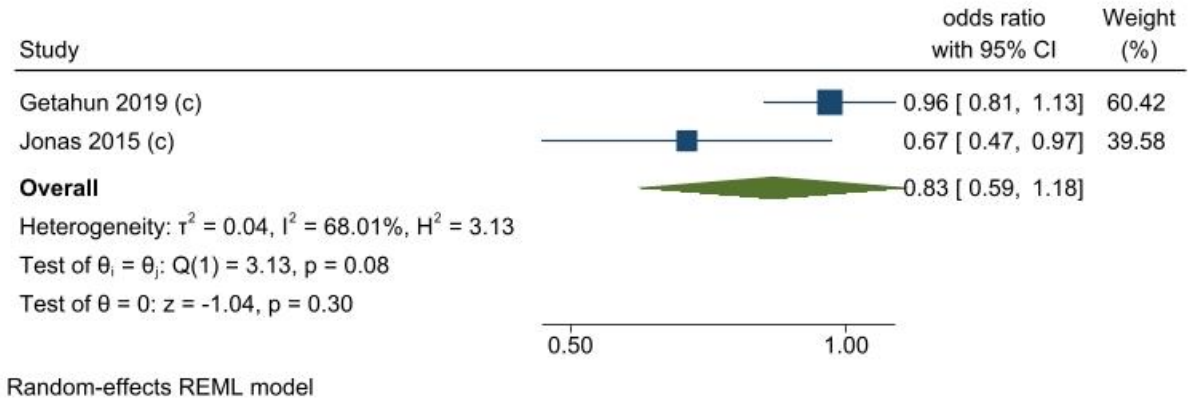
(c) = cohort study design
(cc) = case-control study design
Figure 4-23 Meta-analysis demonstrating the association between antenatally administered H1N1 vaccination versus no H1N1 vaccination and odds of stillbirth.

<u>Trimester specific H1N1 vaccination administration</u>

Three studies included examined the effect of H1N1 vaccination on stillbirth odds by trimester of administration[268, 271, 273]. Studies were combined through meta-analysis and although a minimally protective aOR was seen with first or second trimester vaccine administration compared with none, results failed to reach significance (first trimester H1N1 vaccine administration vs none aOR 0.89 (95% CI 0.77, 1.03) (fig 4-24) and second trimester H1N1 vaccine administration vs none aOR 0.83 (95% CI 0.59, 1.18) – fig 4-25). Meta-analysis of results of third trimester administration of H1N1 vaccine were also associated with protection from stillbirth (aOR 0.78 (95% CI 0.65, 0.93) – fig 4-26).



(c) = cohort study design
(cc) = case-control study design
Figure 4-24 Meta-analysis of the association between maternal vaccination with H1N1 during the first trimester and stillbirth odds compared with non-vaccinated women.



(c) = cohort study design
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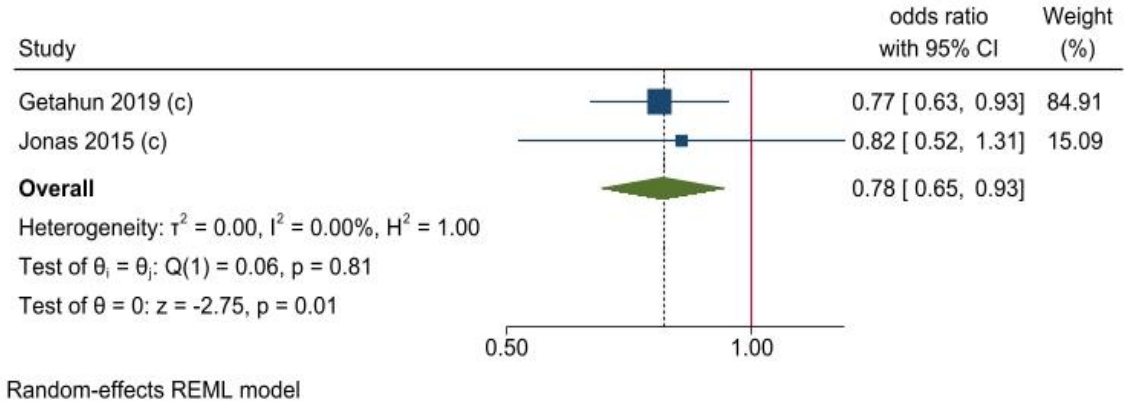
Figure 4-25 Meta-analysis of the association between administration of second trimester H1N1 and stillbirth odds compared with no maternal administration of H1N1 vaccination.



(c) = cohort study design
(cc) = case-control study design
Figure 4-26 Meta-analysis of studies examining the association between administration of third trimester H1N1 and stillbirth odds compared with no maternal administration of H1N1 vaccination.

Regan et al[52] stratified results by gestation at birth (<37 weeks GA and ≥37 weeks GA) demonstrating the H1N1 vaccination decreased stillbirth odds <37 weeks GA in comparison to no vaccination (aOR 0.45 (95% CI 0.26, 0.81)), and no association was shown for stillbirth odds ≥37 weeks GA in vaccinated women compared with non-vaccinated women (aOR 1.13 (95% CI 0.27, 4.71)).

Pertussis vaccination

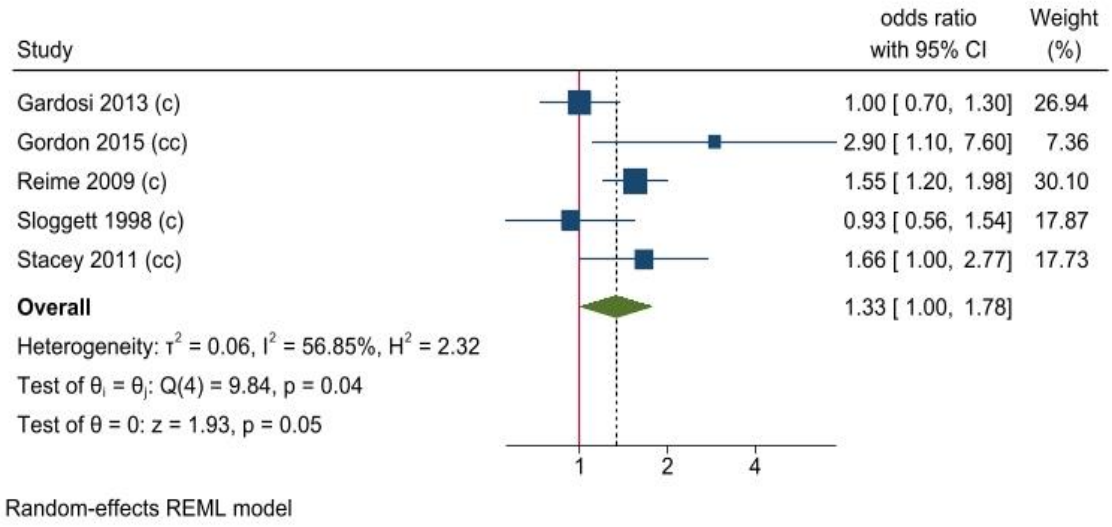
One study examined the association between antenatal pertussis vaccination and stillbirth odds[306]. Vaccination was administered during the third trimester of pregnancy and results demonstrated no association between third trimester pertussis vaccination and stillbirth odds compared with no vaccination (aOR 0.85 (95% CI 0.45, 1.61))[306].

Maternal Occupation

Fifteen studies reported the adjusted odds ratios for stillbirth associated with maternal occupation and/or the characteristics of the maternal occupations (i.e.: lifting, shift work etc)[55, 56, 58, 92, 200, 258, 305, 335, 361, 393-396, 398-400]. Included studies examined the impact of maternal occupation from nine high-income countries. All studies were assessed using the RTI tool of assessment; one study was assessed as having a high risk of bias caused by unclear exposure categories owing to potential for misclassification (identified by authors)[395]. Eleven studies were classified as unclear risk of bias, predominantly due to the complex issues associated with occupation classification, coding, and categorisation[56, 58, 92, 200, 258, 305, 335, 361, 394, 396-398]. Three studies demonstrated low risk of bias[393, 399, 400].

Unemployment

Five studies examined the association between maternal unemployment status reported at birth and the odds of stillbirth[92, 200, 335, 361, 395]. Two examined the impact associated with third trimester stillbirths[92, 361], and three studies examined the impact of unemployment on second and third trimester stillbirths[200, 335, 395]. Meta-analysis showed a possible increase in odds of stillbirth associated with maternal unemployment (aOR 1.33 (95% CI 1.00, 1.78) – fig 4-27). Studies were grouped according to the trimester of stillbirth. Meta-analysis of studies examining second and third trimester stillbirth odds demonstrated no clear association (aOR 1.17 (95% CI 0.83, 1.65) – fig 4-28), whereas studies including exclusively third trimester stillbirth demonstrated an almost two-fold increased odds of stillbirth (aOR 1.87 (95% CI 1.19, 2.94) – fig 4-29).



(c) = cohort study design
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Figure 4-27 Meta-analysis of studies reporting the odds of stillbirth associated with unemployment compared with employment.

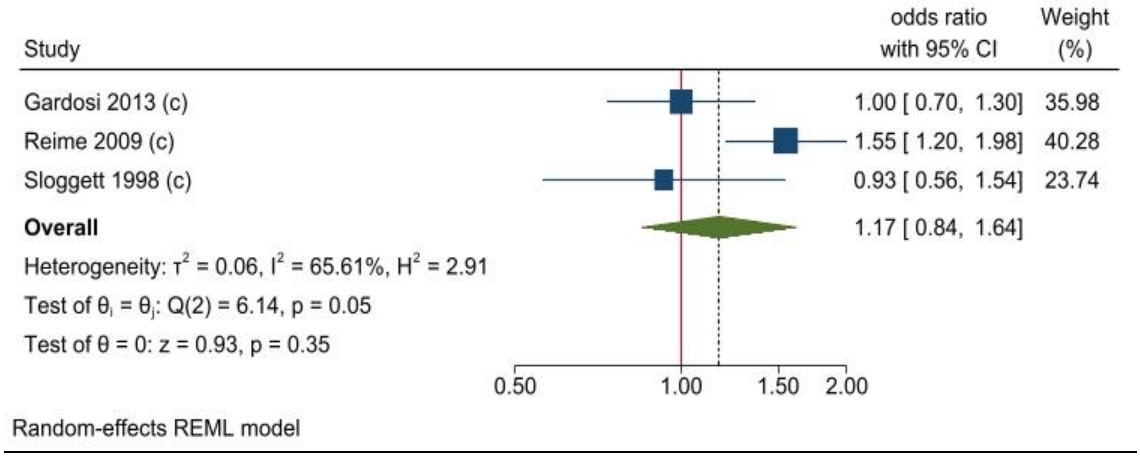

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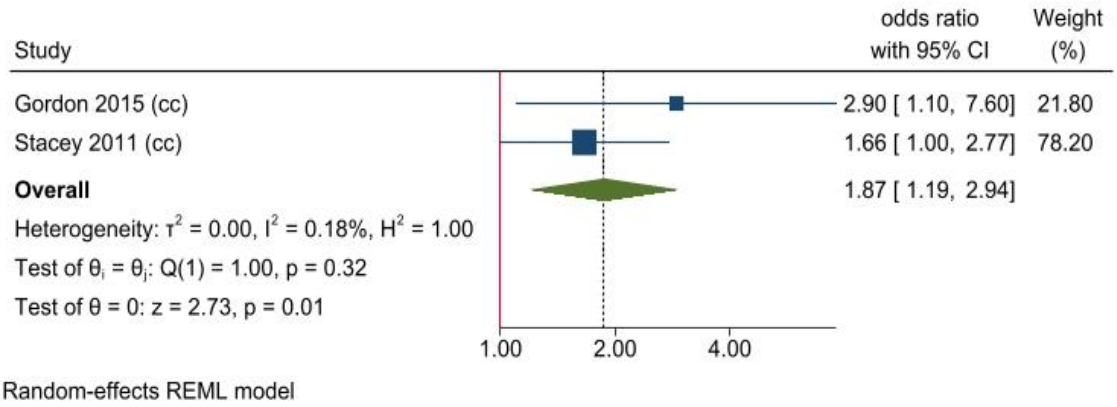
Figure 4-28 Meta-analysis demonstrating the association between maternal unemployment on second and (not or) third trimester stillbirths compared with employment.



(c) = cohort study design
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Figure 4-29 Meta-analysis demonstrating the association between maternal unemployment and third trimester stillbirth odds compared with employed mothers.

Homemaker

Two studies reported the odds of stillbirth associated with homemakers in comparison with employed mothers, one in Germany[395] and the other in the UK[335]. The studies did not report GA parameters of stillbirths included, one study reported birthweight parameters that changed midway through the cohort and were not separated through analysis (until March 1994 > 999g and after March 1999 > 499g)[395]. Meta-analysis demonstrated considerable heterogeneity (83.05%) thought to be due to differences in stillbirth definition between studies and within studies, as well as definitions of homemaker between countries; some included unemployed women as homemakers, and others grouped unemployed women separately to unemployed. Sloggett[335] adjusted results for North/South zone of residency within the England and Wales, whereas Reime[395] adjusted results comprehensively; differences in adjustment may also have contributed to heterogeneity. The analysis demonstrates a possible association between maternal homemaker status and stillbirth (aOR 1.35 (95% CI 0.89, 2.05) – fig 4-30), however large confidence intervals and considerable heterogeneity indicate the need for further research to confirm these results.

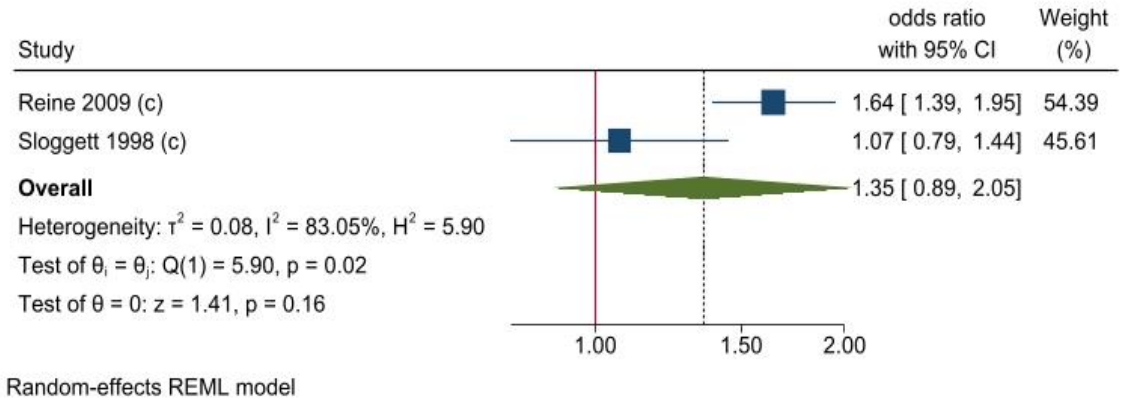

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Figure 4-30 Meta-analysis of association between maternal home-maker status and stillbirth odds compared with employed mothers.

Healthcare workers

Two studies examined the impact of maternal occupation in healthcare and the odds of stillbirth in Norway and Finland compared with cohorts of non-healthcare workers (study reference groups included teachers, upper white-collar workers and the general population)[55, 393, 396]. The healthcare occupations included within exposure groups were dentist, dental hygienist, physicians, nurses, and midwives. Maternal occupation as a nurse was shown to have a possible association with stillbirth odds compared with non-healthcare workers (aOR 1.27 (95% CI 0.98, 1.56))[55], and maternal occupation as a midwife showed an uncertain association with odds of stillbirth (aOR 0.64 (95% CI 0.28, 1.55))[55] compared with non-healthcare workers. Women who work in the healthcare industry demonstrate uncertain associations with stillbirth odds compared with non-healthcare workers (aOR 1.10 (95% CI 0.90, 1.35) – fig 4-31).

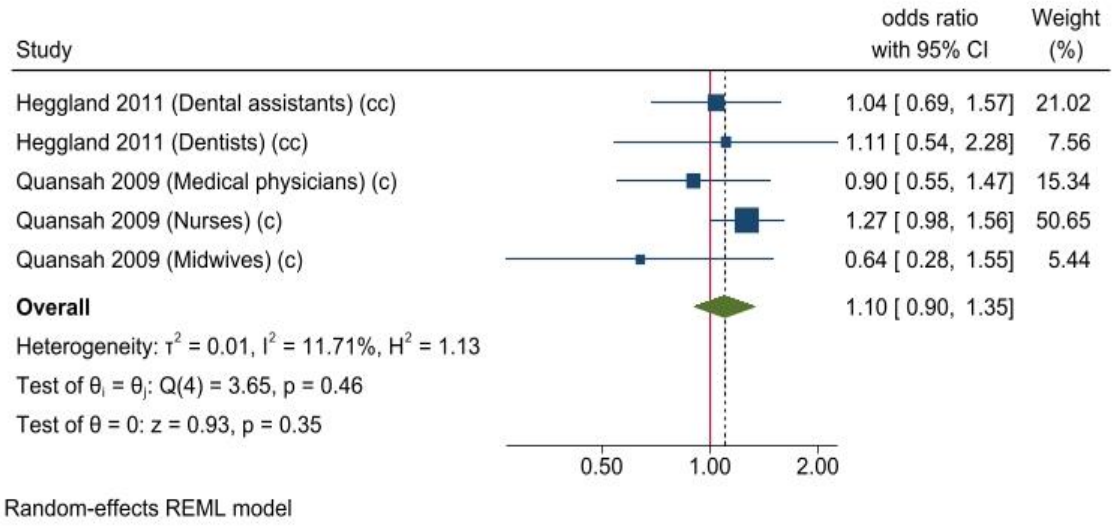

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Figure 4-31 Meta-analysis demonstrating the association between maternal health-care worker status and stillbirth odds compared with non-healthcare workers.

Technical work

Two studies examined the impact of technician work on stillbirth odds in populations from Finland and Canada[305, 394]. One study solely included laboratory technicians[394], and the other combined technician roles e.g. Laboratory technicians, computer technicians etc[305]. Each study used different reference groups: Dodds et al compared technicians odds of stillbirth to that of non-working mothers[305], and Halliday-bell et al compared laboratory workers to teachers[394]. Both studies were combined through meta-analysis and demonstrated moderate heterogeneity (42.54%) thought to result from the differing occupational exposure (different technician occupations) included in the exposure groups, as well as the different referent groups used. Analysis demonstrated a non-significant increased association between technician work and stillbirth odds compared with non-technical workers, but the large confidence interval indicates that further research is required to confirm this association (aOR 1.71 (95% CI 0.86, 3.43) – fig 4-32).

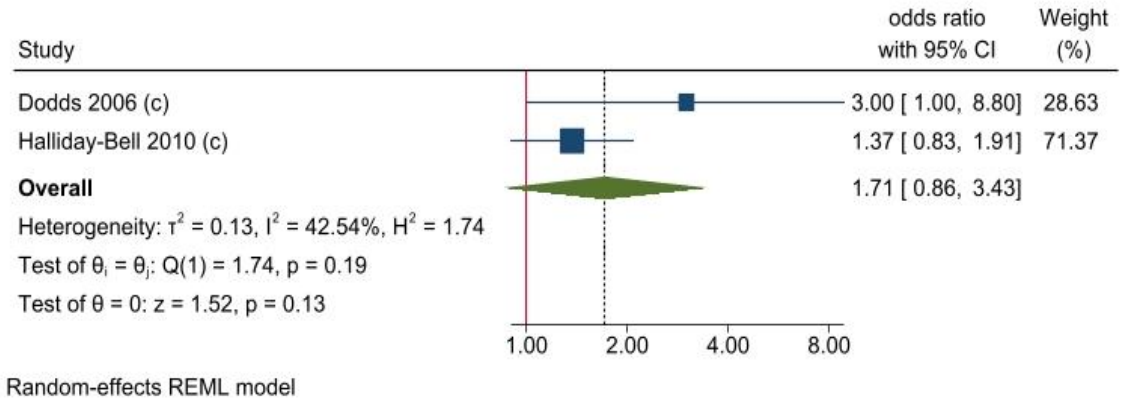

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Figure 4-32 Meta-analysis demonstrating the association between maternal technical workers and stillbirth odds compared with non-technical workers.

Lifting at work

Two studies assessed the impact of self-reported occupational lifting during pregnancy in Denmark[56, 58]. Both studies used the same datasets and therefore were unable to be combined in meta-analysis due to the possibility of double-counting births. Juhl et al[58] demonstrated a protective effect associated with lifting >20kg >3 times per day compared with 0kg lifted per day (aOR 0.51 (95% CI 0.29, 0.92))[58]. Mocevic et al[56] examined heavy lifting and found a possible increased association with lifting 201-975 kg/day compared with 0-14kgs/day (aOR 1.4 (95% CI 0.92, 2.14)). All other workplace lifting categories (kg/day) demonstrated no association with stillbirth odds.

Shift work, workplace strain and occupational autonomy

One study examined the impact of shift work on stillbirth odds and categorised women to one of five groups describing their shift work pattern during pregnancy (day time shift work (referent), fixed evening shift work, fixed night shift work, rotating shift work without night shifts, rotating shift work including nights)[398]. Associations between shift characteristics and third trimester stillbirths (≥28 weeks GA) demonstrated no significant increased odds of stillbirth for any category of shift work compared with day-time shift work. The study further reported an uncertain association between fixed evening shift work (aOR 0.48 (95% CI 0.12, 2.00)), rotating shift work without nights (aOR 0.51 (95% CI 0.22, 1.17)), and rotating shift work with nights (aOR 0.51 (95% CI 0.22, 1.17) compared with day-time shift work. Small numbers in each category resulted in large confidence intervals for results and demonstrate the need for caution when interpreting the results, and the need for further research to validate findings. Zhu et al also examined the impact of workplace physical strain combined with autonomy over tasks that are performed in the workplace, and the association with stillbirth odds[398]. The study demonstrated no clear association between low or high workplace strain combined with high or low autonomy over tasks.

Cosmetology

One study within this review examined the association of maternal work as a cosmetologist with stillbirth odds[258] compared with non-cosmetologists. Cosmetology has previously been implicated as a contributor to stillbirth risk due to the chemical exposure sustained by women during their reproductive years on a daily basis. Gallicchio

et al[258] compared cosmetologists with other professions and demonstrated uncertain association with stillbirth odds (aOR 0.53 (95% CI 0.17, 1.71)).

Veterans

Veterans are thought to be exposed to multiple chemical contaminants during deployment, and one study examined the impact of deployment to the Gulf War and resultant impact on stillbirth odds[399]. This study reported no clear association between classification as a Gulf veteran and stillbirth odds (aOR 1.26 (95% CI 0.46, 3.49)) compared with non-Gulf War veterans. Large confidence interval indicates that the study is underpowered, and a larger cohort of veterans may provide results of greater precision.

Clerical work

One included study examined the impact of clerical work in comparison with non-workers (unemployed mothers) and found no association with stillbirth odds aOR 1.00 (95% CI 0.50, 2.20)[305].

Radiation exposure

There has been continuing concern that low level ionising radiation is associated with poor pregnancy outcomes, specifically damage to genetics of the developing fetus as well as the oocytes. One study used a UK cohort of employees (from establishments operated by either Atomic Energy Authority, Atomic Weapons Establishment, and British Nuclear Fuels) to assess radiation exposure in relation to stillbirth odds[400]. Workers with the potential for any ionising radiation exposure were externally monitored, internal monitoring was used when internal exposure is identified. The findings reported increased stillbirth odds associated with any monitoring (aOR 2.2 (95% CI 1.0, 4.6)) compared with mothers who did not require monitoring (deemed non-exposed). Through stratification by type of monitoring, external monitoring demonstrated increased odds of stillbirth (aOR 2.5 (95% CI 1.1, 5.8)) compared with non-monitored workers. Internally and externally monitored women were analysed, but showed uncertain association with stillbirth odds compared with non-monitored workers (aOR 1.6 (95% CI 0.5, 4.8)). The study further stratified exposure by the timing of monitoring in relation to conception (before and after) and found inconclusive results. On examination of the quantity of exposure to ionising radiation prior to conception 2.5-9.99mSv exposure was associated with a nearly 3-fold increase odds of stillbirth (aOR 2.8 (95% CI 1.0, 7.6)). Association of 10.0-19.99mSv exposure to radiation demonstrated further increased association (non-significant) with stillbirth odds compared with non-monitored women (aOR 3.1 (95% CI 0.9, 10.3)). These results demonstrate possibly significant relationships between maternal ionising radiation and stillbirth risk and warrant further investigation to validate these findings.

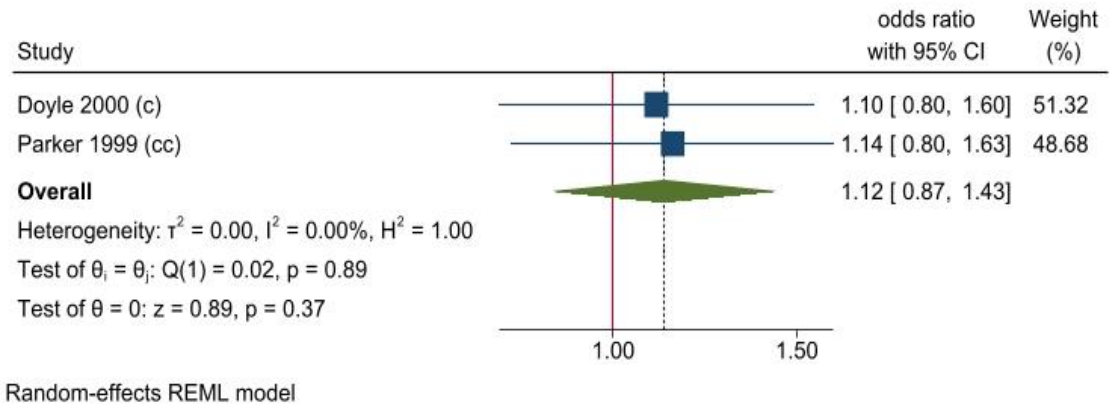
Paternal occupation

Eight studies reported the impact of paternal occupation on stillbirth odds within populations from four high-income countries, the UK, Germany, Norway and the USA[60, 200, 395, 399, 400, 402-406]. Two of the studies examining paternal occupation were deemed as having a high risk of bias[395, 403], one due to self-reporting of employment status; the authors of this study reported potential for misclassification as ‘home-makers’ due to the stigma surrounding unemployment, they also highlight concern regarding lack of adjustment in results[395]. The other study was deemed to have a high risk of bias as two different questionnaires were used through this research; one questionnaire used did not

collect stillbirth outcomes[403]. This study used an unsuitable reference group due to the similar nature and exposures between the exposure and referent groups (flight attendants with reference to air traffic controllers). Two studies were assessed as having an unclear risk of bias[200, 404], and four studies were deemed to have a low risk of bias[60, 399, 400, 402, 405, 406]. Occupations included in this review involved occupational exposure to ionising radiation, exposure to radiofrequency, veterans, flight crew, unemployment, homemaking, and sea diving.

Exposure to ionising radiation

Two studies examined the potential for exposure to ionising radiation during employment to increase the odds of stillbirth[60, 400, 405, 406]. One study included men who worked at a nuclear power plant in the UK[60, 405, 406], and the other included a population of men who worked at the Atomic Energy Authority, Atomic Weapons Establishment and British Nuclear Industry in the UK[400]. The studies detail records of external ionising radiation monitoring, and internal ionising radiation monitoring where an exposure was thought to have occurred, and internal monitoring was indicated. Both studies used different time periods of exposure and examined internal ionising radiation exposure as well as cumulative exposure prior to conception of 100mSv. When internal monitoring for ionising radiation exposure was warranted, results of meta-analysis indicated no clear association between internal monitoring for radiation exposure and odds of stillbirth (aOR 1.12 ((95% CI 0.87, 1.43) – fig 4-33) compared with non-monitored fathers.



(c) = cohort study design
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Figure 4-33 Meta-analysis demonstrating the association between paternal exposure to ionising radiation deemed as requiring internal monitoring and stillbirth odds compared with non-monitored fathers.

Two studies[60, 400] included annual exposure to ionising radiation and included fathers who had recorded 100mSv exposure prior to conception compared with workers who did not require monitoring due to non-exposure to radiation. Combined meta-analysis demonstrated an increased association between this level of ionising radiation exposure and odds of stillbirth (aOR 1.26 (95% CI 1.07, 1.47) -fig 4-34).

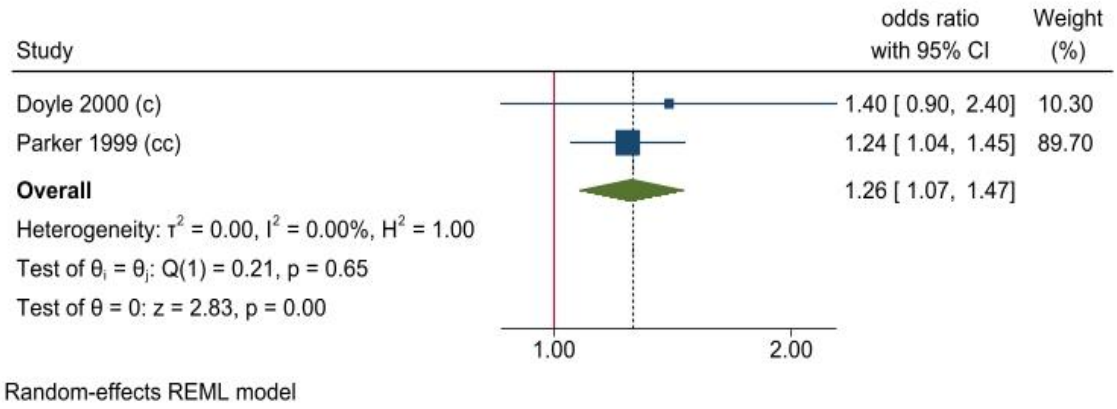

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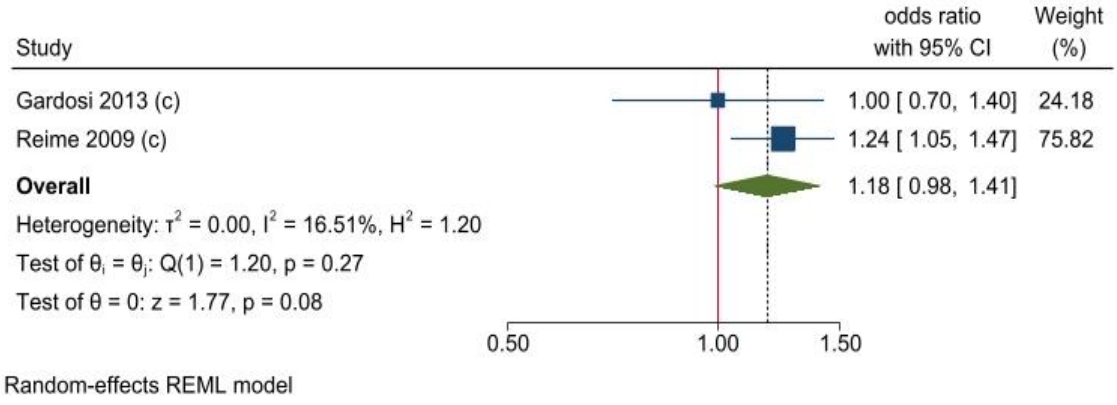
Figure 4-34 Meta-analysis demonstrating the association between paternal exposure to 100mSv (annual cumulative dose) prior to conception and stillbirth odds compared with non-monitored fathers.

Doyle et al[400] also further stratified smaller exposure levels below 100mSv and found no increase in stillbirth odds for lower levels of exposure preceding conception.

Paternal unemployment

Two studies examined the impact of paternal unemployment and odds of stillbirth[200, 395]. One study reported no increased association with stillbirth odds[200], and the other demonstrated a 24% increase in the odds of stillbirth when the father reported unemployment[395]. Meta-analysis demonstrated a non-significant increase in stillbirth odds associated with paternal unemployment (aOR 1.18 (95% CI 0.98, 1.41) – fig 4-35).



(c) = cohort study design
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Figure 4-35 Meta-analysis demonstrating the odds of stillbirth associated with paternal unemployment and stillbirth odds compared with employed fathers.

Homemaker occupation

One study included paternal homemaker status as an occupation category of exposure compared with professional occupations, and the results demonstrated an increased association between paternal homemaker status and stillbirth odds (aOR 1.27 (95% CI 1.00, 1.62))[395]. Results were well adjusted, but authors highlight the potential for

misclassification of unemployed fathers categorised as homemakers due to potential stigma associated with unemployment. The study did not provide clearly defined distinctions for homemaking versus unemployment.

Occupational radiofrequency radiation at the time of conception

One study reported the odds of stillbirth associated with paternal exposure to occupational radiofrequency radiation at conception[404] compared with fathers in occupations where occupational exposure to radiofrequency was minimal. This study used a national Norwegian register dataset and categorised paternal exposure as possible or probable, reporting unclear association with radiofrequency exposure, with "possible" (aOR 1.01 (95% CI 0.92, 1.11)) or "probable" (aOR 1.09 (95% CI 0.89, 1.29)) exposure, compared with fathers who were probably not exposed to occupational radiofrequency[404].

Flight crew

One study examined the impact of paternal occupation as a flight crew member and the odds of stillbirth[403]. The study was conducted in the UK and found that flight crew have a nearly three-fold increased risk of stillbirth compared with air traffic control officers (aOR 2.85 (95% CI 1.30, 6.23)). Results of the quality and bias assessment of this study identified multiple concerns as air traffic control officers have the potential to be exposed to the same levels of pollution, shift work and environment as flight crew, yet an opposing argument presents that the comparability of the occupations results in findings directly related to high altitude exposure. Furthermore, the study did not specify the time of exposure to the occupation in relation to conception and pregnancy. These findings need to be confirmed through further research using larger study populations with potential to reference exposure to the general population.

Gulf war veteran status

One study examined the odds of stillbirth for fathers identified as a Gulf War veterans[399] compared with non-Gulf war veterans. The study found the odds of stillbirth to be possibly increased for couples with paternal Gulf War veteran status (aOR 1.65 (95% CI 0.91, 2.98)), but did not adjust for maternal morbidities or maternal occupation in their final analysis. Wide confidence intervals suggest an underpowered analysis.

Deep-sea divers

Within this review, one study examined the impact of deep sea diving on stillbirths odds within a population of Norwegian fathers[402]. Although the study reported higher risk of miscarriage (aOR 1.21 (95% CI 1.05, 1.39)) in the exposure population, the analysis demonstrated a minimally protective effect on stillbirth odds for men who ever dived (aOR 0.68 (95% CI 0.54, 0.87)), North Sea divers (aOR 0.57 (95% CI 0.24, 1.35)) and divers who held an active diving certificate at the time of conception (aOR 0.90 (95% CI 0.49, 1.67)) compared with the general population. The study did not provide accurate GA or birthweight parameters of stillbirth or births included and therefore the findings should be interpreted with caution.

Maternal sleep characteristics and position

Six studies examined the impact of maternal sleep position on stillbirth odds[32, 89-93]. Five studies sourced data from four high-income countries including the UK, USA, New Zealand, and Australia and one study used a web-based questionnaire encompassing fifteen countries [90]. Of the included studies, two were assessed as having a low risk of bias[89, 91], three had an unclear risk of bias[32, 92, 93], and one demonstrated a high risk of

bias[90]. The high risk of bias was attributed to the online self-reported and web-based nature of the study survey. The study furthermore did not follow-up the control group to ascertain birth outcomes, resulting in differences in follow-up periods for cases and controls. All studies but one included third trimester births in analysis. O'Brien et al[90] was excluded from all meta-analysis due to its use of the same dataset as two larger included studies in this meta-analysis[32, 91].

Maternal sleep quantity per night

Four studies within this review examined the association between number of hours sleep and odds of stillbirth[32, 90, 91, 93]. Two studies[32, 91] reported using the same dataset and therefore the smaller of the two studies was excluded from meta-analysis. All studies used a similar reference group (~6-8.5 hrs of sleep), compared with <6 hours of sleep per night, and >9 hours of sleep per night. Each resultant meta-analysis included three studies[32, 91, 93]. Women who reported <6 hours of sleep per night experienced nearly double the odds of stillbirth (aOR 1.83 (95% CI 1.40, 2.40) – fig 4-36), whereas women who reported >9 hours of sleep per night did not show a clear association compared with women who reported between ~6 to 8.5 hours sleep (aOR 1.26 (95% CI 0.77, 2.06) – fig 4-37).

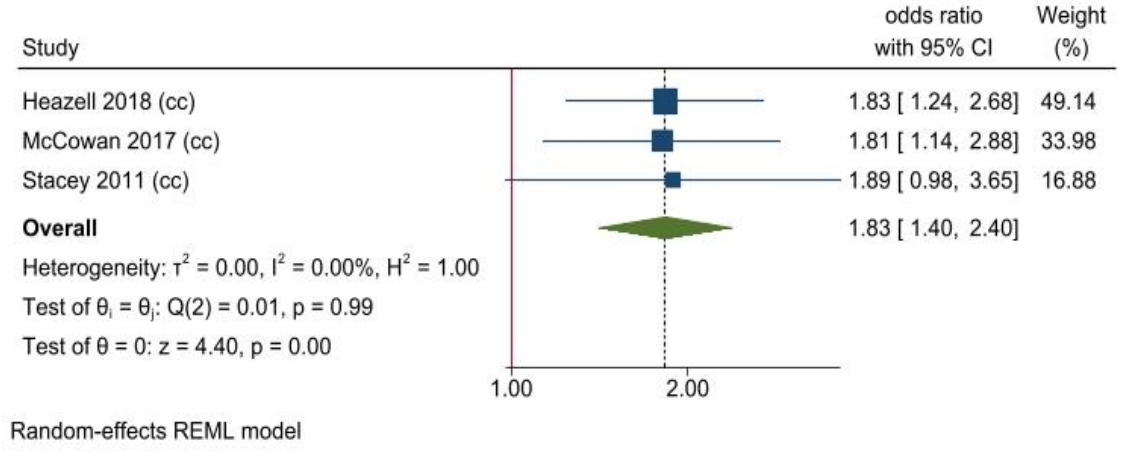

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Figure 4-36Meta-analysis demonstrating the association between <6 hrs sleep per night and stillbirth odds compared with ~6-8.5 hrs sleep per night.

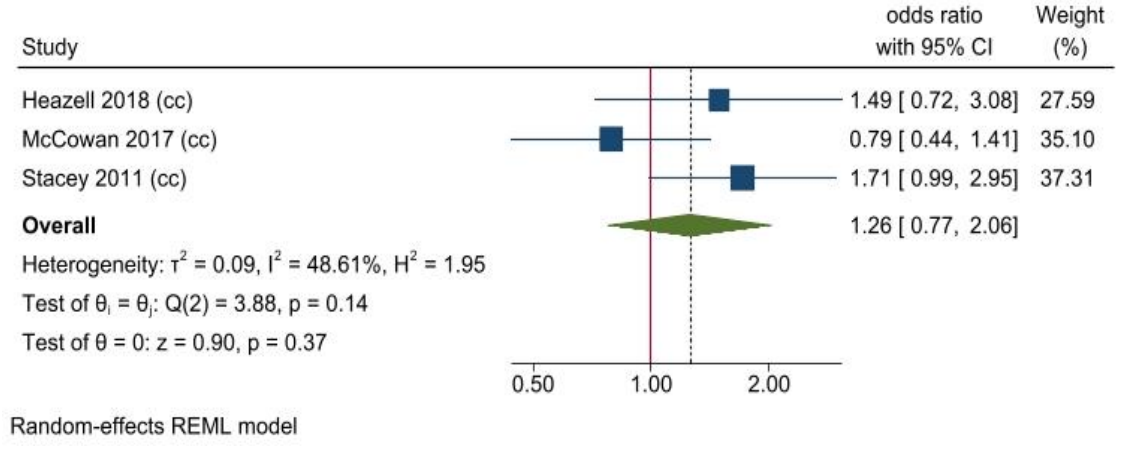

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Figure 4-37Meta-analysis demonstrating the association between >9 hrs sleep per night and stillbirth odds compared with ~6-8.5hrs per night.

Maternal report of awakenings during the night

Four studies examined the odds of stillbirth associated with maternal number of awakenings through the night [32, 90, 91, 93] . Women awaken during the night for several reasons (toileting, hunger, habitual etc), resulting in disturbed sleep, and less time asleep. Women who reported waking ≤1 time during the last night were grouped and compared with women who woke >1 time during the last night. One study[90] contained data from women also included in two larger included studies[32, 91] within this analysis and therefore the smaller study was excluded from analysis. All studies used a similar reference group; women who reported that they were awake more than once during the night prior to stillbirth. The resultant analysis demonstrated that the odds of stillbirth were increased for women who reported only waking once or less during the night compared with multiple awakenings (aOR 2.24 (95% CI 1.58, 3.17) – fig 4-38).

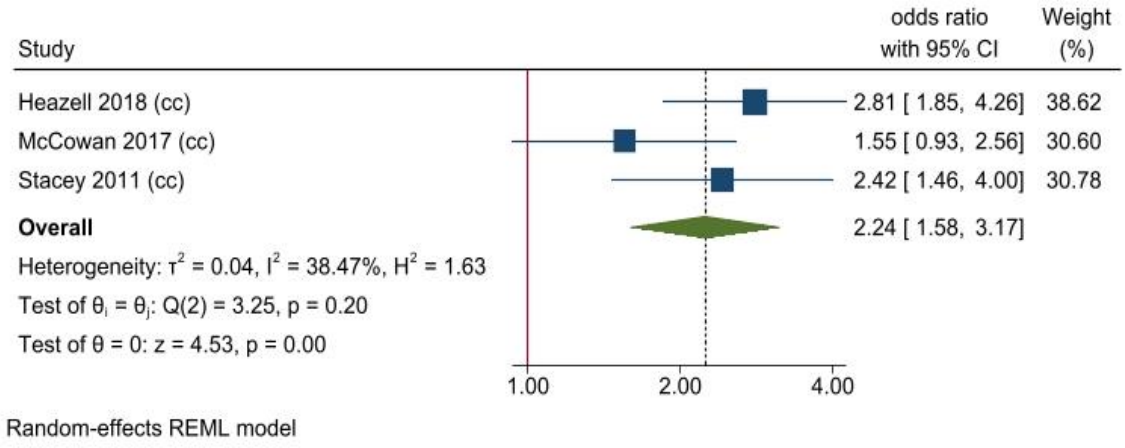

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Figure 4-38 Meta-analysis demonstrating the association between maternal awakening less than once a week and stillbirth odds compared with multiple awakenings per night.

Maternal daytime sleep quantity

Four of the studies examined the impact of maternal daytime sleep on the odds of third trimester stillbirth[32, 90, 91, 93]. Two study cohorts were sourced from New Zealand[32, 93], one from the UK[91], and one utilised a global web based survey across multiple countries[90]. Three studies reported the impact of often, or occasional daytime naps on third trimester stillbirth odds[32, 90, 91]. One study[90] used data that overlaps with cohorts of other included studies[32, 91]. To avoid double-counting births, the smaller study was excluded from analysis[90]. The results of both meta-analyses for occasional (aOR 0.91 (95% CI 0.59, 1.41) – fig 4-39), or often (aOR 1.14 (95% CI 0.63, 2.08) – fig 4-40) daytime naps demonstrated no clear significant association with stillbirth. Four studies reported the association between excessive daytime naps and stillbirth odds, three were included in analysis. There was an almost doubled odds of stillbirth when mothers reported excessive napping during pregnancy compared with no daytime napping, aOR 1.84 (95% CI 1.34, 2.52). Excessive napping was defined as every day by two studies[91, 93], and ≥ 5 times a week by the third study [32].

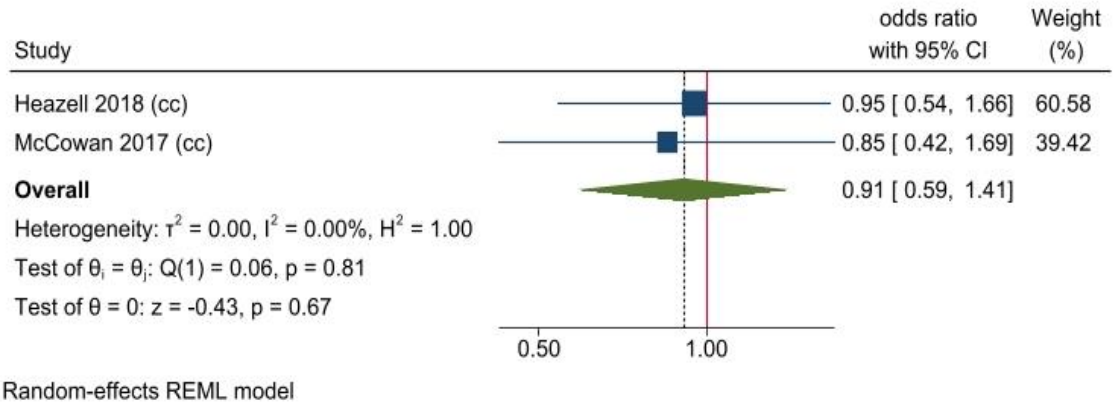

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Figure 4-39 Meta-analysis demonstrating the association between maternal occasional daytime naps and stillbrith odds compared with never having a daytime nap.

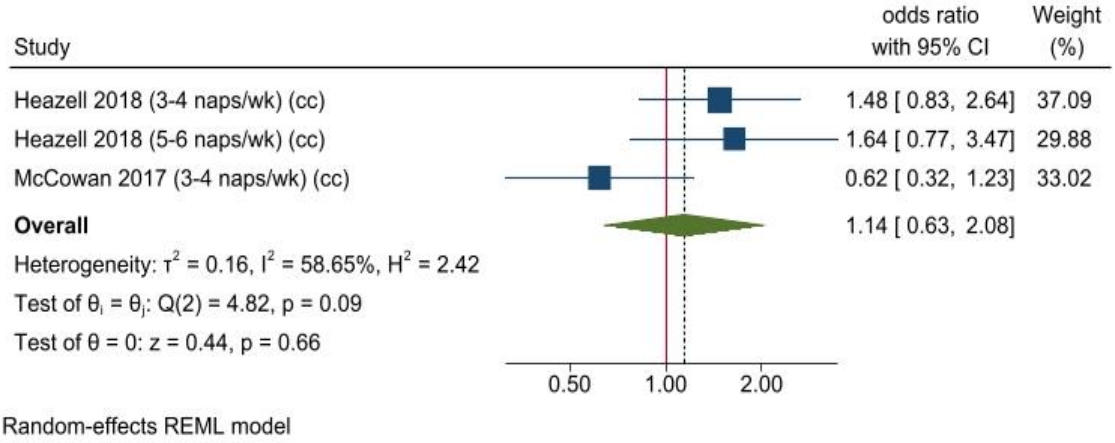

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Figure 4-40 Meta-analysis demonstrating the association between frequent daytime naps (3-6 naps/week) and stillbirth odds compared with women who never nap.

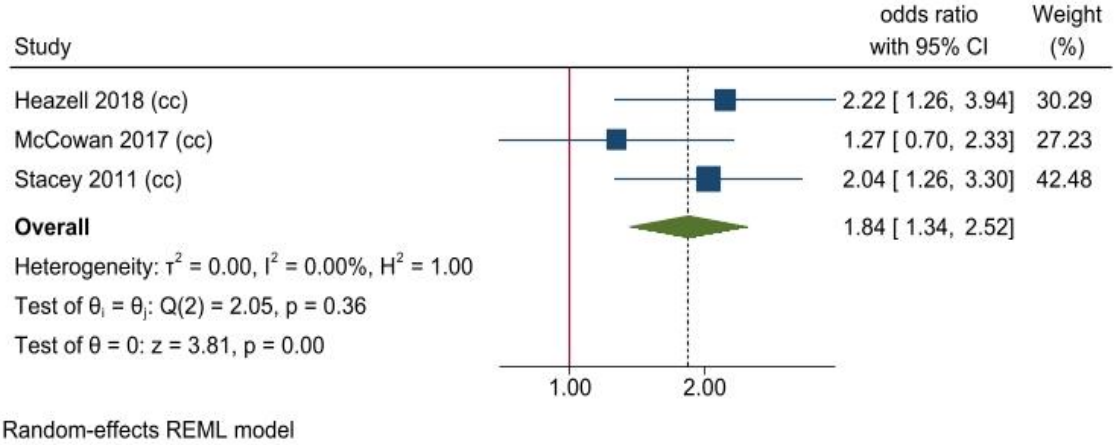

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Figure 4-41 Meta-analysis demonstrating the association between excessive daytime naps and stillbirth odds compared with no daytime naps.

Maternal sleep position

Six studies reported the odds of stillbirth associated with varying going to sleep positions as reported by the mother[32, 89-93]. Positions of going to sleep included right ride, left side, propped, supine, prone, variable, and other.

Supine going to sleep position

Five studies reported the odds of stillbirth associated with supine going to sleep position[32, 90-93], one study included results of a global web-based survey and due to the potential for double counting births, was excluded from analysis. Four of the studies were included in final meta-analysis[32, 91-93]. Results demonstrated a three-fold increase in the odds of stillbirth for women who went to sleep in a supine position, compared with a left lateral position (aOR 3.00 (95% CI 1.92, 4.70) – fig 4-42).

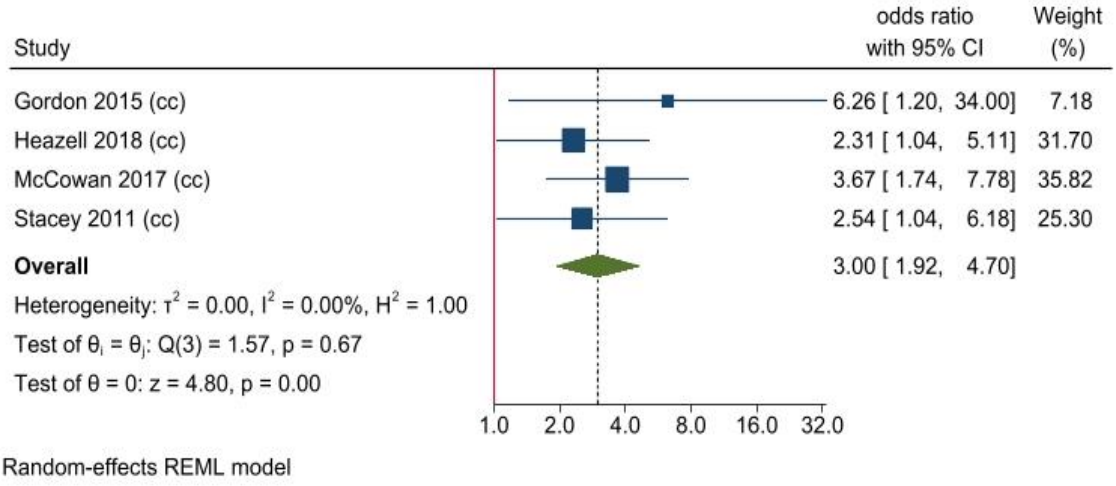

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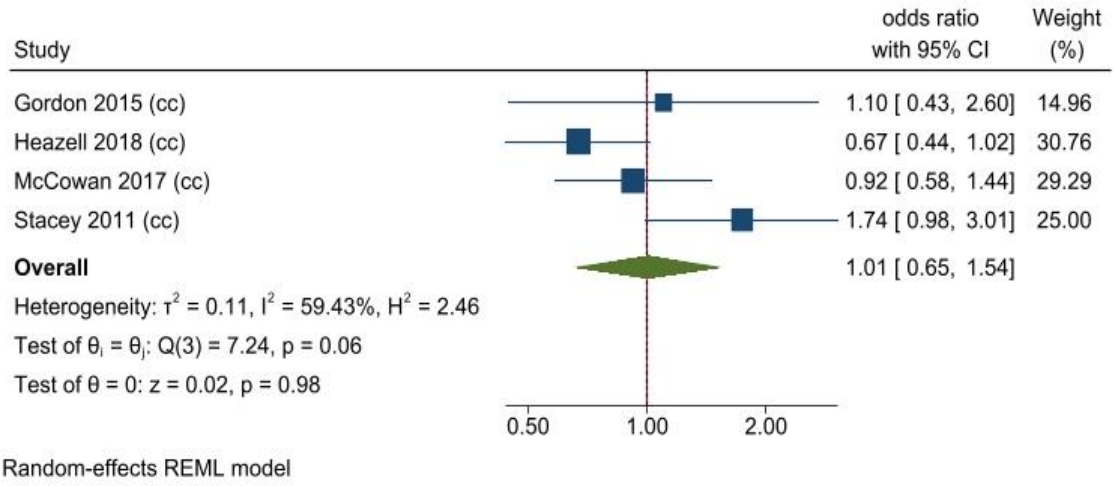
Figure 4-42 Meta-analysis of the association between maternal supine going to sleep position and stillbirth odds compared with left-sided going to sleep position.

Right sided going to sleep position

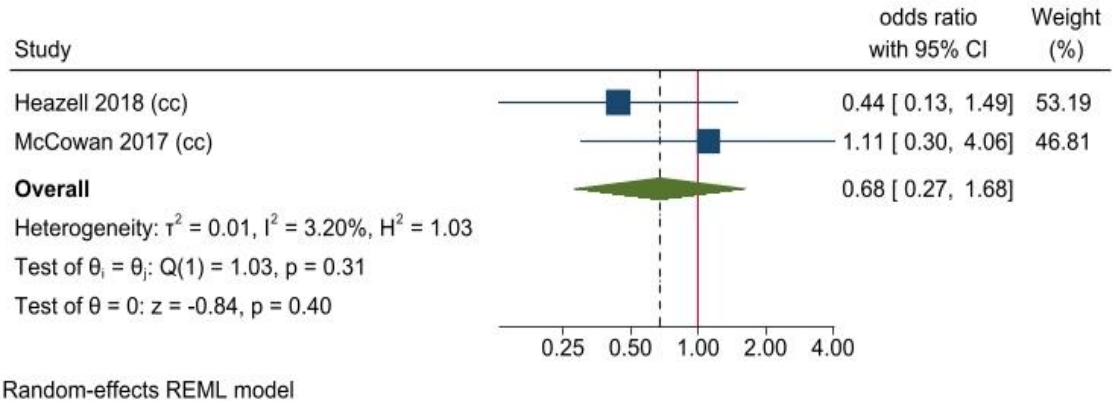
Five studies reported the odds of stillbirth associated with right sided going to sleep position[32, 90-93], and four of the studies were included in final meta-analysis[32, 91-93]. O'Brien et al was excluded due to the cohort overlapping with two larger included studies in this meta-analysis[32, 91]. Final meta-analysis demonstrated no association between a right sided sleep position, and stillbirth odds compared with a left sided sleep position (aOR 1.00 (0.66, 1.54) – fig 4-43).



(c) = cohort study design
(cc) = case-control study design
Figure 4-43 Meta-analysis of the association between right-sided sleep position and stillbirth odds compared with left-sided sleep position.

Maternal propped going to sleep position

Three studies included examined the odds associated with maternal propped position when they fell asleep, and stillbirth[32, 90, 91]. Two studies reported use of the same dataset, therefore the smaller of the studies was excluded from analysis[90]. Results demonstrated a non-significant protective association between sleeping propped and stillbirth odds, compared with left sided sleeping (aOR 0.68 (95% CI 0.27, 1.68) – fig 4-44).



(c) = cohort study design
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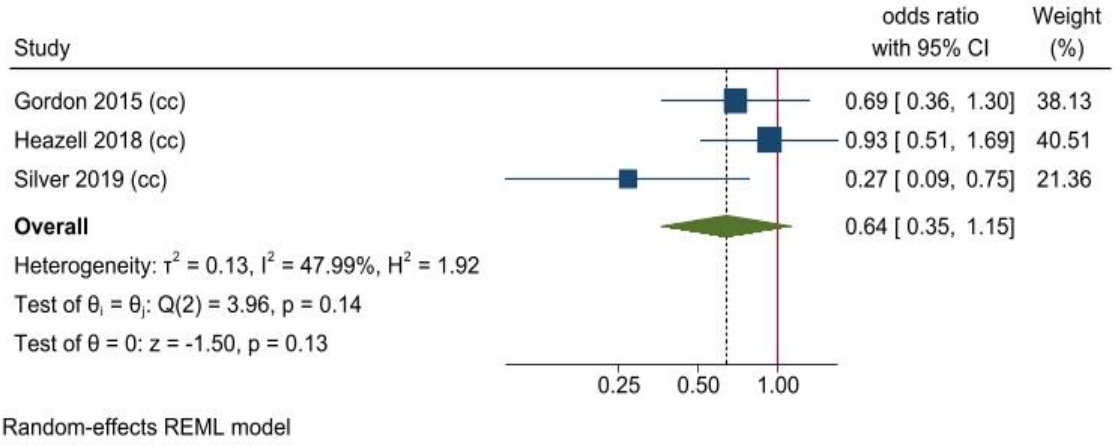
Figure 4-44 Meta-analysis of maternal propped going to sleep position and stillbirth odds compared with left-sided sleep position.

Association between maternal variable/other sleep position

Five studies reported the odds of stillbirth associated with a variable or 'other' sleep position and stillbirth odds[89-93] . Meta-analysis exhibited considerable heterogeneity, thus sensitivity analysis was performed. Stacey et al[93] was shown to contribute greatly to heterogeneity, this was attributed to over-adjustment of results. Final meta-analysis demonstrated a non-significant protective association between variable/other sleep position and stillbirth odds (aOR 0.64 (95% CI 0.35, 1.15) – fig 4-45). Results should be interpreted with caution, due to small cohort sizes.



(c) = cohort study design
(cc) = case-control study design
Figure 4-45 Meta-analysis of a variable maternal going to sleep position and stillbirth odds compared with left-sided going to sleep position.

Maternal nutrition

Nine studies examined maternal dietary nutritional components and their association with stillbirth rates[257, 364, 372-374, 377-379, 381, 382]. Three examined the impact of nutrition programs[364, 373, 379, 381], four investigated the impact of caffeine intake during pregnancy[257, 372, 374, 382], and two investigated the association with maternal supplement use[377, 378]. Study populations spanned four high-income countries, Australia, the USA, Uruguay and Denmark, with six cohort studies and three case-control studies[257, 373, 377]. None of the studies demonstrated a high risk of bias. Five studies exhibited unclear risk of bias[257, 364, 378, 379, 381, 382], and four were deemed to have a low risk of bias[372-374, 377]. Unclear risk of bias was predominantly attributed to method of data collection during pregnancy. Nutritional data collection at a single timepoint was deemed insufficient to adequately assess and draw inferences regarding the associated stillbirth risk.

Nutrition programs

Nutritional programs included in this review included government incentive programs as well as evaluation of maternal diet using established diet scores. Review included three USA studies analysing the odds of stillbirth in relation to one government program, and three pre-defined diet scores.

Two studies examined the benefit of the Women, Infants and Children program (WIC)[1] in prevention of stillbirth odds[373, 381], one stratified the results by maternal ethnicity[373], and the other stratified results by maternal level of education[381]. Differences in

[1] The Special Supplemental Nutrition Program for Women, Infants and Children (WIC) program was established in the 1970s in the USA by the government to improve nutrition of targeted populations[130] .Women in the USA are assessed for eligibility for the WIC program which assists in the purchase of nutritious food [137] Eligibility is based on residency identity (benefits must be received in the state of residency), income eligibility, nutritional risk and categorical eligibility. Pregnant women can be enrolled in the program at any stage during pregnancy until the first 6 weeks following birth, enrolment is voluntary[137]

stratification prevented meta-analysis of the study results. Enrolment in the WIC program was associated with the a decrease in stillbirth odds for black non-Hispanic women compared with black non-Hispanic non-enrolled women (aOR 0.31 (95% CI 0.14, 0.68))[376] Reduction of stillbirth odds was not replicated for enrolled white women (aOR 1.49 (95% CI 0.66, 3.35)) or enrolled Hispanic women (aOR 1.14 (95% CI 0.67, 1.94))[373] compared with their non-enrolled white and Hispanic counterparts.

El-Bastawissi et al[381] compared the association of WIC enrolled women and stillbirth odds compared with WIC eligible women who did not enrol into the nutritional program. Results were stratified by maternal educational level, and demonstrated that enrolment into the nutrition program prevented stillbirth for all women compared with non-enrolment of eligible women[381] (with the exception of women who reported ≥16 years of education) (table 4-6).

Table 4-6 El-Bastawissi et al[381] results demonstrating the association with stillbirths of WIC enrolment versus non-enrolment, stratified by maternal education level

Maternal level of education	**Risk of stillbirth associated with enrolment in WIC (aOR (95% CI))***
<12 years	**0.2 (0.1, 0.3)**
12 years	**0.4 (0.3, 0.7)**
13-15 years	**0.3 (0.1, 0.7)**
≥ 16 years	1.4 (0.4, 4.3)

**aOR are adjusted for education, race, marital status, smoking, adequacy of prenatal care, and gravidity.*

Dietary scores are frequently used to assess the quality of a person's nutrition in relation to predefined criteria. Gaskins et al used pre-pregnancy dietary scores and presented findings of a life-long study of nurses that used a 131-item food frequency questionnaire to assess diet and pregnancy outcomes[364, 379]. Results demonstrated an unclear risk of bias as the dietary information was collected within 4 years prior to pregnancy outcome, and not at the time of pregnancy. The women's diets were compared with the healthy eating Index 2010 (aHEI-2010), an alternative Mediterranean diet (aMED) and the Fertility Diet (FD). Results demonstrated large confidence intervals across all groups, which indicated that the study was underpowered for analysis. Despite this, women in the top quartile of adherence to the Mediterranean diet demonstrated decreased odds of stillbirth when used as the reference group in comparison to all other quartiles of diet adherence. The results of this study were inconclusive and unable to be generalised to a wider population due to the time span between exposure and stillbirth. Further research needs to be conducted regarding maternal diet patterns and stillbirth odds.

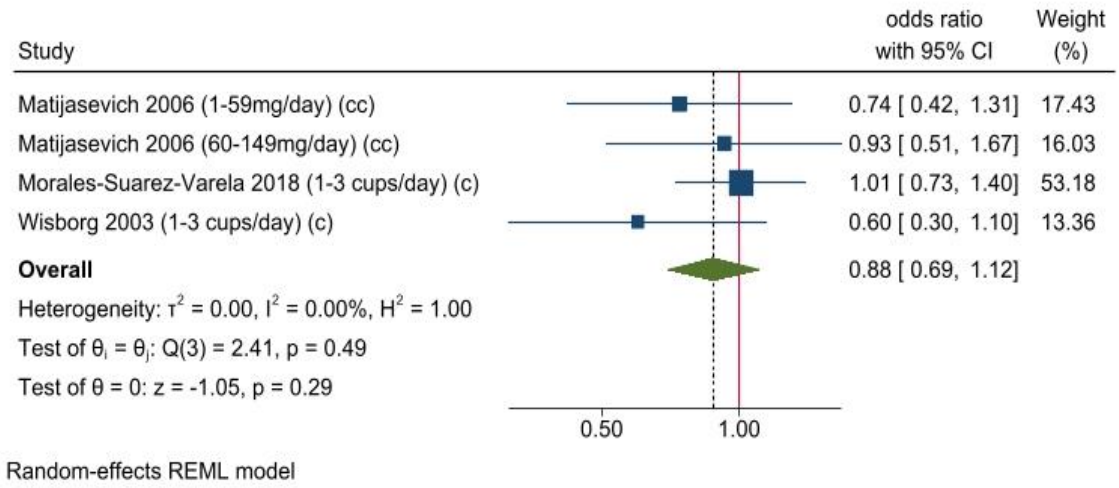
Caffeine intake

Four studies assessed the impact of caffeine intake during pregnancy and its association with stillbirth odds[257, 372, 374, 382]. All studies examined multiple sources of caffeine (tea/cola/coffee), and one examined the consumption of coffee/tea/cola and/or Mate in Uruguay[257]. The study populations included were sourced from three high-income countries; Denmark, Uruguay, and the USA. The timepoint of data collection differed by study, from the first antenatal visit in one study[372], midway through the pregnancy in

another[382], and one study collected data within 24 hours post-birth[257]. One study restricted its analysis to cigarette smokers so was reviewed separately[374].

1-3 cups of caffeine/day

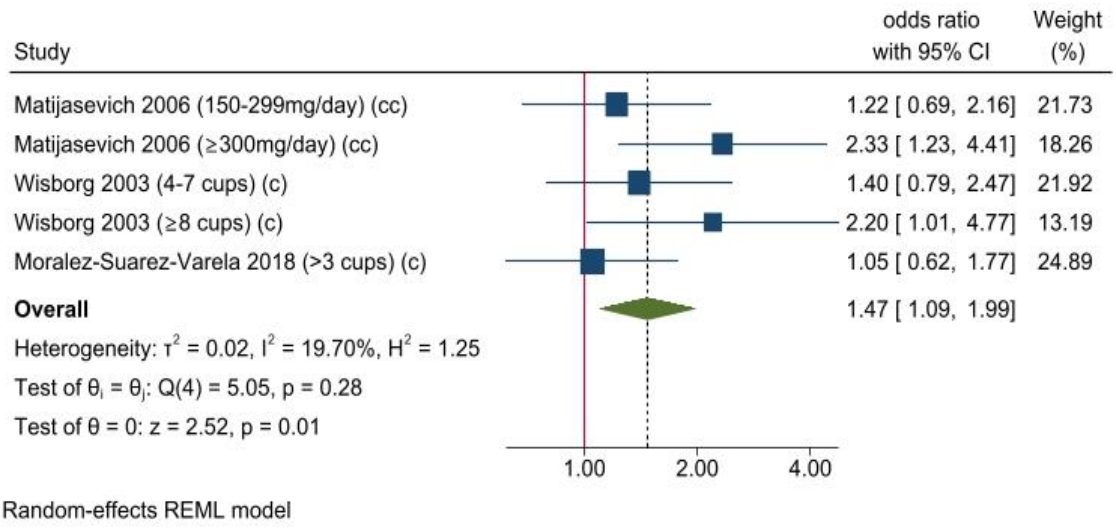
Three studies examined the association between 1-3 cups of caffeine per day during pregnancy with stillbirth odds compared with no caffeine intake[257, 372, 382]. One study stratified analysis by mg/d of caffeine therefore all measures at ≤~120mg/day were included in analysis of 1-3 cups of caffeinated beverages/day (compared with no caffeine intake). The studies included used different stillbirth definitions; two studies included stillbirths ≥28 weeks GA[374, 382] and one study examined stillbirths from 20 weeks GA onwards[257]. The results demonstrated no clear association between 1-3 cups of caffeine per day and stillbirth odds (aOR 0.88 (95% CI 0.69, 1.12) – fig 4-46).



(c) = cohort study design
(cc) = case-control study design
Figure 4-46 Meta-analysis demonstrating the association between 1-3 cups of caffeine/day (<149mg/day) and stillbirth odds compared with no caffeine intake.

≥3cups of caffeine/day

The same three studies also examined the association between high caffeine intake per day (≥3 cups/≥300mg/day) and stillbirth odds. Meta-analysis of all studies examining high caffeine intake demonstrated increased odds of stillbirth associated with ≥3 cups of coffee/day during pregnancy (aOR 1.47 (95% CI 1.09, 1.99) – fig 4-47) compared with no caffeine intake. However, data collection of caffeine intake at one point during pregnancy fails to account for changes in frequency of caffeine intake over the entire pregnancy, which may also alter the odds of stillbirth.



(c) = cohort study design
(cc) = case-control study design
Figure 4-47 Meta-analysis demonstrating the association between >3 cups of caffeine intake per day(>150mg/day) and stillbirth odds comapred to no caffeine intake.

Caffeine intake and smoking status

One study examined caffeine intake in a Danish cohort stratified by smoking quantity and the association with stillbirth odds[374]. The study found that increased caffeine intake increases stillbirth odds. Through further analysis, it was shown that women who had decreased smoking exposure alone did not decrease odds of stillbirth odds, but a combination of reduced caffeine intake as well as cigarette use resulted in decreased odds of stillbirth compared with no caffeine intake (table 4-7).

Table 4-7 Morales-Suarez-Varela et al demonstrating the association between maternal exposure to caffeine and cigarettes, and stillbirth odds compared with women who did not drink caffeine or smoke cigarettes[374]

		Cups of caffeine/day		
		0 cups	≤3 cups *(aOR (95% CI)*	>3 cups *(aOR (95% CI)*
Cigarettes/day	0	Referent	-	-
	≤10	-	0.95 (0.74, 1.25)	**1.33 (1.01, 1.75)**
	>10	-	0.99 (0.59, 1.66)	**1.85 (1.33, 2.56)**

Maternal vitamin D status

One study examined maternal serum vitamin D status within the first trimester (10-14 weeks GA) and odds of stillbirth[377]. The results of this study were inconclusive as subgroups were too small for meaningful analysis. The study also only measured vitamin D status at one point during pregnancy and failed to account for maternal increase in vitamin D status or supplementation with vitamin D during pregnancy.

Maternal multivitamin use

One study examined maternal use of multivitamins before and during pregnancy to investigate the associated stillbirth odds[378]. This large cohort study examined overall multivitamin use as a dichotomous value (y/n) and found no association with stillbirth

between women who did use multivitamins compared with those who did not (aOR 0.97 (95% CI 0.70, 1.35)). The study further stratified women by timing of multivitamin use according to conception, and demonstrated an increase in odds of stillbirth for women who used multivitamins for 5-6 weeks prior to conception (aOR 1.83 (95% CI 1.11, 3.03)). The study adjusted comprehensively for confounders in its analysis.

Maternal folate use

Two studies examined the impact of maternal preconception folate intake and the association with odds of stillbirth[364, 378, 379]. Gaskins et al[364, 379] examined the association within a cohort of ~15,000 American women. Women were grouped by quintiles of folate consumption and included all dietary forms of folate in their analysis alongside supplement use[364, 379]. Through all quintiles of folate consumption, Gaskins et al found marginal protective effects against stillbirth risk, the lowest quintile of folate consumption demonstrated the greatest protective effect against stillbirth (aOR 0.55 (95% CI 0.30, 1.00)) compared with no pre-pregnancy folate supplementation. Nohr et al[378] assessed folate supplement use dichotomously within a large cohort of Danish women (~36,000 women) and found no association between maternal folate supplement use compared with non-use during preconception (aOR 1.01 (95% CI 0.53, 1.92)).

Physical activity

One study examined the impact of physically inactivity during pregnancy and its association with stillbirth odds[126]. The study was assessed by reviewers using the RTI tool of assessment of bias and demonstrated unclear risk of bias due to poor detection of exposure measures. This was predominantly due to poor descriptors of exposure measures (inactive vs active), and also due to lack of adjustment for important confounders (e.g. Maternal BMI). Women were described as active or inactive during pregnancy and inactivity was found to be associated with an increased in stillbirth odds through multivariate analysis adjusted for maternal age, smoking, previous stillbirth and ART use (aOR 1.67 (95% CI 1.00-2.80)). Through further analysis, results demonstrated that inactive women were predominantly from households with an income between $40,000 and $60,000/year, and lowest rates of inactivity were associated with very low-income households (income < $20,000/year).

Maternal dental care

One study[444] examined the association between amalgam dental filling and stillbirth odds within a Norwegian cohort of women. Results demonstrated no association between the number of amalgam fillings at the time of pregnancy. Results further investigated the association between amalgam filling removal during pregnancy, and found no association between amalgam filling removal between 1-30 weeks GA, and stillbirth odds (aOR 1.31 (95% CI 0.61, 2.82))[444].

Place of birth

Seven studies examined the association between place of birth and the odds of stillbirth[113, 157, 408, 410-413]. Studies included cohorts from four high-income countries including Australia, the USA, Norway, and the Netherlands. All studies were assessed

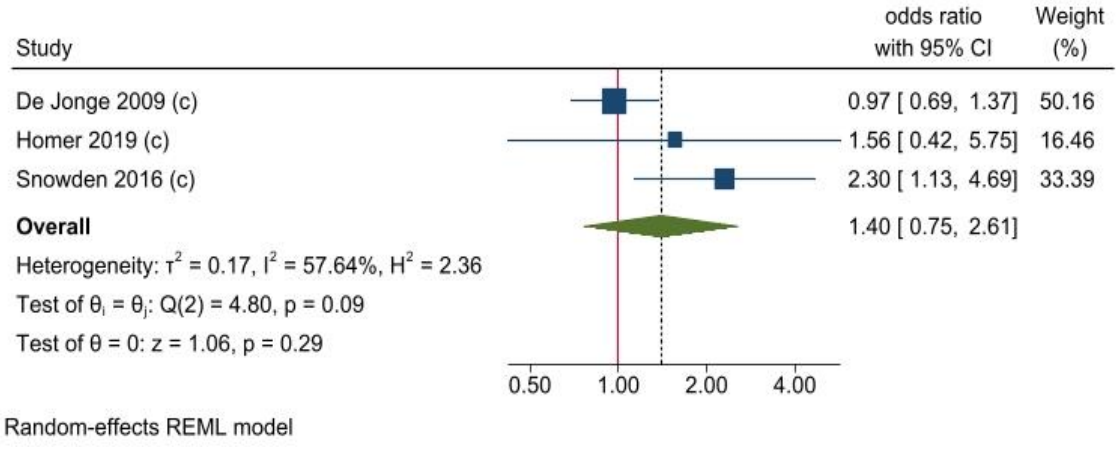
using the RTI tool of assessment and reviewers assessed three studies as having unclear risk of bias [157, 408, 413], and four studies with low risk of bias[113, 410-412]. No studies demonstrated a high risk of bias. Through analysis studies examined stillbirth odds associated with home births, births at birth centres and unplanned place of births.

Birth centres

Two studies assessed the odds of stillbirth associated with birthing at a birth centre[408, 412]. Both studies used Australian perinatal data from overlapping time periods, and thus were unable to be combined in meta-analysis. Within Australia, birth centres are predominantly attached to hospitals, run by teams of midwives and mimic a "home-like" setting for birth. Both studies reported odds ratios for term births (≥ 37 weeks GA) and reported comparable findings: aOR 0.78 (95% CI 0.41, 1.48)[408] and aOR 0.99 (95% CI 0.78, 1.26)[412]. Homer et al's[408] findings demonstrated a greater protective effect of birth centre births on stillbirth odds, the authors explain that this could in part be due to the exclusion of high risk or complicated pregnancies from analysis.

Home births

Four studies examined the impact of delivering at home (term pregnancies (≥37 weeks GA)) and the associated odds of stillbirth[113, 408, 410, 413] compared with hospital births. One study[413] used a cohort that overlapped with another cohort [408], therefore the smaller of the two studies was excluded[413]. The resultant meta-analysis included three studies and demonstrated possible increase in odds of stillbirth associated with home births compared with hospital births (aOR 1.40 (95% CI 0.75, 2.61) – fig 4-48). Heterogeneity between studies is moderate at 57.64% and thought to represent the differences between the populations accessing home births between the countries. In the Netherlands, women have access to universal healthcare, and home births, although declining, are still proportionately high compared with other high-income countries[409].

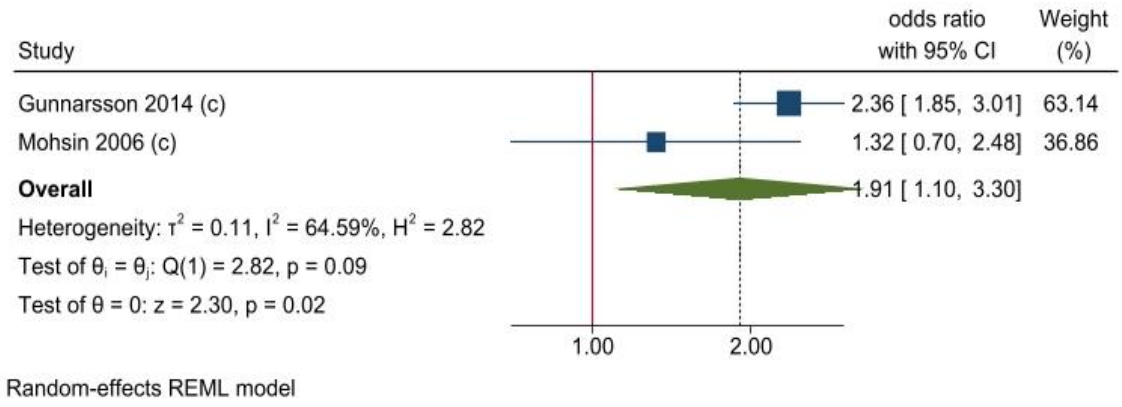


(c) = cohort study design
(cc) = case-control study design

Figure 4-48 Meta-analysis of the association between home births and stillbirth compared with hospital births.

Unplanned place of birth

Two studies examined the impact of unplanned place of birth on stillbirth odds in high-income countries[157, 411]. One study used an Australian population of women in New South Wales[157], and another used a national dataset of births in Norway[411]. Gunnarsson et al[411] further stratified results by birth weight, and demonstrated that the impact of unplanned place of birth showed no association with stillbirth odds when birthweights exceeded 2500 grams (aOR 1.27 (95% CI 0.78, 2.08)). Meta-analysis results demonstrated that unplanned place of birth resulted in nearly double the odds of stillbirth (aOR 1.91 (95% CI 1.10, 3.30) – fig 4-49) compared with planned place of birth.



(c) = cohort study design
(cc) = case-control study design
Figure 4-49 Meta-analysis of the association between unplanned place of birth and stillbirth odds compared with planned place of birth.

Heterogeneity through analysis was considerable (I^2=64.59%) indicating large differences between the study populations. Each study used similar birth parameters for inclusion, comparable methodology, and comparable definitions of exposure measures. Therefore, increased heterogeneity may be due to the differences in populations between the countries included, as well as differences in the birth services and preparedness of emergency services attending births in unplanned places.

Table 4-8 Chapter 4 Summary of meta-analysis findings of modifiable risk factors during the antenatal period.

Factors	Referent group	Exposure group	Findings of meta-analysis aOR (95% CI) (all stillbirths ≥20 weeks GA)	Findings of meta-analysis aOR (95% CI) Second trimester stillbirth	Findings of meta-analysis aOR (95% CI) third trimester stillbirth
Antenatal care adequacy	Adequate antenatal care	*Inadequate antenatal care*	**3.24 (3.12, 3.36)**	-	-
	Adequate antenatal care	*No antenatal care*	**3.51 (1.79, 6.89)**	-	-
	Care initiation in the first trimester	*Care initiation in the second trimester*	0.93 (0.70, 1.25)	-	-
	Care initiation >20 weeks GA	*Care initiation in the first trimester*	1.23 (0.89, 1.70)	-	-
	50-109% of recommended antenatal visits completed	*≤50% of recommended antenatal care visits*	**1.94 (1.89, 1.99)**	-	-
	100% of recommended visits attended	*50-99% antenatal care visits*	**1.21 (1.18, 1.25)**	-	-
	100% of recommended antenatal care visits	*High levels of antenatal care*	1.02 (0.19, 5.35)	-	-
Assault during pregnancy	No record of assault during pregnancy	*Assault during pregnancy*	**3.16 (2.31, 4.32)**	-	-
Drug use	No Drug use	*Any illicit drug use during pregnancy*	1.43 (0.71, 2.88)	-	-
	No drug use	*Cannabis use during pregnancy*	**1.49 (1.39, 1.61)**	-	-

Alcohol use	No Alcohol use during pregnancy	*Any alcohol use during pregnancy*	**1.80 (1.37, 2.35)**	-	-
	No Alcohol use during pregnancy	*1-2 alcoholic drinks/week*	0.90 (0.75, 1.07)	-	-
	No Alcohol use during pregnancy	*3-4 alcoholic drinks/week*	1.19 (0.70, 2.01)	-	-
	No Alcohol use during pregnancy	*4+ alcoholic drinks/week*	1.39 (0.91, 2.11)	-	-
Smoking	Non-smokers	*Smokers*	**1.39 (1.25, 1.54)**	-	-
	Non-smokers	*Smoking during the third trimester*	**1.53 (1.39, 1.67)**	-	-
	Non-smokers	*Smoking cessation during pregnancy*	1.02 (0.94, 1.12)	-	-
	Non-smokers	*1-10 cigarettes/day*	**1.25 (1.05, 1.49)**	-	-
	Non-smokers	*≥10 cigarettes/day*	**1.98 (1.65, 2.36)**	-	-
	Non-smokers	*10-20 cigarettes/day*	**1.40 (1.31, 1.50)**	-	-
	Non-smokers	*≥20 cigarettes/day*	**1.81 (1.06, 3.09)**	-	-
	Women not exposure to second-hand smoke	*Exposure to second hand smoke reported*	1.20 (0.75, 1.91)	-	-
Vaccination	No H1N1 vaccination during or immediately prior to pregnancy	*H1N1 vaccination during pregnancy*	**0.79 (0.68, 0.94)**	-	-
	No H1N1 vaccination during or immediately prior to pregnancy	*H1N1 vaccination during the first trimester of pregnancy*	0.89 (0.77, 1.03)	-	-

	No H1N1 vaccination during or immediately prior to pregnancy	*H1N1 vaccination during the 2nd trimester*	0.83 (0.59, 1.18)	-	-
	No H1N1 vaccination during or immediately prior to pregnancy	*H1N1 vaccination during the 3rd trimester*	**0.78 (0.65, 0.93)**	-	-
Maternal occupation	Employed women	*Unemployed women*	**1.33 (1.00, 1.78)**	1.17 (0.84, 1.64)	**1.87 (1.19, 2.94)**
	Employed women	*Homemaker*	1.35 (0.89, 2.05)	-	-
	non-healthcare workers	*Healthcare workers*	1.10 (0.90, 1.35)	-	-
	non-technical workers (teachers and unemployed women comprised reference groups)	*technical workers*	1.71 (0.86, 3.43)	-	-
Paternal occupation	Worker at nuclear plants not requiring internal radiation monitoring	*Exposed to occupational ionising radiation requiring internal monitoring*	1.12 (0.87, 1.43)	-	-
	Workers not monitored due to non-exposure to radiation	*Exposure to occupational ionising radiation of 100mSv (annual cumulative dose)*	**1.26 (1.07, 1.47)**	-	-
	Employed men	*Unemployed men*	1.18 (0.98, 1.41)	-	-
Maternal sleep characteristics	6-8.5hrs sleep per night	*<6 hrs sleep per night*	**1.83 (1.40, 2.40)**	-	-
	6-8.5hrs sleep per night	*>9hrs sleep per night*	1.26 (0.77, 2.06)	-	-

	>1 awakening during the night	*≤1 awakening during the night*	**2.24 (1.58, 3.17)**	-	-
	Never daytime naps	*Occasional daytime naps*	0.91 (0.59, 1.41)	-	-
	Never daytime naps	*3-6 naps per week*	1.14 (0.63, 2.08)	-	-
	Never daytime naps	*Excessive daytime naps*	**1.84 (1.34, 2.52)**	-	-
Maternal sleep position	Left lateral sleeping position	*Supine going to sleep position*	**3.00 (1.92, 4.70)**	-	-
	Left lateral sleeping position	*Right sided sleep position*	1.01 (0.65, 1.54)	-	-
	Left lateral sleeping position	*Propped going to sleep position*	0.68 (0.27, 1.68)	-	-
	Left lateral sleeping position	*Variable sleep position*	0.64 (0.35, 1.15)	-	-
Maternal diet	No caffeine intake	*1-3 cups of caffeine per day*	0.88 (0.69, 1.12)	-	-
	No caffeine intake	*≥3 cups of caffeine per day*	**1.47 (1.09, 1.99)**	-	-
Place of birth	Hospital birth	*Home birth*	1.40 (0.75, 2.61)	-	-
	Planned place of birth	*Unplanned place of birth*	**1.91 (1.10, 3.30)**	-	-

Discussion and conclusions

Through structured systematic searches, review and meta-analysis of findings, the odds of stillbirth were found to be moderately increased in association with inadequate antenatal care, physical assault during pregnancy, maternal smoking or snuff use, drug and alcohol use, supine sleep position, maternal weight loss, and select parental occupations. These risks associated with increased stillbirth odds may be modifiable through support and intervention during the antenatal period.

Our results indicate that characteristics regarding timing and quantity of antenatal care are, in some instances, associated with a 3-fold increase in stillbirth odds. There is little consensus between antenatal care recommendations across high-income countries. Indeed through our review, included studies referenced five separate guidelines, as well as use of different recommendations outside national guidelines. Four recommendations were that antenatal care be initiated within the first trimester of pregnancy, and two studies recommend initiation prior to 20 weeks GA. Our findings indicate that antenatal care initiation in the second trimester of pregnancy did not increase the odds of stillbirth compared with first trimester, although care initiated after 20 weeks GA was associated with an increased odds of stillbirth compared with earlier initiation. Globally, the recommended number of antenatal care visits during pregnancy differs across high-income country guidelines. The adequate number of visits spanned from seven (Australia) to fourteen (Germany). Through meta-analysis, we were able to examine the effect of maternal attendance at only 50-99% of antenatal care visits in two studies where the recommended number of visits was below 11. Analysis demonstrated an increased odds of stillbirth and maternal attendance of less than 100% of antenatal care visits, indicating that the minimum threshold of care visits before stillbirth odds increase may be 11. This is in line with previous research which has investigated the relationship between the number of antenatal care visits and stillbirth rates. Findings demonstrated a U-shaped curve of stillbirth rates associated with increasing number of antenatal visits, the lowest rate of stillbirth occurred at 14 antenatal care visits [(276)]. Two studies examine the association between high levels of antenatal care and stillbirth odds, but on review, there was high heterogeneity between the studies with differences in adjustment of confounders. Analysis demonstrated no association between high levels of antenatal care attendance and stillbirth odds, and it was acknowledged that the need for an increased number of visits may reflect other morbidities and conditions not examined in this review.

Assault against women is unfortunately common, with estimates that 22% of women in high-income countries have endured physical and/or sexual violence at least once in their lifetime[(277)]. Pregnancy is a time of shift in family dynamics, and can serve to put extra strain on relationships, finances and careers. Antenatal care can act as the crucial point through which to screen women and assess any risk of assault that may occur[(445)]. Previous findings have established domestic violence as a risk factor for poor perinatal outcomes, including low birth weight, preterm birth[(446, 447)], and threatened preterm labour[(447)]. Through our review, it is evident that the availability of data concerning assault and stillbirth outcomes is sparse. Hospital admission data were commonly used as a measure for maternal exposure to violence, as opposed to antenatal reporting through routine interviews. Analysis demonstrates a 3-fold increase in odds of stillbirth associated with assault during pregnancy, this increased when admissions for assault resulted in birth, with the odds of stillbirth at 8-fold that of non-assaulted women. These findings emphasise the crucial nature of reviewing the risk of maternal exposure to violence.

Qualitative surveys of midwives in a high-income setting identified that ongoing repeat family violence screening is the main facilitator assisting women to disclose risk[448, 449]. The same studies further identified the spouse as a barrier to family violence screening, as well as time available to offer adequate support and discussions concerning violence. We have identified that assault during pregnancy is one of the largest risks influencing stillbirth odds, and this suggests that barriers preventing identification and support for behaviour modification should be addressed as a first step towards decreasing stillbirth rates.

Findings pertaining to perinatal outcomes and place of birth differ vastly between high-income countries and regions. Australian and New Zealand findings suggest an increased association between homebirth and stillbirth odds[408], whereas analysis of a Dutch cohort demonstrated that homebirths are safe and cost-effective[409]. Internationally there is mixed consensus to the stance on place of birth[450], with the American College of Obstetricians and Gynaecologists and Australia pregnancy guidelines[286, 451] fail to mention home birth options available to women planning their birth. This is reflected by the latest national data showing that just 0.3% of Australian babies were born at home[286]. This could reflect either a lack of home birth provision of services, or a lack of demand within this population compared with others globally. The UK NICE guidelines have supported home births and indicate that birth at home or a midwife-led unit are equally safe[452]. Our findings suggest that there is no increased odds of stillbirth for birth-centre births (Australian studies only compared with hospital births, but that home births may be associated with a 40% increase in the odds of stillbirth compared with hospital births. In Australia, where poorer perinatal outcomes have been associated with home births[453], privately practicing midwives are not able to access professional indemnity insurance to cover home births, and public home birth providers are sparse[454] resulting in minimal services able to offer this option. In the Netherlands, home birth is commonplace, 30% of births occurring at home, and there is access to ongoing training and support, as well as insurance for healthcare professionals assisting home births[409]. Heterogeneity within our final meta-analysis reflects this difference in national attitude and support for home births, as well a service provision and resource availability to support different places of birth.

Although rates of smoking are decreasing across high-income countries, 20% of the world's tobacco users live in high-income countries[455]. Tobacco use is particularly prevalent in some vulnerable populations, and lower SES groups, for example, 44% of Australian Aboriginal and/or Torres Strait Islander mothers smoked during pregnancy in 2019, compared with 10.2% of all Australian mothers[286]. Smoking during pregnancy and the associations with poor pregnancy outcomes have been widely published. Flenady et al[5] conducted a meta-analysis of large cohort studies and found a 36% increased odds of stillbirth for smokers compared with non-smokers during pregnancy[5], and more recently, Marufu et al[456] demonstrated a 46% increase in odds of stillbirth for smoking during pregnancy compared with not smoking[456]. Our results are consistent with these findings and demonstrate a 39% increase in odds of stillbirth with maternal smoking during pregnancy compared with not smoking. Assessing smoking status of pregnant women is a challenge for care providers due to the stigma associated with tobacco use during pregnancy, thus causing under-reporting[457]. Thirteen of the studies reporting smoking status used self-reported measures owing to high risk of bias. In some studies, self-reporting after giving birth added recall bias, due to known birth outcomes. For other

studies, one timepoint of self-reported smoking was used, causing results to lack adjustment for change in smoking habits and smoking cessation later in pregnancy. One study within this review examined maternal cotinine levels at birth and demonstrated a nearly three-fold increase odds of stillbirth compared with negative cotinine measures at birth. Although this study could not be included in meta-analysis because it was from the same dataset as larger included studies, our results indicate an increase in stillbirth odds associated with maternal smoking of ≥10 and ≥20 cigarettes per day, in line with findings associated with higher maternal cotinine. Exposure to second-hand smoke demonstrated no association with stillbirth odds through our analysis, but it should be noted that a recent meta-synthesis of qualitative studies found a supportive close environment very helpful in assisting maternal smoking cessation[458]. This connection needs to be highlighted as our findings indicate that stillbirth odds associated with smoking cessation were equivalent to that of non-smokers reinforcing the need for a supportive environment conducive to encouraging smoking cessation. Snuff use was moderately associated with increased odds of stillbirth compared with no snuff use, but only one study examined this exposure in Uruguay, with findings corresponding closely to that of maternal tobacco smoking.

Antenatal care globally recommends abstinence from alcohol consumption during pregnancy, yet despite the recommendations, approximately 10% of women continue to consume alcohol while pregnant[459]. Although abstinence from alcohol is advised by care guidelines in high-income countries, less than two thirds of women reported having their alcohol consumption assessed and, in some settings, less than half of assessments are constructed using standardised tests[459, 460]. Our evidence suggests that any alcohol consumption is associated with an almost two-fold increase in stillbirth odds, and binge drinking associated with greater than a two-fold increase in odds compared with no alcohol consumption. These findings emphasise the importance of highlighting and assessing the risk of alcohol consumption during pregnancy. Pre-pregnancy alcohol consumption did not demonstrate an association with stillbirth odds, but a high association was demonstrated between alcohol related hospital admissions and stillbirth outcome of the previous pregnancy. Analysis of any drug use during pregnancy demonstrated increased odds of stillbirth, but there are few studies examining drug use other than cannabis. Given the indications from findings that an almost 50% increase in stillbirth odds is associated with drug use, attention should be given to further research into the true impact of drug use during pregnancy on stillbirth risk to inform public awareness campaigns.

Sleep position during late pregnancy (≥28 weeks GA) has been recently acknowledged as a modifiable risk factor of stillbirth and has received increased attention in the last two decades. The results of recent studies have resulted in campaigns across the UK[297] and Australia[296] to ensure modification of sleep position to prevent stillbirth. A recent meta-analysis of patient aggregated data provided a comprehensive review of characteristics of sleep that were associated with stillbirth including supine sleep position (aOR 3.06), daytime sleepiness (aOR 1.44), >9 hrs sleep in the last month prior to birth (aOR 1.82), and everyday daytime naps (aOR 1.52)[461]. Our findings were mostly in agreement with these published results and in support of resultant public awareness campaigns. Findings at odds with this review include increased stillbirth odds with less than 1 awakening per night and <6 hours of sleep per night, and that no association with stillbirth was observed for maternal sleeping >9hr/night. This indicates that less than adequate duration of sleep

due to awakenings or length of sleep time are associated with increased odds of stillbirth. Cronin et al[461] combined studies examining sleep quantity using meta-aggregation of study data and therefore the findings are robust and complete.

The Institute of Medicine (U.S.) (IOM) guidelines were established in 1990 and have been adopted globally by several countries to inform guideline development, including the UK, and Australia. Gestational weight change forms a component of these guidelines that have been adopted and used by multiple high-income countries. The IOM guidelines were developed in 1990[462] based on a large cohort study conducted in 1980 (the National Natality Survey) of a largely Caucasian population. They were initially developed to decrease the incidence of low birthweight babies. Current recommendations are based upon 30 obstetric and postnatal outcomes (listed below), but alarmingly, stillbirth is missing[463].

- Maternal discomfort
- Hyperemesis
- Abnormal glucose metabolism
- Maternal hypertensive disorders
- Gallstones
- Premature rupture of membranes
- Preterm labour
- Post-term pregnancy
- Induction of labour
- Length of labour
- Mode of birth and vaginal birth after caesarean
- Vaginal lacerations
- Shoulder Dystocia
- Cephalopelvic disproportion
- Labour and birth complications
- Preterm birth
- Birthweight
- Apgar scores
- Neonatal distress
- Neonatal hyperglycemia
- Hyperbilirubinemia
- Neonatal hospitalisation
- Other infant mobility
- Infant BMI
- Infant growth
- Childhood weight status
- Childhood hospitalisation
- Postpartum weight retention
- Premenopausal breast cancer

Our findings suggest that weight loss was associated with increased odds of stillbirth for all pregnancies regardless of maternal BMI. Inadequate weight gain, (defined by Yao et al as <1lb (<0.45kg) gain/week and by Johansson et al as <0.3-0.5lb (<0.14-0.23kg) gain/week differing by maternal initial BMI) was also associated with increased odds of stillbirth in all BMI categories by one of our included studies, but the second smaller study failed to replicate these results. Excessive weight gain (defined by Yao et al[237] as >1.3lb (0.59kg) gain/week and by Johansson et al as >1.0lb (>0.45kg) gain/week) was shown to increase stillbirth odds for obese and morbidly obese women by Yao et al, but only morbidly obese women within Johansson et al's[233] cohort. These findings suggest that increased stillbirth odds were most closely associated with healthy weight and overweight women who experienced weight loss or inadequate weight gain. A recent meta-analysis and review of maternal gestational weight gain found that women experiencing inadequate weight gain had higher risks of small for gestational age babies, and preterm birth, and excessive weight gain was associated with high risk of macrosomia, and caesarean birth[464]. Poorest outcomes were shown for obese women who exhibited weight loss during pregnancy. These findings did not include stillbirth as an outcome measure, and furthermore used the USA's IOM gestational weight gain

guidelines. A summary of our included studies recommended weight gain compared with the IOM guidelines is shown in table 4-9.

Table 4-9 Maternal gestational weight gain recommendations per maternal initial BMI category.

Initial weight category (BMI)	IOM recommendations lb/wk (kg/wk)	Yao et al (USA) lb/wk (kg/wk)	Johansson et al (Sweden) lb/wk (kg/wk)
Underweight (<18.5)	0.97-1.28lb (0.44-0.58kgs)	1-1.3lb (0.45-0.59kgs)	NR
Healthy weight (18.5-24.9)	0.77-1.1lb (0.35-0.50kgs)	1-1.3lb (0.45-0.59kgs)	0.5-1.1lb (0.23-0.50kgs)
Overweight (25.0-29.9)	0.51-0.73lb (0.23-0.33kgs)	1-1.3lb (0.45-0.59kgs)	0.5-1.0lb (0.23-0.45kgs)
Obese (≥30)	0.37-0.60lb (0.17-0.27kgs)	1-1.3lb (0.45-0.59kgs)	0.3-1.0lb (0.14-0.45kgs)

The table serves to demonstrate that the IOM recommendations of weight gain align with Johansson et al's[207] recommendations for healthy weight gain during pregnancy yet align with inadequate weight gain defined by Yao et al[237] for women with a healthy, overweight or obese BMI at the start of the antenatal period. This is of particular concern for healthy weight and overweight women as results shown through systematic review demonstrate a 3 and 4-fold increase in stillbirth odds associated with inadequate weight gain[118, 237]. Global guidelines based on the IOM recommendations need to use strong evidence bases that consider all poor pregnancy outcomes including stillbirth, as shown, by omitting stillbirth in outcomes, the recommendations fall short of preventing this outcome.

Research regarding individual occupations and association with stillbirth odds is sparse, except for unemployment status which demonstrated an increased association with stillbirth for maternal unemployment. Maternal unemployment demonstrated an almost 2-fold increase in third trimester stillbirth odds, which was thought to partially reflect SES in our analysis. Two other maternal occupations demonstrated increased associations with stillbirth odds and they were maternal occupational exposure to ionising radiation (aOR 2.20-3.10), and work as a technician (aOR 1.71). Through analysis of maternal occupational lifting, we demonstrated minimal association between extremely heavy weight lifted during pregnancy, and stillbirth odds (201-975kg/day; aOR 1.4 (95% CI 0.92, 2.14)). Paternal occupations identified as having implications on stillbirth odds were flight attendants (aOR 2.85), and Gulf war veteran status (aOR 1.65). All findings regarding paternal occupation were drawn from single studies, with many lacking quality, and failing to measure exposure just prior to conception, when paternal occupation may impact pregnancy. Although these findings implicate maternal occupation and paternal occupation in the risk of stillbirth, currently there is little focus on occupational exposure and implications for stillbirth odds unless direct hazardous material exposure is known. These findings demonstrate that further research is needed to establish causal links between occupation and stillbirth odds. This in turn will inform national care guidelines about the risks of occupational groups, and examine the potential, if any, to modify risk.

Vaccination during pregnancy has recently been highlighted as a factor of interest following identification of the trans-placental immunity acquired by the fetus following administration[465, 466]. These findings, alongside research indicating an almost 4-fold increase in stillbirth odds (aOR 4.20 (1.42, 12.40)) associated with severe influenza

infection further emphasised the importance of examining the impact of maternal vaccination on stillbirth rates[467]. Our findings that maternal antenatal influenza vaccination was the only factor that demonstrated a protective effect for stillbirth is an important foundation for campaigns to promote maternal vaccination. This finding highlights the importance, of antenatal vaccination programs promotion to not only transplacental immunity, but also stillbirth prevention. Given the availability across high-income countries to vaccination, there is ample opportunity to address and implement this safe and effective prevention strategy.

The strengths of this review include its comprehensive systematic search of literature, combined with extensive extraction of all available data from high-income countries. The associations identified form a strong evidence base and where possible are presented by timing of stillbirth. Results are robust due to the careful investigation of trimester specific relationships of risk factors during the antenatal period. Despite its strengths, given the nature of observational data, the results are limited as none of our results implicated causal relationships between factors and stillbirth odds. Results are also limited by the exclusion of randomised controlled trials that are better suited to the investigation of risk factors such as supplementation during pregnancy, and exercise during pregnancy.

Implications of findings and future research needed

It is evident that modifiable risk spans beyond the scope of current national pregnancy care guidelines, and that there is indeed much room for improvement to decrease stillbirth risk in high-income countries. Findings have highlighted the need to add stillbirth to established national campaigns such as prevention by vaccination, assault, poor antenatal care adequacy, and drug and alcohol use. One modifiable factor that was found to have stillbirth risk modification incorporated into public awareness campaigns was sleep position, yet numerous other identified risk factors have higher associations with stillbirth and are not emphasised through care guidelines of public awareness campaigns.

Implications of findings for policy

It is evident that there is not only a lack of consensus between national pregnancy care guidelines across high-income countries, but also that evidence underpinning guidelines lacks incorporation of stillbirth data.

The findings within this review highlight the importance of developing effective strategies to support women who are pregnant and exposed to situations that could become violent. Although most pregnancy care guidelines worldwide recommend screening for domestic violence, the methods used vary in their delivery and approach, and barriers to effective screening are consistently raised. Given the implications of assault during pregnancy on stillbirth odds, public awareness campaigns are needed to reach out specifically to pregnant families to inform and provide access to support for women at risk.

Current pregnancy guidelines across the USA, Australia and the UK base gestational weight gain recommendations on those set out by the USA IOM in 2009. Although these guidelines are based on high quality evidence from international findings, none of the included studies examined the impact of gestational weight change on stillbirth odds. Through analysis of the impact of gestational weight change on stillbirth odds, it has been identified that the current recommendations are insufficient to prevent stillbirth and require the findings of this review incorporated.

Pregnancy care guidelines lack consensus for the adequate number of antenatal care appointments as well as when care should be initiated. Meta-analysis results combined with previous research findings indicate that care should be initiated prior to 20 weeks GA, and as close to the first trimester a possible to ensure stillbirth prevention. Through analysis it is also evident that the recommended number of antenatal care visit is minimally adequate to prevent stillbirth as less than 100% attendance of 11 visits increased stillbirth risk. It is recommended that the recommended number of antenatal care visits is increased globally so that stillbirths are adequately prevented.

Chapter 5 Exposure to Environmental Pollutants and Stillbirth Risk in High-Income Countries

Abstract

Background

Within high-income countries, different communities may be exposed to differing types and intensities of environmental pollutants. Recent global focus on environmental pollution has highlighted the effect pollution may have on pregnancy outcomes, including stillbirth.

Aim

To systematically review evidence of associations between environmental pollutants and stillbirth

Method

Published cohort and case-control studies (1998-2020) examining populations at risk of exposure to environmental pollutants, were identified through database searches. Adjusted odds ratios of individual pollutants and links with stillbirth were calculated through meta-analysis.

Results

Sixteen studies examined the odds of stillbirth associated with communities exposed to pollution in high-income countries. Moderate associations were seen between exposure to tap water pollutants, haloacetic acid (aOR 1.59 (95% CI 1.04, 2.44)), dichloroacetic acid (aOR 1.64 (95% CI 1.17, 2.31)), no clear associations were shown between some water and air pollutant exposures and stillbirth odds; heavy metal air pollutants (aOR between 1.05 and 1.09), water pollutants; trichloroacetic acid (aOR 1.35 (95% CI 0.95, 1.92)), and brominated haloacetic acid (aOR 1.30 (95% CI 0.89, 1.91)).

Discussion and conclusion

Communities, within high-income countries, exposed to pollution may be at risk of higher incidence of stillbirth. Further research examining environmental pollutants and stillbirth odds are needed to confirm associations. This review reveals the association between specific pollutants and increased risk of stillbirth. Thereby highlighting the potential to decrease stillbirth rates through pollution reduction strategies in high-income countries.

Introduction

Marginalised populations within high-income countries have experienced more than double the odds of stillbirth than their more advantaged counterparts[468]. Inequities across high-income countries contribute to the disparities in health outcomes between advantaged and disadvantaged populations[469]. Increasingly, lower socioeconomic status (SES) communities are located within industrialised areas of cities[470]. These risk factors results in low SES families being exposed to the additional risk of pollutants. Such exposure is generally non-modifiable at an individual level. Pollutant exposure, and monitoring, is a government and national policy responsibility that can be addressed to reduce additional risks for stillbirth, which are often higher in disadvantaged families.

Air pollution may contribute to the pollution of drinking water, for example, through heavy metals leached into rainwater. A recent study in South Australia showed the presence of heavy metals in household rainwater[471] increasing household exposure more than 10 times the local recommendations[471]. The complexities of the relationship between air and water pollution result in multiple sources of exposure for families in industrial districts. Heavy metal exposure to lead, arsenic and cadmium have been linked to poor pregnancy outcomes, such as low birth weight, spontaneous abortion, and stillbirth[472]. Heavy metal exposure has been shown to have endocrine disruption properties that affect the placental development, and subsequently the fetus[473].Despite the knowledge that pollution contributes to poor pregnancy outcomes, effective policies to reduce pollutant exposure have been slow to be implemented[474].

Although in high-income countries, a majority of households use treated potable water, most water treatment plants use chlorination to prevent microbial contamination[475]. The Born in Bradford study examined the risk of low fetal birthweight following exposure to chlorination by-products (trihalomethanes and haloacetic acids (HAA)) in drinking water, and discovered adverse pregnancy outcomes associated with trihalomethane exposure in women of Pakistani origin[476]. The 2011 World Health Organization Guidelines for Drinking-Water Quality (4th edition) recommend monitoring of chlorination by-products[475] due to their teratogenic effects, but that this must be weighed against the risk of microbial water contamination. To date there has not been a complete systematic review examining all environmental pollutants and associations with stillbirth. Thus, it is important to quantify and address any increased risk of stillbirth associated with pollutant exposure.

Aims

To identify association between environmental pollutants and stillbirth odds in high-income countries through systematic review and meta-analysis.

Methods

Literature Search Strategy

Detailed methodology is included in chapter 2 of this thesis. A systematic search of the medical literature was conducted using the major electronic databases PubMed, MEDLINE, Ovid, the Cochrane Library and CINAHL. Literature searches were conducted for the period January 1998-July 2020, restricted to English language. Search strategies and results are included in Appendix B, C and D.

Inclusion/exclusion criteria for studies

Studies included in this review adhered to the inclusion/exclusion criteria (detailed in Chapter 2) and examined the association between environmental pollution and stillbirth odds within high-income countries. Pollutants of interest were limited to environmental exposures associated with the family's local environment, and not caused by natural disasters. Included studies contained adjusted odds ratios for risk factor associations with fetal loss at ≥20 weeks GA or ≥400g birthweight. As described above, reviewer bias was minimised by independent assessment of each study by two research team members. Where disagreement was not resolved by discussion of the researchers, external review from an expert researcher (from SAHMRI Women and Kids theme/The NHMRC Centre for Research Excellence in Stillbirth) was sought to arbitrate and reach consensus.

Extraction and assessment of the studies

To minimise bias, each study was assessed independently by at least two researchers. Where disagreement was not resolved by discussion of the researchers, external review from an expert researcher was sought to arbitrate and reach consensus. All relevant studies selected for this review were assessed independently by two reviewers for their individual methodological quality. This was done by using a quality and bias assessment scale specifically designed by the RTI-University of North Carolina Evidence Based Practice Centre; the RTI item bank (RTI-IB)[85]. The scale includes 29 questions with multiple choice answers and additional space for free-text. The item-bank focuses on believability, incorporating risk and precision of the results. Overall quality and bias assessment was assigned qualitatively as: High, Medium or Low based on the RTI-IB criteria. Quality and bias assessment of studies are included in Appendix D.

Adjusted results were extracted per study and combined through meta-analysis where possible. Random-effects meta-analysis was performed to construct forest plots to account for probable differences in exposure effect between studies as well as variability between cohorts used. Complete analysis were performed using STATA IC v16.1, by first author (A Bowman) and coding framework was checked by SAHMRI Women and Kids Theme Lead Biostatistician (Dr T Sullivan).

Results

Search results

Sixteen studies reported adjusted odds ratios of stillbirth odds associated with environmental pollution exposure during pregnancy[34, 429, 477-491]. Pollutants identified that were associated with the parental environment were polluted air and tap water, and noise pollution. Air pollutants identified included:

- PM2.5 (all, vehicle, heavy vehicle, and heavy metal components)
- PM10
- Environmental smoke
- Waste landfill/incinerator air pollution
- Arsenic
- Ozone
- Nitrogen dioxide
- Sulphur dioxide
- Carbon monoxide

Tap water pollutants identified included:

- Trihalomethanes
- Haloacetic acid
- Dichloroacetic acid
- Trichloroacetic acid
- Brominated haloacetic acid
- Perfluorooctanoic acid
- Tetrachloroethylene

Noise pollution was measured in decibels of exposure during pregnancy across day, and night-time.

Scope, characteristics, and quality of studies

Populations of included studies spanned four high-income countries, Canada, the UK, the USA and Australia. Six studies examined pollution in drinking water sources[477, 480, 481, 484, 486], 10 studies examined the association between air pollution and stillbirth odds[34, 35, 429, 479, 482, 485, 488-491].

Risk of bias assessment suggested that eight of the studies had a low risk of bias[34, 480, 481, 485, 486, 488, 489], five had an unclear risk of bias[429, 479, 482, 483, 490], and the remaining four had a high risk of bias[477, 478, 484, 487] (Appendix D). High risk of bias was due to one study's inclusion restriction to stillbirth attributed to placental abruption or insufficiency[487]. The remaining three studies lacked adjustment, used self-reported pollution exposure, or did not account for other reasonable sources of possible exposure to pollution during pregnancy[477, 478, 484].

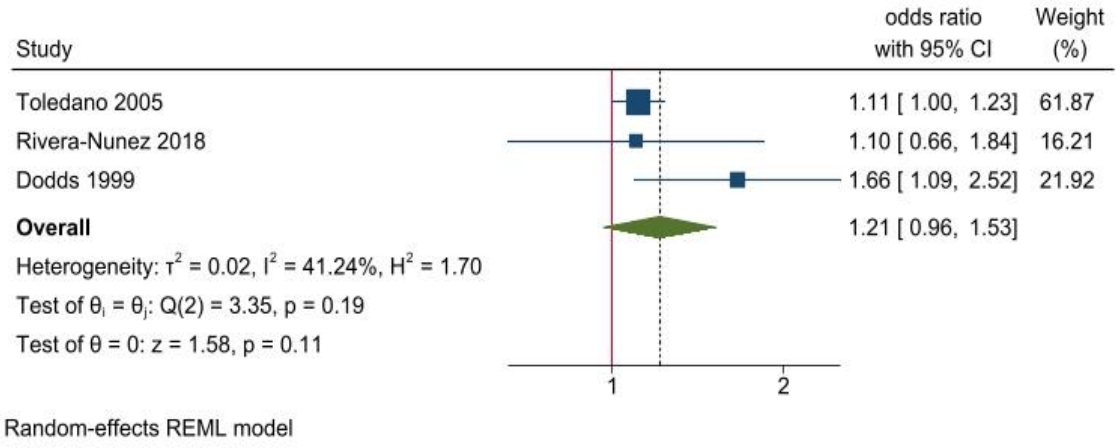
Meta-analysis of findings

Tap water pollution

Trihalomethanes

Trihalomethanes are by-products of chlorination processes used to disinfect water that contains organic matter. Three studies report the association between trihalomethane exposure and stillbirth within populations across three high-income countries: the USA, England and Canada[477, 481, 486]. All studies categorized pollutant exposure into three levels, low medium and high. One study demonstrated a high level of bias[477]and the other two studies demonstrated a low risk of bias[36, 486].

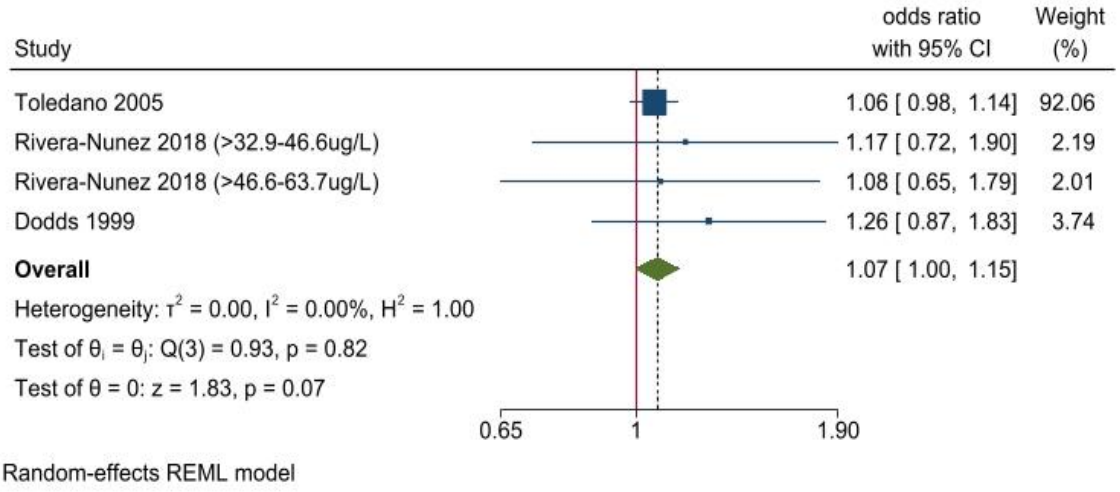
A probably increased association between high trihalomethane exposure (≥60 µg/liter drinking water) in drinking water and stillbirth odds was demonstrated through meta-analysis (aOR 1.21 (95% CI 0.96, 1.53) – fig 5-1). Heterogeneity was accepted at I^2 = 41.24%.



c = cohort study
cc = case-control study
Figure 5-1 Meta-analysis demonstrating the association between tap water pollution with high levels of trihalomethanes and stillbirth odds compared with undetectable trihalomethane levels in tap water.

Meta-analysis of medium level trihalomethane exposure (30-75 µg/liter of water) demonstrated a probable association with stillbirth odds (aOR 1.07 (95% CI 1.00, 1.15)

– fig5-2) in comparison with low levels of trihalomethanes in drinking water[36, 477, 486]. Although the associated odds of stillbirth shown for medium level exposure was smaller than lower high-level exposure, both results show possibly higher odds of stillbirth. Two of the studies[36, 486] included in the meta-analysis have a low risk of bias, and the remaining one, a high risk of bias[477].



c = cohort study
cc = case-control study
Figure 5-2 Meta-analysis of studies demonstrating the association between medium levels of trihalomethanes in tap water and stillbirth odds compared with undetectable levels.

Haloacetic acid (HAA)

HAAs are by-products of water chlorination, ozonation or chloramination. Five are commonly found in water, monochloracetic acid[2], dichloroacetic acid[3], trichloroacetic acid, monobromoacetic acid[3] and dibromoacetic acid[3]. Two studies examined odds of stillbirth[480, 486] associated with exposure to HAA versus non-detectable levels. King et al[480] and Rivera-Nunez et al[486] both correlated the impact of total HAA found in samples of tap water with stillbirth odds. Each study grouped exposure to lowest, medium, and highest exposure using minimally different parameters.

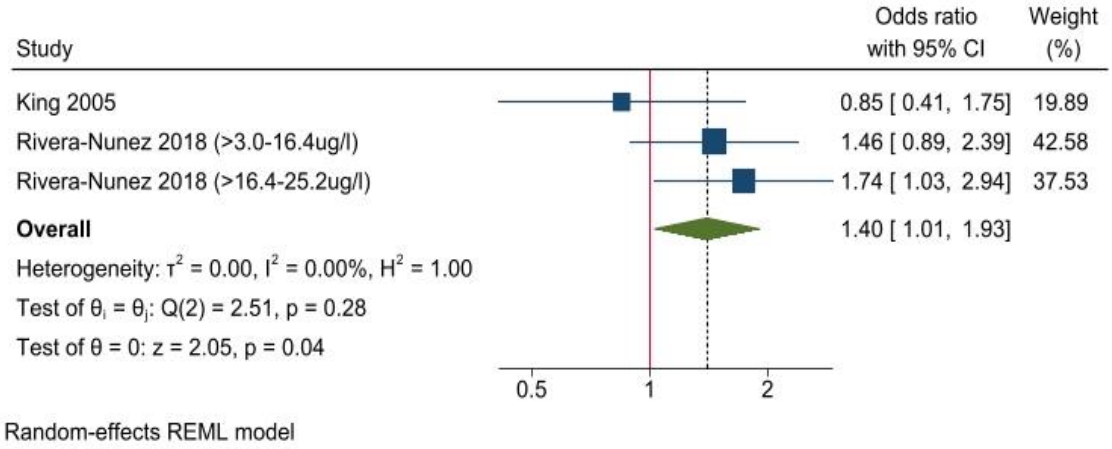
Table 5-1 HAA µg/l parameters per exposure group

	Reference group	**Lowest exposure**	**Medium exposure**	**Highest exposure**
King 2005[480]	<3.0 µg/l/day	3.0-28.2 µg/l/day	28.3-57.5µg/l/day	57.6-88.1 µg/l/day
Rivera-Nunez 2018[486]	<3.0 µg/l/day	>3.0-16.4 µg/l/day & >16.4-25.2 µg/l/day	>25.2-35.4 µg/l/day	>35.4-126.1 µg/l/day

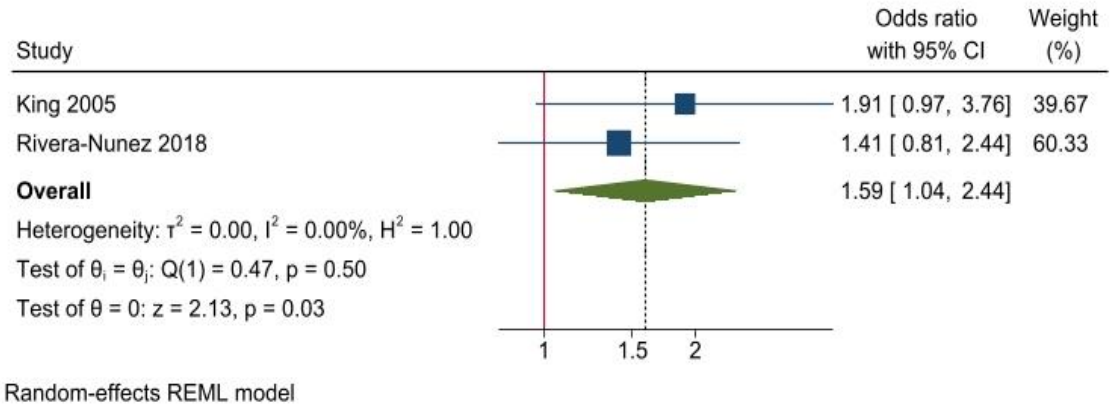
Meta-analysis of results showed an increased association between the lowest (aOR 1.40 (95% CI 1.01, 1.93) – fig 5-3) and medium levels (aOR 1.59 (95% CI 1.04, 2.44) – fig 5-4) of exposure to total HAA through tap water, with stillbirth rates. Exposure to the

[2] World Health Organization Water Safety and Quality guidelines recommend <20µg/liter of water
[3] The World Health Organization Water Safety and Quality Guidelines have inadequate data to form a guide value 475. World Health Organization. Guidelines for drinking-water quality. 4th ed. Geneva: World Health Organization; 2011.

highest levels of total HAA through tap water demonstrated a possible increase in stillbirth (aOR 1.37 (95% CI 0.80, 2.34) – fig 5-5).



c = cohort study
cc = case-control study
Figure 5-3 Meta-analysis demonstrating the association between lowest total HAA pollution in tap water and stillbirth odds compared with undetectable HAA in drinking water.



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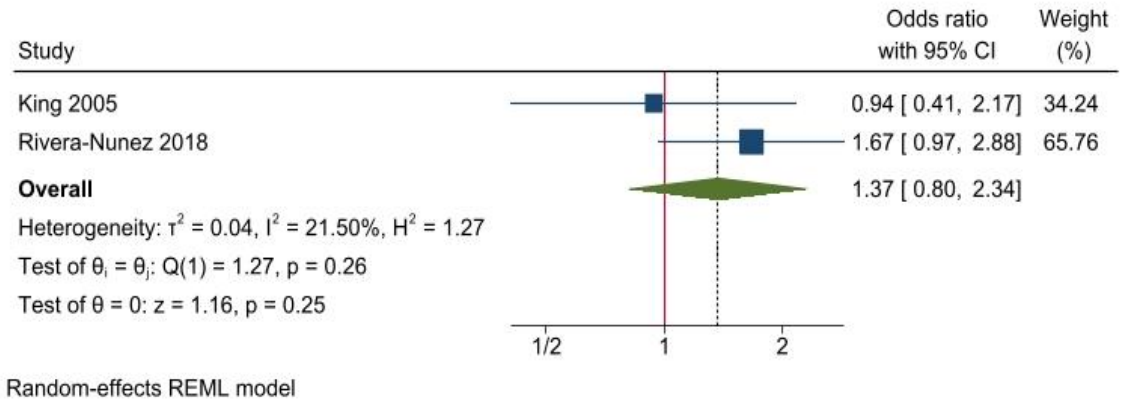
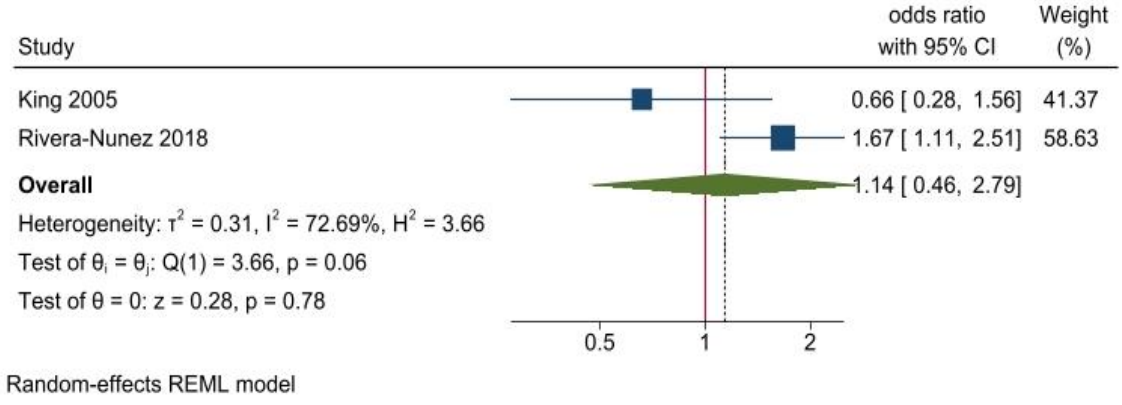
cc = case-control study
Figure 5-4 Meta-analysis demonstrating the association between medium levels of total HAA tap water pollution and odds of stillbirth compared with undetectable levels of total HAA.



c = cohort study
cc = case-control study
Figure 5-5 Meta-analysis demonstrating the association between highest levels of total HAA in tap water pollution and odds of stillbirth compared with undetectable levels of total HAA.

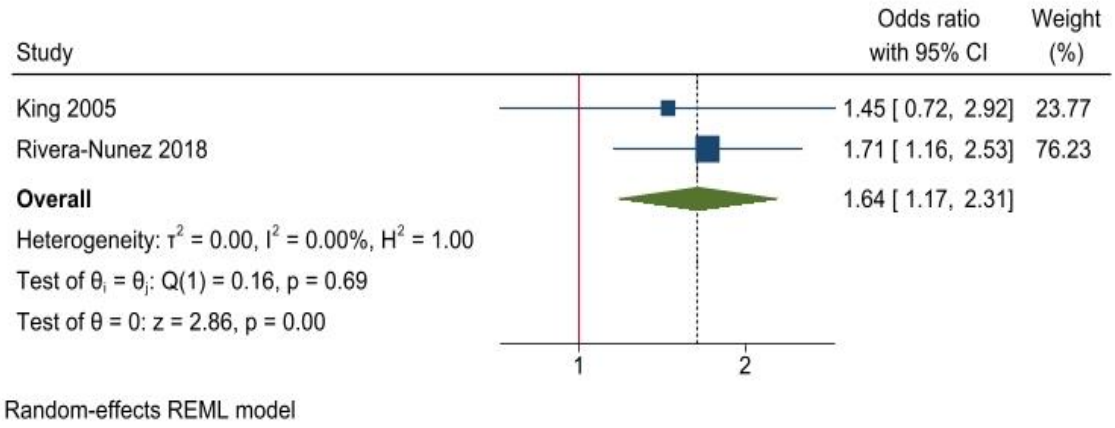
Dichloroacetic acid

Studies examining the association between stillbirth odds and dichloroacetic acid grouped exposure into four exposure levels: highest, medium, lowest, and no/minimal exposure (referent group). The highest level of dichloroacetic acid exposure measured within a study was >14.1-40.9 µg/liter[486], and in the remaining study was provided as a quartile without measures [480]. Meta-analysis including both studies resulted in no clear association with stillbirth odds (aOR 1.14 (95% CI 0.46, 2.79) – fig 5-6). High heterogeneity between studies contributed to uncertainty in these findings. Both studies demonstrated low risk of bias (Appendix D).



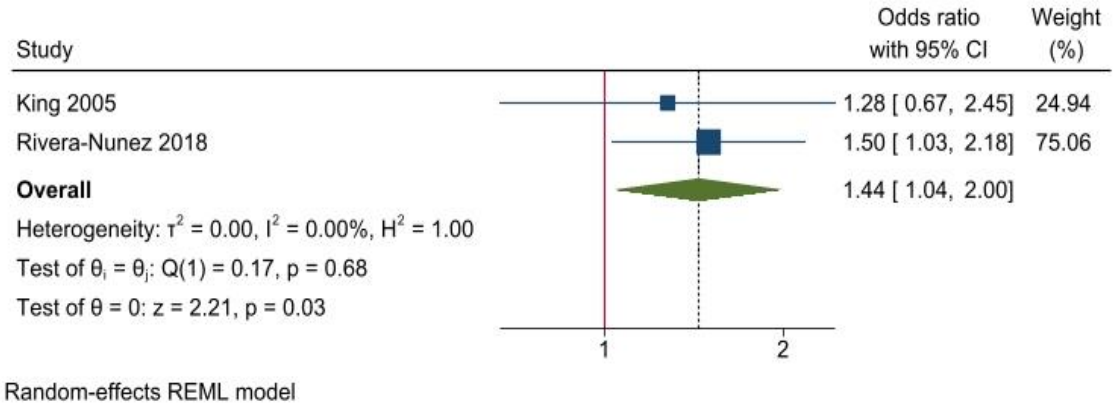
c = cohort study
cc = case-control study
Figure 5-6 Meta-analysis demonstrating the association between highest dichloroacetic acid levels and stillbirth odds compared with no dichloroacetic exposure.

Medium levels of exposure to dichloroacetic acid were measured by two studies. One measured medium exposure as >9.3-14.1 µg/liter[486], and in the other study measures were provided as quartiles[480]. Both studies were combined through meta-analysis, and results demonstrated an increased association with stillbirth for medium levels of exposure to dichloroacetic acid in drinking water compared with no/minimal exposure (aOR 1.64 (95% CI 1.17, 2.31) – fig 5-6).



c = cohort study
cc = case-control study
Figure 5-7 Meta-analysis demonstrating the association between medium dichloroacetic acid levels and stillbirth odds compared with no dichloroacetic exposure

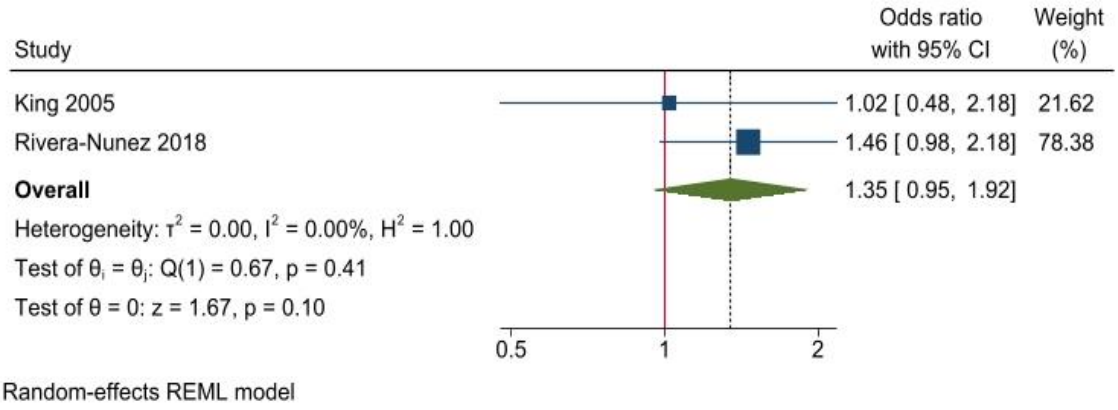
Low levels of dichloroacetic acid were compared with minimal (<2.5 µg/liter of tap water), no detected levels in two studies. Through meta-analysis, the odds of stillbirth were shown to be increased at the lowest levels of exposure to dichloroacetic acid compared with no/minimal exposure (aOR 1.44 (95% CI 1.04, 2.00) – fig 5-8).



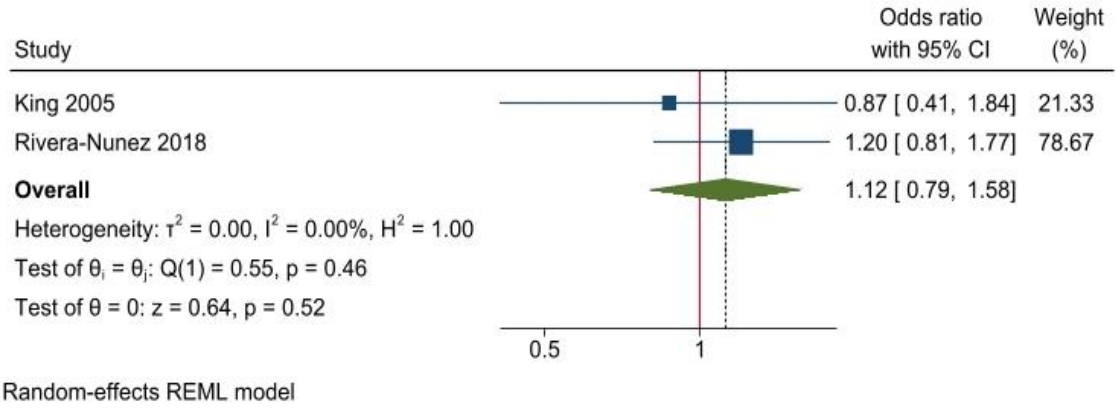
c = cohort study
cc = case-control study
Figure 5-8 Meta-analysis demonstrating the association between lowest dichloroacetic acid levels and stillbirth odds compared with no dichloroacetic exposure

Trichloroacetic acid

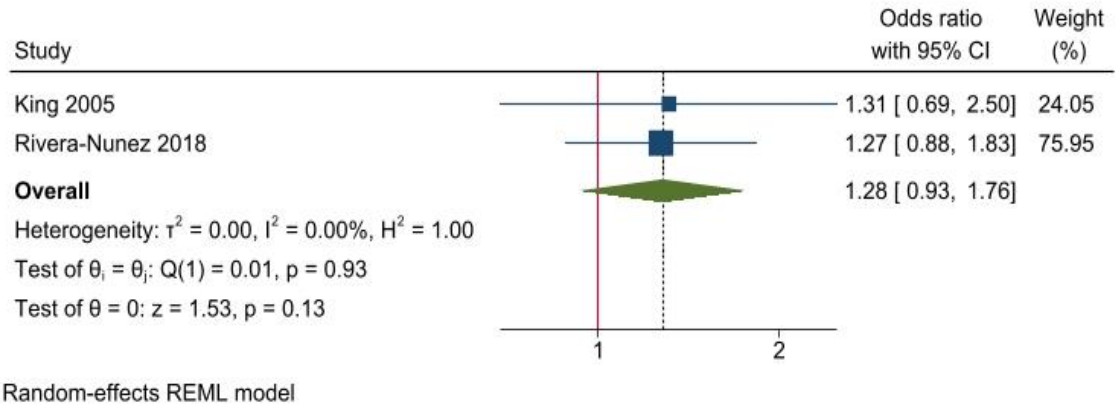
Two studies examine the association between trichloroacetic acid exposure and the association with stillbirth odds[480, 486]. Levels present in tap water were grouped as highest, medium, and lowest levels. All were compared with undetectable levels of trichloroacetic acid in tap water. Meta-analysis of all levels demonstrated a possible increase in stillbirth odds associated with the presence of trichloroacetic acid in tap water (fig 5-9, 5-10 and 5-11).



c = cohort study
cc = case-control study
Figure 5-9 Meta-analysis of studies demonstrating the association between highest levels of trichloroacetic acid and stillbirth odds compared with undetectable trichloroacetic acid.



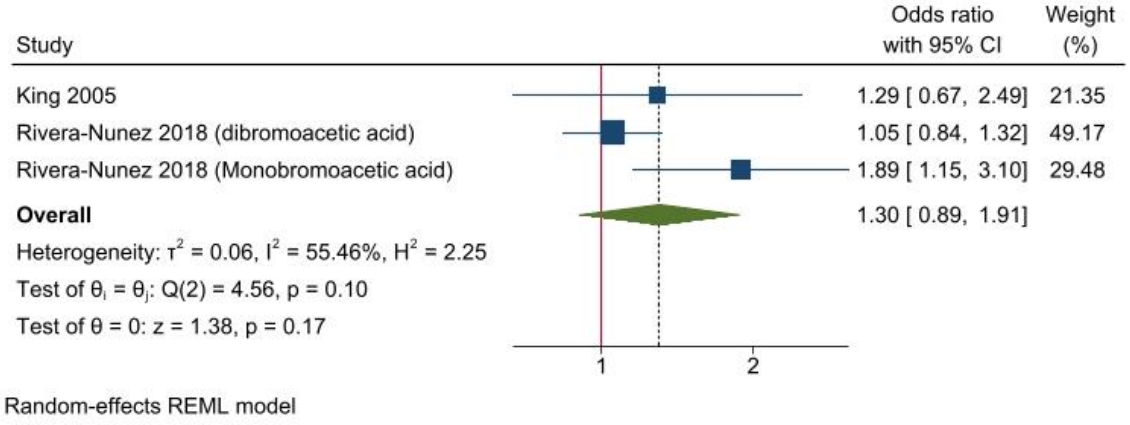
c = cohort study
cc = case-control study
Figure 5-10 Meta-analysis of the association between medium levels of trichloroacetic acid and stillbirth odds compared with undetectable levels.



c = cohort study
cc = case-control study
Figure 5-11 Meta-analysis of studies demonstrating the association between lowest levels of trichloroacetic acid in tap water and stillbirth odds compared with undetectable levels.

Brominated haloacetic acid

Two studies[480, 486] measured brominated haloacetic acid in tap water serving communities within high-income countries and examine the association with stillbirth odds. One study stratified results by mono and di-brominated haloacetic acid, and both studies adjusted the odds ratio for the presence of trihalomethanes within tap water samples. Final analysis demonstrated a non-significant increased association between the presence of brominated haloacetic acids in tap water and stillbirth odds compared with no brominated haloacetic acid (aOR 1.30 (95% CI 0.89, 1.91) – fig 5-12).



c = cohort study
cc = case-control study

Figure 5-12 Meta-analysis of studies demonstrating the association between brominated haloacetic acids in tap water and stillbirth odds compared with no brominated haloacetic acid.

Perfluorooctanoic acid

Stillbirth odds associated with perfluorooctanoic acid pollution in tap water were reported by one study[483] . The study stratified results by levels of exposure up to 717.6 ng/ml and reported no increased association with stillbirth odds at any level of exposure.

Tetrachloroethylene (perchloroethylene (PCE))

One case-control study from the USA utilised a leaching and transport model to assess pregnant women's exposure to PCE in tap water and reported the association with stillbirth odds due to placental abruption or insufficiency[484]. This study was assessed to have a high risk of bias due to reported missing confounder data of up to 76% for included cases and/or controls (appendix D). Study findings reported consistently higher stillbirth odds associated with the presence of any PCE in tap water (aOR 1.70 (95% CI 1.20, 2.40)). The study further stratified results to percentiles and µg/L of exposure. Results demonstrated that at the highest levels of exposure (≥ 40 µg/L), increased odds of stillbirth were shown (aOR 2.6 (95% CI 1.40, 4.80)). Through step-wise exposure classification, this study demonstrated a dosage dependent relationship between PCE exposure and stillbirth risk[484].

Chloroform presence in tap water and associated stillbirth odds.

Chloroform ($CHCl_3$), originally a potent anaesthetic, is now a byproduct in production of refrigerants, plastics and pharmaceuticals[492]. Its presence in tap water is due largely to

the chlorination of water and wastewater[492]. One study demonstrated a possibly increased association between the presence of chloroform in tap water and stillbirth odds[486] compared with ≤6.2 μgL^{-1}, though a dose response effect was not apparent. Results stratified by exposure were:

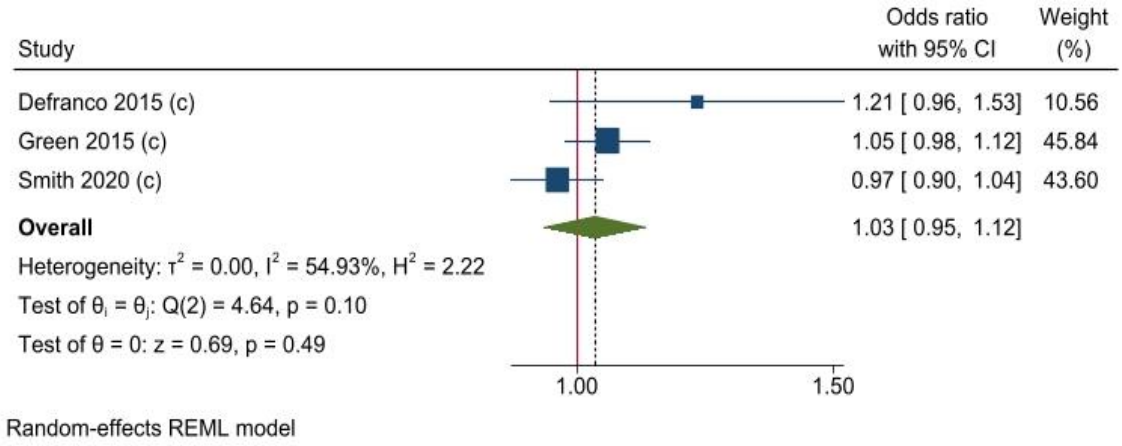
- >6.2-23.5 μgL^{-1} (aOR 1.36 (95% CI 0.85, 2.17))
- >23.5-37.4 μgL^{-1} (aOR 1.51 (95% CI 0.94, 2.42))
- >37.4-54.0 μgL^{-1} (aOR 1.37 (95% CI 0.83, 2.26))
- >54.0-192.1 μgL^{-1} (aOR 1.29 (95% CI 0.78, 2.16))

Air Pollution

Eleven studies examined the odds of stillbirth associated with air pollution in high-income countries[34, 35, 429, 479, 482, 485, 487-490]. All studies examining the impact of air pollution used cohorts from either the UK or the USA.

PM2.5 pollutants

PM2.5 pollutants encompass particles associated with second hand smoke, vehicle emissions and ambient pollution deposited into the air[493]. Due to the small size of PM2.5 pollutants, they can become embedded deep within human lungs and enter the bloodstream. Four studies investigated the impact of total pregnancy exposure to PM2.5 molecules and the associated stillbirth odds[34, 333, 485, 490]. Two studies reported use of the same dataset, and therefore to avoid double-counting of births, the smaller study[485] was excluded from meta-analysis. Results demonstrated a possible association between exposure to PM2.5 with each interquartile range increase in pollution (3.2-10 µg increase in PM 2.5), and stillbirth odds (aOR 1.03 (95% CI 0.95, 1.12) – fig 5-13). Moderate heterogeneity (I^2=54.93%), is thought due to the difference in interquartile range parameters between studies.

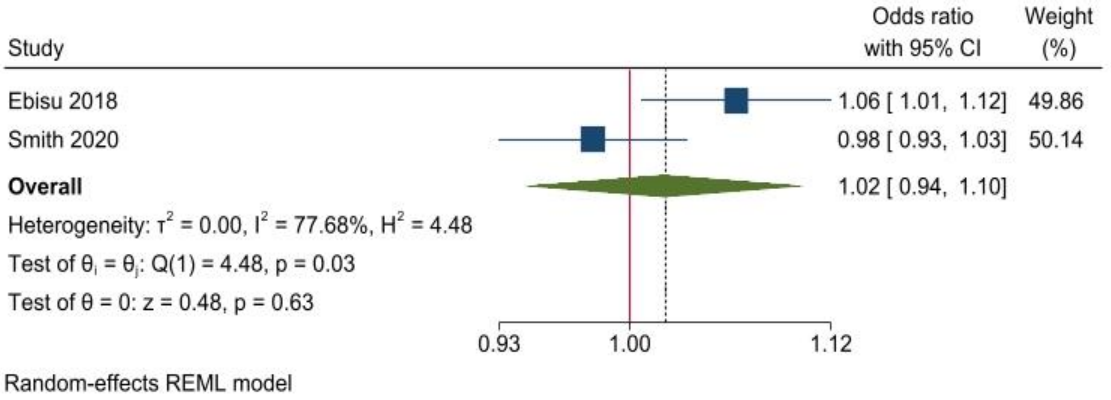


c = cohort study
cc = case-control study
Figure 5-13 Meta-analysis demonstrating the association between each interquartile range increase in pollution and stillbirth odds.

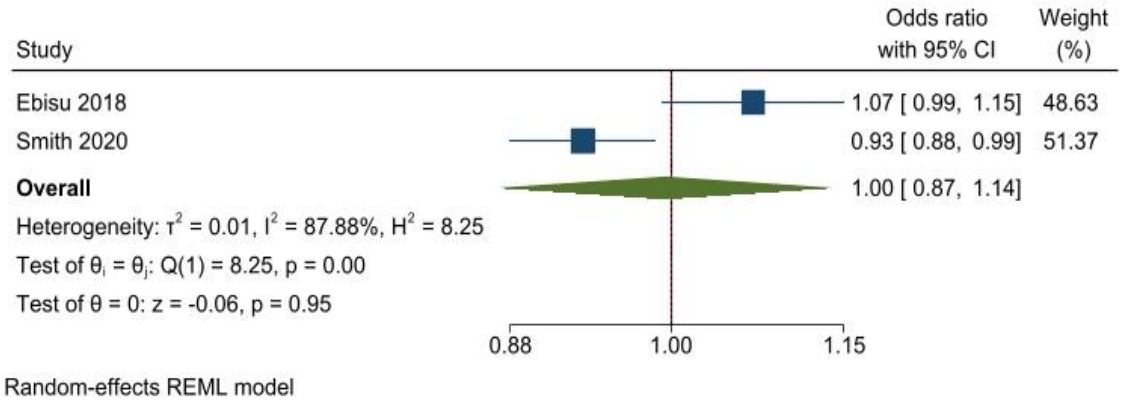
PM2.5 vehicle emissions

A major contributor to PM2.5 air pollution is vehicle emission, measured as a subgroup in two studies included in this review[34, 490]. Meta-analysis of the results demonstrated a

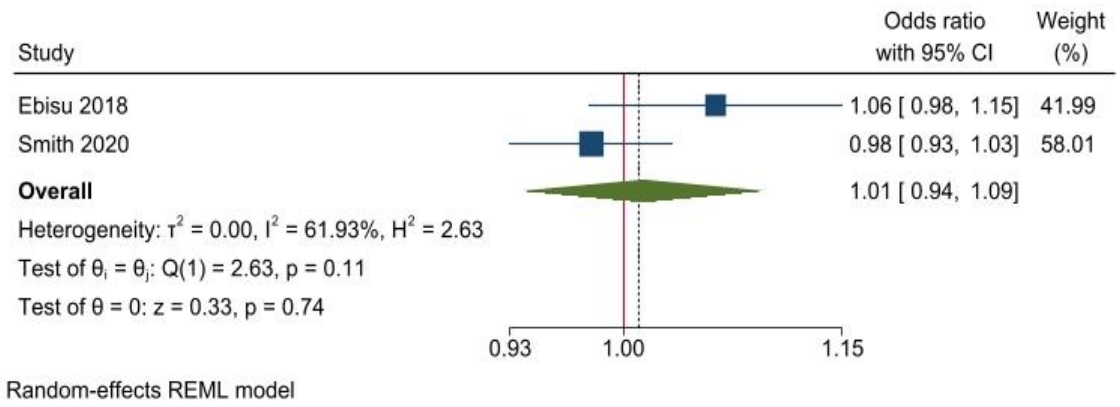
possible association between PM2.5 (from vehicle emissions) and stillbirth odds (aOR 1.02 (95% CI 0.94, 1.10) – fig 5-14). Exposure to PM2.5 from vehicle emissions was further stratified by the two studies to second and third trimester exposure, and associated stillbirth odds[485, 490]. Meta-analysis demonstrated that neither second (aOR 1.00 (95% CI 0.87, 1.14) – fig 5-15), nor third trimester (aOR 1.01 (95% CI 0.94, 1.09) – fig 5-16) exposure was clearly associated with stillbirth odds. Considerable heterogeneity, thought due to the differences in exposure group interquartile range parameters between the studies (Ebisu et al[485] – 1.68 ug/m^3, Smith et al[490] – 0.35 ug/m^3).



c = cohort study
cc = case-control study
Figure 5-14 Meta-analysis of the association between each IQR increase in PM2.5 pollution from vehicle emissions (entire pregnancy exposure) and stillbirth odds.



c = cohort study
cc = case-control study
Figure 5-15 Meta-analysis demonstrating the association between each IQR increase in PM2.5 emissions from vehicles (second trimester exposure) and stillbirth odds.

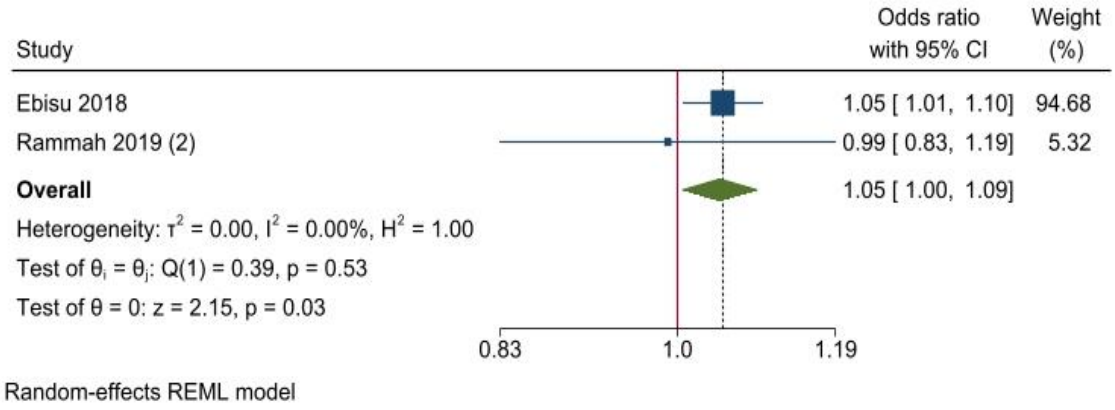


c = cohort study
cc = case-control study
Figure 5-16 Meta-analysis of studies examining the association between each IQR increase in PM2.5 vehicle pollution (third trimester exposure) and stillbirth odds.

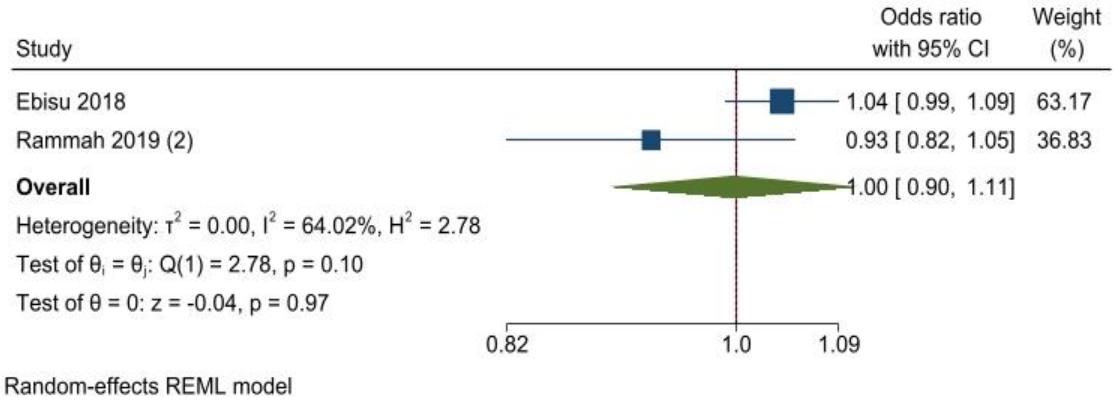
Although personal monitors of air pollution are the gold standard for assessment of exposure[493], one included study measured the distance of maternal residence to the nearest highway, as a proxy for exposure, and assessed the associated stillbirth odds [487]. Through analysis of stillbirth due to placental abruption or placental insufficiency, proximities of <50 meters to ≥200 meters demonstrated no increased association with stillbirth odds. Stillbirths associated with placental abruption demonstrated a non-significant increased association when maternal residence was <50 meters from a highway compared with ≥200 meters (aOR 1.60 (95% CI 0.6, 4.0)). Future research will require larger samples sizes to confirm this potential association[487].

PM2.5 individual heavy metal components

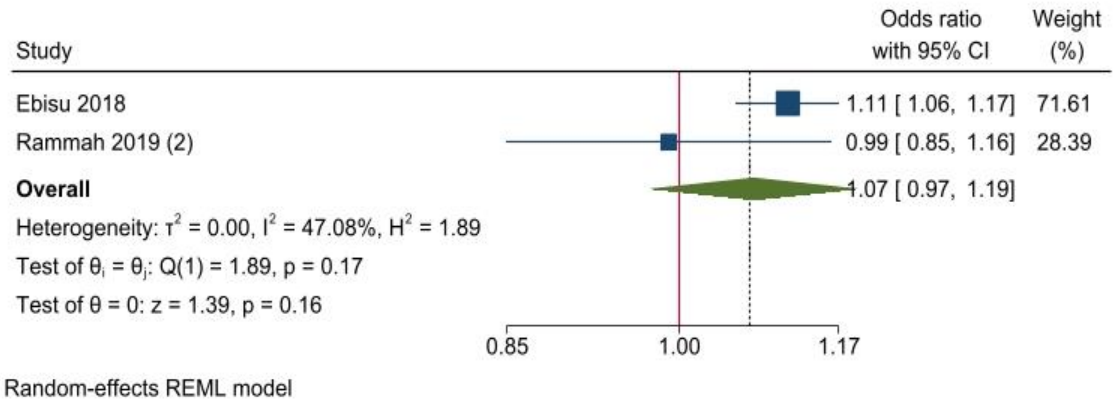
Two studies included in this review examined the association between heavy metal pollutants in air, and their associated stillbirth risks[485, 489]. Heavy metals examined include aluminum (Al), copper (Cu), iron (Fe), nickel (Ni), titanium (Ti) and zinc (Zn). Both studies used data from states within the USA, one in Texas, and one in California. Meta-analysis of adjusted odds ratios reported within the studies resulted in no clear association between maternal antenatal exposure to Cu (aOR 1.00 (95% CI 0.90, 1.11) – fig 5-18), Fe (aOR 1.01 (95% CI 0.97, 1.19) – fig 5-19), Ni (aOR 1.00 (95% CI 0.98, 1.02) – fig 5-20) and stillbirth odds. Results of meta-analysis of exposure to Al, Ti and Zn all demonstrated significant associations with stillbirth odds (Al: aOR 1.01 (95% CI 1.00, 1.09) (fig 5-17), Ti: aOR 1.09 (95% CI 1.03, 1.16) (fig 5-21), Zn: aOR 1.07 (95% CI 1.02, 1.13) (fig 5-22)). Uncertainty in these results is driven by wide confidence intervals of Rammah et al[489], despite a low risk of bias, and large sample sizes.



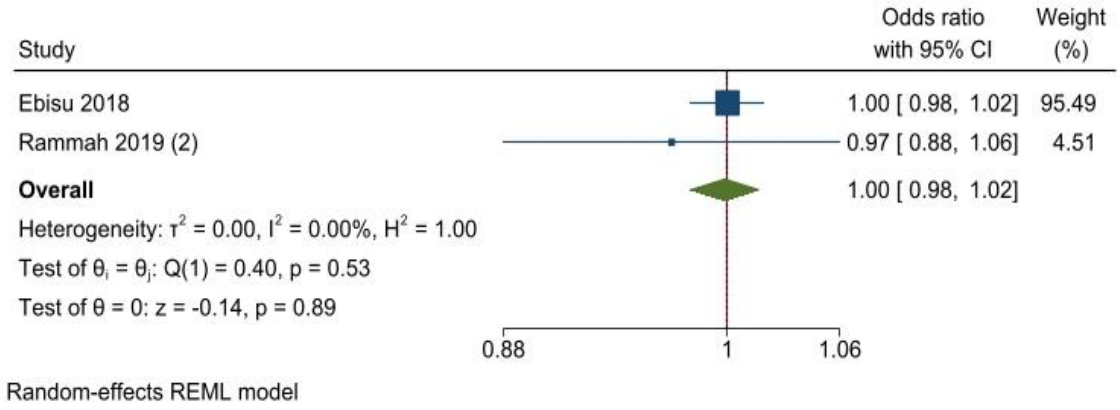
c = cohort study
cc = case-control study
Figure 5-17 Meta-analysis of the association between 1 increase in IQR of maternal exposure during pregnancy to aluminium air pollution and stillbirth odds.



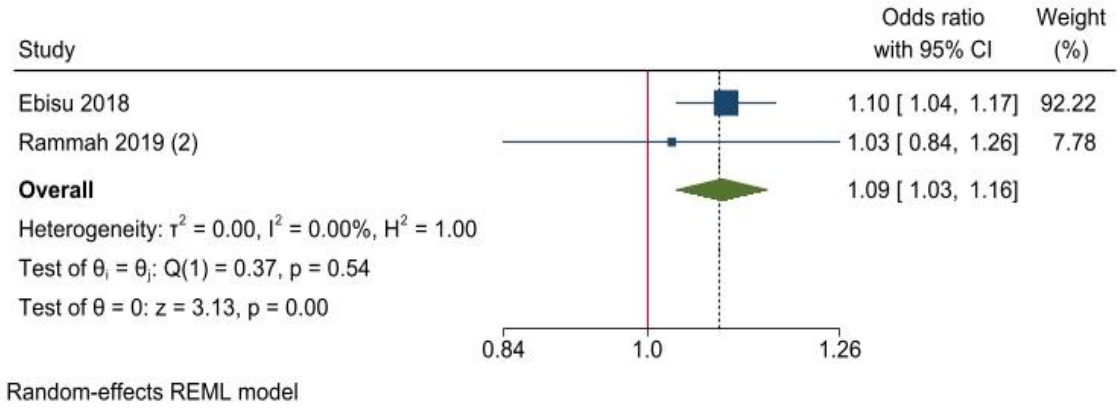
c = cohort study
cc = case-control study
Figure 5-18 Meta-analysis demonstrating the association between 1 increase in IQR of maternal exposure during pregnancy to copper in air pollution and stillbirth odds.



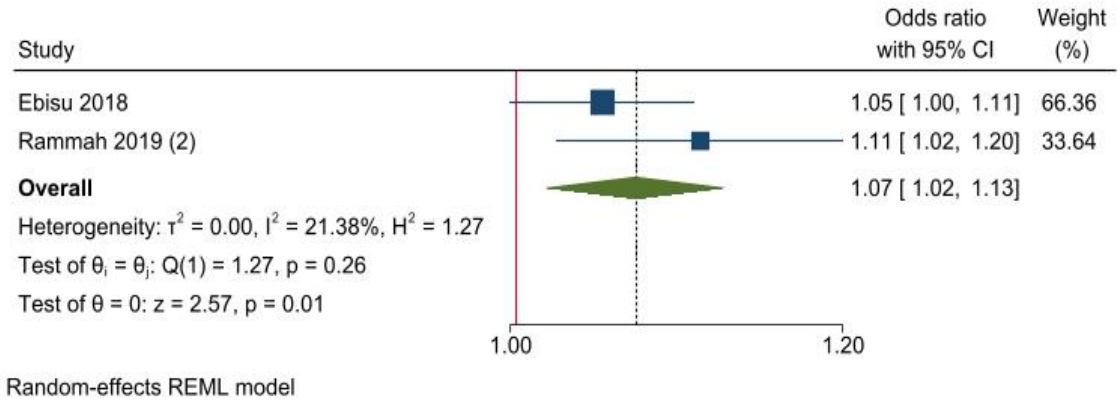
c = cohort study
cc = case-control study
Figure 5-19 Meta-analysis demonstrating the association between 1 increase in IQR of maternal exposure during pregnancy to iron in air pollution and stillbirth odds.



c = cohort study
cc = case-control study
Figure 5-20 Meta-analysis demonstrating the association between 1 increase in IQR of maternal exposure during pregnancy to nickel in air pollution and stillbirth odds.



c = cohort study
cc = case-control study
Figure 5-21 Meta-analysis demonstrating the association between 1 increase in IQR of maternal exposure during pregnancy to titanium in air pollution and stillbirth odds.



c = cohort study
cc = case-control study
Figure 5-22 Meta-analysis demonstrating the association between 1 increase in IQR of maternal exposure during pregnancy to zinc in air pollution and stillbirth odds.

PM10 air pollution

Two studies examined antenatal PM10 air pollution exposure and reported the associated stillbirth odds in the UK[488, 490]. As both studies reported use of the same dataset for analysis, they could not be combined through meta-analysis due to potential for double counting of births. Ghosh et al[488] demonstrated no clear association between doubling of PM10 pollution exposure during pregnancy and stillbirth odds (aOR 0.99 (95% CI 0.97, 1.00))[488], whereas Smith et al reported odds of stillbirth per interquartile range (IQR) increased (4.0 ug/m3). Analysis of trimester one and two exposure demonstrated a marginally protective effect on stillbirth odds (trimester one exposure per IQR 4.0 ug/m3: aOR 0.82 (95% CI 0.78, 0.87), and trimester two exposure per IQR 4.0 ug/m3: aOR 0.90 (95% CI 0.85, 0.96)). Smith et al[490] also reported no clear association between odds of stillbirth and PM10 exposure per increase in IQR during the last three months or pregnancy (aOR 0.98 (95% CI 0.92, 1.04))[490].

Environmental smoke

Ebisu et al[485] reported minimally decreased association between exposure during pregnancy to biomass burning (per increase in IQR) and stillbirth odds aOR 0.88 (95% CI 0.82, 0.93), and results did not differ when the cohort was stratified by trimester of stillbirth[485]. Pearce et al[482] similarly demonstrated no clear association between black smoke exposure (per 10 ug/m^3 increase/week) during pregnancy and stillbirth (aOR 1.01 (95% CI 0.99, 1.02))[482].

One study[429], conducted in the USA, used maternal serum levels of cotinine, a blood serum marker for exposure to smoke, to assess the odds of stillbirth associated with exposure during the first trimester[429]. Cotinine levels (ng/mL) were measured at 15-19 weeks GA, and were grouped into 5 categories (<0.026, 0.026-0.53, 0.54-0.96, 0.97-0.235, >0.235) but due to the very small sample sizes, the results were non-significant, as shown below:

- 0.026-0.53Ng/mL - aOR 1.08 (95% CI 0.21, 5.34)
- 0.54-0.96Ng/mL - aOR 1.47 (95% CI 0.32, 6.71)
- 0.97-0.235Ng/mL - aOR 0.37 (95% CI 0.04, 3.66)
- >0.235Ng/mL - aOR 3.36 (95% CI 0.81, 13.96)

Waste landfill/incinerator air pollution

Two studies included examined the distance between the primary place of residence for mothers and waste-incinerators[479, 488]. One study reported the odds associated with each additional kilometer between maternal place of residence to the waste facility, and found no increased odds of stillbirth (aOR 0.99 (95% CI 0.97, 1.00))[488]; the second study[488] confirmed these findings, demonstrating that residing within 2km of the waste facility, did not increase odds of stillbirth (aOR 0.91 (95% CI 0.77, 1.09)).

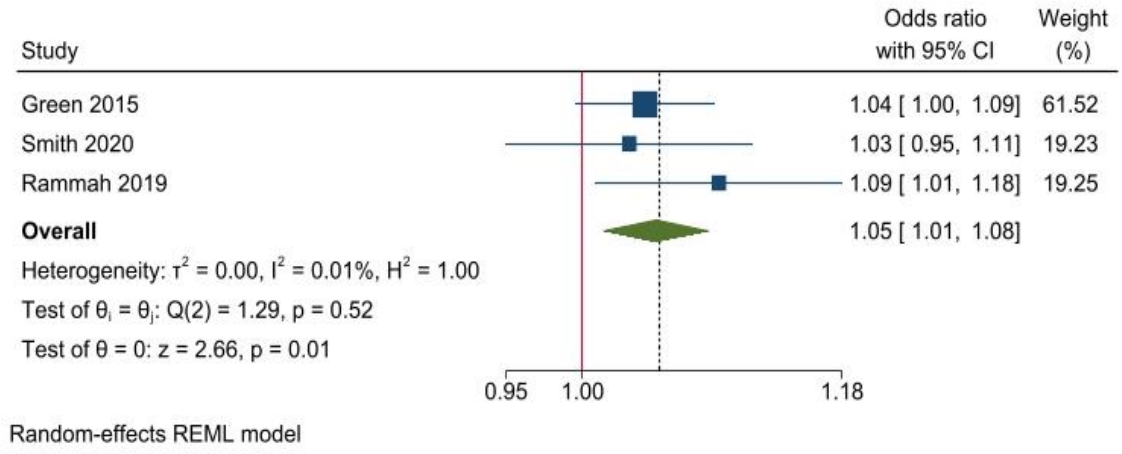
Arsenic

One study examined the association between arsenic air pollution exposure during pregnancy and stillbirth odds in Texas, USA[35]. Arsenic is found within air pollution from a variety of sources, including natural (bush fires) and industrial sources (mining, industrial combustions and smelters)[35]. The study used atmospheric dispersion models

of annual arsenic release from a processing plant, combined with residential postcode to estimate exposure during pregnancy. Results suggested that >100 ng per m^3 was associated with a fourfold increase in stillbirth odds (aOR 4.0 (95% CI 1.2, 13.7)), but small sample sizes contributing to large confidence intervals reduced confidence in these findings. The quality and bias assessment of this study was unclear due to lack of methodological detail concerning case and control selection, as well as concerns regarding exposure status measures.

Ozone (O_3)

Ozone air pollution was measured in three included studies and association with stillbirth odds were reported for cohorts in the USA and UK[34, 489, 490]. All three studies were combined in meta-analysis and demonstrated a marginally increased association with stillbirth odds for women exposed to increased ozone pollution compared with no increased levels (aOR 1.05 (95% CI 1.01, 1.08) – fig 5-23). Exposure groups varied between 3.6 ppb to 17.6 ppb unit increases per exposure group.



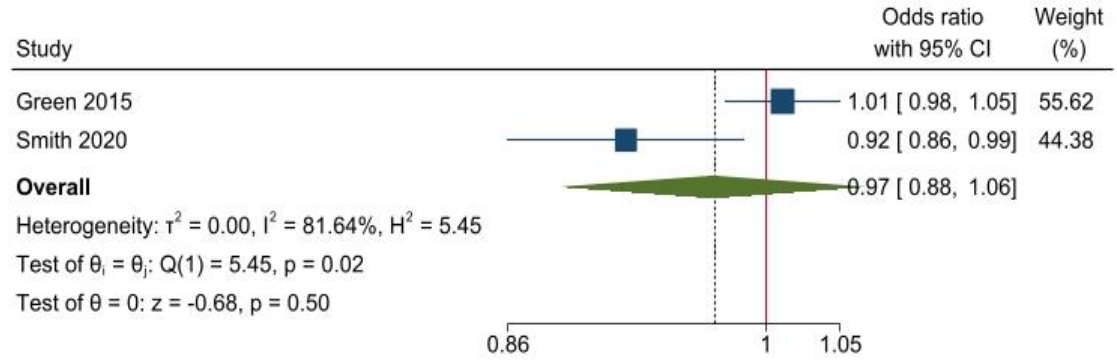
c = cohort study
cc = case-control study

Figure 5-23 Meta-analysis demonstrating the association between ozone air pollution and stillbirth odds compared with undetectable ozone air pollution.

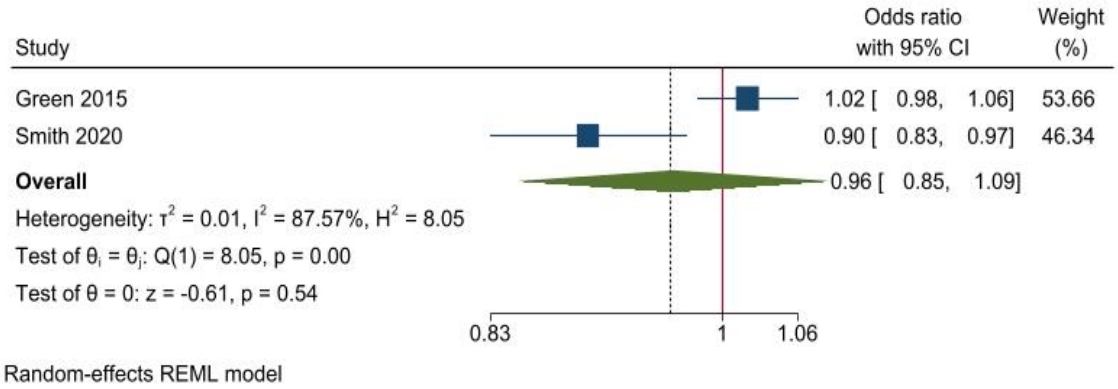
Smith et al combined O_3 pollution with primary traffic non-exhaust related PM2.5. and demonstrated an increase in stillbirth odds associated with trimester one (aOR 1.25 (95% CI 1.13, 1.38)), and trimester two (aOR 1.29 (95% CI 1.15, 1.46)), exposure compared with no increased exposure. Stillbirth odds were not increased when exposure was limited to the last 3 months of pregnancy[490].

Nitrous Dioxide (NO_2)

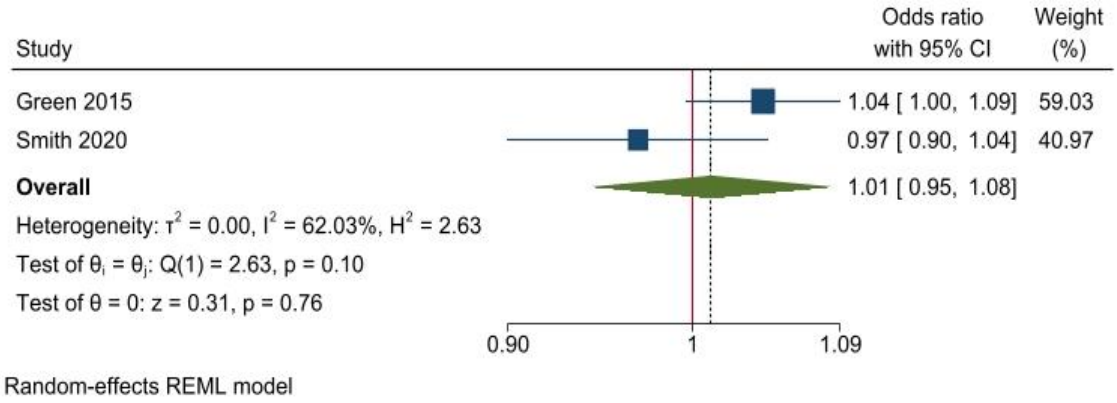
Exposure to NO_2 was examined by two studies, cohorts included populations from the UK and the USA[34, 490]. One study measured the exposure across the entire pregnancy and reported increased odds of stillbirth (aOR 1.08 (95% CI 1.03, 1.13))[34]. Both studies stratified exposure by trimester of pregnancy exposure and reported odds of stillbirth accordingly[34, 490]. Studies were combined through meta-analysis for each trimester of exposure to NO_2 air pollution exposure, with no clear associations with stillbirth demonstrated (fig 5-24, 5-25 and 5-26).



c = cohort study
cc = case-control study
Figure 5-24 Meta-analysis of the association between <u>first trimester</u> exposure to NO^2 within air pollution and stillbirth odds compared with undetectable nitrous oxide air pollution.



c = cohort study
cc = case-control study
Figure 5-25 Meta-analysis of the association between <u>second trimester</u> exposure to NO^2 within air pollution and stillbirth odds compared with undetectable nitrous oxide air pollution.



c = cohort study
cc = case-control study
Figure 5-26 Meta-analysis of the association between <u>third trimester</u> exposure to NO^2 within air pollution and stillbirth odds compared with undetectable nitrous oxide air pollution.

Sulphur dioxide

Only one study within this review reported adjusted odds of stillbirth associated with antenatal exposure to sulphur dioxide[34]. Green et al[34] examined association within a Californian birth cohort and demonstrated no clear association between sulphur dioxide exposure per 10 ppb increase, and stillbirth odds (aOR 1.02 (95% CI 0.91, 1.14))[34]. This study further stratified results by trimester of exposure, and again demonstrated no clear association between sulphur dioxide pollution and stillbirth odds.

Carbon monoxide

Carbon monoxide exposure during the antenatal period and its association with stillbirth odds was examined by one included study[34]. Through analysis of exposure, during the entire antenatal period, as well as stratification to trimesters of exposure, Green et al[34] reported no increased association with stillbirth with each 1ppb increase of carbon monoxide exposure during pregnancy:

- 1st trimester aOR 1.0 (95% CI 0.96, 1.05)
- 2nd trimester aOR 1.01 (95% CI 0.96. 1.07)
- 3rd trimester aOR 1.01 (95% CI 0.95, 1.07)
- entire pregnancy aOR 1.04 (95% CI 0.97, 1.12))

Nitrogen oxide (NOx)

Nitrogen oxide pollution is emitted during very high temperature combustions, like that seen in vehicular combustion, or residential and gas combustion[494]. The predominant contributor to NOx pollution in one New England study was found to be gasoline and diesel emission from vehicles[495]. One study, conducted within London, UK, measured the antenatal exposure to nitrogen oxide (NOx) and association with stillbirth risk. An increased association with stillbirth odds was demonstrated when women were exposed to NOx and increased O_3 in trimesters one (aOR 1.22 (95% CI 1.08, 1.37)) and two (aOR 1.27 (95% CI 1.10, 1.46)) of pregnancy, compared with no increased exposure.

Noise pollution

Smith et al[490] examined the impact that day-time noise pollution (per IQR, 3.5 dB) and night-time noise pollution (per IQR, 3.9 dB) had on stillbirth odds, and found that no increased association was reported for congenital anomaly-related stillbirths (aOR 1.00 (95% CI 0.94, 1.05)) or asphyxia-related stillbirths (aOR 0.99 (95% CI 0.94, 1.05))[490] compared with lower levels of noise exposure.

Table 5-2 Chapter 5 Summary of meta-analysis findings of the association between environmental pollutants and stillbirth odds

	Reference group	Exposure group	**All stillbirths ≥20 weeks GA or ≥400 grams** *(aOR (95% CI)*	**2nd trimester stillbirths** *(aOR (95% CI)*	**3rd trimester stillbirths** *(aOR (95% CI)*
Tap water pollution	Undetectable trihalomethanes	*Trihalomethanes ≥60 µ/liter*	1.21 (0.96, 1.53)	-	-
	Undetectable trihalomethanes	*Trihalomethanes 30-75 µ/liter*	**1.07 (1.00, 1.15)**	-	-
	Haloacetic acid <3.0 µ/liter	*Haloacetic acid 3.0-25.2 µ/liter*	**1.40 (1.01, 1.93)**	-	-
	Halo acetic acid <3.0 µ/liter	*Haloacetic acid 25.2-57.5 µ/liter*	**1.59 (1.04, 2.44)**	-	-
	Halo acetic acid <3.0 µ/liter	*Haloacetic acid 35.4-88.1 µ/liter*	1.37 (0.80, 2.34)	-	-
	No dichloroacetic acid exposure	*Highest levels of dichloroacetic acid*	1.14 (0.46, 2.79)	-	-
	No dichloroacetic acid exposure	*Medium levels of dichloroacetic acid*	**1.64 (1.17, 2.31)**	-	-
	No dichloroacetic acid exposure	*Lowest levels of dichloroacetic acid*	**1.44 (1.04, 2.00)**	-	-
	Undetectable trichloroacetic acid	*Highest levels of trichloroacetic acid*	1.35 (0.95, 1.92)	-	-
	Undetectable trichloroacetic acid	*Medium levels of trichloroacetic acid*	1.12 (0.79, 1.58)	-	-
	Undetectable trichloroacetic acid	*Lowest levels of trichloroacetic acid*	1.28 (0.93, 1.76)	-	-
	Undetectable Brominated haloacetic acids	*Brominated haloacetic acids detected*	1.30 (0.89, 1.91)	-	-
Air pollution	NA	*PM2.5 pollutants – risk per IQR increase*	1.03 (0.95, 1.12)	-	-
	NA	*PM2.5 pollutants entire pregnancy exposure – risk per IQR increase*	1.02 (0.94, 1.10)	-	-
	NA	*PM2.5 pollutants second trimester exposure – risk per IQR increase*	1.00 (0.87, 1.14)	-	-
	NA	*PM2.5 pollutants third trimester exposure – risk per IQR increase*	1.01 (0.94, 1.09)	-	-

NA	*Aluminium air pollution (+1 IQR increase)*	**1.05 (1.00, 1.09)**	-	-
NA	*Copper air pollution (+1 IQR increase)*	1.00 (0.97, 1.19)	-	-
NA	*Iron air pollution (+1 IQR increase)*	1.07 (0.97, 1.19)	-	
NA	*Nickel air pollution (+1 IQR increase)*	1.00 (0.98, 1.02)	-	-
NA	*Titanium air pollution (+1 IQR increase)*	**1.09 (1.03, 1.16)**	-	-
NA	*Zinc air pollution (+1 IQR increase)*	**1.07 (1.02, 1.13)**	-	-
NA	*Ozone (O_3) pollution (+1 IQR increase)*	**1.05 (1.01, 1.08)**	-	-
NA	*NO_2 pollution (+1 IQR increase)*	0.97 (0.88, 1.06)	0.96 (0.85, 1.09)	1.01 (0.95, 1.08)

Discussion and conclusions

To our knowledge, this is the only systematic review and meta-analysis to date that presents the association between pollutant exposure and stillbirth odds. Women living in areas of high tap water pollution, particularly from chlorination by-products (dichloroacetic acid and haloacetic acid) or chemical leaching pollutants (tetrachloroethylene) demonstrated higher odds of stillbirth compared with non-exposed pregnancies. Tetrachloroethylene water pollution was shown to have moderate associations with stillbirth odds, increasing by over 2-fold for exposed women[484]. Tetrachloroethylene pollution is primarily due to chemical run off leaching into waterways supplying drinking water sources[496]. Following pollutant level peaks in the 1980s, they have slowly declined due to increased awareness of the health implications of exposure[496]. Most tetrachloroethylene presence is due to dry-cleaning, domestic or industrial cleaning products, solid fuel burning, chemical production, and the production of fluorocarbons[496]. Only a single study examined the relationship between tetrachloroethylene and stillbirth odds. This study included stillbirths due to placental abruption or insufficiency and reported up to 76% of confounders missing, thereby limiting the generalisability of findings to other populations. The study was assessed as having a high risk of bias and poor quality, therefore our confidence in findings is low, although the effects of tetrachloroethylene pollution warrant further investigation.

Chlorination treated water is the main source of household drinking water in most high-income countries. Since water processing plants acknowledged the relationship between chlorination by-products and poor pregnancy outcomes, kidney failure and cancers[497], they have implemented alternative disinfectant means such as ozone filtration or UV radiation. These methods are preferable as they do not produce halogenated by-products[498, 499]. Results demonstrate moderate associations between these pollutants in tap water and stillbirth odds. The gold standard is to individually measure pollutant exposure for each person in samples of water, but our included studies that sampled local water distribution centres to estimate exposure status. Despite included data inherently affected by misclassification bias due to poor exposure measure methods, findings still demonstrate clear association with several pollutants analysed. Thus, our findings support the need to use alternative methods for water treatment prior to consumption to minimise the exposure to chlorination by-products. No studies included analysis of the relationship between phthalate or paraben exposure and stillbirth.

Most air pollutants are associated with waste incineration and traffic fumes that accumulate in industrial areas. In high-income countries, such areas are generally associated with lower SES communities. Another reported source of pollution exposure is heavy metal air pollution concentrated in potable household rainwater collection[471]. Many high-income countries encourage the use of roof collected rainwater, but conflicting results regarding safe consumption mean increased monitoring is encouraged[500]. Although none of the included studies examined the impact of heavy metal exposure in water pollution, heavy metal exposure due to air pollution was associated with minimally increased stillbirth odds. Slight association with stillbirth odds were shown in association with interquartile range increases in titanium, aluminium, and zinc pollution exposure, demonstrating a dose-response relationship. Confidence in these results is high due to the low risk of bias and high quality of the included studies. Where results of exposure to air pollution could be stratified by trimester of exposure (PM2.5, sulphur dioxide and NO2 pollution), meta-analysis demonstrated that the trimester of

exposure was not related to an increase in stillbirth risk. A stand-alone study identified 4-fold increased odds of stillbirth association with annual estimations of residential arsenic air pollution exposure during pregnancy However, unclear bias and quality assessment meant confidence in these findings was lacking. Our review included environmental pollutants not associated with unprecedented natural or provoked disasters. Arsenic pollution has been associated with bushfire and large combustion incidents, but due to exclusion of studies examining the association between pollution caused by natural disasters, we were unable to form any conclusions regarding the association with bushfire or combustion incidents on stillbirth odds.

Our findings are limited by the low number of studies examining the association between pollution and stillbirth odds. Furthermore, many of those studies did not adjust results for SES or by ethnicity, both of which have known associations related to pollution during pregnancy. In most instances, measures of pollution within included studies were largely generalised to the areas monitored by pollutant measuring stations. There caused is concern that residential areas with higher industrial pollution warranting monitoring are associated with low SES populations experiencing high levels of poverty and educational disadvantage. This to confounder bias affecting the results of analysis and means findings should be interpreted with caution. While measuring air pollution rather than maternal personal monitors can lead to exposure misclassification, by pooling international data we were able to demonstrate the effect on stillbirth of tap water pollution and air pollution across high-income countries. Findings are limited to average and long-term exposure which does not reflect associations with the exposure peaks and troughs associated with natural and/or provoked disasters, or occupational exposure.

Implications of findings and future research needed

Future research examining the impact of environmental pollutants on stillbirth odds needs to account for the multiple sources of exposure through analysis. Measures should encompass water and air samples at an individual level to fully examine the impact of pollution. A large prospective cohort study of pollution and its impact on stillbirth would strengthen findings and provide insight into an individual's direct source of pollution (air, water, food, or occupation).

Implications of findings for policy

These findings support the need for updating the World Health Organization guidance to limit exposure to chlorination by-products in drinking water and highlight the urgency for setting specific goals to reduce exposure globally. Exposure to chlorination by-products and leached pollutants is shown to have the highest association with stillbirth odds and is not a risk factor easily avoided at the individual level. Therefore, to ensure the safety of communities, it is beholden upon government and national policy to monitor and reduce pollutant exposure. Our findings confirm the need for national efforts to reduce pollution exposure through traffic and exhaust fumes, but cannot be generalised to exposure due to natural or provoked disasters. Despite many high-income countries adopting incentive programs for alternative fuel options, and reduced national emissions, to achieve global targets, our findings suggest that the most harmful pollutant exposure is found in drinking water. There exists a need for better monitoring and safety guidance for air quality and all drinking water, including rainwater used for consumption where heavy metals could be leached and consumed.

Chapter 6 Identification of Populations at Increased Risk of Stillbirth in High-income Countries

Abstract

Background

Multiple populations and communities, within high-income countries, have been identified as experiencing higher risk of stillbirth than the general population.

Methods

Cohort and case-control studies published between 1998-2020 examining stillbirth risk for populations within high-income countries were identified through database searches. Adjusted odds ratios were calculated through meta-analysis for individual populations according to ethnicity, country of birth, insurance status and residence in remote and rural areas.

Results

One hundred and five studies examined the odds of stillbirth associated with populations at risk within high-income countries. Associations with stillbirth were shown for very remote living (aOR 2.66 (95% CI 1.35, 5.22)), black maternal ethnicity (USA and UK) (aOR 1.99 (95% CI 1.78, 2.23)), Indian maternal ethnicity (aOR 1.72 (95% CI 1.35, 2.18)), Indian country of birth (aOR 1.58 (95% CI 1.03, 2.41)), African maternal ethnicity (aOR 1.82 (95% CI 1.56, 2.12)) and Aboriginal and Torres Strait Islander ethnicity (aOR 1.61 (95% CI 1.08, 2.37)). Other important associations with aOR ranging from 1.05-1.64 were: maternal Pacific or Asian ethnicity, maternal Middle Eastern country of birth and rural place of residence.

Conclusion

Several populations are at increased risk of stillbirth within high-income countries, including communities with different ethnicities and those living in remote and rural areas. Strategies are needed to identify and address drivers of disparities in stillbirth rates affecting these communities.

Introduction

Marginalised populations across high-income countries demonstrate more than double the odds of stillbirth than their advantaged counterparts[5]. Inequities within high-income countries, widening disparity, and complex relationships between disadvantage and the consequent adverse health outcomes have never been more apparent[469]. Multiple factors have been implicated in contributing to inequity in accessing health care, such as cultural insensitivity, institutional racism, lack of interpreter presence, and travel and physical accessibility barriers[501, 502]. Ethnicity, migration, remoteness, and poor living conditions have all been identified as factors that increase the risk of poor health outcomes within marginalised populations, especially during vulnerable periods such as pregnancy. Stillbirth rates for women living in very remote Australia are almost three times that of women living in major cities, and these rates are further increased for Indigenous women residing in remote areas. There is increasing national concern that the impact of colonisation on Indigenous women's health, and the consequent intergenerational cycles of poor health outcomes, need to be addressed[503].

In Australia and the UK, programs to reduce preventable stillbirths, such as the Safer Baby Bundle and the Saving Babies' Lives programs, have used a multifaceted approach to raise awareness of prevalence and risk, encourage improved fetal monitoring, and assist

in strategies to reduce stillbirths[504, 505]. Both preventative programs have seen encouraging outcomes in the UK and Australia by engaging families through antenatal care and public campaigns. Although this is encouraging, women within marginalised groups generally fall outside of both campaign and healthcare reach, thereby reducing the effectiveness of prevention strategies and increasing the risk of inadequate antenatal care[349, 438, 506]. Without access to safe, culturally sensitive, risk awareness programs some families remain at increased risk of stillbirth.

Quantifying the risk of stillbirth associated with marginalised groups will help guide the focus of future prevention strategies. By focusing on identifying and overcoming barriers to the effectiveness of prevention campaigns, it may be possible to address come of the disparity in stillbirth rate within high-income countries.

Aims

To identify which populations and communities within high-income countries are at higher risk of stillbirth.

Methods

Literature Search Strategy

Detailed methodology is included in chapter 2 of this thesis. A systematic literature search of the medical literature was conducted using the major electronic databases PubMed, MEDLINE, Ovid, the Cochrane Library and CINAHL. Literature searches were conducted for the period 1998-July 2020, restricted to English language. Search strategies and results are included in Appendix B and C.

Inclusion/exclusion criteria for studies

Studies included in this review adhered to the inclusion/exclusion criteria outlined in Chapter 2. Literature reporting adjusted odds ratios for risk factor associations with fetal loss at ≥20 weeks GA or ≥400g birthweight were included. To minimize the potential bias resulting from individual reviewer judgment bias, each study was assessed independently by at least two members of the review team (SAHMRI Women and Kids researchers). Where disagreement was not resolved by discussion of the researchers, external review from an expert researcher (from SAHMRI Women and Kids theme/The NHMRC Centre for Research Excellence in Stillbirth) was sought to arbitrate and reach consensus.

Extraction and assessment of the studies

To minimise bias, each study was assessed independently by at least two researchers. Where disagreement was not resolved by discussion of the researchers, external review from an expert researcher was sought to arbitrate and reach consensus. All relevant studies selected for this review were assessed independently by two reviewers for their individual methodological quality. This was done by using a quality and bias assessment scale specifically designed by the RTI-University of North Carolina Evidence Based Practice Centre; the RTI item bank (RTI-IB)[85]. The scale includes 29 questions with multiple choice answers and additional space for free-text. The item-bank focuses on believability, incorporating risk and precision of the results. Overall quality and bias assessment was assigned qualitatively as: High, Medium or Low based on the RTI-IB criteria. Quality and bias assessment of studies are included in Appendix D.

Adjusted results were extracted per study and combined through meta-analysis where possible. Random-effects meta-analysis was performed to construct forest plots to account for probable differences in exposure effect between studies as well as variability between cohorts used. Complete analyses were performed using STATA IC v16.1, by first author (A Bowman) and coding framework was checked by SAHMRI Women and Kids Theme Lead Biostatistician (Dr T Sullivan).

Results

Search results

Systematic review and meta-analysis included 105 studies reporting adjusted odds ratios of factors that were associated with populations and or communities at risk in high-income countries[32, 35, 40, 42, 62-69, 71, 73, 86, 87, 91, 93, 104-108, 110, 111, 113, 118, 122, 125, 127, 132, 145, 146, 150-154, 157, 158, 164, 168, 177, 181, 185, 188, 192, 197, 200, 218, 231, 240, 250, 252, 253, 258, 275, 309, 313, 318, 323, 327, 330, 333, 340, 345, 361, 373, 442, 507-537]. Factors identified were; maternal country of birth, ethnicity, maternal remote living, insurance type, and residential segregation.

Scope, characteristics and quality of studies

Study populations were sourced from 16 high-income countries including Australia, Belgium, Denmark, Germany, the Netherlands, Norway, Sweden, Switzerland, Canada, the UK, Italy, New Zealand, Spain, the USA, Alaska, and Hawaii. Studies included 95 cohort studies, 8 case-control studies, and 2 cross-sectional studies. The quality and risk of bias of each study was assessed as low, medium or high. The quality and bias assessment details are provided in Appendix D.

Meta-analysis of findings

Country of birth

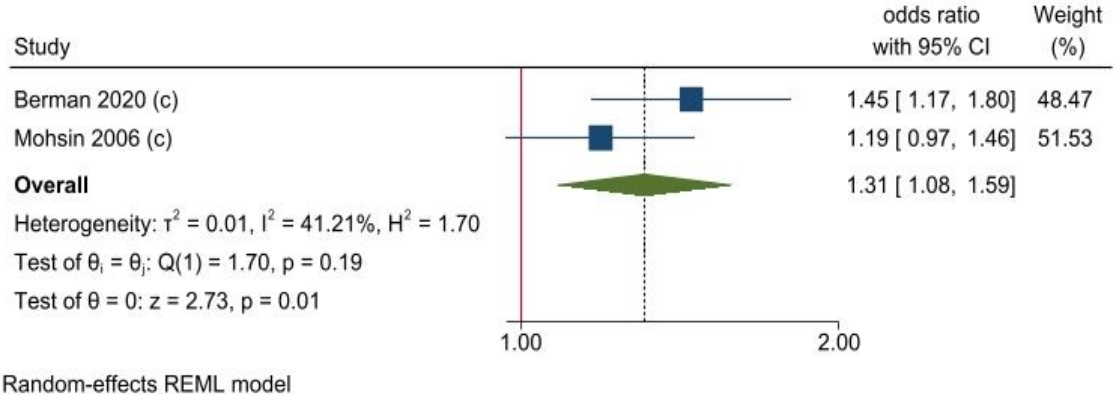
Twenty-seven studies examined the impact of maternal country of birth on stillbirth rates[42, 71, 73, 104, 125, 132, 151-153, 157, 192, 197, 200, 231, 240, 252, 509, 521-523, 530, 531, 533, 534, 536-538]. During extraction, two exposure measures were noted; self-reported ethnicity and country of birth. Results were accordingly stratified by exposure measure reported. The studies sourced data from 11 high-income countries and the EU15 (number of countries in the European Union prior to 2004 – Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Netherlands, Portugal, Spain, Sweden, UK). Using the RTI tool of assessment, fourteen of the studies were judged to have a low risk of bias[42, 73, 104, 125, 132, 153, 231, 240, 252, 509, 531, 533, 534, 536]. Nine of the studies were assessed as having an unclear risk of bias predominantly due to attrition bias, inadequate methodology detail, missing outcomes between study groups, as well as omitting descriptions of missing or unlinked data[71, 151, 152, 157, 197, 200, 522, 537, 538]. Four studies were assessed to have a high risk of bias[192, 521, 523, 530], one study poorly described the inclusion and exclusion criteria, and used a registry that detailed stillbirth reporting was "non-mandatory"[530]. Two studies reported results that were minimally adjusted and methodology demonstrated high potential for exposure misclassification[521, 523], and the final study compared pre-viable stillbirths with viable live births that resulted in inconsistent inclusion criteria across comparison groups[192].

Countries were grouped into global regions:

- Oceania (Including Micronesia, Melanesia, Polynesia and New Zealand, excluding Australia)
- Middle East (2nd trimester, 3rd trimester, term births)
- America (definitions include - Central South America, America/Africa, Latin America, America and Caribbean, Latin America and the Caribbean)
    - American born women all stillbirth odds
    - American born primiparous women stillbirth odds
- African born women (2nd trimester, 3rd trimester, term births)
- European born women
    - European born women stillbirth odds (all, 3rd trimester, term births)
    - Eastern European born (primiparous and multiparous)
- Asian born women
    - Indian born women
    - Southeast Asian born women
    - South Asian born women
    - West Asian born women
    - Northeast born Asian women

Oceanic maternal country of birth

Three studies examined the impact of maternal country of birth in Oceania[157, 197, 531] on stillbirth odds. One study was excluded from meta-analysis because although analysis was of Oceanic births, the focus of findings detailed comparison of maternal BMI rendering analysis non-comparable with other included studies[197]. The two remaining studies were combined through meta-analysis and results demonstrate increased odds of stillbirth for women born in Oceania compared with Australian born women (aOR 1.31 (95% CI 1.08, 1.59) – fig 6-1).



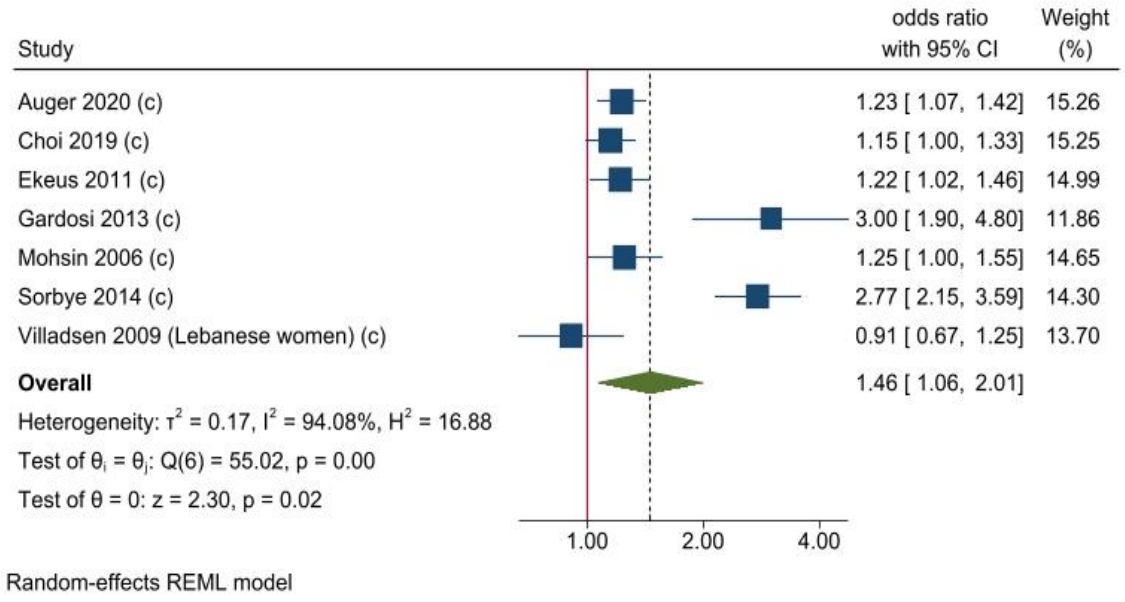
c = cohort study
cc = case-control study

Figure 6-1 Meta-analysis demonstrating the association between maternal Oceania country of birth and stillbirth odds compared with Australian born women.

Heterogeneity was moderate (I^2= 41%), possibly reflecting differences in populations included in the exposure groups. Mohsin et al[157] included births to New Zealander women within the exposure group, whereas Berman et al[531] did not.

Middle Eastern maternal country of birth

Ten studies examined the association between births to women born within Middle Eastern countries, and associated stillbirth odds[73, 104, 125, 157, 200, 509, 521, 522, 533, 536]. Three studies reported the use of the same dataset as other included studies. Thus, to avoid double-counting births, the three smaller studies were excluded from meta-analysis[73, 125, 521]. Initial analysis demonstrated high heterogeneity at 94.08%, therefore sensitivity analysis was performed. Two studies were identified that contributed considerably to heterogeneity, one excluded births where only one parent was foreign born, and the other included a smaller data-set from the UK West Midlands. Neither were accepted as reasonable grounds for exclusion, and therefore both were retained for analysis[200, 536]. Final meta-analysis of seven studies demonstrated an increased odds of stillbirth for women who were born in countries within the Middle East (aOR 1.46 (95% CI 1.06, 2.01) – fig 6-2) compared with births to Australian and European born women.

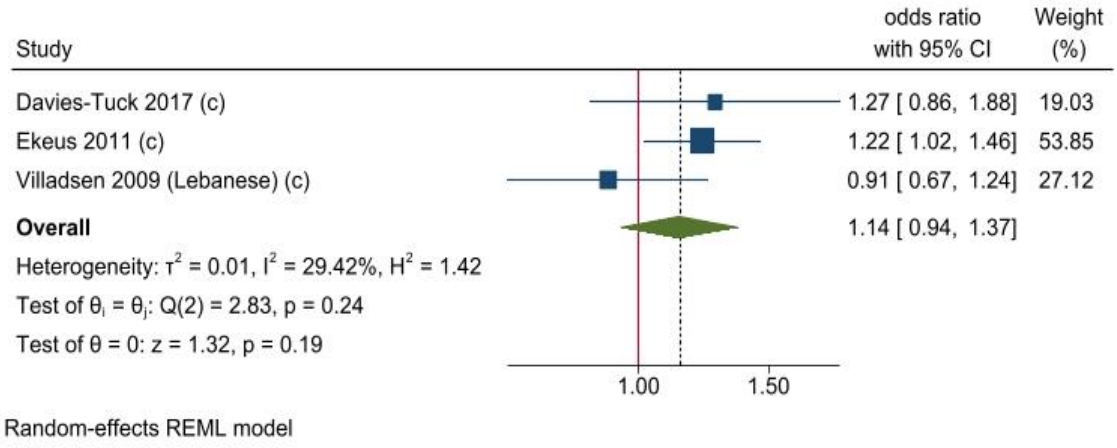


c = cohort study
cc = case-control study

Figure 6-2 Meta-analysis demonstrating the association between Middle Eastern country of birth and stillbirth odds compared with women not born in a Middle eastern country.

Middle Eastern maternal country of birth (third trimester stillbirth)

Three studies examined the impact on third trimester stillbirth odds of women born in the Middle East[73, 522, 533]. When combined through meta-analysis it was shown that the odds of third trimester stillbirth for Middle Eastern born women, residing in high-income countries, were slightly higher than women not born in the Middle East (aOR 1.14 (95% CI 0.94, 1.37) – fig 6-3).



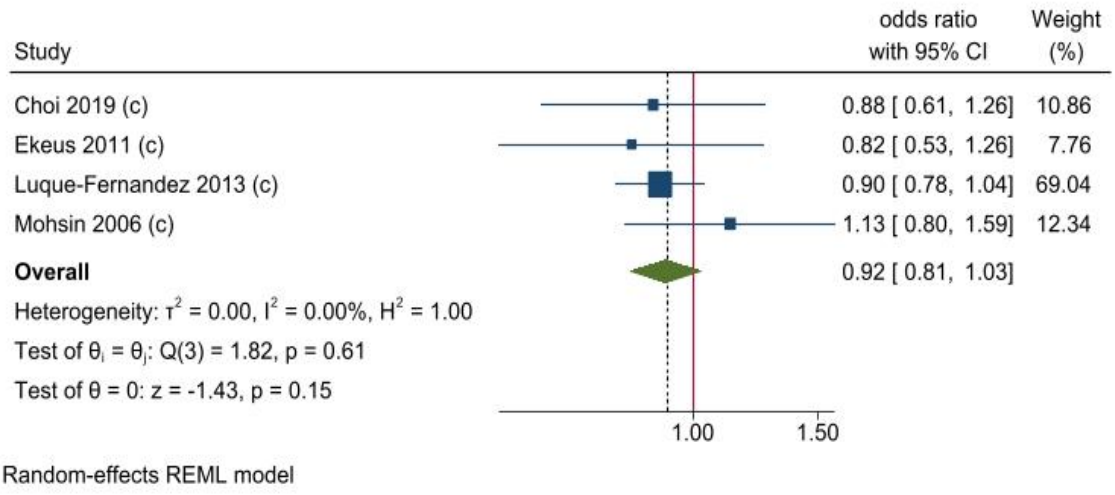
c = cohort study
cc = case-control study

Figure 6-3 Meta-analysis demonstrating the association between maternal Middle Eastern country of birth and third trimester stillbirth odds compared with women with a non-Middle Eastern country of birth.

One study[533] stratified third trimester births to women born in the Middle East by parity, and results demonstrated an increase in the odds of stillbirth for Middle Eastern born primiparous women compared with primiparous Swedish women (aOR 1.61 (95% CI 1.25, 2.09)).

American maternal country of birth

Seven studies examined the impact of maternal American country of birth on stillbirth odds[125, 151, 152, 157, 509, 530, 533] compared with women who were born elsewhere. Of the studies included in analysis, three examine the association within populations from Australia[125, 157, 509], three within Spanish cohorts[151, 152, 530], and one used a Swedish cohort[533]. Six studies reported use of the same dataset within analysis, therefore to avoid double counting of births, the smaller study subsets[125, 152, 530] were excluded from analysis, and the larger, and more robust analysis were retained[152, 157, 509]. Final meta-analysis included four studies, results demonstrated no association between maternal American country of birth and odds of stillbirth compared with women born outside America (aOR 0.92 (95% CI 0.81, 1.03) – fig 6-4).

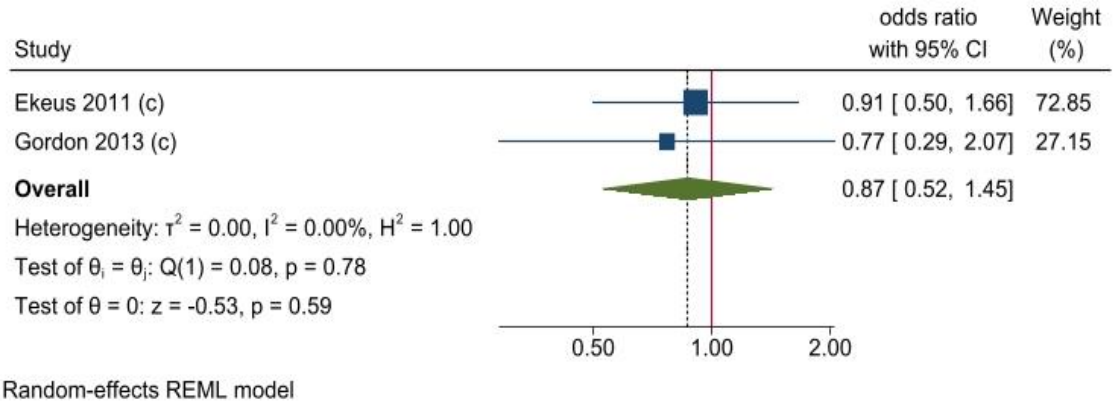


c = cohort study
cc = case-control study

Figure 6-4 Meta-analysis of the association between American born women and stillbirth odds compared with women not born outside America.

American maternal country of birth (per parity)

Two studies stratified American born women by parity[125, 533], and subgroup meta-analysis was performed for primiparous American born women. Although the findings of the meta-analysis demonstrated large confidence intervals, indicating that the analysis is under-powered, the results suggest odds of stillbirth for primiparous American-born women were not increased compared with primiparous non-American born women (aOR 0.87 (95% CI 0.52, 1.45) – fig 6-5).



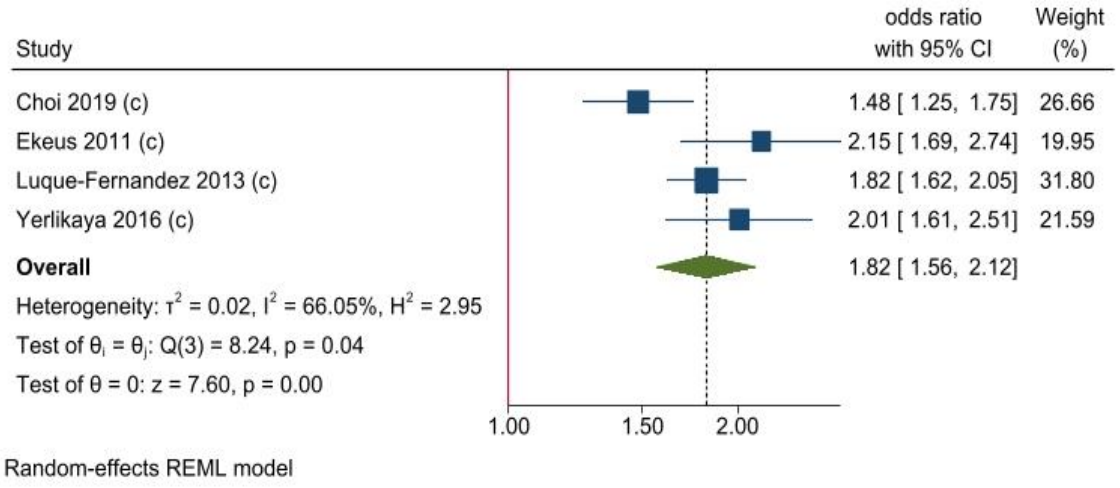
c = cohort study
cc = case-control study

Figure 6-5 Meta-analysis demonstrating the association between primiparous American born women, and stillbirth odds compared with primiparous non-American country born women.

African maternal country of birth

Ten studies reported adjusted odds ratios for women reporting an African country of birth[73, 151, 152, 200, 240, 252, 509, 530, 531, 533]. Studies included cohorts from Spain, Australia, the UK and Sweden. Of the ten studies six were excluded[73, 152, 200, 252, 530, 531] as they reported use of datasets encompassed within larger study populations[151, 240, 509]. Final meta-analysis included four studies, sourcing cohorts from Australia, Sweden, Spain and

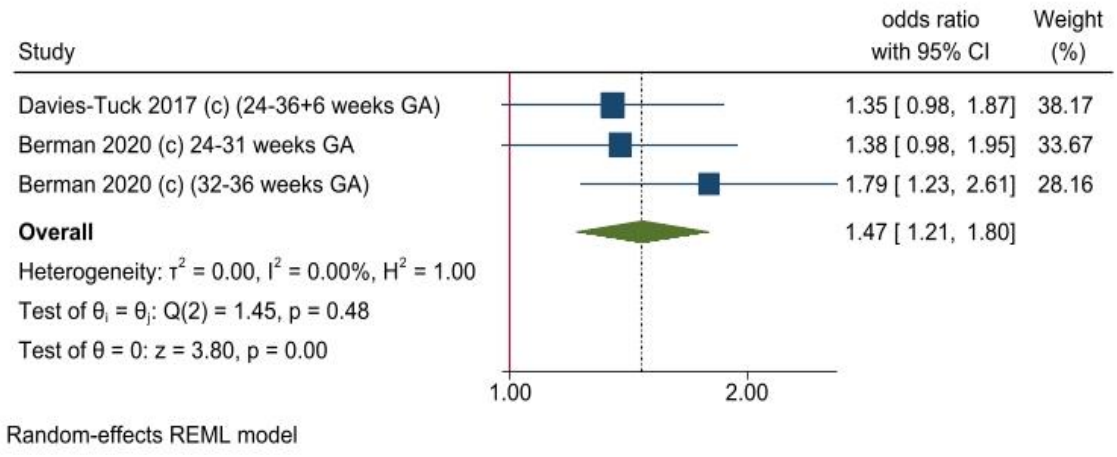
England[152, 240, 509, 533]. Heterogeneity between studies was considered substantial (I^2 = 66%) and therefore sensitivity analysis was performed, identifying Choi et al as the main contributor. On exclusion, heterogeneity decreased to 0% but review of the study methodology and population characteristics did not identify substantial differences warranting exclusion. Therefore Choi et al remained in analysis. Results demonstrated a nearly 2-fold increase in stillbirth odds associated with African country of birth compared with non-African country of birth (aOR 1.82 (95% CI 1.56, 2.12) – fig 6-6).



c = cohort study
cc = case-control study
Figure 6-6 Meta-analysis demonstrating the association between maternal African country of birth and stillbirth odds compared with non-African maternal country of birth.

African maternal country of birth (preterm stillbirth)

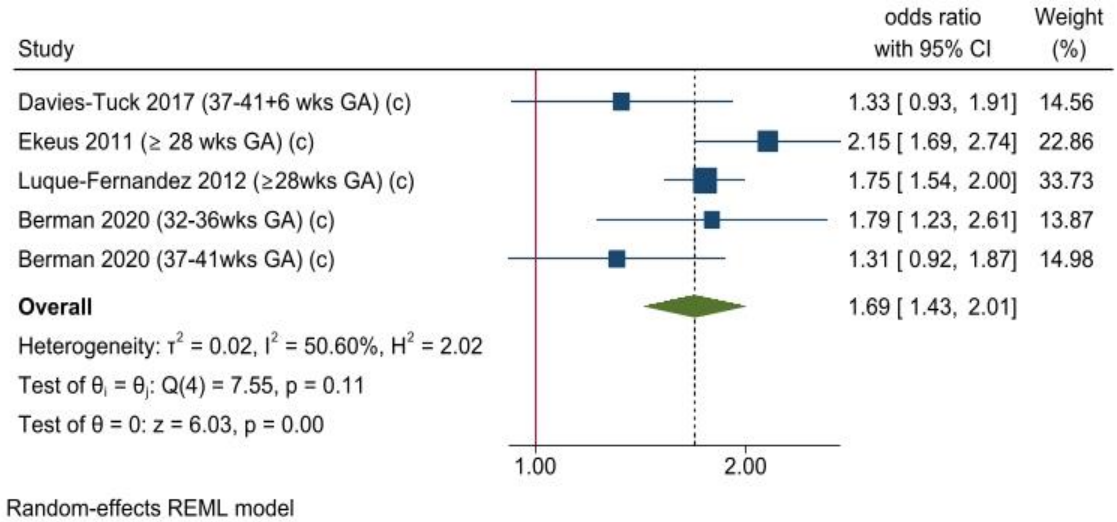
Two studies examined the association between maternal African country of birth and preterm stillbirth odds[73, 531]. Results of meta-analysis demonstrated 47% increased odds of stillbirth associated with maternal African country of birth, compared to Australian country of maternal birth (aOR 1.47 (95% CI 1.21, 1.80) – fig 6-7).



c = cohort study
cc = case-control study
Figure 6-7 Meta-analysis of studies examining the association between maternal African country of birth and preterm stillbirth compared with Australian country of birth

African maternal country of birth (third trimester stillbirth)

Four studies examined the impact of maternal African country of birth on third trimester stillbirths[73, 152, 531, 533]. Final meta-analysis demonstrated an increased odds of third trimester stillbirth (aOR 1.69 (95% CI 1.43, 2.01) – fig 6-8) compared with non-African born women. Moderate heterogeneity was demonstrated through analysis (I^2 = 51%) and was thought to reflect differing definitions of stillbirth (GA inclusion parameters at birth) used by the included studies (Detailed in figure 6-8, and also Appendix C).

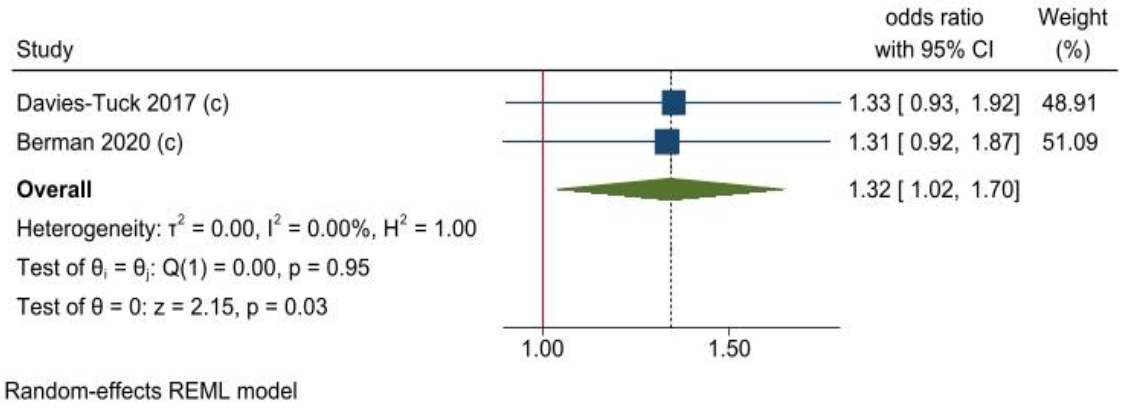


c = cohort study
cc = case-control study
Figure 6-8 Meta-analysis demonstrating the association between African maternal country of birth and third trimester stillbirth odds compared with non-African born women in high-income countries.

African maternal country of birth (term stillbirth)

Two Australian studies reported odds associated with an African maternal country of birth and term stillbirth (≥37 weeks GA) [73, 531]. Results of meta-analysis demonstrated

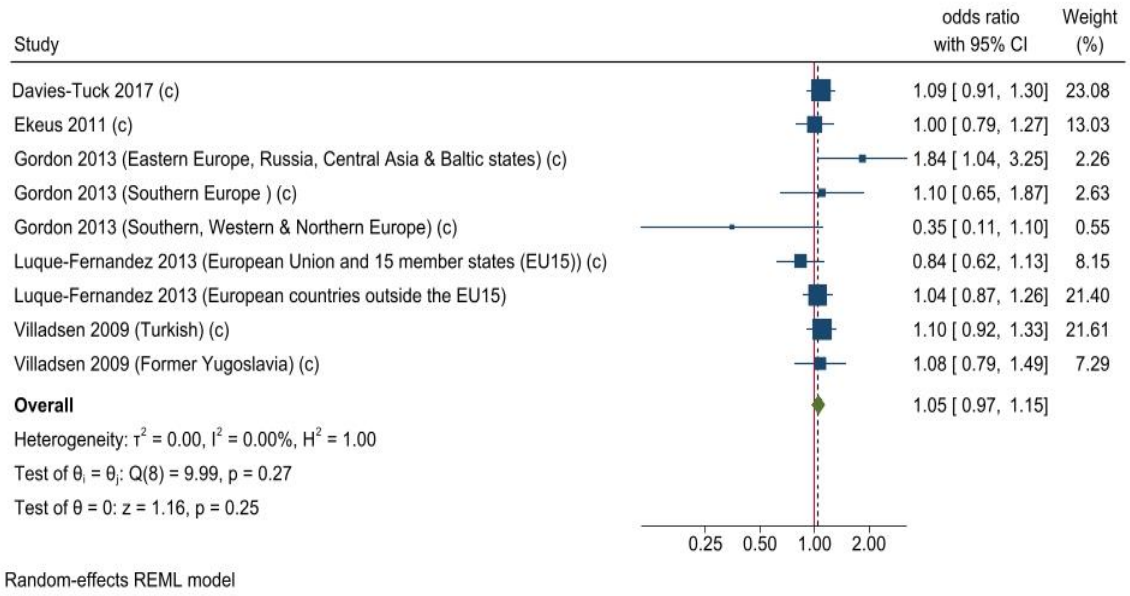
increased odds of term stillbirth odds associated with African maternal country of birth, compared with non-African maternal country of birth (aOR 1.32 (95% CI 1.02, 1.70) – fig 6-9). This indicate that the risk of stillbirth for African born women is still high but may decreases later in gestation, as the pregnancy approaches term.



c = cohort study
cc = case-control study
Figure 6-9 Meta-analysis demonstrating the association between African maternal country of birth and term stillbirth odds compared with non-African country of birth.

European maternal country of birth

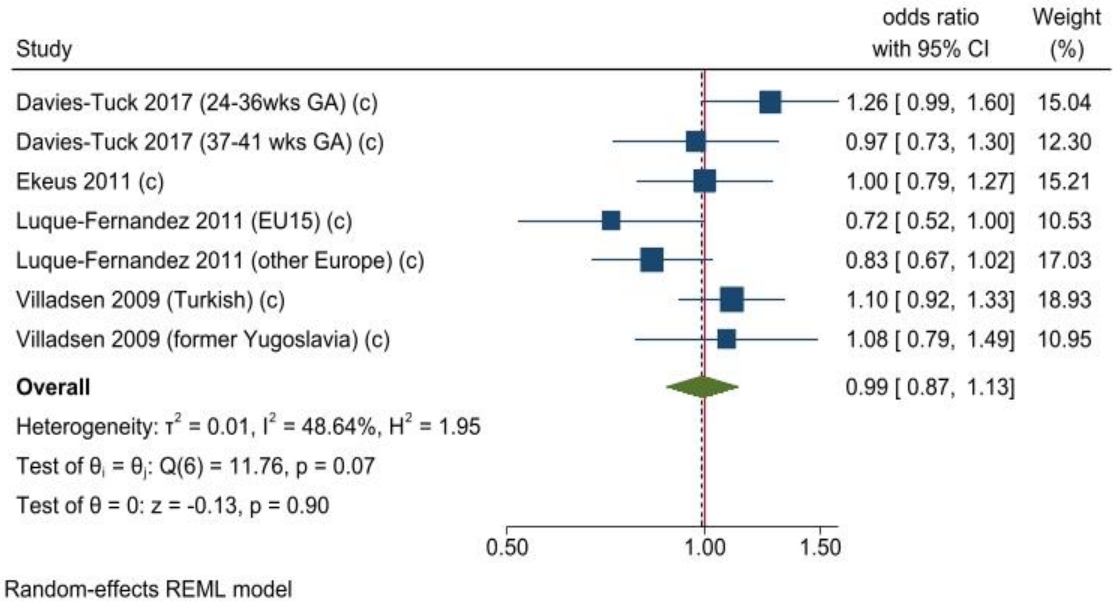
Nine studies examined the relationship between European maternal country of birth and the odds of stillbirth[73, 125, 151, 152, 157, 522, 523, 530, 533]. Seven studies[125, 152, 157, 530, 533] [151, 523] reported use of the same dataset and therefore to avoid potentially double counting births, three smaller studies were excluded from meta-analysis[152, 157, 530]. The final analysis included six studies but demonstrated substantial heterogeneity (I^2 = 73.2%). Through sensitivity analysis, Villadsen et al[523] was identified as a contributor to heterogeneity, likely due to only adjusting results for year of birth. Due to minimal adjustment of one confounder, Villadsen et al[522] was excluded from analysis. Final meta-analysis of five studies[73, 125, 151, 522, 533] demonstrated the possibility of a small increase in odds of stillbirth associated with European maternal country of birth (aOR 1.05 (95% CI 0.97, 1.15) – fig 6-10).



c = cohort study
cc = case-control study
Figure 6-10 Meta-analysis demonstrating the association between European maternal country of birth and stillbirth odds compared with non-European country of birth

<u>European maternal country of birth (third trimester stillbirth)</u>

Five studies examined the association between European maternal country of birth and third trimester stillbirth odds[73, 152, 522, 523, 533]. One study[523] was excluded to avoid double counting births as it used a dataset encompassed within a larger study[533]. Final meta-analysis included four studies and demonstrated moderate heterogeneity (I^2 = 48.64%) that was accepted and attributed to the stratifications within the included studies. Results indicate no clear association between European maternal country of birth and third trimester stillbirth compared to non-European country of birth (aOR 0.99 (95% CI 0.87, 1.13) – fig 6-11) .



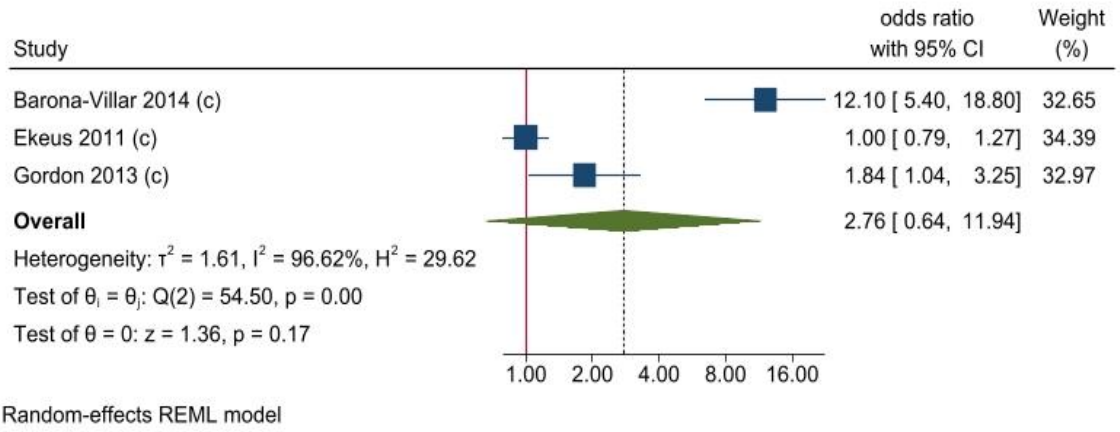
c = cohort study
cc = case-control study
Figure 6-11 Meta-analysis of the association between maternal European country of birth and third trimester stillbirth odds compared with women born outside of Europe.

European maternal country of birth (term stillbirths)

One study examined the association between European maternal country of birth and term stillbirth odds (≥37 weeks GA)[73]. Results demonstrated no clear association with term stillbirth odds for European maternal country of birth in comparison with Australian born women (aOR 0.97 (95% CI 0.73, 1.30))[73].

Eastern European maternal country of birth

Three studies stratified results by Eastern European region of maternal birth[125, 530, 533]. Results were combined through meta-analysis and considerable heterogeneity was demonstrated between studies (I^2 = 96.62%). Sensitivity analysis was performed, and heterogeneity was not decreased substantially, therefore was accepted. Results were under-powered due to small sample sizes but demonstrate an almost 3-fold increase in stillbirth odds for women born in an Eastern European country compared with other countries (aOR 2.76 (95% CI 0.64, 11.94) – fig 6-12).

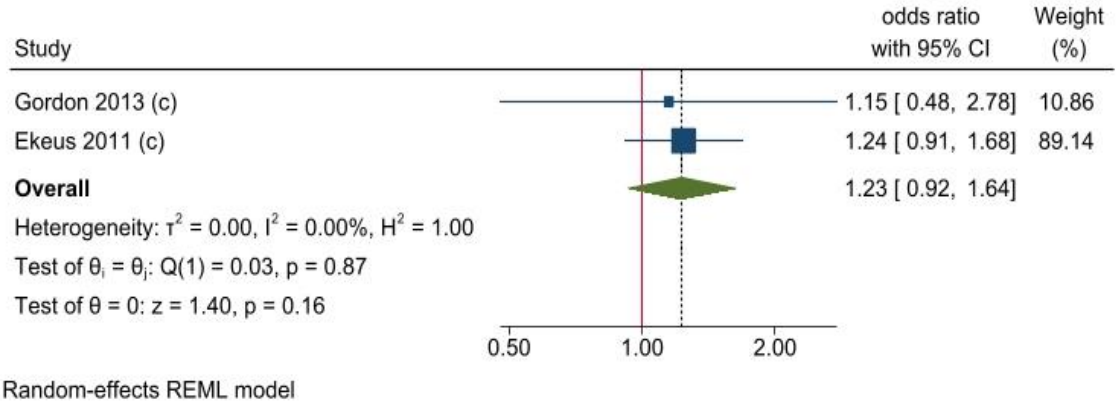


c = cohort study
cc = case-control study

Figure 6-12 Meta-analysis demonstrating the association between maternal Eastern European country of birth and stillbirth odds compared with women born outside of Eastern Europe

Eastern European maternal country of birth (primiparous women)

Two studies examined the association between primiparous Eastern European maternal country of birth and stillbirth odds[125, 533]. Final meta-analysis did not demonstrate a clear association between Eastern European country of birth and stillbirth in primiparous women compared to primiparous women born outside of Eastern Europe (aOR 1.23 (95% CI 0.92, 1.64) – fig 6-11).



c = cohort study
cc = case-control study

Figure 6-13 Meta-analysis of studies demonstrating the association between Eastern European maternal country of birth and stillbirth odds for primiparous women compared with births to primiparous women born outside of Eastern Europe.

Eastern Europe maternal country of birth (multiparous women)

One study examined the relationship between Eastern European country of birth and stillbirth odds for multiparous women within an Australian cohort[125]. Results demonstrated a three-fold increased risk of stillbirth for multiparous women who were born in a country in Eastern Europe compared with multiparous Australian born women (aOR 3.27 (95% CI 1.54, 6.94)).

Asian-born women

West Asian maternal country of birth

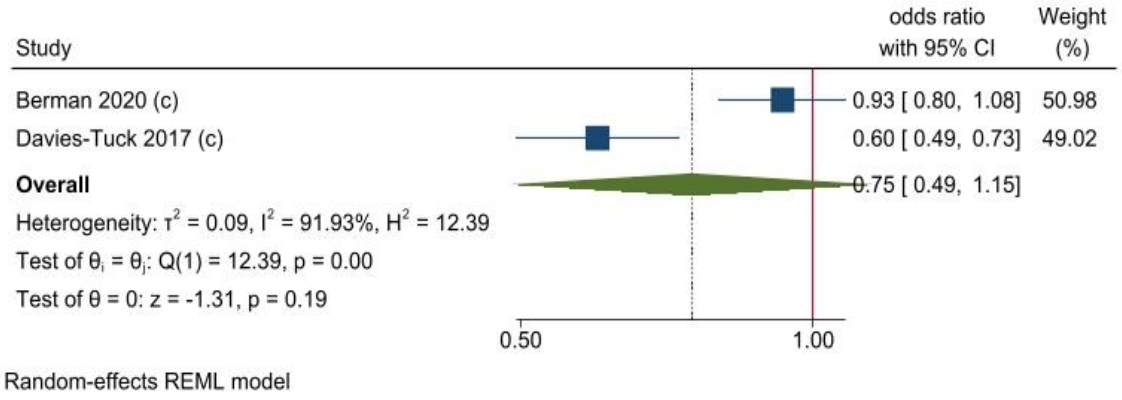
One study reported adjusted odds ratios for stillbirth among women born in West Asian countries[531]. The study used an Australian cohort of women sourced from one state (New South Wales). Results suggest a possible non-significant increased risk of stillbirth for women born in a West Asian country compared to Australian born women (aOR 1.13 (95% CI 0.95, 1.34)).

Northeast Asian maternal country of birth

One study reported adjusted odds ratio of stillbirth for Northeast Asian maternal country of birth, compared with Australian born women[125]. Results did not suggest increased odds of stillbirth (aOR 0.72 (95% CI 0.49, 1.06)) compared with women born in non-Northeast Asian countries. Stratification by parity demonstrated no clear association with stillbirth for nulliparous (aOR 0.81 (95% CI 0.51, 1.29)) or multiparous women (aOR 0.57 (95% CI 0.28, 1.15)) born in Northeast Asian countries compared with women born in predominantly English-speaking countries[125].

Southeast-East Asian maternal country of birth

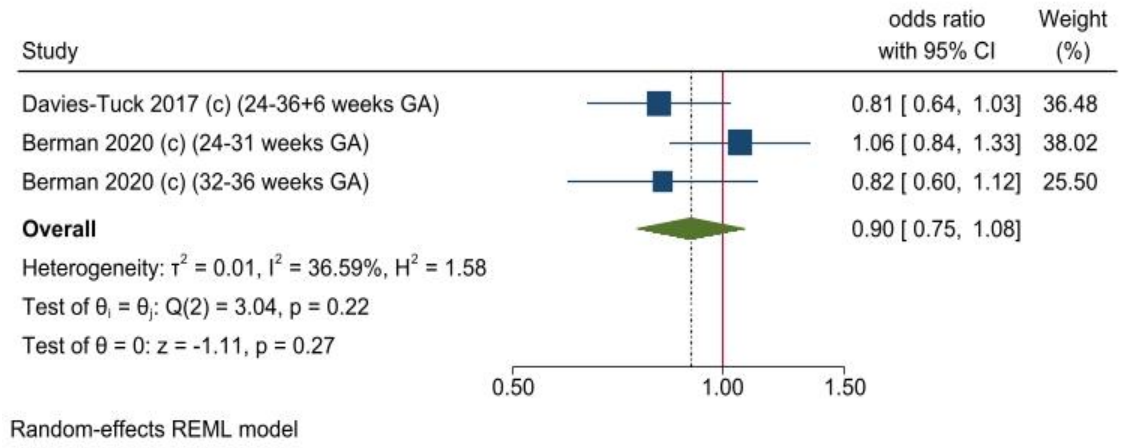
Two studies examined the odds of stillbirth associated with a Southeast-East Asian maternal country of birth[73, 531]. Final meta-analysis included both studies and results showed considerable heterogeneity (I^2 = 91.93%). No causes for high heterogeneity were identified. The results do not suggest an association between Southeast-East Asian born women and stillbirth odds (aOR 0.75 (95% CI 0.49, 1.15) – fig 6-14), but results should be interpreted with caution due to the high heterogeneity.



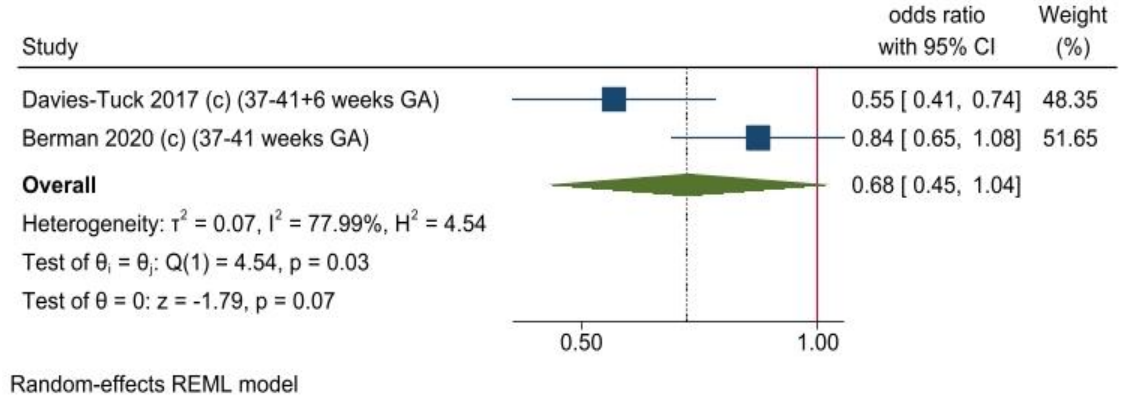
c = cohort study
cc = case-control study
Figure 6-14 Meta-analysis of the association between maternal Southeast/South Asian country of birth and stillbirth odds compared with non-Southeast/South Asian maternal country of birth.

Both Davies-Tuck et al[73] and Berman et al[531] stratified results of analysis by GA at birth to preterm and term stillbirth odds analysis. Analysis demonstrated that the odds of stillbirth remain unchanged as gestation reached term for women born in Southeast-East Asian countries, and possibly trends towards a non-significant protective association

(preterm; aOR 0.90 (95% CI 0.75, 1.08) (fig 6-15) and term; aOR 0.68 (95% CI 0.45, 1.04) (fig 6-16)).



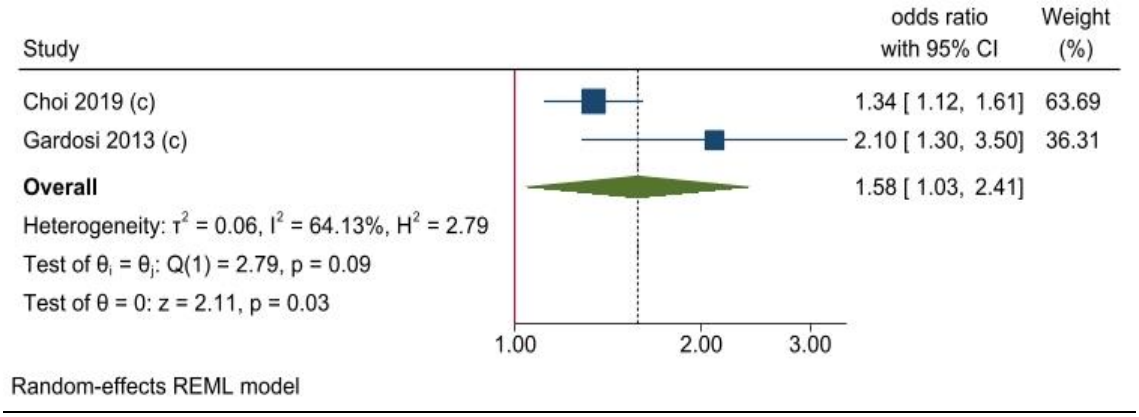
c = cohort study
cc = case-control study
Figure 6-15 Meta-analysis of the association between Southeast Asian maternal country of birth and preterm stillbirth versus non-Southeast Asian country of birth.



c = cohort study
cc = case-control study
Figure 6-16 Meta-analysis of the association between Southeast Asian maternal country of birth and term stillbirth versus non-Southeast Asian country of birth.

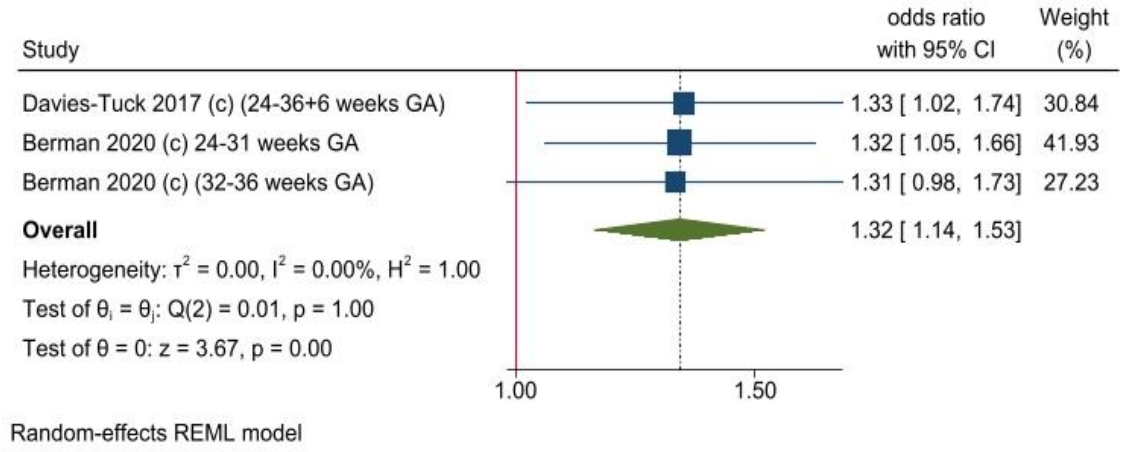
South Asian maternal country of birth

Four studies examined the association between maternal South Asian country of birth and stillbirth odds compared with UK and Australian born women[73, 200, 509, 531]. Three of the studies reported use of the same Australian dataset, therefore the largest and most comprehensive study was included[509], and the smaller two were excluded to avoid double counting births within analysis[73, 531]. Both remaining studies were included in meta-analysis and the association between South Asian born women and stillbirth odds was shown to be increased, compared with UK and Australian born women (aOR 1.58 (95% CI 1.03, 2.41) – fig 6-17).



c = cohort study
cc = case-control study
Figure 6-17 Meta-analysis of the stillbirth association between South Asian maternal country of birth versus UK or Australian country.

Two studies examined the impact of South Asian maternal country of birth stratified to preterm and term stillbirth[73, 531]. Through meta-analysis of both groups, results demonstrate an increase in stillbirth odds as pregnancy gestation approaches term (preterm; aOR 1.32 (95% CI 1.14, 1.53) (fig 6-18) and term; aOR 1.50 (95% CI 1.27, 1.77) (fig 6-19)).



c = cohort study
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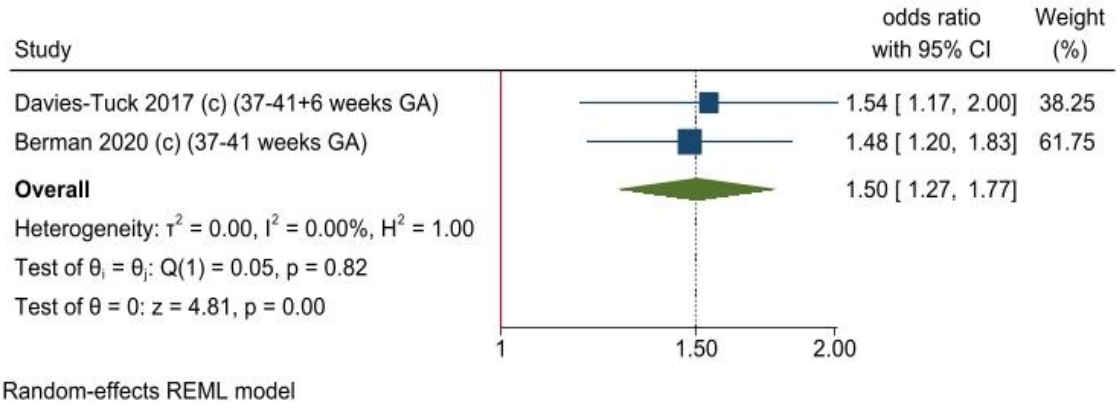
Figure 6-18 Meta-analysis of studies examining the association between South Asian maternal country of birth and preterm stillbirth odds, compared to Australian and English maternal country of birth

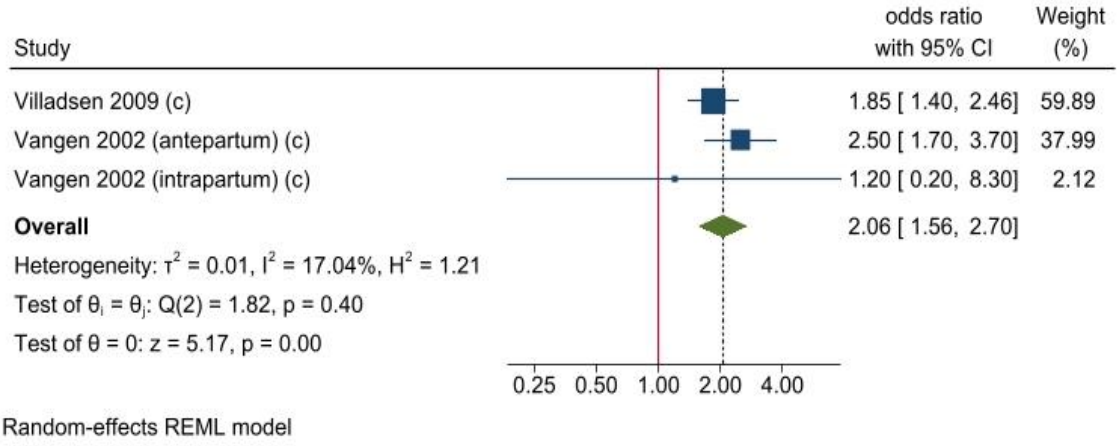


c = cohort study
cc = case-control study

Figure 6-19 Meta-analysis of studies examining the association between maternal South Asian country of birth and term stillbirth odds compared with Australian and English maternal country of birth

Somalian maternal country of birth

Two studies reported the odds of stillbirth associated with Somalian maternal country of birth compared with women in two cohorts, one from Norway[522], and one from Denmark[521]. Vangen et al[521] stratified births by timing of fetal death (antepartum or intrapartum), both groups were included within meta-analysis. Results of meta-analysis demonstrated a two-fold increased odds of stillbirth for women living in Norway or Denmark who reported Somalia as their country of birth, compared with Norway or Denmark as the reported maternal country of birth (aOR 2.06 (95% CI 1.56, 2.70) – fig 6-20).



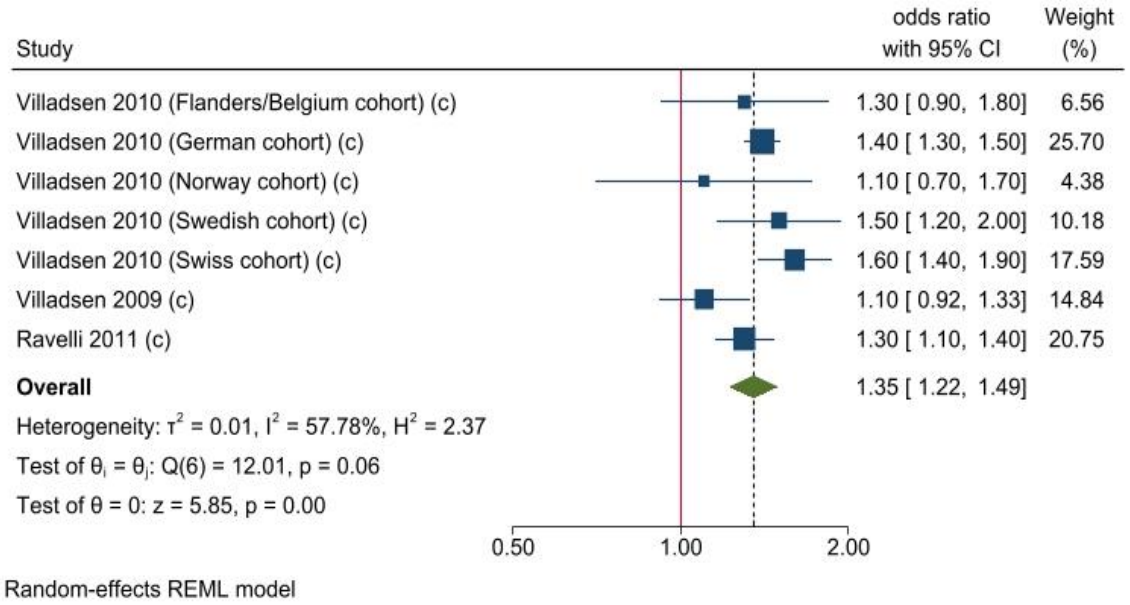
c = cohort study
cc = case-control study

Figure 6-20 Meta-analysis demonstrating the association between Somalian country of birth and stillbirth odds compared with Danish and Norwegian born women.

Turkish maternal country of birth

Three studies examined the impact of maternal Turkish country of birth and stillbirth odds[69, 522, 523]. All three studies used cohorts from different countries, and one study, Villadsen et al[523], included cohorts from five separate European countries. Results demonstrated an increased association between Turkish maternal country of birth and

stillbirth compared with other countries of birth (aOR 1.35 (95% CI 1.22, 1.49) – fig 6-12).



c = cohort study
cc = case-control study
Figure 6-21 Meta-analysis demonstrating the association between mothers born in Turkey and stillbirth odds, compared with mothers born in the host countries.

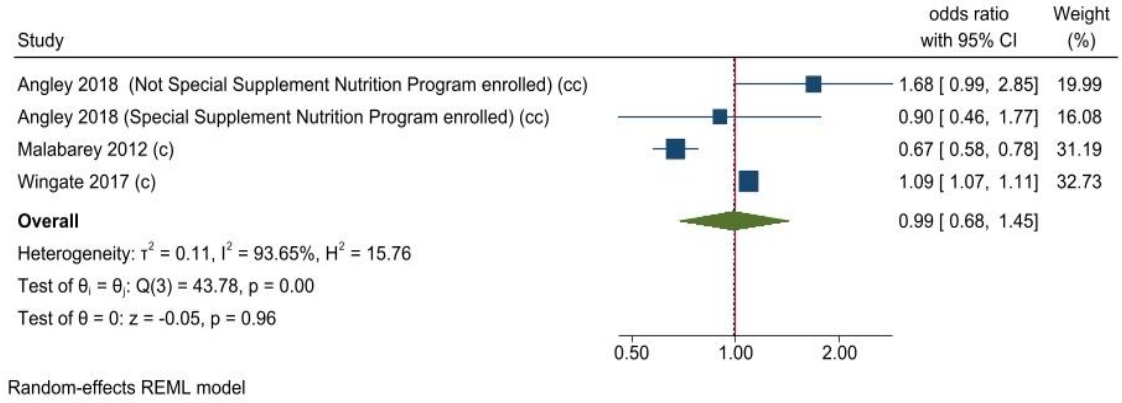
Maternal ethnicity

Fifty-two studies examined maternal ethnicity and the associated odds of stillbirth[32, 63, 65-69, 86, 91, 104, 106, 110, 118, 125, 145, 152, 154, 156, 157, 164, 169-171, 179, 181, 185, 190, 218, 258, 309, 318, 324, 327, 330, 340, 345, 362, 373, 507, 508, 510-512, 514-516, 518, 519, 522-527, 539-543]. Fifteen high-income countries including Australia, Austria, Belgium, Denmark, Germany, the UK, Norway, Netherlands, Sweden, Switzerland, Canada, Italy, New Zealand, Spain, and the USA were included in analysis. Twenty-five of the included studies were assessed as having a low risk of bias[65, 66, 69, 91, 104, 118, 125, 145, 154, 156, 181, 185, 190, 218, 309, 318, 373, 507, 508, 512, 518, 519, 524, 527, 539]. Twenty-one studies included were assessed to have an unclear risk of bias[32, 67, 68, 106, 110, 152, 157, 164, 169-171, 179, 258, 324, 327, 340, 345, 362, 514-516, 522, 526, 540-542].The remaining six studies demonstrated a high risk of a bias[63, 86, 510, 511, 523, 543], attributed to poor adjustment for confounders, poor selection criteria, and poor methodology[63, 86, 510, 511, 523, 543]. Three studies described selection criteria for their cohort that limited the generalisability of the results[510, 523, 543]. One study poorly described the cohort used in the reference group[510], and three studies described poor methods of data collection as well as high portions of missing data[63, 511, 523]. Furthermore one study, did not adequately describe the definition of stillbirth used[63].

Hispanic maternal ethnicity

Eight studies examined the association between maternal Hispanic ethnicity and stillbirth odds in the USA[154, 169, 333, 373, 507, 514, 525, 526]. All studies reported use of overlapping datasets for analysis, therefore smaller studies[169, 333, 507, 514, 525] were excluded from

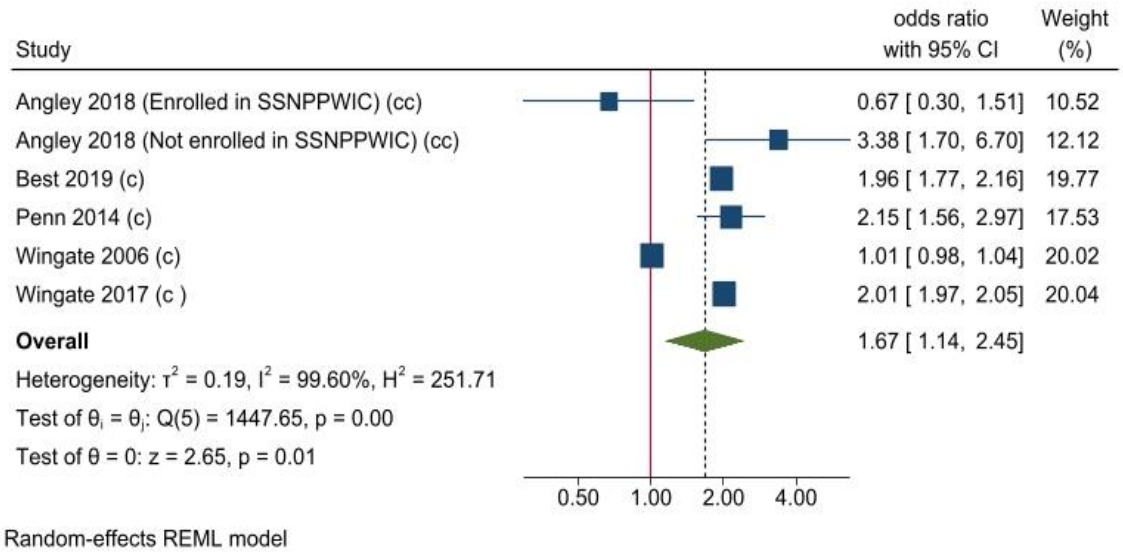
analysis to avoid double counting of births. Final meta-analysis included three studies[154, 525, 526], but due to considerable heterogeneity (I^2 = 93.65%) step-wise exclusion sensitivity analysis was performed, and identified Malabarey et al[154] as a major contributor to heterogeneity. On exclusion, heterogeneity decreased to 30.6%. On review of Malabarey et al[154], no reason for heterogeneity was identified and potential for bias was assessed as low. Therefore, all studies were retained for analysis. Final analysis demonstrated no association between Hispanic ethnicity and stillbirth odds (aOR 0.99 (95% CI 0.68, 1.45) – fig 6-22). Of the included studies, one restricted analysis to women who were eligible for a special supplement program, and stratified by program enrolment during analysis. Both subgroups were included within meta-analysis.



c = cohort study
cc = case-control study
Figure 6-22 Meta-analysis demonstrating the association between maternal Hispanic ethnicity and stillbirth odds compared with non-Hispanic maternal ethnicity.

Black (USA and UK) maternal ethnicity

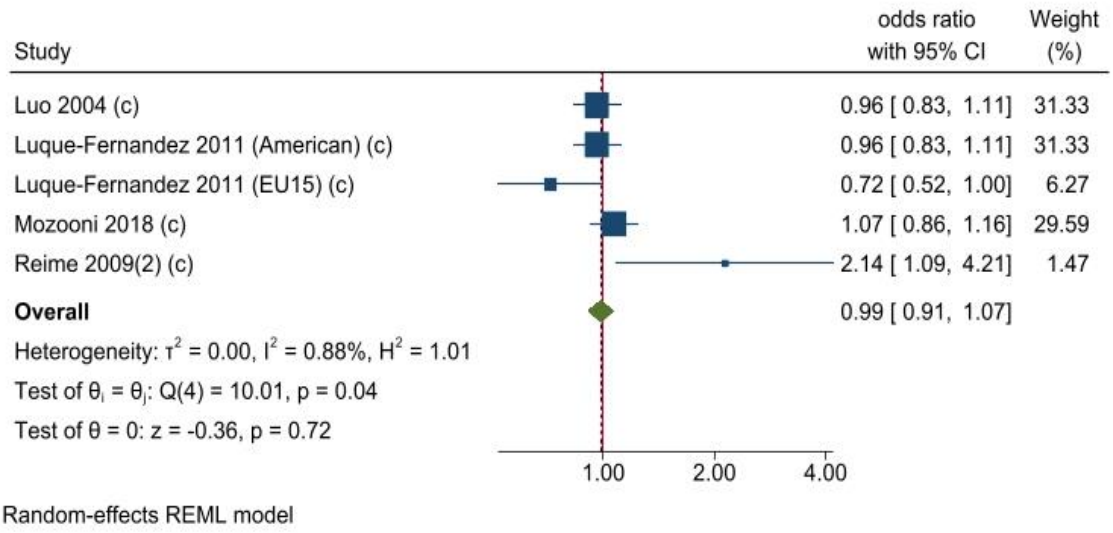
Seventeen studies reported the odds of stillbirth for black women in the USA and the UK[91, 106, 110, 118, 154, 164, 181, 185, 333, 340, 373, 507, 508, 514, 520, 525, 526]. Fourteen of the studies reported use of the same dataset, thus, in an effort to avoid double counting births, the larger and most robust of the studies[164, 340, 525, 526] were retained for meta-analysis, and the smaller excluded[91, 110, 118, 154, 181, 185, 333, 507, 508, 514, 520]. The remaining studies were combined through meta-analysis and exhibited considerably high heterogeneity (I^2 = 99.6%) Wingate et al[525] was found to contribute greatly to heterogeneity. Upon exclusion, heterogeneity decreased to a moderate level (I^2 = 58.8%) but as no reason for heterogeneity was identified, the study was retained within analysis. Final meta-analysis included five studies[164, 340, 373, 525, 526] and demonstrated an increased association between maternal black ethnicity and stillbirth odds (aOR 1.67 (95% CI 1.14, 2.45) -fig 6-23).



c = cohort study
cc = case-control study
*SSNPPWIC = Special Supplement Nutrition Program
Figure 6-23 Meta-analysis demonstrating the association between Black maternal ethnicity and stillbirth odds compared with non-Black women.*

Caucasian maternal ethnicity

Four studies examined the association between maternal Caucasian ethnicity (American, European, English) and stillbirth odds compared with Spanish and German women[86, 152, 518, 540]. It was noted through review that the referent groups of included studies also include Caucasian women. Analysis demonstrated no association between Caucasian ethnicity and stillbirth (aOR 0.99 (95% CI 0.91, 1.07) – fig 6-24) but it should be noted that three studies used European cohorts of women (Spanish, German and French cohorts of women) in the reference population[86, 152, 313], therefore the reference population may also have included Caucasian mothers.



c = cohort study
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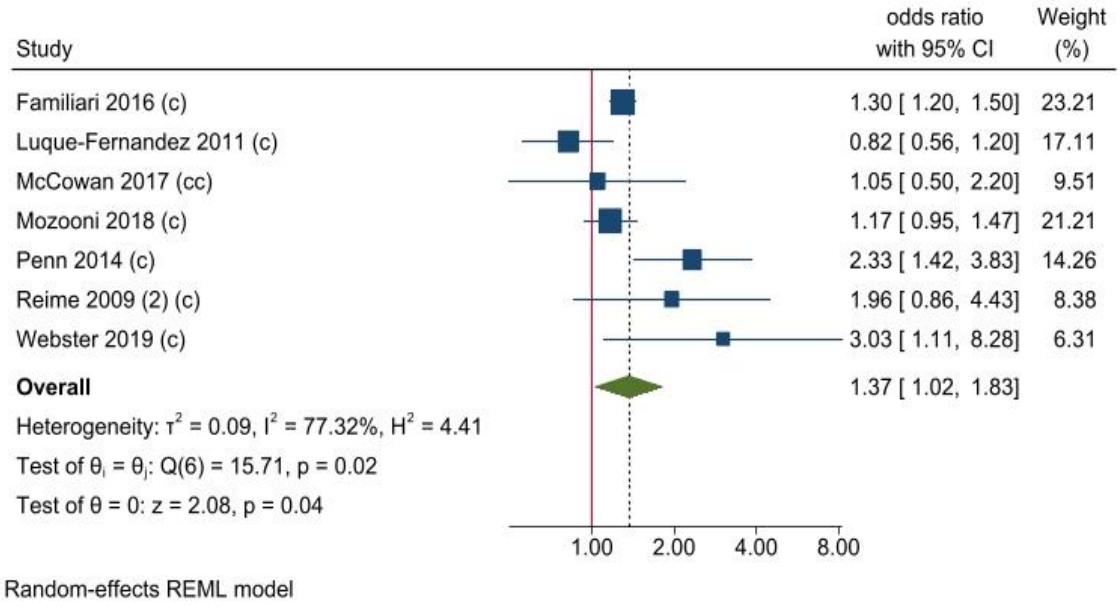
Figure 6-24 Meta-analysis demonstrating the association between Caucasian women (American, other European and English) and stillbirth odds compared with that of a Spanish and German cohort of women.

Asian maternal ethnicity (second or third trimester stillbirth)

Eight studies examined the odds of stillbirth associated with Asian maternal[32, 86, 152, 164, 185, 340, 510, 518]. Two studies report use of the same dataset and therefore the smaller of the studies was excluded from meta-analysis to avoid double-counting births. [185, 340] Initial meta-analysis demonstrated substantial heterogeneity (I^2 = 72.7%). Through step-wise exclusion sensitivity analysis, two studies[152, 340] were identified as main contributors of heterogeneity. On review, both demonstrated unclear bias due to minimal adjustment of confounders, and one also included Oceanic women within their analysis of Asian women's association with stillbirth[152]. This study was therefore excluded from analysis due to non-comparable exposure groups, and the other retained. Final analysis demonstrated increased odds of stillbirth for Asian women compared with Caucasian women (aOR 1.37 (95% CI 1.02, 1.83) – fig 6-24) with moderate-high heterogeneity between studies (I^2 = 77.32%) was accepted.



c = cohort study
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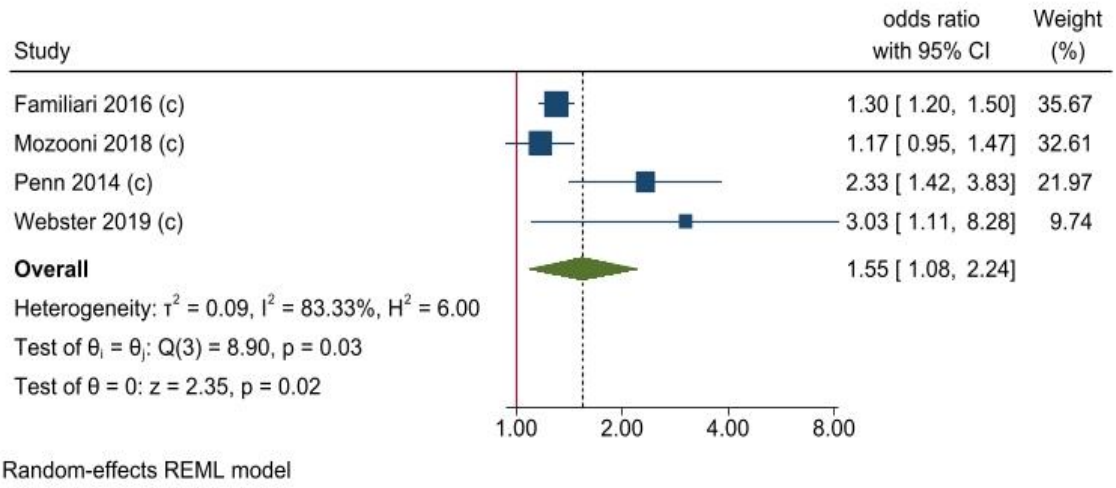
Figure 6-25 Meta-analysis of studies examining the association between maternal Asian ethnicity and stillbirth compared with other ethnicities.

Asian maternal ethnicity (second and third trimester stillbirth)

Five studies used definitions of stillbirth that encompassed both second and third trimester stillbirths odds in outcome analysis of Asian maternal ethnicity, and associated stillbirth odds compared with other ethnicities[164, 185, 340, 510, 518]. Two studies detailed use of the same dataset for analysis, therefore to avoid double counting of births, the study detailing a larger, more comprehensive analysis of the dataset was retained[185] and the smaller dataset analysis study excluded[340]. Results of meta-analysis demonstrated increased odds of second and third trimester stillbirth for Asian maternal ethnicity compared with women of other ethnicities (aOR 1.55 (95% CI 1.08, 2.24) – fig 6-26).



c = cohort study
cc = case-control study
Figure 6-26 Meta-analysis of studies examining the association between maternal Asian ethnicity and second and third trimester stillbirth compared with births to non-Asian women.

Asian maternal ethnicity (third trimester)

Three studies reported the odds of third trimester stillbirth associated with women of Asian ethnicity[32, 86, 152]. Results of analysis demonstrated no clear association between maternal Asian ethnicity and third trimester stillbirths (aOR 1.07 (95% CI 0.66, 1.74) – fig 6-27).

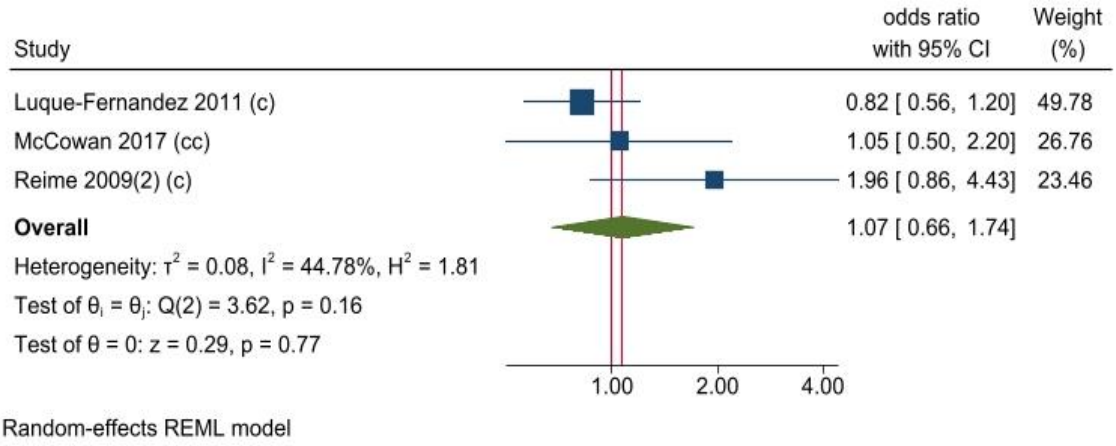


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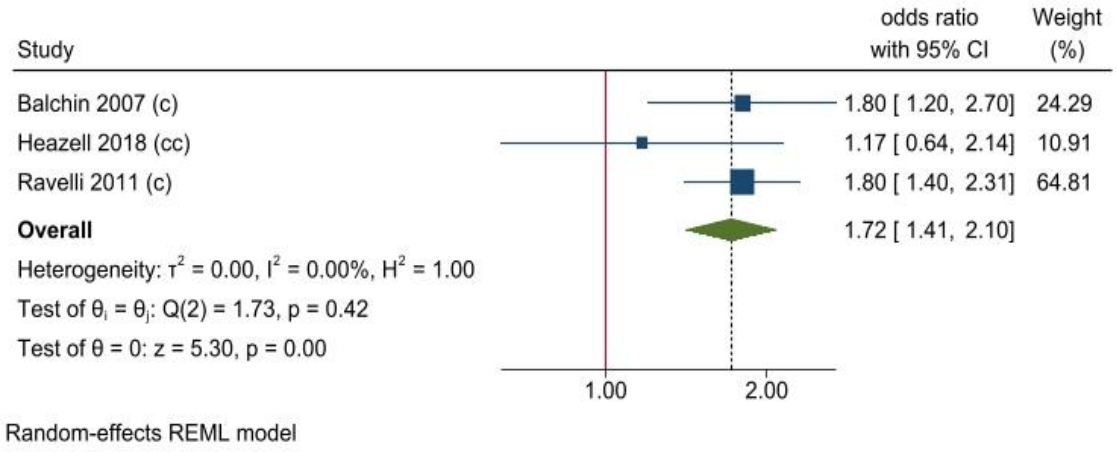
Figure 6-27 Meta-analysis of studies examining the association between maternal Asian ethnicity and third trimester stillbirths compared with non-Asian women.

South Asian maternal ethnicity

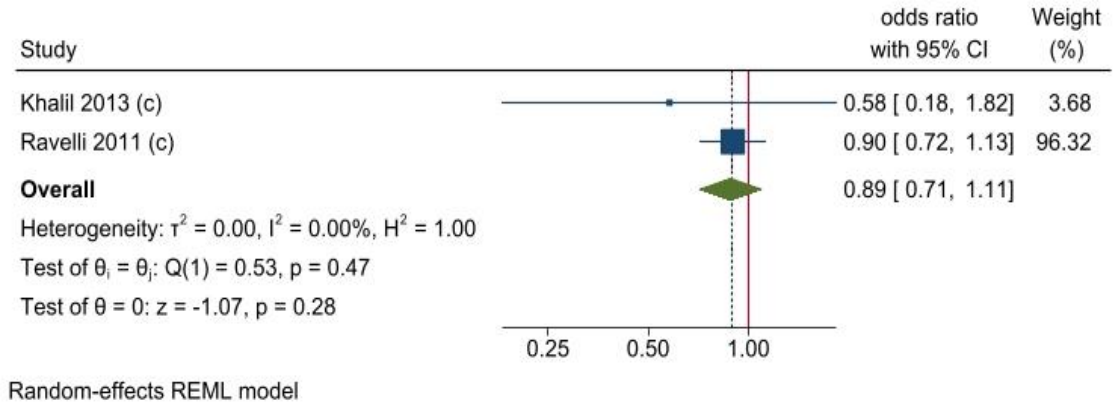
Four studies examined the impact of South Asian ethnicity on stillbirth odds[69, 91, 106, 345]. One of the studies did not report study period dates, and the location of the population overlapped with other studies. Therefore the decision was made to exclude this study from analysis to avoid potential double counting of births[345]. Meta-analysis of the remaining studies[70, 106, 274] demonstrated an almost doubled odds of stillbirth for women of South Asian ethnicity compared with Caucasian women (aOR 1.72 (95% CI 1.41, 2.10) – fig 6-28).



c = cohort study
cc = case-control study
Figure 6-28 Meta-analysis of studies demonstrating the association between maternal South Asian ethnicity and stillbirth odds compare to Caucasian maternal ethnicity.

East Asian maternal ethnicity

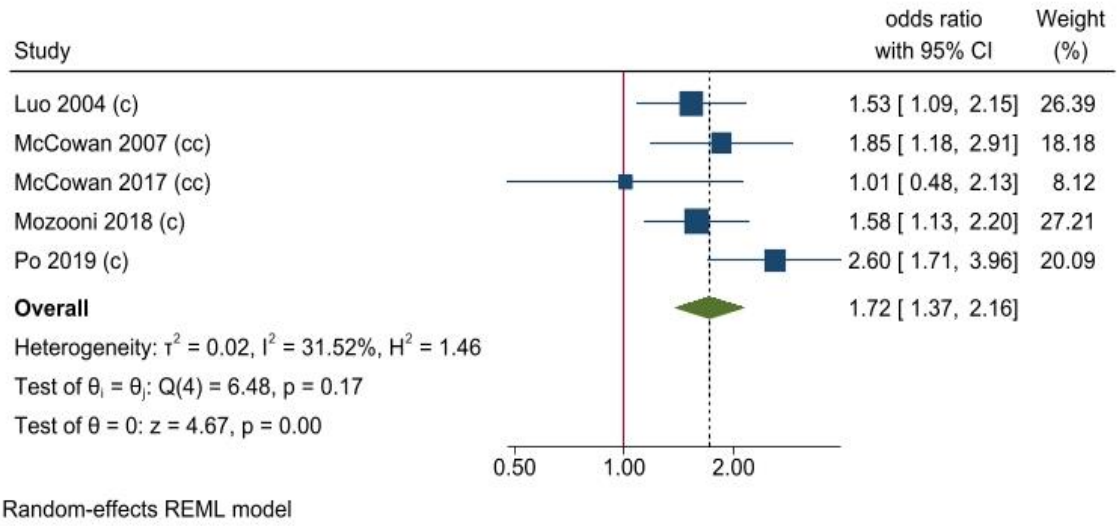
Two studies examined the impact of East Asian ethnicity on stillbirth odds within two high-income countries; the UK and the Netherlands[69, 345]. Meta-analysis included both studies and demonstrated no clear association between East Asian maternal ethnicity and stillbirth odds compared with Caucasian maternal ethnicity (aOR 0.89 (95% CI 0.71, 1.11) – fig 6-29).



c = cohort study
cc = case-control study
Figure 6-29 Meta-analysis of studies demonstrating the association between maternal East Asian ethnicity compared with Caucasian ethnicity.

Indian maternal ethnicity

Five studies examined the odds of stillbirth for women of Indian ethnicity in comparison with Caucasian reference groups[32, 156, 218, 518, 540]. Studies used populations from four high-income countries including New Zealand, Canada, Australia and Italy. The results were similar to those for all South Asian women (see above). Final meta-analysis demonstrated an increase in odds of stillbirth associated with Indian maternal ethnicity compared with Caucasian women (aOR 1.72 (95% CI 1.37, 2.16) – fig 6-30).

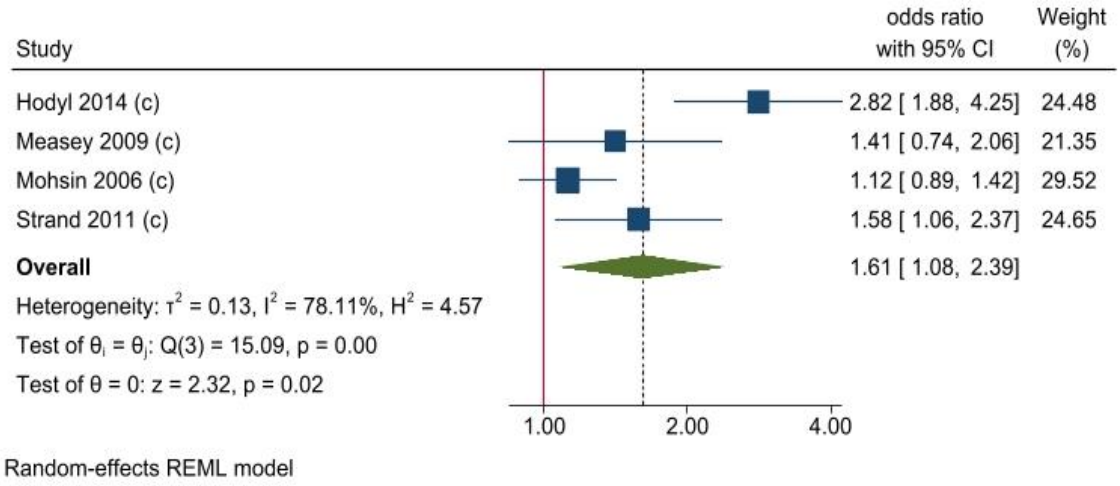


c = cohort study
cc = case-control study
Figure 6-30 Meta-analysis of studies demonstrating the association between maternal Indian ethnicity and stillbirth odds compared with Caucasian ethnicity.

Indigenous populations

Australian Aboriginal or Torres Strait Islander maternal ethnicity

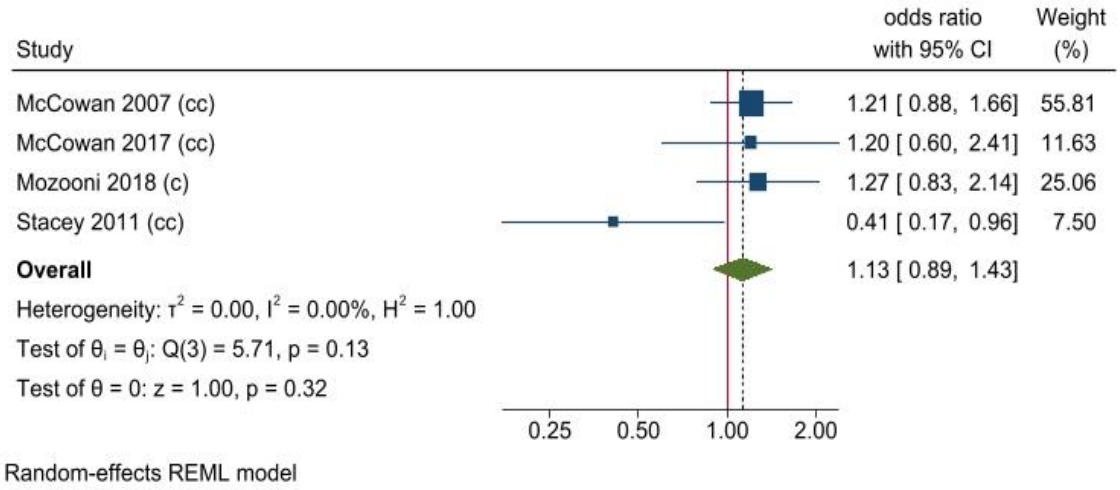
Six studies examined the association between maternal Australian Aboriginal or Torres Strait Islander ethnicity and stillbirth odds[68, 125, 145, 157, 327, 544]. One study[125] reported use of the same dataset as a larger included study[157] thus, to avoid double counting births, the smaller study was excluded from analysis and larger robust analysis included. Of the five remaining studies, a further study was excluded, as publication was noted to contain errors, and authors were uncontactable through the provided methods[145]. Subsequent meta-analysis demonstrated considerable heterogeneity (I^2 = 86.7%). The results indicate that Australian Aboriginal or Torres Strait Islander women have a 61% increase in the odds of stillbirth compared with non-indigenous Australian women (aOR 1.61 (95% CI 1.08, 2.39) – fig 6-31).



c = cohort study
cc = case-control study
Figure 6-31 Meta-analysis of studies demonstrating the association between Australia Aboriginal and/or Torres Strait Islander ethnicity and stillbirth odds compared with non-indigenous Australian women.

Māori maternal ethnicity

Four studies examined the association between Māori ethnicity and stillbirth odds across populations from Australia and New Zealand[32, 156, 179, 324, 362, 518]. Results of meta-analysis did not demonstrate significantly increased association between Māori maternal ethnicity and stillbirth odds (aOR 1.13 (95% CI 0.89, 1.43) – fig 6-32).



c = cohort study
cc = case-control study
Figure 6-32 Meta-analysis of study results demonstrating the association between maternal Māori ethnicity and stillbirth odds compared with non-Māori maternal ethnicity

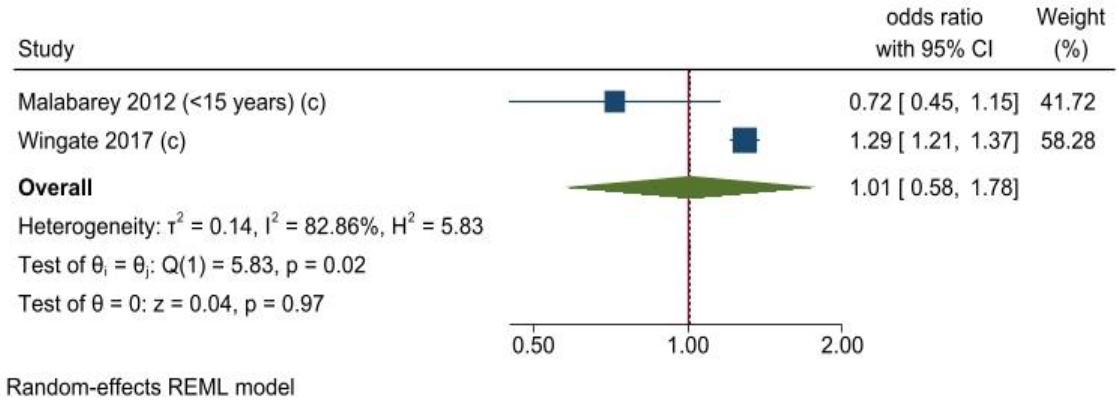
Inuit and/or Cree Canadian maternal ethnicity

Five studies examined the odds of stillbirth associated with Inuit and/or Cree status in Canada[63, 515, 516, 527, 540]. Shapiro et al[63] examined the differences in birth outcomes for Inuit women according to maternal place of residence within Canada. Results indicate no difference in stillbirth odds associated with community living, compared with living outside of communities for Inuit women (aOR 0.89 (95% CI 0.51, 1.53))[63]. The

remaining four studies all reported use of the same dataset for analysis, and therefore to avoid double counting of births, were not combined through meta-analysis[313, 515, 516, 527]. The largest and most comprehensive of the included studies reported an almost 2-fold increase in stillbirth odds for women in Inuit inhabited areas of Canada compared with non-Inuit inhabited areas (aOR 1.89 (95% CI 1.54, 2.33))[515]. Findings of this study were supported by one of the remaining studies; Xiao et al[527] that indicated an almost 2-fold increase for births to Cree women (aOR 1.84 (95% CI 1.15, 2.95)), and increased odds of stillbirth for other First Nation women compared with non-Aboriginal Canadian women (aOR 1.63 (95% CI1.12, 2.63)). In a later study, Luo et al[516] stratified results per ethnicity, and area of residence within Quebec. Results indicate no increase in stillbirth odds for Inuit or First nation women residing in northern Quebec compared with non-indigenous women residing in northern Quebec (aOR 0.60 (95% CI 0.23, 1.60) and aOR 0.87 (95% CI 0.40, 1.91) respectively). Yet results demonstrated a 2-fold increase in stillbirth odds for First nation women living in Southern Quebec (2.09 (95% CI 1.29, 3.39)) compared with non-indigenous women residing in the same area.

American Indian/First Nation maternal ethnicity

Two studies reported the odds of stillbirth for American Indian/First Nation women compared with white women in the USA[154, 526]. One study limited analysis to women who were <15 years of age at time of birth, and therefore the study populations differed considerably. Results reflected considerable heterogeneity (I^2= 82.9%), with no clear association between American Indian/Native ethnicity and stillbirth odds (aOR 1.01 (0.58, 1.78) – fig 6-33), despite the larger and more comprehensive of the studies demonstrating an increased association with stillbirth (aOR 1.29 (95% CI 1.21, 1.37))[524].

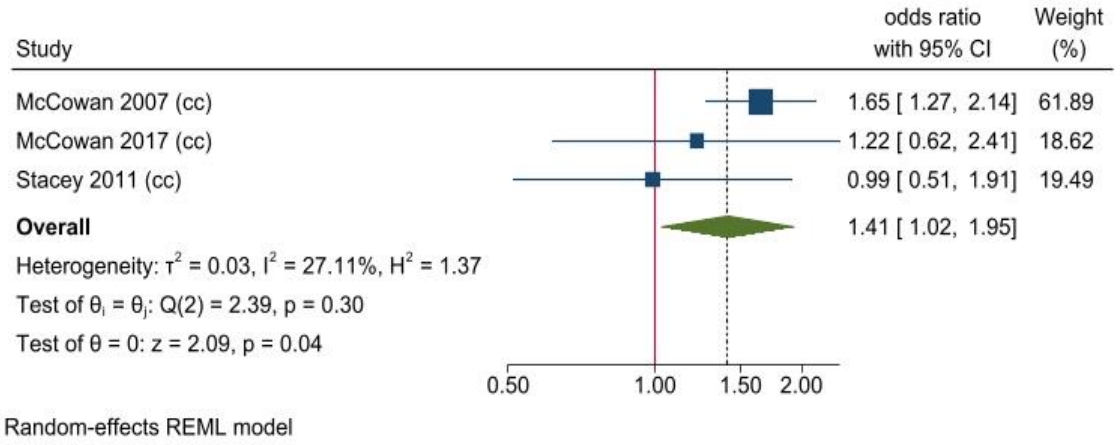


c = cohort study
cc = case-control study
Figure 6-33 Meta-analysis of the studies reporting the association between maternal American Indian/Native ethnicity and stillbirth odds compared with non-American Indian/First Nation ethnicity.

Pacific maternal ethnicity

Three studies of New Zealand cohorts examined the impact of Pacific maternal ethnicity on stillbirth odds compared with other New Zealand mothers[32, 156, 179, 324, 362]. Results of analysis demonstrated an increased association between maternal Pacific ethnicity and

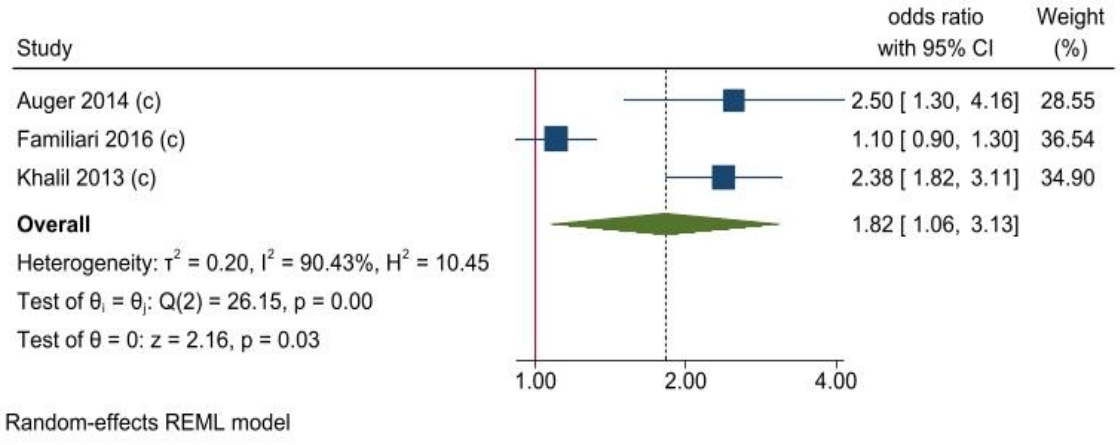
stillbirth odds (aOR 1.41 (95% CI 1.02, 1.95) – fig 6-34), however the results appear to be largely weighted by the oldest cohort study included, McCowan et al[517].



c = cohort study
cc = case-control study
Figure 6-34 Meta-analysis of the studies associated with Pacific maternal ethnicity (New Zealand) and stillbirth odds compared with other maternal ethnicities in New Zealand

Afro-Caribbean maternal ethnicity

Three studies examined the association between maternal Afro-Caribbean ethnicity and stillbirth odds in populations from the UK and Canada[66, 345, 510]. Inclusion of all studies in meta-analysis resulted in considerable heterogeneity (I^2 =92.4%) and thus sensitivity analysis was performed. Familiari et al[510] was identified as a major contributor to heterogeneity[510], yet as no clear cause for heterogeneity was identified, it was accepted. Final meta-analysis demonstrated a moderate increase in stillbirth odds associated with maternal Afro-Caribbean ethnicity compared with Caucasian, and non-Haitian, ethnicity (aOR 1.82 (95% CI 1.06, 3.13) – fig 6-35).



c = cohort study
cc = case-control study
Figure 6-35 Meta-analysis of studies examining the association between maternal Afro-Caribbean maternal ethnicity and stillbirth odds compared with Caucasian and non-Haitian ethnicity.

Parental combined ethnicity

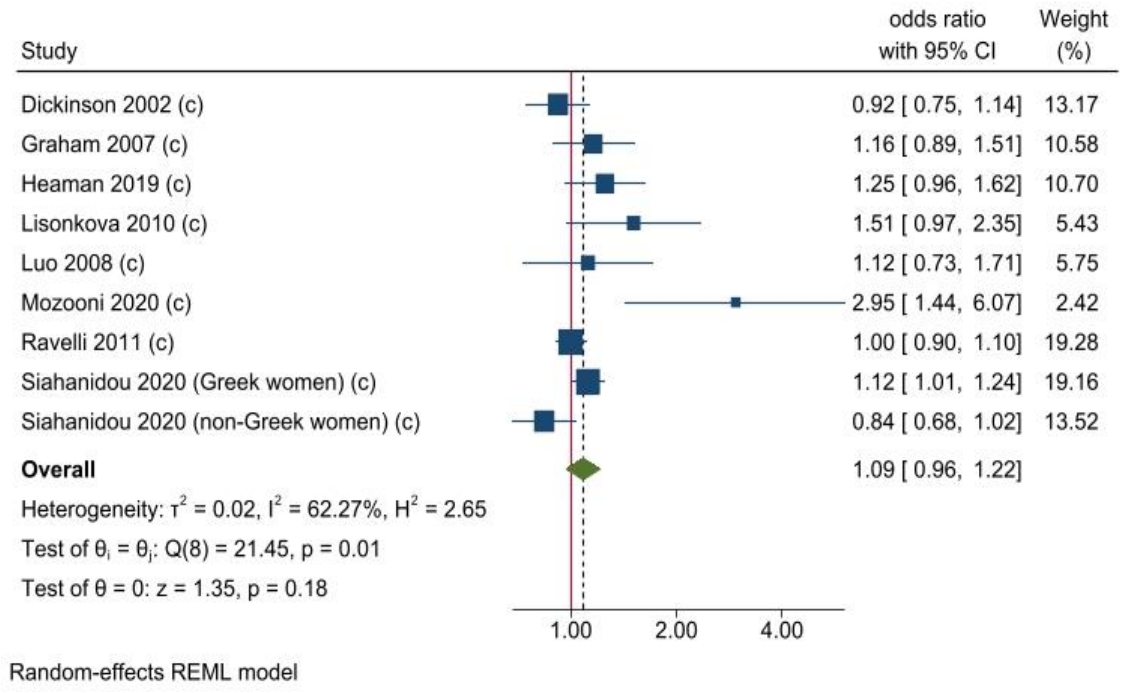
Three studies[104, 511, 539] examined the impact of parental ethnicity, and the associated stillbirth odds in the USA and Canada. Two studies[511, 539] examined the association within the same dataset from the USA and examined the combination of Black or White ethnicity on stillbirth odds. Results of the larger and more robust study suggest that increased odds of stillbirth are associated with either Black maternal (aOR 1.37 (95% CI 1.21, 1.54)), paternal (aOR 1.17 (95% CI 1.10, 1.26)) or both (aOR 1.67 (95% CI 1.62, 1.72)) ethnicity compared to both White parental ethnicities. The final study[104] used a Quebec cohort of births that examined parental Arabic ethnicity compared to non-Arabic. No association was shown for Arabic maternal (aOR 1.39 (95% CI 0.94, 2.04)), or both (aOR 0.97 (95% CI 0.84, 1.11)) ethnicities compared to French/English maternal and paternal ethnicity. Paternal Arabic ethnicity and non-Arabic maternal ethnicity was shown to have a protective association with stillbirth odds compared to French/English parental ethnicities (aOR 0.67 (95% CI 0.46, 0.97)).

Place of residence – remoteness

Eleven studies reported the odds of stillbirth associated with the remoteness status of maternal place of residence[62-64, 87, 146, 168, 177, 249-252]. Studies analysed the effect of maternal residential remoteness status within populations spanning across five high-income countries, Canada, the UK, Australia, the Netherlands and Greece. Risk of bias assessment suggested that three of the studies had a high risk of bias, one due to lack of methodological detail[168] and the remaining two reported exposure measures that were inherently affected by misclassification of residential location[63, 64]. Two studies demonstrated an unclear risk of bias[62, 249] and six studies; a low risk of bias[87, 146, 177, 250-252].

Maternal rural residential status

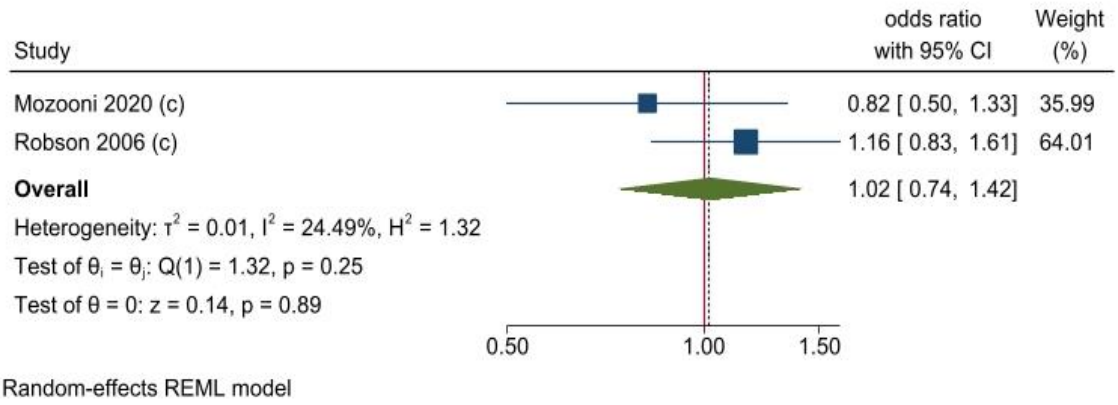
Included studies examined rural, remote and community residential status and the associated stillbirth odds using slightly different classifications. All studies were included in an overarching analysis examining remote/non-accessible/community residential status in comparison to urban residential status[62-64, 87, 146, 168, 177, 249-252]. Six studies reported use of the same dataset for analysis. To avoid double counting of births, the smaller studies were excluded from meta-analysis[63, 64, 168], larger and more robust studies were retained. Heterogeneity between studies was substantial (62.7%), sensitivity analysis identified that Moozoni et al[252] as the main contributor to heterogeneity, and exclusion resulted in a decrease to 48.3%. On review of Moozoni et al, it was noted that the study was performed on a population that excluded Indigenous Australians in Western Australia. As no further reason for heterogeneity could be identified, it was accepted and included. Analysis demonstrated a possible, but non-significant, increase in stillbirth odds with rural/remote/non-accessible/community residential status compared with stillbirth odds and urban residential status (aOR 1.09 (95% CI 0.96, 1.22) – fig 6-36).



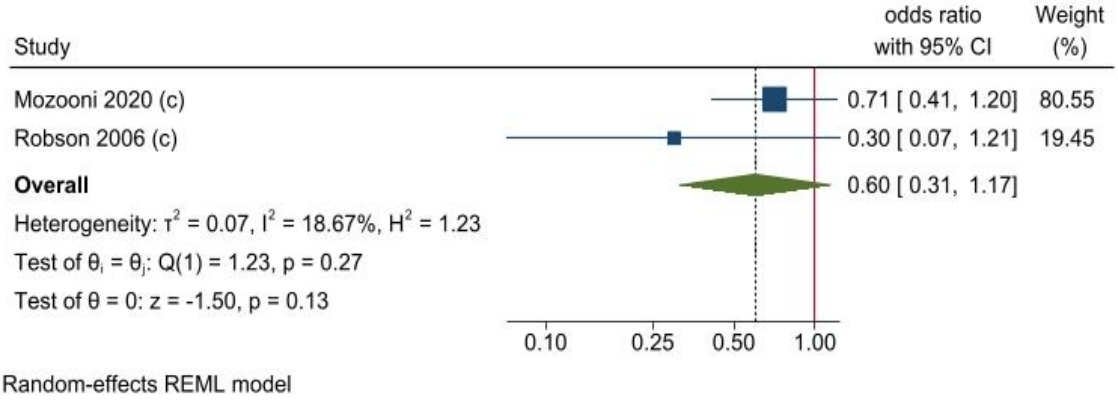
c = cohort study
cc = case-control study
Figure 6-36 meta-analysis demonstrating the association between maternal rural residential status of living and stillbirth odds compared with urban residential status.

Maternal residential remoteness status in Australia

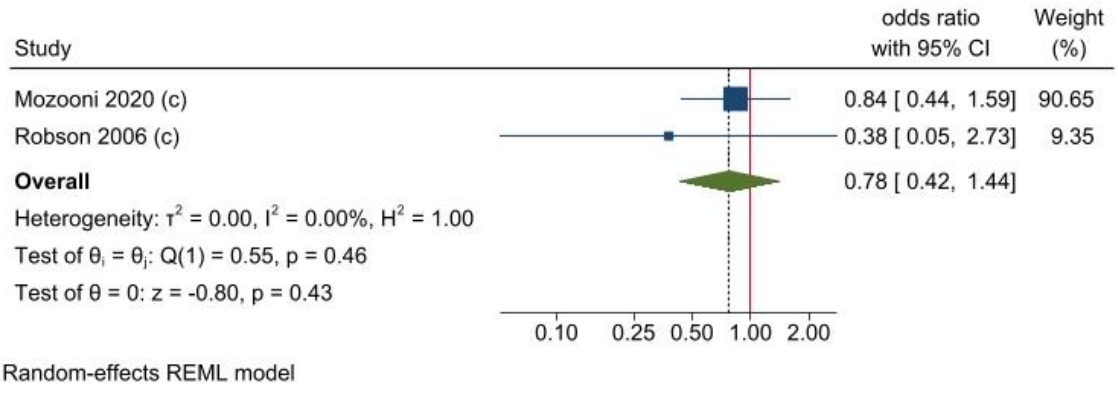
Three studies examined the effect of residential remoteness status in Australia. One study included teenage mothers in New South Wales births[168], another included Western Australian births[252], and the last included a national dataset to examine the effects within a population of Aboriginal women[62]. Graham et al[62] assigned births to Aboriginal women to one of three classifications; rural, regional or city. In comparison to Aboriginal women living in a city postcode, findings did not demonstrate significant associations with stillbirth odds. For regional postcodes, the adjusted odds ratio was reported as 0.97 (95% CI 0.76, 1.26) and for rural postcodes, aOR 1.16 (95% CI 0.89, 1.51). Both Robson et al[168] and Mozooni et al[252] used the ARIA (Accessibility/Remoteness Index of Australia) classification to assess remoteness and accessibility of maternal area of residence. Through meta-analysis, no association was demonstrated for mothers living in an "accessible" area (fig 6-37), and a slightly protective effect was demonstrated with residence in a "moderately accessible" area (aOR 0.60 (95% CI 0.31, 1.17) – fig 6-38). However, an almost three-fold rise in stillbirth odds was associated with very remote residence in Australia (aOR 2.66 (95% CI 1.35, 5.22) – fig 6-39).



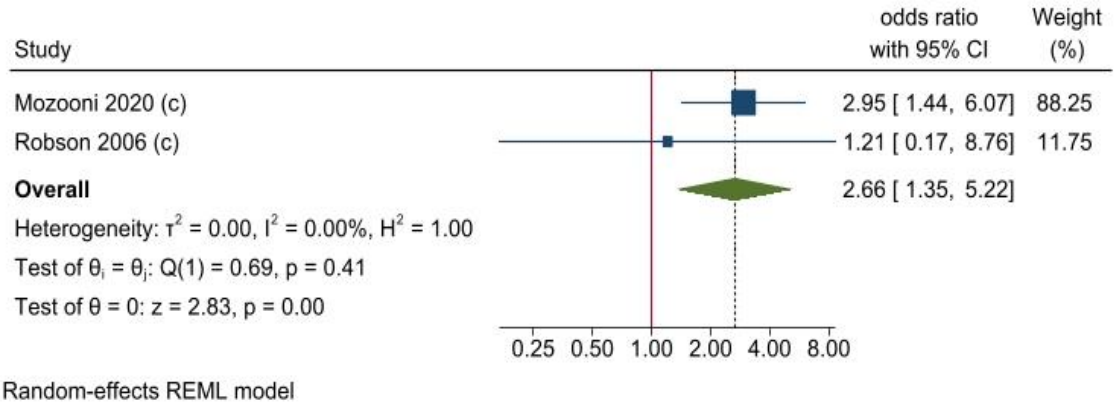
c = cohort study
cc = case-control study
Figure 6-37 Meta-analysis demonstrating the effect of "accessible" maternal residential status on stillbirth odds compared with "very accessible" status.



c = cohort study
cc = case-control study
Figure 6-38 Meta-analysis demonstrating the effect of "moderately accessible" maternal residential status on stillbirth odds compared with "very accessible" status



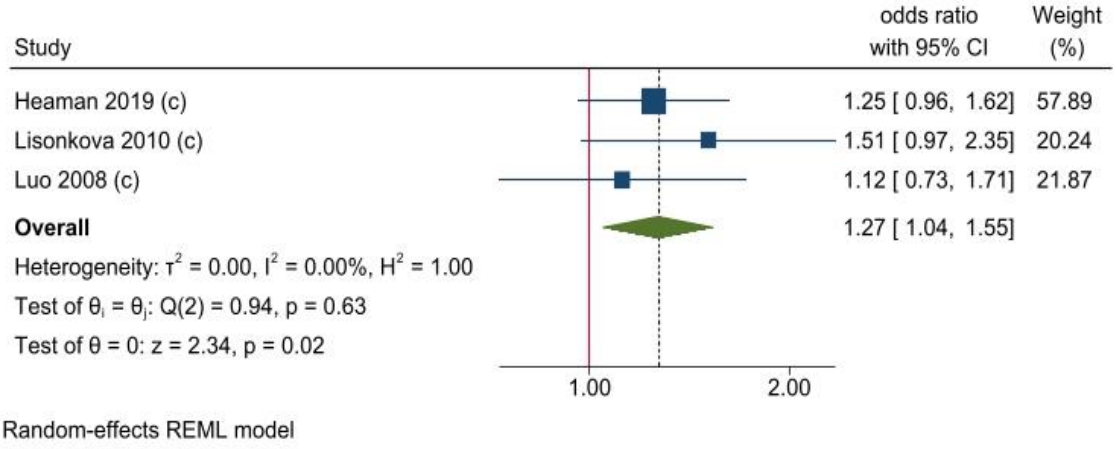
c = cohort study
cc = case-control study
Figure 6-39 Meta-analysis demonstrating the effect of "remote" maternal residential status on stillbirth odds compared with "very accessible" status



c = cohort study
cc = case-control study
Figure 6-40 Meta-analysis demonstrating the effect of "very remote" maternal residential status on stillbirth odds compared with "very accessible" status

Maternal residential remoteness status in Canada

Five studies examined the association between maternal residential remoteness status in comparison to urban areas in Canada[63, 64, 87, 146, 250], and resultant stillbirth odds. Three studies[63, 64, 250] reported use of the same dataset in analysis, and therefore the smaller cohorts[64] were excluded from meta-analysis to avoid double-counting births, and larger more robust analysis retained. Final meta-analysis included three studies, and the most remote category of each study was included for analysis. Results indicated an increase in the odds of stillbirth for women with rural residential status compared to city residential status (aOR 1.27 (95% CI 1.04, 1.55) – fig 6-41).



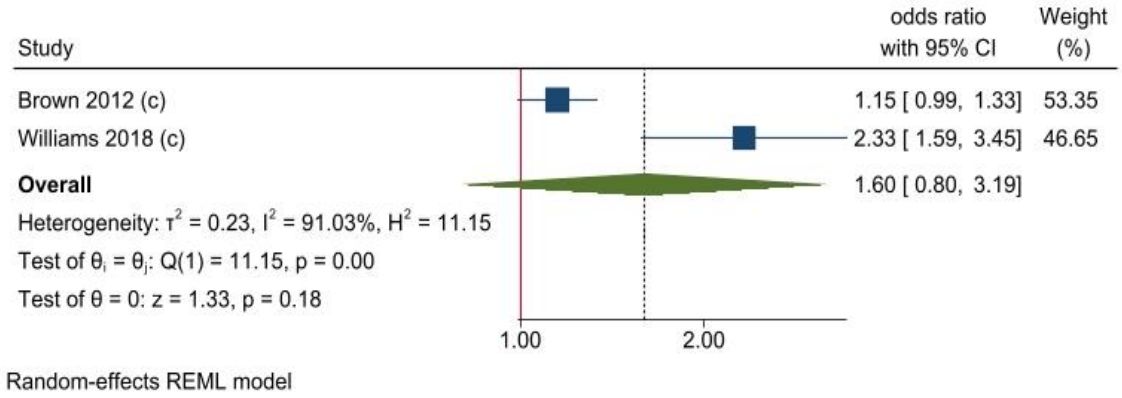
c = cohort study
cc = case-control study
Figure 6-41 Meta-analysis of studies examining the association between maternal rural residential status in Canada and stillbirth odds compared with city residential status.

Residential segregation

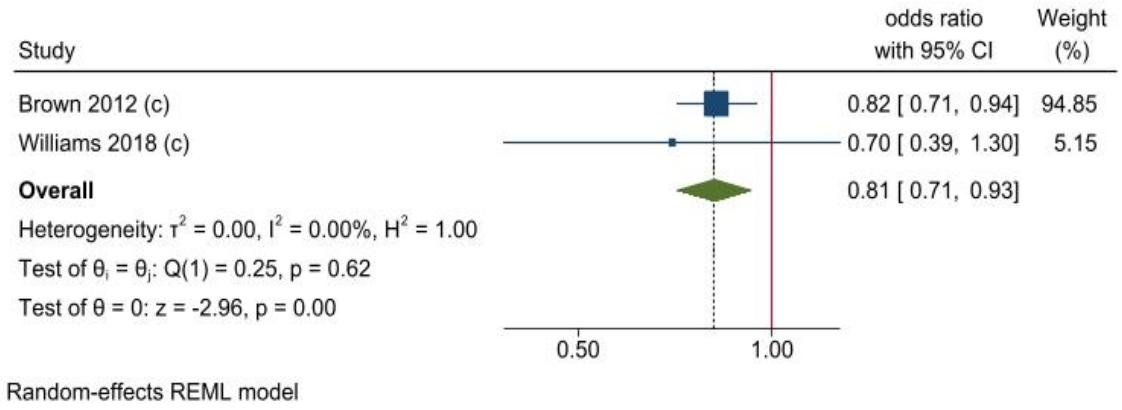
Dissimilarity index

Two studies examined the impact of residential segregation in USA communities[111, 275]. Residential segregation was measured using the dissimilarity index. The dissimilarity

index indicated high dissimilarity reflecting higher segregation levels, and lower dissimilarity index's reflecting low segregation levels. Risk of bias was unclear due to a lack of detail within the methodology for both studies. Segregation was assessed by maternal ethnicity (black women or white women). A higher residential dissimilarity index was found protective for stillbirth odds in white women (aOR 0.81 (95% CI 0.71, 0.93) – fig 6-41) with a possible marginal increase in stillbirth odds for births to black women (aOR 1.60 (95% CI 0.80, 3.19) – fig 6-42), though heterogeneity was high (I^2 = 91%) and thus, results should be interpreted with caution.



c = cohort study
cc = case-control study
Figure 6-42 Meta-analysis demonstrating the association between high dissimilarity index (higher segregation) on the odds of stillbirth in black women compared with low dissimilarity index.



c = cohort study
cc = case-control study
Figure 6-43 Meta-analysis demonstrating the association between high dissimilarity index on the odds of stillbirth for births to white women compared with low dissimilarity index.

Isolation index

Williams et al[275] further explored residential segregation through use of the isolation index, a measure to assesses the probability that a member of one racial group will interact with a member of the same racial group[275]. A low isolation index indicates more interactions between members of the same racial group. The study found that black women experience lower odds of stillbirth associated with a low isolation index (aOR

0.25 (95% CI 0.16, 0.41)) and even a moderate level isolation index decreased the odds of stillbirth in comparison to high levels of isolation (aOR 0.61 (95% CI 0.42, 0.91)). For white women, low isolation was similarly protective against stillbirth odds (aOR 0.33 (95% CI 0.21, 0.53)), but moderate isolation did not have a clear impact (aOR 1.06 (95% CI 0.71, 1.59)).

Williams et al[275] investigated the impact on stillbirth rates in black and white women from racial residential segregation. In areas of persistently high dissimilarity index scores and isolation, black women had a constantly higher stillbirth rate than white women. Any decrease in dissimilarity index score was associated with a protective effect against stillbirth odds for black women (aOR 0.53 (95% CI 0.32, 0.89)), although the association for white women was not apparent (aOR 0.75 (95% CI 0.41, 1.37)).

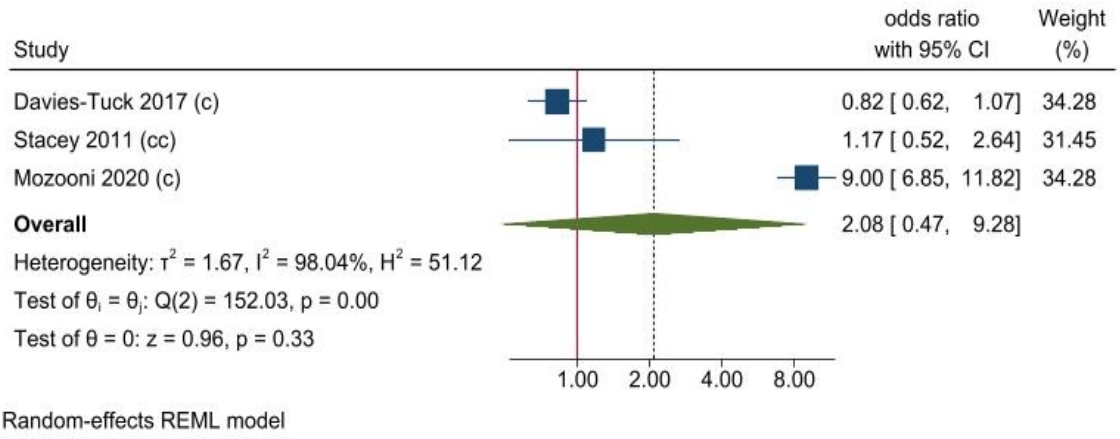
Antenatal care type and healthcare insurance status.

Eight studies examined the impact of insurance type and care type on stillbirth odds and used cohorts from four high-income countries[73, 127, 150, 158, 179, 192, 324, 362, 528, 529]. Different models of care are used worldwide, and definitions between countries differ slightly. Risk of bias assessment suggested that one study had a high risk of bias due to its inclusion of different gestational age for stillbirths (20-25 weeks GA) and live-births (26-42 weeks GA) in the cohort[192]. Three of the studies were assessed as having an unclear risk of bias, and four studies had a low risk of bias.

Midwife only antenatal care

Three studies examined midwife only care and the association with stillbirth odds[73, 158, 179, 324, 362]. Reference groups contained a combination of obstetrician care, doctor care, and any model other than midwife. One study[158] observed a nine-fold increase in the odds of stillbirth associated with midwife only care aOR (9.00 (95% CI 6.85, 11.82)). However, further analysis established that this increase was restricted to migrant women receiving midwife only antenatal care in Australia and was not replicated for non-migrant women receiving midwife only antenatal care. Stacey et al[179, 324, 362] also found possibly increased odds of stillbirth associated with midwife led maternity care in New Zealand (aOR 1.17 ((95% CI 0.52, 2.64)), but the study was underpowered, and therefore results inconclusive.

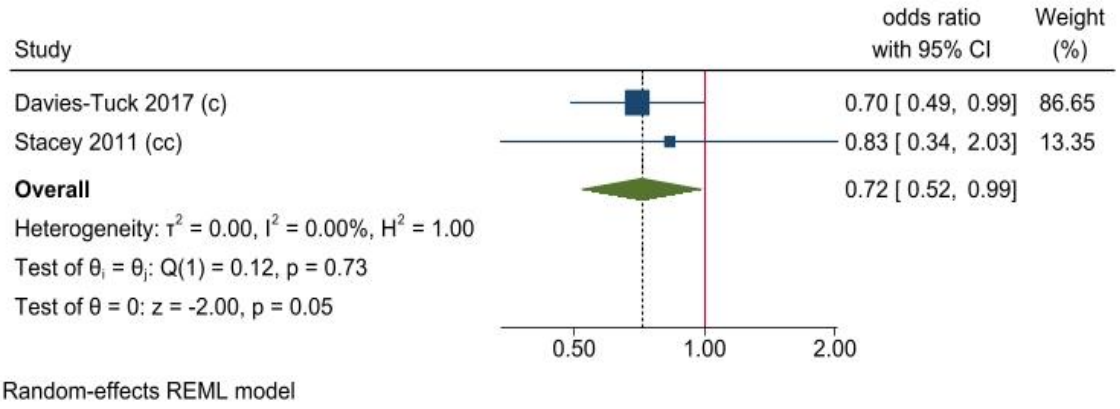
Meta-analysis including all three studies resulted in considerable heterogeneity (I^2= 98.7%). Through sensitivity analysis heterogeneity decreased to 0% on exclusion of Mozooni et al[158], possibly as a result of large study cohorts, as well as discrepancies between definitions of midwife only care. Exclusion was not judged to be justified for these differences, therefore Mozooni et al was not excluded from analysis. Meta-analysis results demonstrated doubled odds of stillbirth (OR 2.08 (95% CI 0.47, 9.28) – fig 6-44) associated with midwife-only maternity care. However large confidence intervals suggest results are underpowered, and should be interpreted with caution.



c = cohort study
cc = case-control study
Figure 6-44 meta-analysis demonstrating the association between midwife only care and stillbirth odds compared with other care types.

General practitioner (GP) shared antenatal care

New Zealand and Australia offer a type of care for pregnant women during the antenatal period classed as shared care (care shared between a midwife and the pregnant woman's GP). Two studies in this review examined the effect of GP shared care on stillbirth odds[73, 179, 324, 362]. Meta-analysis demonstrated a slightly protective association with GP shared care compared with obstetrician or midwife only care (aOR 0.72 (95% CI 0.52, 0.99) – fig 6-45).

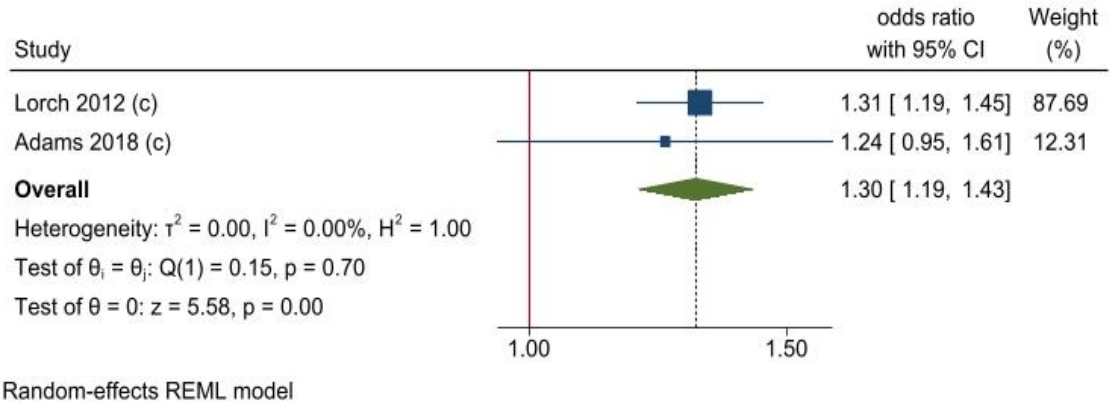


c = cohort study
cc = case-control study
Figure 6-45 Meta-analysis demonstrating the association between general practitioner (GP) or shared antenatal care and stillbirth odds compared with obstetrician or midwife only care.

Publicly insured maternity care

Three studies examined the odds of stillbirth associated with publicly insured maternity care versus privately insured maternity care[150, 192, 528]. Two of the included studies were conducted in the USA[150, 192] and one in Australia[528], in all studies publicly funded maternity care referred to women whose health care was paid for by government bodies. Although it should be noted that in the USA this level of cover does not result in the

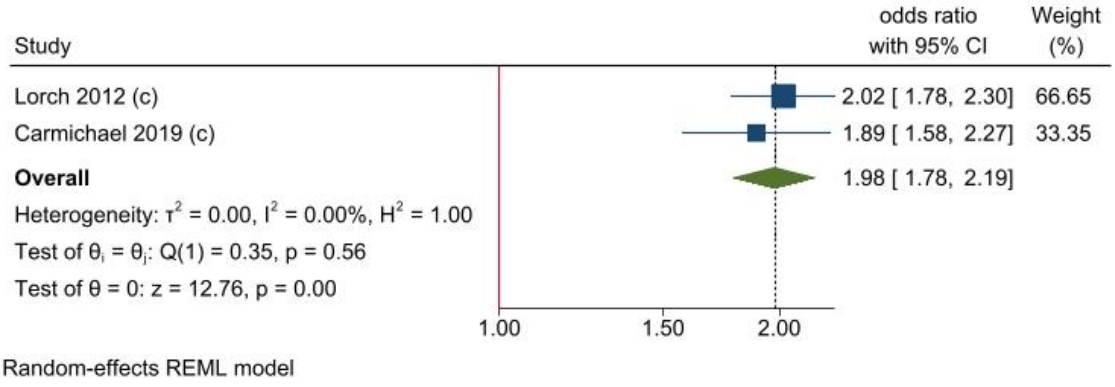
government assumes responsibility for all costs. Meta-analysis demonstrated very high heterogeneity, likely due to Carmichael et al[192] assessing risk of stillbirths born at gestational age 20-25 weeks in comparison to a control group of different GAs. Carmichael et al was excluded due to methodological differences. Final meta-analysis demonstrated higher odds of stillbirth with the use of public health care versus private health care (aOR 1.30 (95% CI 1.19, 1.43) – fig 6-46).



c = cohort study
cc = case-control study
Figure 6-46 Meta-analysis demonstrating the association between publicly insured maternity care and stillbirth odds compared with privately insured maternity care.

Uninsured maternity care (USA only)

In the USA, health care is paid for by the patient, partially covered by the government, or costs are paid by an insurer. Uninsured women personally assume responsibility for the cost of their own maternity care during pregnancy. Three studies examined the effect of uninsured status on stillbirth odds in the USA[127, 150, 192]. Two studies[127, 192] reported use of the same dataset, therefore to avoid double-counting of births, the smaller of the studies was excluded from analysis[192]. Final analysis demonstrated an almost 2-fold increase in stillbirth odds amongst women who have uninsured for maternity care compared with insured maternity care in the USA (aOR 1.98 (95% CI 1.78, 2.19) -fig 6-47).



c = cohort study
cc = case-control study
Figure 6-47 Meta-analysis demonstrating the association between uninsured maternity care and stillbirth odds for American women, compared with insured maternity care.

Continuity of care

One study examined the impact of continuity of care on stillbirth odds amongst Swedish women and found continuity of care to be statistically non-significant in protecting against stillbirth (aOR 0.40 (95% CI 0.14, 1.13))[529], compared with multiple health carers throughout pregnancy. Continuous care ensures that the same health care provider looks after the woman throughout their pregnancy, improving trust between the woman and carer, resulting in better detection of any pregnancy complications[529].

Privately insured maternity care

One study examined care provided by a private obstetrician during pregnancy compared with women using self-employed midwives in New Zealand[179, 324, 362]. The analysis showed uncertain results as the sample size was too small to statistically demonstrate any association (aOR 0.90 (95% CI 0.35, 2.30)).

Acculturation following maternal migration

One study examined the association between acculturation and stillbirth odds in Australian migrants from different countries[518]. Acculturation was measured in years since maternal arrival into Australia, to the time of birth. Results of Mozooni et al[518] are shown below (table 6-1. Results indicate that for all maternal country of birth categories, stillbirth odds are highest in the first 2 years following immigration, and then decrease. Although this trend is seen for women born in African countries, results demonstrate that even after 5 years of residence within Australia, risk is still increased almost 2-fold that of women born in Australia.

Table 6-1 Results of Moozoni et al[518] demonstrating the stillbirth odds associated with acculturation in migrant women measured as the time from migration to birth*

	Acculturation - length of residence in Australia*		
Country of birth	*<2 years (aOR (95% CI)*	*2-5 years (aOR (95% CI)*	*>5 years (aOR (95% CI)*
Caucasian	0.88 (0.52, 1.50)	1.20 (0.90, 1.59)	1.02 (0.84, 1.23
Asian	**1.93 (1.21, 3.05)**	1.01 (0.66, 1.53)	1.06 (0.77, 1.44)
Indian	**2.71 (1.58, 4.65)**	1.38 (0.82, 2.32)	0.67 (0.25, 1.80)
African	**3.32 (1.70, 6.47)**	**2.77 (1.70, 4.52)**	**1.96 (1.10, 3.49)**
Māori	0.75 (0.19, 3.03)	1.71 (0.70, 3.62)	1.07 (0.51, 2.28)
Other	1.24 (0.61, 2.49)	**1.63 (1.04, 2.56)**	1.08 (0.74, 1.80)

*adjusted for marital status, maternal age group, socioeconomic status, parity, plurality, previous stillbirth, medical conditions, pregnancy complications, sex of baby and smoking during pregnancy. **Bold** = statistically significant results.

Maternal asylum and undocumented refugee status

One study of Swedish births examined stillbirth odds associated with asylum and undocumented refugee status compared with documented refugee women[534]. All exposure group women were from Syria, Iraq, Somali, Eritrea or Afghanistan Refugee/asylum status was identified through registry data indicators for undocumented and documented status. Analysis of asylum-seeking women and undocumented women

demonstrated a 30% increase in stillbirth odds compared with refugee women (aOR 1.30 (95% CI 0.74, 2.29))[534].

Table 6-2 Chapter 6 Summary of meta-analysis findings of populations at risk of stillbirth

	Reference group	Exposure group	All stillbirths	Preterm stillbirth	3rd tri stillbirth	Term stillbirth
Maternal country of birth	Australia	*Oceania*	**1.31 (1.08, 1.59)**	-	-	-
	Australia and Europe	*Middle East*	**1.46 (1.06, 2.01)**	-	1.14 (0.94, 1.37)	-
	Non-American	*American*	0.92 (0.81, 1.03)	-	0.87 (0.52, 1.45)	-
	Non-African	*African*	**1.82 (1.56, 2.12)**	**1.47 (1.21, 1.80)**	**1.69 (1.43, 2.01)**	**1.32 (1.02, 1.70)**
	Australia, Sweden, Spain, Denmark	*European*	1.05 (0.97, 1.15)	-	0.99 (0.87, 1.13)	-
	English speaking countries	*Eastern European*	2.76 (0.64, 11.94)	-	-	-
	Australia, UK and New Zealand	*Southeast Asia*	0.75 (0.49, 1.15)	0.90 (0.75, 1.08)	-	0.68 (0.45, 1.04)
	Australia and UK	*South Asia*	**1.58 (1.03, 2.41)**	**1.32 (1.14, 1.53)**	-	**1.50 (1.27, 1.77)**
	Danish and Norwegian born women	*Somalia*	**2.06 (1.56, 2.70)**	-	-	-
	Non-Turkey	*Turkey*	**1.35 (1.22, 1.49)**	-	-	-
Ethnicity	Non-Hispanic white women	*Hispanic women*	0.99 (0.68, 1.45)	-	-	-
	Non-Hispanic white women	*Black women*	**1.67 (1.14, 2.45)**	-	-	-
	Spanish, German and French women	*European/American women*	0.99 (0.91, 1.07)	-	-	-
	European and non-Indigenous Australian women	*Asian women*	**1.37 (1.02, 1.83)**	-	1.07 (0.66, 1.74)	-
	Caucasian and Dutch women	*South Asian women*	**1.72 (1.41, 2.10)**	-	-	-
	Caucasian and Dutch women	*East Asian women*	0.89 (0.71, 1.11)	-	-	-

	European and non-Indigenous Australian women	*Indian women*	**1.72 (1.37, 2.18)**	-	-	-
	Non-Indigenous Australian women	*Australian Aboriginal and Torres Strait Islander*	**1.61 (1.08, 2.39)**	-	-	-
	Non- Māori European and Australian women	*Māori ethnicity*	1.13 (0.89, 1.43)	-	-	-
	Non-Hispanic white women	*American Indian/native women*	1.01 (0.58, 1.78)	-	-	-
	European women	*Pacific women*	**1.44 (1.02, 1.95)**	-	-	-
	Caucasian and non-Haitian women	*Afro-Caribbean women*	**1.82 (1.06, 3.13)**	-	-	-
Place of residence	Major city	*Rural area*	1.09 (0.96, 1.22)	-	-	-
Australian place of residence	Very accessible	*Accessible*	1.02 (0.74, 1.42)	-	-	-
	Very accessible	*Moderately accessible*	0.60 (0.31, 1.17)	-	-	-
	Very accessible	*Remote*	0.78 (0.42, 1.44)	-	-	-
	Very accessible	*Very remote*	**2.66 (1.35, 5.22)**	-	-	-
Canadian place of residence	Urban areas	*Rural living*	**1.27 (1.04, 1.55)**	-	-	-
	Other care types	*Midwife only care*	2.08 (0.47, 9.28)	-		

Maternity care type	Other care types	*General practitioner or shared care*	0.72 (0.52, 0.99)	-		
	Private health care	*Public health care*	**1.30 (1.19, 1.43)**	-		
	Insured women (USA)	*Uninsured women (USA)*	**1.98 (1.78, 2.19)**	-		
Residential segregation	Low dissimilarity (Black women)	*High dissimilarity (Black women)*	1.60 (0.80, 3.19)	-	-	-
	Low dissimilarity (White women)	*High dissimilarity (White women)*	**0.81 (0.71, 0.93)**	-	-	-

Discussion and conclusions

To our knowledge this is the largest review of populations and communities at risk of stillbirth in high-income countries. Results identify multiple populations experiencing increased odds of stillbirth than that of the general population, within high-income countries. Of the populations at risk, very remote Australian communities, women born in Africa, and maternal black ethnicity (USA and UK), Indian country of birth or ethnicity, and Australian Aboriginal and/or Torres Strait Islander ethnicity all demonstrate moderately increased odds of stillbirth. Marginal increases in stillbirth odds were shown in association with Pacific Islander ethnicity, and Canadian Inuit ethnicity. Most identified populations at increased risk of stillbirth have clear barriers to accessing antenatal care.

Country of birth and ethnic minority groups have long been a focus of health inequalities and social disadvantage within high-income countries. Through meta-analysis, both Indian maternal country of birth and Indian self-reported ethnicity were shown to increase the odds of stillbirth within high-income countries. In addition, African, Middle Eastern and Oceanic countries of birth demonstrated association with an independent risk for stillbirth in high-income countries. Asian, Indian, South Asian, Australian Aboriginal or Torres Strait Islander women, Pacific and Afro-Caribbean women also demonstrated increased odds for stillbirth in high-income countries. Indian maternal ethnicity demonstrated greater odds of stillbirth than Indian country of birth, suggesting that risks associated with this factor could be intergenerational following migration. This was despite the results of one included study that indicated a reduction in stillbirth odds, for all ethnicities, with increasing length of time since migration (acculturation)[518]. The increased odds of stillbirth for the identified ethnic minority groups may reflect barriers associated with institutional racism, and systemic inequalities of social and political influences. With meta-analysis results maternal Middle Eastern country of birth, or Asian maternal ethnicity, were shown to have decreased odds of stillbirth when analysis was restricted to third trimester stillbirths compared to analysis including both second and third trimester stillbirths. Further research should prioritise the examination of second trimester risk of stillbirth for women born in the Middle East or reporting Asian ethnicity. The difference in results may indicate that stillbirth risk is greater for women of these minority groups during the second trimester of pregnancy. These findings contradict recent studies that implicate term stillbirth as the driving force behind higher stillbirth rates amongst maternal Asian country of birth[73, 531]. However, we are unable to confirm or dispute the findings because a subgroup analysis for term stillbirths for women with Asian countries of birth was not possible. These findings support the conclusion that maternal Indian and Asian ethnicity, regardless of place of birth, independently increases the odds of stillbirth, and should therefore be factored into risk assessment measures independent to maternal country of birth.

Findings demonstrate that women reporting a Southeast Asian country of birth were not at increased risk of stillbirth, but that women who reported South Asian ethnicity, or women who were classified as Black women in the UK or USA have almost 2-fold increased odds of stillbirth. These findings are aligned with recent research completed in the UK that reported increased attributable fractions of stillbirth associated with maternal South Asian ethnicity (36.5%), and Black maternal ethnicity (51.2%)[545]. Recent analysis of a large UK cohort demonstrated that half of the stillbirths to South Asian women, and

two thirds of stillbirths to Black UK women could be attributed to socioeconomic status and ethnic inequalities within high-income countries[545]. Although this review found no such studies within the search dates, policy change in many high-income countries acknowledges, and attempts to address, the need for adaption of care guidelines and integration of culturally appropriate policy, despite impetus progress has been slow. Women within vulnerable groups are likely to be further disadvantaged by such delayed progress in meeting their needs and reducing stillbirth risk.

Women from disadvantaged groups are less likely to receive adequate antenatal care, and this in turn contributes to poorer outcomes, especially for vulnerable populations in rural and remote areas[546]. Analysis of maternal rural living and the associated risk of stillbirth did not demonstrate increased odds compared with major cities[546]. Yet as this analysis included Greece, the Netherlands, the UK, Australia and Canadian datasets, it is possible that differences between rural settings makes results non-comparable between countries. Stratification of results suggest that maternal rural living has the greatest effect on stillbirth odds firstly in Australia, followed by Canada, compared with major city residence. Rural and remoteness affect the delivery methods of health care within Australia and Canada, and changes to delivery have been shown to influence adequacy of antenatal care[547]. Such large inequity, not only between communities but within communities, results in health care measures, and public campaigns, that struggle to reach the populations most in need and to address health issues to prevent stillbirth[548]. National campaigns designed for population wide coverage can be insensitive to the access, and complexity of circumstances, affecting remotely living women. Through public health campaigns, behaviours contributing to poor health outcomes can be addressed, but only if we know where, and how to target and structure such campaigns. In Australia, The Centre of Research Excellence in Stillbirth has endeavoured to bridge the gap between blanket national campaigns and communities at risk by tailoring a prevention package developed through extensive community consultation, the Safer Baby Bundle, to hospitals[19, 295].

Some factors included within this review were not internationally generalizable, and therefore conclusions at an international level were not possible. Antenatal care type is dependent upon national healthcare plans and therefore our results are restricted to country specific healthcare types. Midwife led care in Australia and New Zealand was shown to results in a two-fold increased odds of stillbirth compared with other modes of care. Wide variation in results and confidence intervals, combined with migrant stillbirth rates drive this increase[158]. These findings indicate the need for further research into the impact of midwife lead care. Uninsured maternity care in the USA was also shown to increase stillbirth odds almost 2-fold compared with insured maternity care. Lack of insurance in the USA results in families being out-of-pocket for a large portion of maternity costs, this in turn can serve to inhibit antenatal care engagement. In Australia, public health care models differ to that in the USA, as the Australian government pays for public maternity care through a public hospital/maternity facility. An increase in stillbirth odds associated with publicly insured maternity care demonstrated again the inequalities between health care insurance status and birth outcomes. Fundamentally, the differences in health care insurance accessibility are perpetuated by maternal socioeconomic status. Increased rates of stillbirth among the uninsured, and public health

care systems globally serves to widens the gap of inequality within high-income countries.

Our review incorporates 105 studies spanning across 16 high-income countries. This review is the largest and most comprehensive to our knowledge. It forms a strong evidence base on which maternity care programs and interventions can be based. Despite its strengths, our findings for individual factors were limited by availability of results, as some factors were disproportionately represented by three high-income countries, Australia, Canada and the UK. This results in findings concerning antenatal care type, and rural residence, to lack generalisability to other high-income countries. Country of birth is a good indicator for a mother who has migrated within her lifetime to a host high-income country, but lack of data concerning time since arrival, and proficiency in the host country language limit the results. Further research incorporating this data would assist in minimising assumptions that language and acculturation form barriers and subsequent stillbirth risk.

Implications of findings and future research needed

The research findings indicate the need for further research to investigate the pathogenesis and causal pathways between different maternal ethnicities and GA specific stillbirth odds.

Findings that uninsured, and publicly funded health care, increase the odds of stillbirth in comparison with private/insured maternity care (USA, Australia and New Zealand), indicate the need to investigate the difference between the models of care, and the barriers to effectively delivering adequate care.

The independent association between country of birth and maternal ethnicity with increased stillbirth risk warrants further investigation into causal pathways between risk and stillbirth. Finally, research is needed to establish the role of biological causes, stillbirth and/or acculturation and the barriers that persist at an intergenerational level for minority groups, within high-income countries.

Implications of findings for policy

The impact shown by publicly funded, or uninsured, maternity care highlights the need for national policy to address differences in healthcare delivery, and barriers to effective care programs between the private/insured and the uninsured/public care. This will serve to break the perpetual cycle of inequality within high-income countries.

As demonstrated by preliminary findings from the Safer Baby Bundle implementation in Australia, prevention strategies require tailoring to marginalised group's needs. There are large variations in stillbirth odds between areas of residence, insurance type, and linguistically diverse and ethnic minority groups that maternity care programs have been unable to address.

Chapter 7 Lifestyle and Sociodemographic Stillbirth Risk Factors in a South Australian Cohort (1998-2016) (The ILSSA study)

Abstract

Background

Stillbirth rates in Australia have shown little improvement over several decades. Better understanding of potentially modifiable risk factors will help to prevent stillbirths.

Objectives

To identify and quantify sociodemographic, lifestyle and parental factors associated with stillbirth odds in a large South Australian (SA) cohort.

Methods

All births registered in the SA routine data collection over the period of 1998-2016 were included. Terminations of pregnancy were excluded from analysis. The primary outcome of interest, stillbirth, is defined as a birth with no signs of life ≥20 weeks gestational age (GA) or ≥400grams birthweight. Associations between stillbirth risk and lifestyle, environmental and social determinant factors were explored, using multivariable logistic regression incorporating confounders with known associations with stillbirth odds. Population Attributable Fractions (PAF) were calculated for factors demonstrating strongest associations with stillbirth in SA.

Results

A total of 363,959 births were included. An inadequate number of antenatal visits was associated with the strongest odds of stillbirth (aOR 3.93 (95% CI 3.41, 4.52)) Other factors found to have important associations with stillbirth odds were: maternal plant or machine operators (aOR 1.99 (95% CI 1.16, 2.45)), maternal age ≥40 years (aOR 1.92 (95% CI 1.50, 2.45)), paternal pensioners (aOR 1.83 (95% CI 1.12, 2.99)), Southern Asian country of birth (aOR 1.58 (95% CI 1.19, 2.10)) and Aboriginal/Torres Strait Islander women (aOR 1.50 (95% CI 1.20, 1.88)). Odds of stillbirth were increased in regional and remote areas in association with inadequate antenatal care visits (aOR 4.64 (95% CI 2.98, 7.23)), maternal age 35-40 years (aOR 1.92 (95% CI 1.02, 3.64)), Aboriginal and/or Torres Strait Islander women (aOR 1.90 (95% CI 1.12, 3.21)), paternal occupations; tradesperson (aOR 1.69 (95% CI 1.17, 6.16)) or unemployment (aOR 4.06 (95% CI 1.41, 11.73)).

Discussion and conclusion

In Australia, stillbirth rates have shown very little improvement over several decades. This research highlights the importance of strategies for modifiable risk factors (such as smoking cessation programs or culturally appropriate antenatal care programs) to improve antenatal care engagement, and decrease stillbirth rates across South Australia, with likely relevance to the rest of Australia.

Introduction

Globally, more than 2.64 million babies are stillborn each year with the highest rates are experienced by families in lower- and middle-income countries. Following the omission of stillbirth from the UN Millennium Development Goals, the *Lancet* 2011 stillbirth series[4, 5, 13-16] highlighted the need for global unity in the effort to end preventable stillbirth[14]. This series identified key areas for improvement and set goals for decreasing global stillbirth rates. In 2016, this was followed by an urgent call for further effort, as stillbirth rates in Australia, and many other countries globally, remained unchanged[6, 18]. More recently, in 2020, Women and Birth published a series which focused solely on stillbirths in Australia, identifying the national action needed to decrease stillbirth in

Australia[19-24]. Flenady et al demonstrated that overall, Australian stillbirth rates have shown encouraging downward trends, particularly third trimester stillbirths (≥28 weeks GA), but alarmingly showed an increase in very early stillbirth rates (20-23 weeks GA)[6] reinforcing earlier findings of the same trend[549]. The clear discrepancies in stillbirth rates between high-income countries indicates that in Australia there is room for improvement and prevention[6, 17]. In particular, Rumbold et al[24] highlight the impact of inequity within select Australia populations with high stillbirth rates. This is of particular concern within communities experiencing isolation and socioeconomic disadvantage [24]. Inequity has been shown to be linked with high rates of smoking, poverty, young maternal age and poor health literacy within disadvantaged communities that results in the culmination of multiple risk factors increasing stillbirth risk[6, 67]. Within Australia this intersection of risk factors within disadvantaged communities contributes to the widening gap of health inequality, further hindering stillbirth prevention[550].

In 2018, the Australian government appointed a Senate Select Committee on Stillbirth Research and Education[551, 552]. The report released following the inquiry ranked stillbirth rates across high-income countries and summarised progress made between 2009 and 2015. This report revealed that Australia had slipped in rank compared with other countries, and recently published 2019 data from UNICEF reveals that Australia is currently ranked 11th of all high-income countries indicating further potential for reduction of stillbirth rates (Appendix A).

Reports from the Senate Select Committee on Stillbirth Research and Education demonstrated that babies born to mothers in remote and very remote areas were 65% more likely to be stillborn than babies born in major cities. Table 1, included in the committee's report, demonstrated an almost doubling of stillbirth rates for women living remotely compared with their major city dwelling counterparts (2013-2014). The overall stillbirth rate for Australia (7.1/1000 births in 2013-14) aligned closely with the stillbirth rate of major cities and inner regional areas.

Table 7-1 Stillbirth deaths by maternal remoteness and residence, Australia 2013-14 (table 2.4, p12, Chapter 2 [552])

Remoteness of usual residence (ARIA+)	Total births[a]	Live births	Stillbirths	
			n	Rate[b]
Major cities	444,729	441,737	2,938	6.6
Inner regional	101,768	100,993	744	7.3
Outer regional	53,716	53,266	446	8.3
Remote	9,368	9,274	93	10.0
Very remote	6,204	6,141	64	10.2
Not stated	6,253	6,189	55	8.8
Total	**622,037**	**617,600**	**4,419[a]**	**7.1**

(a) Total births comprise live births and s illbirths collected by the National Perinatal Data Collection. The sum of stillbirths and live births may not add up to total births. See Appendix C for further detail.
(b) The rate is the number of deaths per 1,000 births. Stillbirth and perinatal death rates were calculated using total births (live births and stillbirths). Neonatal rates were calculated using live bir hs.
Source: AIHW 2018 - analysis of National Perinatal Mortality Data Collec ion and the National Perinatal Data Collection, Table A22: Perinatal deaths by maternal remoteness of residence (ARIA+), Australia, 2013–2014

Aims

This research aims to review parental sociodemographic factors, lifestyle and environmental factors, as well as antenatal care characteristics and a woman's reproductive history to identify risk factors of stillbirth relevant to SA, and to

subsequently identify the patterns of risk factors by remoteness classification of area of residence. Within a sub-cohort from this dataset, the association between maternal BMI and stillbirth odds will be assessed, and the role of maternal BMI as a confounder of other risk factors identified. This will enable insight into where resources should be focused on prevention strategies to decrease stillbirth risk.

Methods

Data sources and study population

Within Australia, data are collated within perinatal datasets, containing births in each state and territory. The South Australia Perinatal Outcomes dataset provides detailed information regarding factors caused by, and contributing to, inequity and stillbirth rates within sub-populations. Barriers to adequate health care such as area of residence, country of birth, maternal comorbidities as well as parental occupation, are included within this dataset to enable scrutiny of the overall risk factor prevalence in SA, as well as in regional and remote areas.

Cohort 1

Cohort 1 uses the SA perinatal data collection including all births over the period 1998 to 2016 inclusive. In SA, all births are reported to the SA Perinatal Outcomes Unit of the Department of Health and Wellbeing by midwives, birth attendants and obstetricians on a standardised supplementary birth record. Each birth is allocated a unique identifier, and maternal sociodemographic characteristics, pregnancy and birth outcome data are recorded. Information for all births (live or stillborn) ≥ 20 weeks completed gestational age (GA), or ≥400g birthweight are reported. Although validation studies of the SA perinatal data collection have been conducted and have shown high validity and reliability of the data, the data validated predates our dataset[553]. For the purpose of ongoing quality assurance, the Department of Health and Wellbeing have integrated continuous validation of the dataset by comparing data collected on the supplementary birth record to electronic hospital records at the time of coding. Our analysis includes all births ≥ 20 weeks completed gestational age (GA), or ≥400g birth weight during the years 1998-2016 in South Australia. Terminations of pregnancy were excluded.

Cohort 2

Due to the later introduction of maternal BMI within the perinatal data collection, analyses involving BMI were restricted to study years 2007-2016 (cohort 2). Replication of the analysis is performed for cohort 2. Where variables are continuous, larger category definitions are explored and applied to enable analysis with larger numbers of stillbirth per group.

Ethics approval for this project was obtained from the South Australian Department of Health and Wellbeing Committee (ID HREC19SAH13) as well as ethical approval from the Aboriginal Health Council of SA Human Research Ethics Committee (ID 04-19-816).

Study Variables

The dataset contains pregnancy outcome categorised as live birth (includes neonatal deaths and inpatient babies to 28 days of life) or stillbirth. All data were obtained

anonymously with all identifying fields removed by the SA Perinatal Outcome Unit prior to provision for research purposes.

All available variables were considered for inclusion within analysis, the dataset did not include variables such as sleep position, or domestic violence, and access was not granted to maternal alcohol or substance use data.

Table 7-2 The ILSSA study variables included

Variable (availability)	Time point of collection	Definition/Categorisation
Study Variables		
Maternal race (1998-2016)	First antenatal visit (booking visit)	Self-reported Caucasian, Aboriginal, Torres Strait Islander, Aboriginal and Torres Strait Islander or Asian status. Aboriginal and/or Torres Strait Islander status includes identification by Aboriginal or Torres Strait Islander descent, self-identification of community acceptance of Aboriginal and/or TSI status. Births to women recorded as Aboriginal, Torres Strait Islander, and/or Aboriginal were categorised as Aboriginal and/or Torres Strait Islander women for analysis. Women recorded as Asian were categorised as Asian, and women recorded as Caucasian were categorised as Caucasian.
Maternal country of birth (1998-2016)	First antenatal visit (booking visit)	Australia, Oceania, Europe/USSR, Middle East/Nth Africa, SE Asia, NE Asia, Southern Asia, Nth America, South/Central America, Africa as reported by women.
Statistical areas Level 3 (SA3) areas (1998-2016)	At birth	Maternal place of usual residence data. Australia Bureau of Statistics modified Accessibility and Remoteness Index of Australia (ARIA+) score average for each SA3 area compiled from SA2 area ARIA+ scores. SA3 area was assigned on maternal usual place of residence at birth. Areas were classified as; major cities (geographic distance imposes minimal restrictions upon accessibility to the widest range of goods, services and opportunities for social interaction), inner regional areas (geographic distance imposes some restrictions upon accessibility to the widest range of goods, services and opportunities for social interaction), outer regional areas (geographic distance imposes a moderate restriction upon accessibility to the widest range of goods, services and opportunities for social interaction), remote/very remote areas (geographic distance

		imposes the highest restriction upon accessibility to the widest range of goods, services and opportunities for social interaction). Map of South Australia areas according to the ABS modified ARIA+ score with superimposed SA3 boundaries shown below (figure 1).
Adequacy of antenatal care (1998-2016)	At birth	Adequacy of antenatal care was assessed per pregnancy according to the Australian Clinical Practice Guidelines: Pregnancy Care that recommends nulliparous women have a minimum of 10 antenatal visits, and multiparous women; a minimum of 7 antenatal visits [(554)]. Adequacy was assigned separately by parity (nulliparous and multiparous) stratified by gestational age.
Maternal age (1998-2016)	At birth	Categories: 12-19 years, 20-24 years, 25-29 years, 30-34 years, 35-40 years, ≥40 years
Marital status (1998-2016)	At birth	Categories: Married/Unmarried (encompasses; never married, widowed, divorced, separated)
Smoking status (1998-2016)	First antenatal visit (booking visit) and again at 20 weeks GA	Non-smokers as self-reported smoking status at booking visit and 20 weeks GA. Women were classified as smokers if any smoking was reported at either visit.
Parity (1998-2016)	First antenatal visit (booking visit)	Nulliparous, multiparous
Chronic health medical conditions	At birth	Previous diabetes or chronic hypertension
Parental occupation	Father's occupation at birth, mother occupation prior to and/or during pregnancy before 'home duties'.	One of 13 occupation groups according to the ABS Australia Standard Classification of Occupations (ASCO) first edition
Inter-pregnancy interval		Calculated as the number of months between the previously recorded birth, and date of conception of the current pregnancy (>6 months, < 6 months).
Maternal BMI (2007-2016)	First antenatal visit (booking visit) measurements	Calculated as weight in kgs divided by height (in meters) squared. Underweight (<19), healthy (19-24), overweight (25-29) and class 1 obesity (30-34 years), class 2 obesity (35-39 years), morbid obesity (40+)

Anaemia	At any stage during pregnancy	Anaemia diagnosed as maternal Hb <10gms/100ml
Study Confounders		
Obstetric conditions	At birth	Placental abruption, multiple pregnancy, post-term birth (>41 completed weeks GA)
Prolonged labour	At birth	Labour duration of >18 hrs
Past obstetric history	At birth	Previous caesarean section, previous stillbirth.
Medical conditions	At birth	Asthma during pregnancy, urinary tract infection during pregnancy
Babies born small for gestational age	After birth	SGA; below the 10th percentile were determined using Australian national birthweight percentiles estimated from a large Australian cohort of infants born between 1997 and 2007[555].

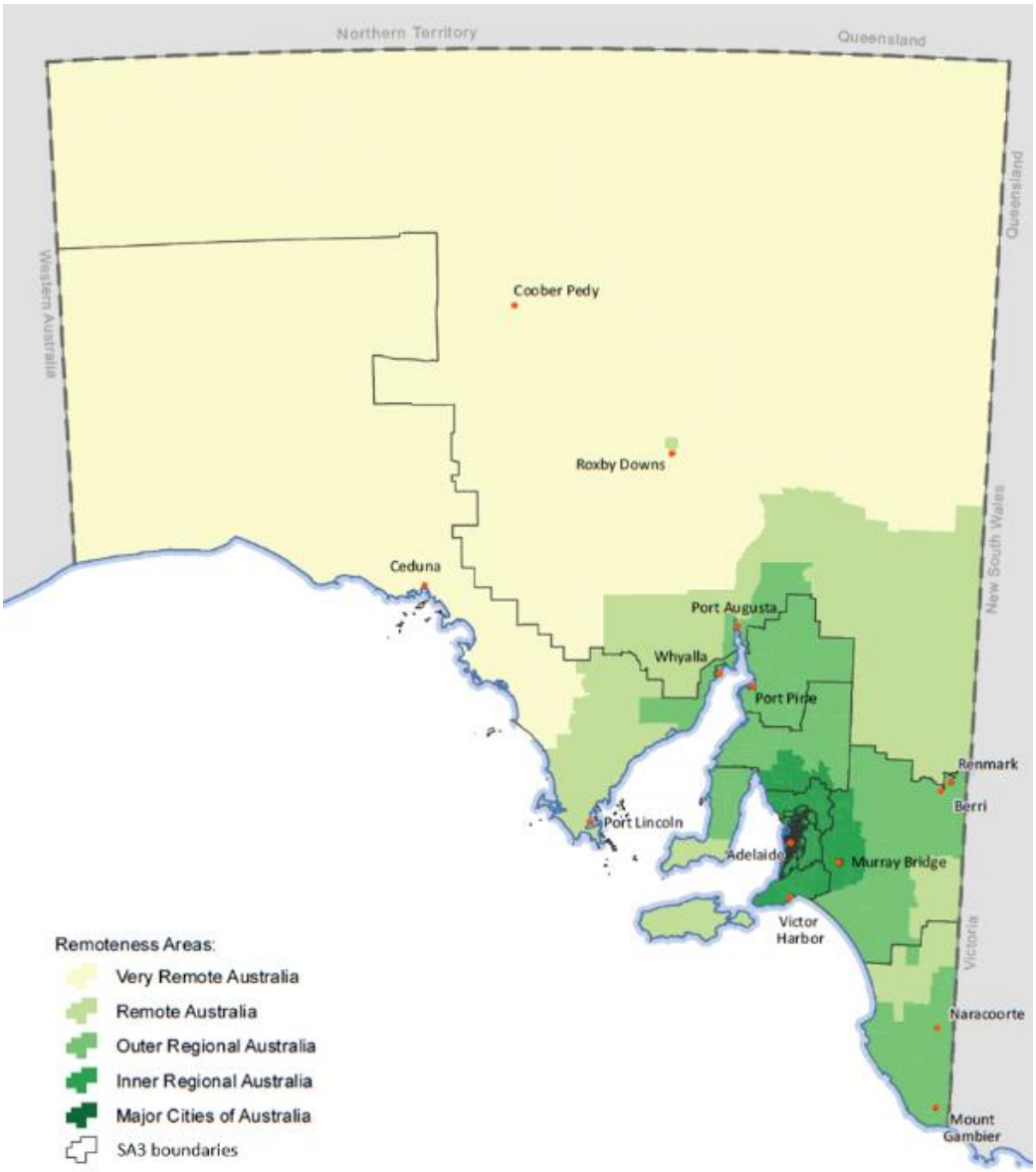


Figure 7-1 Geographic areas of South Australia demonstrating major cities, inner regional, outer regional, remote, and very remote areas of SA[4] .

Statistical analysis

Variables within the dataset were categorised as outlined above in table 7-2. Variable categories with less than 10 stillbirths per groups were reported as '<10' and crude odds ratios concealed. Within multivariable analysis where categories have less than 5 stillbirths, analysis is reported as '<5'. Logistic regression was performed using professional statistics software STATA 16 IC (by first author A Bowman) to determine the association between risk factors and stillbirth, with associations described using odds ratios and 95% confidence intervals. Both unadjusted and adjusted models were

[4] This image is based on data from the Australian 2011 Census of Population and Housing compiled by the Australian Bureau of Statistics. The data plotted is from the Basic Community Profile from the Department of Communities and Social Inclusion. The raw data is made available as part of data packs (Australian Statistical Geography Standard (ASGS) Volume 5 – Remoteness Structure) and is licensed under the Creative Commons Attribution 2.5 license (Australia). This file is licensed under the Creative Commons Attribution-4.0 Australia license.

considered, with adjustment made for variables selected *a priori* that also demonstrated significance during univariate analysis (indicated by $p<0.001$). For each risk factor, adjustment variables included year of birth, adequate ANC visits (adjusted for gestational age at birth), marital status, maternal race, smoking status, parity, remote/rural status, maternal age, previous stillbirth, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, antepartum haemorrhage (APH)). The cohort was stratified by region of residence (major city, inner regional, outer regional and remote/very remote) and analysis repeated using the same adjustment variables as described above (excluding rural/remote status).

Analysis was repeated using cohort 2 with the addition of maternal BMI to model of multivariable adjustment. Factors demonstrating the strongest association with stillbirth odds were further explored to calculate SA specific population attributable fractions (PAF)[556] and subsequent factor attributable stillbirths (n).

Results

Over the 18-year study period, from 1998 to 2016, the SA perinatal data collection contained 363,959 births following the exclusion of pregnancy terminations (n=95,487). Birth <20 weeks GA (n=18) or with a birthweight of <400g if GA was unknown (n=8), were excluded leaving 363,933 births, including 1767 stillbirths, available for analysis. Women within the study population were predominantly Australian born (81%) and 86% identified as Caucasian. Of the cohort's births, 3% were multiple births. Most women within the cohort were non-smoking (78%), gave birth in the Australian public health care system (70%), and were 30-34 years of age (32%) at the time of giving birth, the average age of mothers at the time of birth over the study period is 29.5years. Maternal occupation was predominantly 'home duties' (25.8%) and a large majority of women reporting their occupation as 'home duties' were multiparous (88.4%). During pregnancy 13.5% of women in SA had less than their required number of antenatal care visits during pregnancy. Following application of the same inclusion and exclusion criteria, cohort 2 encompassed 201,315 total births (918 stillbirths) between 2007 and 2016. The same inclusion and exclusion criteria were applied to cohort 2 for analysis of maternal BMI and adequacy of antenatal care. Within cohort 2, 16.5% of women attended an inadequate number of antenatal care visits during pregnancy. Births to women living in major cities formed most of the cohort (71%), followed by those in inner regions (14%), the outer regional areas (8%) and lastly remote and very remote regions (1%).

Crude analysis (table 7-3) demonstrated strong associations between several variables and stillbirth odds including maternal smoking compared with non-smokers (cOR 1.47 (95% CI 1.32, 1.63), public health insurance status compared with private (cOR 1.57 (95% CI 1.40, 1.76)), as well as unmarried status compared with married (cOR 1.70 (95% CI 1.51, 1.92)). More than four times the odds of stillbirth were demonstrated for an inadequate number of antenatal care visits compared with women who attended the adequate number of appointments (cOR 4.02 (95% CI 1.65, 4.44)), maternal age groups of 12-19 years (cOR 1.71 (95% CI 1.39, 2.09)) or ≥40 years of age (cOR 1.75 (95% CI 1.40, 2.19)) are associated also with increased odds of stillbirth compared with 25-29 years. Maternal occupation as well as employment status was analysed in comparison to professionals, demonstrating that unemployed mothers have a more than 2-fold increase in stillbirth odds (cOR 2.44 (95% CI 1.94, 3.06)), as well as maternal plant/machine operators (cOR 2.38 (95% CI 1.40, 4.05)), and pensioners (cOR 2.63 (95% CI 1.38,

4.99)). Aboriginal/Torres Strait Islander status (cOR 2.55 (95% CI 2.11, 3.08)) also demonstrated important associations with stillbirth odds, as did maternal country of birth, specifically, women who were born in the Middle East/North Africa (cOR 1.53 (95% CI 1.09, 2.14)), Southern Asia (cOR 1.29 (95% CI 1.01, 1.65) and Africa (cOR 1.64 (95% CI 1.15, 2.32)). Nulliparous women were shown to have higher odds of stillbirth than multiparous women who have 1-2 previous births ((cOR 1.30 (95% CI 1.18, 1.44)), parity demonstrated a u-shaped association with stillbirth odds as parity >2 also demonstrated increased odds compared with parity of 1-2 (cOR 1.67 (95% CI 1.43, 1.96)). Major pre-existing medical conditions were associated with more than double the odds of stillbirth; pre-existing diabetes (type 1 or 2) (cOR 4.00 (95% CI 2.94, 5.43)) and chronic hypertension cOR 2.15 (95% CI 1.59, 2.90)). Also women with anaemia (cOR 1.23 (95% CI 1.04, 1.44)) and women who experienced urinary tract infections during pregnancy were at increased odds of stillbirth (cOR 1.71 (95% CI 1.35, 2.17)).

Table 7-3 The ILSSA study cohort characteristics, including obstetric factors and maternal health conditions

Variables		Stillbirths	Total births	rate/1000 births	Crude OR (95% CI)	p-value
Sociodemographic, lifestyle and environmental factors						
Smoking	*Non-smoker*	1,197	282,737	4.23	Referent	
	Smoker	472	76,130	6.20	**1.47 (1.32, 1.63)**	
	unknown	98	5,066	19.35	**4.64 (3.75, 5.75)**	<0.001
Insurance type	*Private*	379	109022	3.48	Referent	
	Public	1,388	254911	5.45	**1.57 (1.40, 1.76)**	<0.001
Marital status	*Married*	1440	321,088	4.48	Referent	
	Unmarried	326	42,737	7.63	**1.70 (1.51, 1.92)**	<0.001
	Unknown	<10	108	NR†	NR†	
Adequate antenatal care visits	*Adequate antenatal care visits*	1,090	314,810	3.46	Referent	
	Inadequate antenatal care visits	677	49,123	1.38	**4.02 (3.65, 4.44)**	<0.001
Maternal age	*12-19 years*	119	15,838	7.51	**1.71 (1.39, 2.09)**	
	20-24 years	298	54,316	5.49	**1.24 (1.07, 1.44)**	
	25-29 years	472	106,830	4.42	Referent	
	30-34 years	483	117,263	4.12	0.93 (0.82, 1.06)	<0.001
	35-39 years	302	57,622	5.24	**1.19 (1.02, 1.38)**	
	≥40 years	93	12,064	7.71	**1.75 (1.40, 2.19)**	
Maternal occupation	*Professionals*	169	50,280	3.36	Referent	
	Managers/Admin	91	26,607	3.42	1.02 (0.79, 1.32)	
	Paraprofessionals	93	22,528	4.13	1.23 (0.95, 1.59)	
	Tradespersons	45	11,594	3.88	1.16 (0.82, 1.63)	

	Variables	Stillbirths	Total births	rate/1000 births	Crude OR (95% CI)	p-value
	Clerks	149	44,340	3.36	1.00 (0.80, 1.25)	
	Sales and service workers	228	53,632	4.25	**1.27 (1.03, 1.55)**	
	Plant and machine operators	15	1,882	7.97	**2.38 (1.40, 4.05)**	
	Labourers	60	12,051	4.98	**1.48 (1.10, 1.99)**	
	Student	81	13,106	6.18	**1.84 (1.41, 2.41)**	
	Pensioner	10	1,139	8.78	**2.63 (1.38, 4.99)**	
	Home duties	504	93,854	5.37	**1.60 (1.34, 1.91)**	
	Unemployed	134	16,434	8.15	**2.44 (1.94, 3.06)**	
	Unknown	188	16,486	11.40	**3.42 (2.76, 4.23)**	<0.001
Partner's occupation	*Professionals*	176	50581	3.48	Referent	
	Managers/Admin	187	57678	3.24	0.93 (0.76, 1.15)	
	Paraprofessionals	62	18511	3.35	0.96 (0.72, 1.29)	
	Tradespersons	251	64480	3.89	1.12 (0.92, 1.36)	
	Clerks	44	9805	4.49	1.29 (0.92, 1.81)	
	Sales and service workers	80	20395	3.92	1.13 (0.86, 1.48)	
	Plant and machine operators	92	22489	4.09	1.18 (0.91, 1.52)	
	Labourers	205	47252	4.34	**1.25 (1.02, 1.53)**	
	Student	47	8081	5.82	**1.68 (1.21, 2.31)**	
	Pensioner	21	2057	10.21	**2.95 (1.87, 4.65)**	
	Home duties	<10	1476	NR†	NR†	
	Unemployed	145	18454	7.86	**2.27 (1.81, 2.84)**	
	Unknown	452	42674	10.59	**3.07 (2.57, 3.66)**	<0.001

Variables		Stillbirths	Total births	rate/1000 births	Crude OR (95% CI)	p-value
Country of birth (maternal)	*Australia*	1,424	294863	4.83	Referent	
	Europe/USSR	91	20115	4.52	0.94 (0.76, 1.16)	
	Middle east/Nth Africa	37	5014	7.38	**1.53 (1.09, 2.14)**	
	SE Asia	59	14334	4.12	0.85 (0.65, 1.11)	
	NE Asia	26	6583	3.95	0.82 (0.55, 1.22)	
	Southern Asia	69	11097	6.22	**1.29 (1.01, 1.65)**	
	Nth America	<10	1725	NR†	NR†	
	South/Central America	<10	1392	NR†	NR†	
	Africa	34	4318	7.87	**1.64 (1.15, 2.32)**	
	Oceania	13	4450	2.92	0.60 (0.35, 1.04)	
	Unknown	<10	42	NR†	NR†	0.003
Maternal race	*Caucasian*	1,404	311,232	4.51	Referent	
	Aboriginal/Torres Strait Islander	123	10,773	11.42	**2.55 (2.11, 3.08)**	
	Asian	151	29,154	5.18	1.15 (0.97, 1.36)	
	Unknown	89	12,774	6.97	**1.55 (1.24, 1.93)**	<0.001
Remoteness classification	*Major city*	1,210	257128	4.71	Referent	
	Inner regional area	238	51219	4.65	0.99 (0.86, 1.14)	
	Outer regional area	163	30880	5.28	1.12 (0.95, 1.32)	
	Remote/Very remote area	123	22305	5.51	1.17 (0.97, 1.42)	
	Unknown/interstate	33	2401	13.74	**2.95 (2.06, 4.22)**	<0.001
Obstetric factors						
Interpregnancy interval*	*>6 months*	613	150178	4.08	Referent	

	Variables	Stillbirths	Total births	rate/1000 births	Crude OR (95% CI)	p-value
	< 6 months	115	23245	4.95	1.21 (0.99, 1.49)	
	missing	226	38591	5.86	**1.44 (1.23, 1.68)**	<0.001
Parity	*Nulliparous*	813	151,919	5.35	**1.30 (1.18, 1.44)**	
	1-2 previous births	747	181,823	4.11	Referent	
	3+ previous births	207	30,191	6.86	**1.67 (1.43, 1.96)**	<0.001
Previous stillbirth*	*No previous stillbirth*	905	208,379	4.34	Referent	
	Previous Stillbirth	49	3,635	13.48	**3.13 (2.34, 4.19)**	<0.001
Previous caesarean*	*No previous caesarean*	659	152792	4.33	Referent	
	Previous caesarean	295	60176	4.93	1.14 (0.99, 1.31)	0.071
Gestational hypertension	*No gestational hypertension*	1,654	336395	4.92	Referent	
	Gestational hypertension	113	27538	4.10	0.83 (0.69, 1.01)	0.065
UTI during pregnancy	*No UTI during pregnancy*	1,693	354852	4.77	Referent	
	UTI during pregnancy	74	9081	8.15	**1.71 (1.35, 2.17)**	<0.001
Multiple pregnancy	*Singleton*	1,610	352415	4.57	Referent	
	Multiple	157	11518	13.63	**3.01 (2.48, 3.66)**	<0.001
Prolonged labour (>18 hrs)**	*No prolonged labour*	1,444	243,367	5.93	Referent	
	Prolonged labour	73	4,310	16.94	**2.89 (2.27, 3.67)**	<0.001
GDM	*No GDM*	1,698	342261	4.96	Referent	
	GDM	69	21672	3.18	0.64 (0.50, 0.82)	<0.001
Placental abruption	*No placental abruption*	1,610	361640	4.45	Referent	
	Placental abruption	157	2293	68.47	**16.44 (13.84, 19.52)**	<0.001
	No threatened miscarriage/APH	1,657	357602	4.63	Referent	

Variables		Stillbirths	Total births	rate/1000 births	Crude OR (95% CI)	p-value
Threatened miscarriage/APH (<20 weeks GA)	*Threatened miscarriage/APH*	110	6331	17.37	**3.85 (3.35, 4.42)**	<0.001
SGA	*Not SGA*	1,177	326547	3.60	Referent	
	SGA	590	37386	15.78	**4.43 (4.01, 4.90)**	<0.001
GA at birth	*Term*	452	330508	1.37	Referent	
	All preterm (<37+0wks)	1,308	31321	41.76	**31.82 (28.55, 35.47)**	
	Post-term (≥41+7wks)	<10	2096	NR†	NR†	
	Unknown	<10	<10	NR†	NR†	<0.001
Maternal health						
Asthma	*No asthma*	1,636	339648	4.82	Referent	
	Asthma	131	24285	5.39	1.12 (0.93, 1.34)	0.221
Pre-existing diabetes	*No pre-existing diabetes*	1,724	361644	4.77	Referent	
	Pre-existing diabetes	43	2289	18.79	**4.00 (2.94, 5.43)**	<0.001
Chronic hypertension	*No chronic hypertension*	1,721	359434	4.79	Referent	
	Chronic hypertension	46	4499	10.22	**2.15 (1.59, 2.90)**	<0.001
Anaemia	*No anaemia during pregnancy*	1,597	334841	4.77	Referent	
	Anaemia during pregnancy	170	29092	5.84	**1.23 (1.04, 1.44)**	<0.001

†Not publishable because of small numbers
*Analysis only includes multiparous women
**Analysis only includes vaginal births

Multivariable analysis (table 7-4), showed no clear associations with stillbirth for a number of factors that demonstrated increased odds initially through crude analysis; between publicly insured women, compared with private (aOR 1.11 (95% CI 0.96, 1.28)), smokers (aOR 1.11 (95% CI 0.96, 1.28)), young mothers (12-19 years (aOR 1.04 (95% CI 0.82, 1.32)) and maternal age of 20-25 years (aOR 0.99 (95% CI 0.84, 1.16)) in comparison to mothers aged 25-30. This was also shown when adjustments were applied for nulliparous women compared with multiparous women (aOR 1.03 (95% CI 0.90, 1.17)), and anaemic women compared with non-anaemic women (aOR 0.99 (95% CI 0.82, 1.18)).

Aboriginal and/or Torres Strait Islander race was shown to be an independent risk factor for stillbirth women compared with Caucasian women (aOR 1.50 (95% CI 1.20, 1.88)) for the entire SA cohort (cohort 1) but analysis within cohort 2 (2007-2016) demonstrated a weaker effect that was no longer significant (aOR 1.17 (95% CI 0.80, 1.72)). Through stratification of cohort 1 by maternal residence remoteness classification, odds of stillbirth for Aboriginal and/or Torres Strait Islander women were double that of Caucasian women within inner regional (aOR 1.91 (95% CI 1.06, 3.46)) and remote/very remote areas (aOR 1.90 (95% CI 1.12, 3.21)). Although marginally increased for Aboriginal and/or Torres Strait Islander women within major cities compared with Caucasian women, confidence intervals did not reach statistical significance (aOR 1.26 (95% CI 0.90, 1.75)). Asian race (self-reported) was not shown to be an independent risk factor of stillbirth in cohort 1, (aOR 1.12 (95% CI 0.93, 1.35)) but was associated with increased stillbirth odds cohort 2 (aOR 1.43 (95% CI 1.13, 1.82)) compared with Caucasian women. Stratification by areas of remoteness was unable to be performed due to small case numbers per subgroup.

The association between maternal region of birth and stillbirth odds within cohort 1 analysis demonstrated increased odds for women born in Southern Asia compared with women born in Australia (aOR 1.58 (95% CI 1.19, 2.10)), and although slightly lower, these findings were similar through analysis of cohort 2 (aOR 1.67 (95% CI 1.24, 2.24)) where adjustment for maternal BMI was possible. Following stratification for area of residence, South Asian born women residing in major cities compared with Australian born women showed a 64% increase in odds (aOR 1.64 (95% CI 1.21, 2.21)). Analysis of South Asian maternal country of birth in regional and remote areas was not possible due to small numbers of cases.

Table 7-4 The ILSSA study - Findings of multivariable analysis (cohort 1)

Factors		Adjusted OR for risk factors of stillbirth*	Adjusted OR for risk factors of stillbirth stratified by region of residence*			
			Major city	Inner Regional	Outer Regional	Remote/Very remote area
		aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Smoking	Non-smoker	Referent	Referent	Referent	Referent	Referent
	Smoker	1.13 (0.99, 1.28)	1.16 (0.99, 1.35)	1.28 (0.92, 1.77)	**1.13 (1.00, 1.28)**	0.65 (0.42, 1.00)
Insurance type	Private	Referent	Referent	Referent	Referent	Referent
	Public	1.11 (0.96, 1.28)	1.08 (0.91, 1.28)	1.29 (0.85, 1.96)	1.13 (0.98, 1.31)	1.66 (0.77, 3.57)
Marital status	Married	Referent	Referent	Referent	Referent	Referent
	Unmarried	**1.20 (1.04, 1.39)**	1.18 (0.98, 1.41)	1.41 (0.95, 2.09)	**1.19 (1.02, 1.37)**	1.17 (0.73, 1.90)
Adequate ANC visits	Adequate ANC visits	Referent	Referent	Referent	Referent	Referent
	Inadequate ANC visits	**3.93 (3.41, 4.52)**	**3.53 (2.95, 4.22)**	**5.56 (3.91, 7.92)**	**3.89 (3.38, 4.47)**	**4.64 (2.98, 7.23)**
Maternal age	12-19 years	1.04 (0.82, 1.32)	0.94 (0.69, 1.28)	0.84 (0.45, 1.59)	1.05 (0.83, 1.33)	1.20 (0.55, 2.61)
	20-25 years	0.99 (0.84, 1.16)	1.03 (0.85, 1.26)	0.69 (0.43, 1.11)	0.99 (0.85, 1.17)	1.42 (0.83, 1.43)
	25-29 years	Referent	Referent	Referent	Referent	Referent
	30-34 years	1.01 (0.88, 1.16)	1.00 (0.85, 1.18)	0.96 (0.64, 1.43)	1.00 (0.87, 1.15)	1.11 (0.61, 2.04)
	35-40 years	**1.31 (1.11, 1.54)**	1.15 (0.94, 1.40)	**2.02 (1.34, 3.03)**	**1.29 (1.10, 1.52)**	**1.92 (1.02, 3.64)**
	≥40 years	**1.92 (1.50, 2.45)**	**2.02 (1.52, 2.67)**	1.14 (0.48, 2.72)	**1.90 (1.49, 2.43)**	<5 SBs
Maternal occupation	Professionals	Referent	Referent	Referent	Referent	Referent
	Managers/Admin	1.00 (0.77, 1.31)	1.18 (0.87, 1.60)	0.80 (0.40, 1.61)	1.01 (0.77, 1.31)	<5 SBs
	Paraprofessionals	1.09 (0.83, 1.43)	1.28 (0.94, 1.73)	0.72 (0.32, 1.64)	<5 SBs	<5 SBs
	Tradespersons	1.04 (0.74, 1.48)	1.09 (0.71, 1.66)	1.46 (0.69, 3.10)	<5 SBs	<5 SBs
	Clerks	0.94 (0.74, 1.18)	1.03 (0.79, 1.36)	0.64 (0.31, 1.31)	0.94 (0.74, 1.18)	0.67 (0.26, 1.72)
	Sales and service workers	1.04 (0.84, 1.30)	1.11 (0.86, 1.45)	0.78 (0.42, 1.45)	1.04 (0.84, 1.30)	0.49 (0.19, 1.27)

Factors		Adjusted OR for risk factors of stillbirth*	Adjusted OR for risk factors of stillbirth stratified by region of residence*			
			Major city	Inner Regional	Outer Regional	Remote/Very remote area
	Plant and machine operators	**1.99 (1.16, 3.43)**	**2.76 (1.55, 4.90)**	<5 SBs	<5 SBs	<5 SBs
	Labourers	1.08 (0.78, 1.49)	1.02 (0.67, 1.54)	0.84 (0.35, 2.04)	1.10 (0.79, 1.52)	<5 SBs
	Student	1.28 (0.94, 1.75)	1.28 (0.89, 1.94)	1.83 (0.75, 4.45)	<5 SBs	<5 SBs
	Pensioner	1.55 (0.80, 3.01)	0.94 (0.34, 2.60)	<5 SBs	<5 SBs	<5 SBs
	Home duties	1.21 (0.98, 1.49)	1.26 (0.98, 1.62)	1.10 (0.64, 1.88)	1.21 (0.99, 1.49)	1.13 (0.55, 2.31)
	Unemployed	**1.34 (1.01, 1.76)**	1.32 (0.93, 1.86)	1.14 (0.52, 2.50)	**1.35 (1.02, 1.78)**	1.35 (0.54, 3.39)
Paternal occupation	Professionals	Referent	Referent	Referent	0.75 (0.29, 1.92)	<5 SBs
	Managers/Admin	0.90 (0.72, 1.11)	0.86 (0.66, 1.11)	1.10 (0.60, 2.02)	Referent	Referent
	Paraprofessionals	0.92 (0.68, 1.24)	0.89 (0.63, 1.25)	1.53 (0.69, 3.41)	<5 SBs	<5 SBs
	Tradespersons	0.97 (0.78, 1.19)	0.93 (0.73, 1.18)	0.86 (0.46, 1.64)	0.82 (0.46, 1.48)	**1.69 (1.17, 6.16)**
	Clerks	1.26 (0.90, 1.77)	1.30 (0.90, 1.88)	1.78 (0.65, 4.90)	<5 SBs	<5 SBs
	Sales and service workers	0.95 (0.72, 1.26)	0.95 (0.69, 1.30)	0.59 (0.21, 1.64)	1.30 (0.57, 2.96)	<5 SBs
	Plant and machine operators	0.93 (0.71, 1.23)	0.88 (0.63, 1.23)	1.10 (0.52, 2.30)	0.70 (0.30, 1.61)	<5 SBs
	Labourers	0.96 (0.77, 1.20)	0.91 (0.70, 1.18)	0.81 (0.40, 1.65)	1.11 (0.64, 1.90)	
	Student	1.11 (0.76, 1.63)	1.19 (0.80, 1.77)	<5 SBs	<5 SBs	<5 SBs
	Pensioner	**1.83 (1.12, 2.99)**	**2.01 (1.14, 3.54)**	<5 SBs	<5 SBs	<5 SBs
	Home duties	0.61 (0.23, 1.65)	0.44 (0.11, 1.82)	<5 SBs	<5 SBs	<5 SBs
	Unemployed	**1.33 (1.01, 1.76)**	1.19 (0.85, 1.67)	1.61 (0.73, 3.57)	1.39 (0.71, 2.69)	**4.06 (1.41, 11.73)**
Interpregnancy interval	>6 months	Referent	Referent	Referent	Referent	Referent
	< 6 months	1.05 (0.85, 1.29)	1.18 (0.92, 1.52)	0.82 (0.46, 1.47)	1.05 (0.85, 1.29)	0.70 (0.32, 1.55)

Factors		Adjusted OR for risk factors of stillbirth*	Adjusted OR for risk factors of stillbirth stratified by region of residence*			
			Major city	Inner Regional	Outer Regional	Remote/Very remote area
Country of birth**	Australia	Referent	Referent	Referent	NA	NA
	Europe/USSR	0.90 (0.71, 1.13)	0.92 (0.71, 1.18)	1.10 (0.59, 2.05)	<5 SBs	<5 SBs
	Middle east/Nth Africa	1.17 (0.53, 2.63)	1.29 (0.58, 2.89)	<5 SBs	<5 SBs	<5 SBs
	SE Asia	0.84 (0.64, 1.12)	0.89 (0.66, 1.19)	<5 SBs	<5 SBs	<5 SBs
	NE Asia	0.77 (0.50, 1.18)	0.76 (0.47, 1.20)	<5 SBs	<5 SBs	<5 SBs
	Southern Asia	**1.58 (1.19, 2.10)**	**1.64 (1.21, 2.21)**	<5 SBs	<5 SBs	<5 SBs
	Nth America	0.67 (0.04, 2.11)	0.72, 0.27, 1.93)	<5 SBs	<5 SBs	<5 SBs
	South/Central America	0.29 (0.04, 2.11)	0.32 (0.45, 2.30)	<5 SBs	<5 SBs	<5 SBs
	Africa	0.82 (0.29, 2.27))	0.85 (0.26, 2.74)	<5 SBs	<5 SBs	<5 SBs
	Oceania	0.57 (0.30, 1.07)	0.64 (0.31, 1.28)	<5 SBs	<5 SBs	<5 SBs
Ethnicity	Caucasian	Referent	Referent	Referent	Referent	Referent
	Aboriginal/Torres Strait Islander	**1.50 (1.20, 1.88)**	1.26 (0.90, 1.75)	**1.91 (1.06, 3.46)**	**1.55 (1.25, 1.93)**	**1.90 (1.12, 3.21)**
	Asian	1.12 (0.93, 1.35)	1.17 (0.96, 1.42)	<5 SBs	<5 SBs	<5 SBs
Parity	Nulliparous	1.03 (0.90, 1.17)	1.00 (0.85, 1.17)	1.19 (0.85, 1.69)	1.02 (0.89, 1.16)	1.12 (0.69, 1.82)
	Multiparous	Referent	Referent	Referent	Referent	Referent
Remoteness	Major City	Referent	NA	NA	NA	NA
	Inner regional area	1.01 (0.93, 1.27)	NA	NA	NA	NA
	Outer regional area	**1.31 (1.10, 1.55)**	NA	NA	NA	NA
	Remote/Very remote area	1.11 (0.91, 1.37)	NA	NA	NA	NA
Anaemia	No anaemia	Referent	Referent	Referent	Referent	Referent

Factors		Adjusted OR for risk factors of stillbirth*	Adjusted OR for risk factors of stillbirth stratified by region of residence*			
			Major city	Inner Regional	Outer Regional	Remote/Very remote area
	Anaemia	0.99 (0.82, 1.18)	0.96 (0.78, 1.20)	1.17 (0.70, 1.94)	0.97 (0.81, 1.17)	1.02 (0.55, 1.87)

aOR adjusted for year, adequate ANC visits, marital status, smoking status, parity, remote/rural status, maternal age, previous stillbirth, maternal race, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, APH)

*aOR adjusted for year, adequate ANC visits, marital status, maternal race, smoking status, parity, maternal age, previous stillbirth, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, APH)

** model of adjustment excluding maternal race

The impact on stillbirth odds associated with inadequate antenatal care visits was consistently high across all analyses and areas of residence. Between the cohorts, inadequate care visits demonstrated an increased association in cohort 2 (aOR 4.02 (95% CI 3.19, 5.06)) than in analysis of cohort 1 (aOR 3.93 (95% CI 3.41, 4.52)). Women living in inner regional areas who attended fewer than the recommended number of antenatal visits had a more than five-fold increase in stillbirth odds (aOR 5.56 (95% CI 3.91, 7.92)), and women living remote/very remotely were found to have an almost 5-fold increase in stillbirth odds (4.64 (95% CI 2.98, 7.23)) than women attending the recommended number of antenatal care visits.

Older maternal age (35-40 and ≥40 years) demonstrated independent associations with increased odds of stillbirth. Through multivariable analysis of both cohort 1 (table 7-4) and 2 (table 7-6) (additionally adjusted for BMI), the association of older maternal age remained significant (cohort 1 (maternal age 35-40 years (aOR 1.31 (95% CI 1.11, 1.54)) and ≥40 years (aOR 1.92 (95% CI 1.50, 2.45)), cohort 2 (≥40 years (aOR 2.00 (95% CI 1.40, 2.86)). Analysis stratified by remoteness demonstrated that older maternal age had the greatest association with increased stillbirth odds for women residing in regional and remote areas of SA compared with women aged 25-29 years at time of birth (table 7-4). Women residing in inner regional areas aged 35-40 years had more than double the odds of stillbirth than their 25–29-year-old counterparts (aOR 2.02 (95% CI 1.34, 3.03)), as did women aged ≥ 40 years compared with their 25-29 years old counterparts within stratified subgroups of women residing in major cities (aOR 2.02 (95% CI 1.52, 2.67)) and outer regional areas (aOR 1.90 (95% CI 1.49, 2.43)).

Two maternal occupation codes showed increased associations with stillbirth odds in SA. Maternal plant and machine operators were found to have nearly double the odds of stillbirth compared with professionals in SA (aOR 1.99 (95% CI 1.16, 3.43)), and for women living in major cities, the odds of stillbirth were nearly 3-fold for women working as plant and machine operators compared with professionals (aOR 2.76 (95% CI 1.55, 4.90)). Analysis of maternal unemployment demonstrated increased association with stillbirth odds compared with professional women (aOR 1.34 (95% CI 1.01, 1.79)). Increased association was maintained for women living in outer regional areas (aOR 1.35 (95% 1.02, 1.78)) and remote/very remote areas (aOR 1.35 (95% CI 0.54, 3.39)) compared with major cities. Through analysis of the later cohort 2, student occupation demonstrated non-significantly increased stillbirth odds aOR 1.45 (95% CI 0.97, 2.17) compared with professionals/managers/administration maternal occupations.

Paternal unemployment (aOR 1.33 (95% CI 1.01, 1.76)) and pensioners (aOR 1.83 (95% CI 1.12, 2.99)) compared with professionals showed increased odds of stillbirth. Paternal tradespeople (aOR 1.69 (95% CI 1.17, 6.16)) and paternal unemployment (aOR 4.06 (95% CI 1.41, 11.73)) were independently associated with stillbirth within remote/very remote areas of SA, compared with managers and administrative roles.

Smoking status was shown to marginally increase the odds of stillbirth (aOR 1.13 (95% CI 1.00, 1.28)) compared with non-smoking women in outer regional areas of SA. Women residing in inner regional areas of SA were shown to have a probable increased odds of stillbirth if they reported smoking at any stage during their pregnancy, compared

with non-smokers, (aOR 1.28 (95% CI 0.92, 1.77)). Analysis within cohort 2 demonstrated comparable results (aOR 1.16 (95% CI 0.95, 1.42)).

Analysis of BMI through cohort 2 (table 7-5) demonstrated an increased risk of stillbirth in crude analysis for obesity class 2 (BMI 35-40) compared with a healthy maternal BMI (BMI 20-25) (cOR 1.38 (95% CI 1.04, 1.83)). This association remained increased through multivariable analysis (aOR 1.48 (95% CI 1.08, 2.02)). Due to small sample sizes, BMI groups were consolidated to healthy (BMI <25), overweight (BMI 25-30) and obese (BMI >30). There was an independent association with stillbirth odds for maternal obesity (aOR of 1.33 (95% CI 1.05, 1.68)) compared with women with a healthy BMI in inner regional areas.

Table 7-5 The ILSSA study - findings of multivariable analysis of maternal BMI stratified by ARIA remoteness classification (cohort 2)

Maternal BMI category	Total Births	Stillbirth rate/1000 births	Crude OR (95% CI)	Adjusted OR for risk factors of stillbirth*	Adjusted OR for risk factors of stillbirth stratified by region of residence**			
					Major city†	Inner regional†	Outer regional†	Remote/very remote†
Underweight (<19)	5,421	3.49	0.80 (0.50, 1.27)	0.72 (0.44, 1.19)	0.66 (0.08, 5.17)	Referent	Referent	Referent
Healthy weight (19-24)	67,664	4.37	Referent	Referent	Referent			
Overweight (25-29)	45,594	4.32	0.99 (0.82, 1.19)	1.02 (0.84, 1.24)	1.44 (0.82, 2.54)	0.96 (0.76, 1.20)	1.23 (0.60, 2.52)	1.10 (0.54, 2.26)
Obese class 1 (30-34)	22,518	4.38	1.15 (0.96, 1.38)	1.06 (0.82, 1.36)	1.06 (0.50, 2.23)			
Obese class 2 (35-39)	10,426	6.01	**1.38 (1.04, 1.83)**	**1.48 (1.08, 2.02)**	1.24 (0.49, 3.12)	**1.33 (1.05, 1.68)**	1.39 (0.67, 2.86)	0.69 (0.28, 1.70)
Morbidly Obese (40+)	6,750	5.60	1.28 (0.91, 1.08)	1.29 (0.89, 1.87)	0.99 (0.34, 2.92)			
Missing	42,228	4.83	NA	NA	NA	NA	NA	NA

* aOR adjusted for year of birth, adequate ANC visits, marital status, rural/remote status, maternal race, smoking status, parity, maternal age (<35, 35-39, >40), previous stillbirth, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, APH)

** aOR adjusted for year, adequate ANC visits, marital status, smoking status, parity, maternal age, previous stillbirth, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, APH)

†stratified analysis conducted using populations designated as living within a major city (n=110,075 (407 stillbirths)), Inner regional area (n=19,569 (73 stillbirths)), outer regional area (n=11,363 (51 stillbirths), or remote/very remote area (n=7795 (40 stillbirths)). Due to cohort size, BMI categories were grouped (healthy (BMI <25), overweight (BMI 25-29), obese (BMI >30)).

Table 7-6 The ILSSA study - findings of multivariable analysis (cohort 2)

Variables		**Adjusted OR**
Smoking	Non-smoker	Referent
	Smoker	1.16 (0.95, 1.42)
Insurance type	Private	Referent
	Public	0.82 (0.65, 1.03)
Marital Status	Married	Referent
	Unmarried	1.23 (0.97, 1.55)
Adequate ANC visits	Adequate antenatal care visits	Referent
	Inadequate antenatal care visits	**4.02 (3.19, 5.06)**
Maternal age	12-19 years	1.20 (0.81, 1.78)
	20-24 years	0.98 (0.76, 1.27)
	25-29 years	Referent
	30-34 years	1.07 (0.96, 1.32)
	35-39 years	1.17 (0.90, 1.51)
	≥40 years	**2.00 (1.40, 2.86)**
Maternal occupation	Professionals/Managers/Admin	Referent
	Clerks/Sales people	1.02 (0.81, 1.29)
	Tradespersons/Labourers/Lab & machine operators	1.08 (0.75, 1.56)
	Student	1.45 (0.97, 2.17)
	Unemployed/Pensioner/Home duties	1.19 (0.93, 1.53)
Paternal occupation	Professionals/Managers/Admin	Referent
	Clerks/Salespeople	1.02 (0.73, 1.43)
	Tradespersons/Labourers/Lab & machine operators	1.10 (0.89, 1.36)
	Student	1.13 (0.66, 1.93)
	Unemployed/Pensioner/Home duties	**1.46 (1.04, 2.07)**
Interpregnancy interval	>6 months	Referent
	≤ 6 months	1.21 (0.90, 1.62)
Country of birth*	Australia	Referent
	Europe/USSR	1.14 (0.80, 1.63)
	Middle east/Nth Africa	**1.87 (1.23, 2.83)**
	SE Asia	0.93 (0.62, 1.40)
	NE Asia	0.90 (0.54, 1.50)
	Southern Asia	**1.67 (1.24, 2.24)**
	Nth America	<5 SBs
	South/Central America	<5 SBs
	Africa	**1.96 (1.30, 2.97)**
	Oceania	<5 SBs
Race	Caucasian	Referent
	Aboriginal/Torres Strait Islander	1.17 (0.80, 1.72)
	Asian	**1.43 (1.13, 1.82)**
Parity	Nulliparous	0.80 (0.65, 1.00)
	Multiparous	Referent
Remoteness	Major City	Referent
	Inner regional area	1.08 (0.83, 1.40)

Variables		Adjusted OR
	Outer regional area	1.30 (0.97, 1.75)
	Remote/Very remote area	1.36 (0.96, 1.91)
Anaemia	No anaemia during pregnancy	Referent
	Anaemia during pregnancy	1.17 (0.91, 1.52)

aOR adjusted for year of birth, adequate ANC visits, marital status, maternal BMI, maternal race, smoking status, parity, remote/rural status, maternal age, previous stillbirth, medical conditions (pre-existing diabetes or hypertension, anaemia), plurality, interpregnancy interval, insurance status, obstetric complications (gestational diabetes, gestational hypertension, APH)
*maternal race excluded from model of adjustment

Maternal factors demonstrating strongest independent association with stillbirth odds through complete analysis of cohort 1 were selected for further analysis of population attributable fraction (PAF) (Table 7-7). The population attributable fraction enabled examination of the direct percentage of stillbirths attributed to each risk factor within our population according to the populational prevalence. The strongest impacts on stillbirth rates in SA were shown to be inadequate antenatal care with a PAF of 27.65%, and maternal Aboriginal and/or Torres Strait Islander status (PAF = 24.03%). For maternal Southern Asian country of birth these were PAF 13.30%) and maternal age >35 years (PAF = 6.32%).

Table 7-7 The ILSSA study - results of multivariable analysis for select factors, populations attributable fractions (PAF) and attributable stillbirths*

Variables		aOR (95% CI)	PAF (%)**	Total preventable SB for SA dataset (1998-2016)	Average preventable SB per year in SA
Smoking status	Non-smoker	Referent	..	..	
	Smoker	1.13 (0.99, 1.28)	3.31%	52	3
Adequate ANC visits	Adequate ANC visits	Referent	..	..	
	Inadequate ANC visits	3.93 (3.41, 4.52)	27.65%	437	24
Maternal age	≤35 years	Referent	..	..	
	>35 years	1.40 (1.23, 1.60)	6.32%	100	6
Maternal Occupation	All other occupations	Referent	..	..	
	Plant or machine operators	1.74 (1.04, 2.91)	0.40%	6	0.3
Maternal Aboriginal and/or Torres Strait Islander status	Non-Aboriginal and/or Torres Strait Islander	Referent	..	..	
	Aboriginal and/or Torres Strait Islander	1.49 (1.20, 1.87)	2.40%	38	2
Maternal country of birth	All other countries (excluding only population of interest below)	Referent	..	..	
	Southern Asian countries	1.64 (1.23, 2.18)	1.33%	21	1
	African countries	1.55 (1.21, 1.99)	1.52%	24	1
Remoteness	Major city/Inner regional	Referent	..	..	
	Outer regional/remote/very remote	1.23 (1.08, 1.41)	3.24%	51	3

*SB = stillbirths, Remoteness = remoteness classification of the maternal residential postcode at the time of birth, aOR = adjusted odds ratio, odds adjusted for year of birth, adequate antenatal care visit attendance, marital status, smoking status, parity, remoteness, maternal age, maternal pre-existing medical conditions (diabetes, hypertension, anaemia), insurance status, interpregnancy interval, plurality, gestational diabetes or hypertension, antepartum haemorrhage (adjustments of individual factors exclude the factor of interest within adjustment).

**PAF calculated using methods described by Mansournia et al[556]

Discussion

To our knowledge this is the first analysis of a large Australian cohort stratified by remoteness (including births to Aboriginal and/or Torres Strait Islander women). Results indicate that the factor associated with the strongest odds of stillbirth in SA is an inadequate number of antenatal care visits compared with women who attend the recommended number per the Australian Pregnancy Care guidelines[451]. Through adjustment for known important confounders, the association remained robust, indicating that there is an independent association between antenatal care visits and a four-fold increase in stillbirth odds outside major cities. PAF calculations indicate that if all women attended the recommended number of antenatal care visits, 437 stillbirths could have been prevented over this study period, equating to an average of 24 stillbirths per year. Antenatal care engagement in Australia has been highlighted as a marker of inequity between areas of remoteness and major cities[551, 552]. The inequity, and subsequent poorer engagement in rural and remote areas affects stillbirth odds as well as other perinatal outcomes. Barriers to adequate attendance (such as distance to care, interpreter services availability, cultural appropriateness, and institutional racism and ageism), the failure of state-wide and national policy to appropriately supply accessible and suitable care for Australian families are major underlying factors in increased risk of stillbirth[19, 22-24].

Adequate antenatal care is well established as the best means to ensure a healthy pregnancy, and effective preventative care for poor pregnancy outcomes. The number of antenatal care visits recommended by the Australian Pregnancy Care guidelines is a schedule of ten visits for first pregnancies, and seven visits for subsequent uncomplicated pregnancies[451]. Women who do not have the requisite number of antenatal visits have much high odds of stillbirth within the SA population. Previous research has examined the impact of antenatal care visits and found a U-shaped curve associated with the number of antenatal care visits and stillbirth odds revealing that 14 visits is optimal to minimise risk[276]. Globally, there are large variations in the minimum recommended number of visits; German studies recommend 12 ANC visits[86], whereas USA studies recommend 11[88, 154], and Canada recommends 13 through the antenatal period[87, 557]. These differences indicate a lack of consensus and evidence informing this aspect of pregnancy care guidelines amongst high-income countries. It is evident that Australian guidelines offer the lowest minimum recommendations, and through calculation of PAF and resultant average stillbirths per year, this may be contributing to almost one fifth of stillbirths occurring. Raising the minimum number of recommended antenatal care visits should be considered for the South Australia population.

Remote and rural status has previously been implicated as having an independent association with stillbirth odds for remotely residing women. This was demonstrated through a study of remote areas in Western Australia, yet analysis excluded Aboriginal and/or Torres Strait Islander women[252]. While other studies have examined the impact that regional and remote living has on stillbirth rates in Australia[62, 168], their findings were limited by cohort size, and limited adjustment through multivariable analysis. Graham et al[62] examined the impact of rural and remote status, and results were comparable to our findings that living in regional areas of Australia increases the risk of stillbirth[62]. Our analysis found higher odds of stillbirth within regional areas (outer and inner regional areas), and in women who smoke during pregnancy, who are unmarried

and are older (over 35 years), and Aboriginal and/or Torres Strait Islander women were at increased risk of stillbirth in inner and outer regional areas. Conversely, stillbirth odds for women with a maternal age of 35-40 years compared with 25-29 years did not show an increased association with stillbirth when analysis was restricted to women living in major cities, compared with the state-wide analysis. This trend was replicated for maternal unmarried status compared with married, unemployed women compared with professional women, and Aboriginal and/or Torres Strait Islander women compared with Caucasian women living in major cities. These findings indicate differences in the demographics of women at increased risk of stillbirth by residential remoteness, indicating that preventative care requires tailoring, not only for specific groups, but also to populations living in regional and remote areas.

Research using Australian cohorts examining the association between Aboriginal and/or Torres Strait Islander race and stillbirth odds have reported mixed findings. Some report increased odds of stillbirth[68, 327], and others report that stillbirth odds for Aboriginal and/or Torres Strait Islander women are diminished though multivariable analysis, indicating non-independence of this factor[125, 157]. Results of this research indicate that the risk associated with maternal Aboriginal and/or Torres Strait Islander status contributes to an average of 21 stillbirths per year in SA and is an independent risk factor across all areas of SA. In comparison to Caucasian women, Aboriginal and/or Torres Strait Islander women residing in inner regional and remote/very remote areas experience higher stillbirth odds than their city dwelling counterparts, highlighting that there is a lack of culturally appropriate and easily accessible antenatal care in regional and remote areas of SA for Aboriginal and Torres Strait Islander women. Accessibility to culturally appropriate care is fundamental for improving perinatal outcomes at a local level. Cultural safety training of health care professionals is needed to establish effective communication, care and to improve understanding of trauma informed care where appropriate[558, 559]. Stratification of ethnicity by area of residential remoteness within SA showed heightened inequity of stillbirth odds in remote areas.

Maternal South Asian race has previously been shown to have an independent relationship with increased stillbirth odds in western populations globally[71, 73, 91, 106, 158, 167, 345, 509, 531]. Analysis examining maternal South Asian race differ between stillbirth in South Asian women self-reporting their race[91, 106, 167, 345], compared with research utilising maternal country of birth as a proxy for race[71, 73, 125, 200, 252, 509, 531]. National registries and datasets have described differing methods of classification for maternal race, some using maternally self-reported race, and others reporting maternal country of birth. Although country of birth is a commonly used proxy for race, there is potential for misclassification and maternal race should not be confused with maternal country of birth due to the differences between these factors. Analysis of maternal race distinguished from country of birth allowed the findings of our research to differentiate between the separate factors. Findings of this study demonstrate that South Asian country of birth is associated with stronger odds of stillbirth (compared with Australian country of birth), than self-reported Asian ethnicity (compared with Caucasian). Through analysis of the later cohort 2 (table 7-4), the addition of BMI into multivariable analysis did not alter results. Southern Asian country of birth remained an independent risk factor for stillbirth compared with Australian born women. This highlights that although maternal race demonstrated increased odds of stillbirth compared with Caucasian women, country of

birth should also be considered when assessing risk of stillbirth at an individual level. Further research should seek to stratify self-reported Asian race by country of birth to investigate the independent association that these factors have with stillbirth odds in Australia.

Certain occupations and their associated exposures to chemicals or lifting and rotating shift work have been implicated as contributors to preventable stillbirth rates in high-income countries, including Australia[55-60, 396]. To our knowledge there has been no research to date examining the association between occupational groups within an entire population and stillbirth odds. Strong associations between maternal plant or machine operators and stillbirth odds remained independent throughout multivariable analysis. The increased association was among the highest demonstrated for women residing in major cities and warrants further research into sub-occupational groups/careers to confirm and explain these findings. In South Australia's remote and very remote areas, paternal occupation showed strong independent relationships with stillbirth odds differing to that demonstrated in inner-regional and major city areas of SA. Strongest associations were seen for paternal unemployment and tradespeople in remote and very remote areas. These associations remained significant despite robust analysis adjusting for potential confounders. This is the first research to our knowledge that was able to examine stillbirth odds associated with occupation, and the impact in regional and remote areas of South Australia.

Through previous research of high-income populations, maternal obesity has consistently demonstrated an independent association with increased stillbirth odds[195, 200, 209, 223, 226, 228, 230, 236, 237]. Our findings are similar, demonstrating a maternal BMI between 35 and 39 is associated with increased odds of stillbirth but we were unable to demonstrate increased stillbirth odds when maternal BMI was ≥40. There are two reasons that this may differ to previous findings, firstly, the number of cases for maternal BMI ≥40 is low, rendering the analysis underpowered. Secondly, care pathways for this group of women differ to non-morbidly obese women. In SA women with a BMI ≥40 at their first antenatal appointment are automatically entered into specific antenatal care programs focusing on pregnancy risks and complications association with morbid obesity. Resultant intensive monitoring and care may have reduced the risk of stillbirth within this group of women.

Strengths and limitations

Strengths of this study lay in the comprehensive and detailed measures included for each birth, that are lacked by data collection in other states and territories, as well as internationally. The comprehensiveness of this dataset enabled robust identification of stillbirth risk factors for specific to SA. Inclusion of detailed maternal and parental occupational coding is unique to this dataset, as is maternal race alongside country of birth. A majority of factors included within this dataset are collected routinely for the entire study period without periodic changes in definition, or classification of diseases. Due to the large number of stillbirths included within this study, analysis of smaller factors, such as smaller occupational groups, was possible resulting in meaningful and generalisable results.

Despite many strengths, this research has several limitations. Omission of maternal BMI collection prior to 2007 prevents analysis incorporating BMI across the study period.

Cohort 2 encompasses maternal BMI, but due to a smaller cohort size, comprehensive analysis of all factors across regional and remote areas was not possible. As with all observational studies, this study has the same limitations ubiquitous to research examining routinely collected perinatal data, that may not have been intended solely of research purposes. This results in a need for careful interpretation of the data and definitions encompassed as they relate clinically. Lack of data concerning domestic assault, pollution exposure, consanguinity, paternal BMI, sleep position and drug and alcohol use all leave potential for residual bias due to unmeasured covariates in analysis. Unmeasured confounders may have affected the stratification of result and impacted the findings for births to women residing in remote and very remote areas. Factors such as overall parental health, nutrition and individual proximity and access to care were unable to be incorporated into analysis and cannot be ruled out as confounding stillbirth risk across SA.

The independent association between Aboriginal and/or Torres Strait Islander status and stillbirth odds indicates that there may be complexities at play unable to be quantified using routinely collected perinatal data such as in this study. Through this dataset, we did not have access to measures of stress, severity of chronic diseases, or culturally appropriate care; all factors that form a wholistic measure of a woman's health status and trust in the health care system. National centralisation of data collection regarding access to culturally appropriate care for Aboriginal and/or Torres Strait Islander women and other minority groups may provide further insight. Within ethnic minority groups, research regarding gestational age at birth has provided insight into strategies for earlier frequent monitoring that could prevent stillbirths[73, 197]. Further stratification of gestational age at birth for remote and rural Aboriginal and/or Torres Strait Islander women, as well as Southern Asian born women in major cities, could identify specific periods during gestation that may require additional support and monitoring.

Although multivariable analysis included year of birth, it cannot be presumed that this accounts for the temporal changes of individual risk factor impact over the course of the study period. Further analysis is needed to investigate the temporal trends of risk factor association in SA.

Data timepoint collection affects the exposure measure bias as many risk factors examined are liable to change over the course of the antenatal period. Partner occupation, collected at the time of birth of the baby, does not account for occupation change over the course of the pregnancy. Similarly postcode and maternal occupation collected at birth may have changed over the course of pregnancy. Furthermore, cigarette use may change over pregnancy in quantity and frequency, and our dataset contains no information for smoking status after 20 weeks GA. Our use of maternal first antenatal appointment smoking status, as well as smoking status at 20 weeks GA attempts to capture all smokers within the dataset. It is well established that smoking cessation decreases the odds of stillbirth and we were unable to account for this within analysis. Further misclassification may occur due to occupational coding we were unable to isolate specific jobs but used over-arching occupational groups assigned by the Australia Bureau of Statistics (ABS).

Geographical areas are defined by the size of the population they encompass, and within our dataset, we were provided with SA3 areas for South Australia. The ABS modified ARIA+ classification is commonly assigned to SA2 areas, encompassing smaller

populations. The use of average ARIA+ scores from SA2's encompassed within each SA3 has potential to result in misclassification of remoteness status for some populations encompassed within our assigned categories.

Conclusions

This research presents a robust and comprehensive analysis of a large South Australian cohort spanning almost two decades. While medical advances have seen improvements in antenatal care and better monitoring of medical conditions during pregnancy, effects of social determinants continue to impact stillbirth rates[560]. Despite limitations, our findings highlight gaps in national and state/territory level analysis of stillbirth. By omitting stratification by remoteness, previous research has masked disparity between marginalised groups within regions that are shown to have the highest rates of stillbirth. Although this disparity has been well established, and highlighted as a focus of addressing preventable stillbirth, further research stratified by remoteness is required. It is clear from our findings that the stillbirth odds for Aboriginal and/or Torres Strait Islander women, women aged 35-40 years, and specific parental occupations differ according to remoteness classification of their usual area of residence. Our findings support recommendations that culturally appropriate care should be accessible to all women, and that the recommended number of antenatal care visits needs reviewing to enable Australia to align itself with recommendations of other high-income countries. Developing specific pregnancy care guidelines appropriate to regions of remoteness may assist in addressing inequity in rates of stillbirth, and in turn decrease stillbirth rates.

Implications of findings and future research needed

The findings of this research make a substantial contribution to the evidence base informing pregnancy care in Australia. This further highlights the need for future research to examine characteristics and factors associated with stillbirth, at a local community level. The evidence presented indicates that further research is needed to underpin the required minimum number of antenatal care visits, and that the Australian Pregnancy Care Guidelines[451] should consider recommending a higher number of care visits to fall in line with global standards. This should not be done without considering the implications to current health care systems in place, especially in remote and regional areas. While our research methodology did not enable us to identify barriers to antenatal care engagement, it is clear that effective antenatal care is fundamental and this should be researched further within SA.

Given the differences between stillbirth odds in marginalised groups within regional and remote SA, results of pregnancy outcomes need to be stratified by area of residence. To enhance our findings, larger datasets, encompassing additional variables, are needed to examine the risk of stillbirth by gestational age at birth, for all identified populations at risk. Further research in the form of prospective case-control studies would further enrich this evidence base and enable in-depth analysis of pathways between risk factors and stillbirth odds in SA.

Implications for future policy

Pregnancy care guidelines and protocols within Australia address prevention strategies for risk of stillbirth based on national data. Although this approach is rigorous and evidence based at a national level, areas of ambiguity and difference exist for health care providers in regional and remote areas – overlaid with finite access to resources. Our

findings indicate that poor antenatal care attendance is the largest risk factor for stillbirth in South Australia, worsening in areas of increased remoteness. Robust analysis indicates that there are complexities at play preventing maternal engagement in care, and that poor attendance may reflect access and acceptability of antenatal care programs across all facets of society. Limitations of national policy and guidelines for antenatal care in regional and remote areas results in care that is complex to deliver within limited resource settings, and accessibility is often limited. It is imperative that tailored, accepted and culturally appropriate care policies, especially for minority groups are implemented. The NHMRC Pregnancy Care Guidelines detail specific recommendations care concerning Aboriginal and/or Torres Strait Islander women, reinforcing our findings and recommendations, but this approach needs broadening to regional areas, culturally and linguistically diverse, and occupational groups. This approach has already been implemented for morbidly obese women in SA and is one example of tailored care that may have resulted in stillbirth prevention explaining our findings.

Chapter 8 Overall Conclusions

Summary of all findings

This thesis provides evidence synthesis of stillbirth risk associated with lifestyle, environmental and sociodemographic risk factors across high-income countries. Following a systematic review and analysis of evidence of global research findings, risk of stillbirth was examined within a large cohort study of birth in South Australia (the ILSSA study). The ILSSA study provides detailed knowledge and descriptions of the differences in risk factor prevalence of locally (South Australia) collected data. The combination of findings from the systematic review and the ILSSA study indicates that there is much improvement to be made through focus through preconception and antenatal care, as well as through overarching national health policy within high-income countries, towards reducing stillbirth rates. During preconception, the antenatal period and at national policy level, strategies to modify the identified risk factors such as maternal obesity, lifelong health, antenatal care engagement and ingrained inequality within communities will aid in countries meeting their targets of reducing the numbers of stillbirths.

Through identification and quantifying modifiable antenatal risk factors of stillbirth, the need for risk prevention has been identified and requires addressing through the antenatal period. This research's repeat identification of antenatal care adequacy as a major risk factor adds complexity to enacting preventative strategies and assisting families to decrease stillbirth risk. Antenatal care inadequacy increases the odds of stillbirth four-fold for families within high-income countries and contributes to stillbirth odds at a local level as shown through analysis of the ILSSA study. The global confusion over definitions of adequate antenatal care further add to limitations of findings, as differences in definitions increase heterogeneity between study populations. Results indicate that care should be initiated prior to 20 weeks GA, and that any less than 11 antenatal care visits during pregnancy increases stillbirth odds, thereby indicating that 11 visit should be the minimum number recommended during the antenatal period. Within findings from the ILSSA study analysis, 16.5% of women in cohort 2 attended less than the recommended number of antenatal care visits, and calculation of population attributable fractions indicate that 24 stillbirths per year could be avoided in SA if women attended an adequate number of visits. Preventing stillbirths across high-income countries due to inadequate care lies in the adaption of care and facilitation of engagement including removal of barriers including: culturally inappropriate care, lack of at home provision of care, universal free health care, and lack of appropriate translation services. During pregnancy, alongside inadequate antenatal care. assault, maternal smoking or snuff use, drug and alcohol use, supine sleep position, ≤1 awakening during the night, maternal weight loss, and select parental occupations were identified as contributors of stillbirth risk. Assault during pregnancy is not uncommon. In high-income countries, 22% of women experience family violence[277] during their lives, and a quarter of women report that violence first occurred during pregnancy[278]. Reinforcing findings, studies using national Australian data have revealed that nearly 5% of women report experiencing domestic violence at their first antenatal visit, and this is increased within linguistically diverse populations[447, 561]. Assault during pregnancy remains a challenge due to the stigma associated with domestic violence, as well as complexities for healthcare professionals in building trusting patient relationships to facilitate discussion, in the absence of continuity of care models. Results within this thesis highlight the importance of identification of women

assaulted during pregnancy, as findings reveal a three to eight-fold increased risk of stillbirth. Continuity of care alongside general practitioner (GP) shared care demonstrate a protective effect for stillbirth, reinforcing global consensus that models of maternity care should all involve continuity of care[562]. Findings were limited in being unable to examine all identified risk factors within the ILSSA study, but these results complement previous findings that demonstrate strong associations between physical assault and other composite adverse perinatal outcomes[96, 279] reinforcing that efforts need to be focused on increased antenatal care engagement to identify potential assault prevention during pregnancy.

The preconception period paves the way for a healthy pregnancy, and indeed, completes the continuum of care from childhood to the antenatal period. Despite opportunities to optimise health (maternal body mass index (BMI), monitoring and treatment of diabetes and hypertension disorders, discussions regarding interpregnancy interval, and parental age) prior to pregnancy, preconception care is largely ignored[349, 350, 355]. None of the included studies examined the impact of preconception care programs on stillbirth odds, despite many mentioning the value of this care model for at risk families. Recent research has indicated that 40% of adult women are overweight or obese in the USA[563], and it is well established that BMI usually increases with maternal age[564]. Global increases in maternal obesity as well as maternal age are concerning, as through this work, both were associated with increased stillbirth odds across high-income countries. A maternal BMI ≥35 results in a two-fold increase in odds of stillbirth compared with a BMI of 20-25 at the start of pregnancy. Women whose BMI is ≥40 at the start of pregnancy were shown to experience triple the odds of stillbirth. This association was not replicated through the analysis of the ILSSA study since maternal BMI was only recently introduced to the dataset, and so limitations of sample size affected this analysis. Despite limitations, an almost 50% increase in stillbirth odds was demonstrated for maternal BMI ≥35 in SA. Within SA, almost 30% of births were to women with a maternal age of over 35 years, and analysis confirmed an increase in stillbirth odds associated with maternal age over 35 years. Of women included in cohort 2 of the ILSSA study, 54% were observed to have a BMI above the healthy range, and as shown through review of global studies examining weight change during pregnancy, modification of BMI through weight loss during the antenatal period compounds stillbirth risk. Although the implications for paternal obesity on reproductive health are known[565-567], findings of this work identified a gap in knowledge regarding the associations between paternal obesity and stillbirth odds were not identified, as no studies examined this factor. Pre-existing morbidity (pre-existing hypertension and/or diabetes) is of particular concern during the antenatal period due to the association with poor pregnancy outcomes such as preterm birth, stillbirth and low birth weight[5, 244]. The pathological relationship between increased maternal BMI and age, with hypertension and diabetes results in a multifactorial clinical risk picture at conception that has severe implications for stillbirth risk. Given the sequalae of events following a high-risk pregnancy on stillbirth risk, or in the event of a live birth - long term health implications for mother and baby[5, 238, 564, 568], it is prudent to re-focus efforts within high-income countries to the continuum of care prior to the antenatal period. Such efforts would encourage improved national health alongside decreasing stillbirth rates. Findings of this review show that pre-existing diabetes carries a 2.5-fold increase in stillbirth odds. Through stratification to diabetes sub-diagnosis, type 1 diabetes was shown to drive this association. The lack of association between type 2 diabetes and stillbirth odds is

attributed to preconception, and very early pregnancy care in Canada and Finland. Other factors found to have associations with increased stillbirth odds include unmarried marital status, and sexual orientation – both factors that may indicate issues of societal stigma and taboo, which may affect stillbirth risk. The causes of increased stillbirth odds within these groups is beyond the scope of this thesis, but increased risk, health counselling prior to pregnancy, and the role of stigma should be considered in caring for vulnerable populations of women.

Within high-income countries, migration, refugee and asylum seeking rates have steadily increased, resulting in multi-cultural and linguistically diverse populations accessing maternity and healthcare services[569, 570]. Research of health indicators have attempted to examine maternal country of birth, and maternal ethnicity in tandem[571], but throughout literature, these factors have been used interchangeably through stillbirth risk analysis. Through analysis of maternal country of birth or reported ethnicity, the ILSSA study findings demonstrate differences in the associated stillbirth odds between maternal country of birth and ethnicity. Although South Asian ethnicity demonstrates an almost two-fold increase in stillbirth odds, South Asian maternal country of birth was shown to have lower odds of stillbirth throughout gestation in comparison. Comparable risk association was demonstrated for maternal Indian ethnicity, leading to probable assumptions that women born in India could be driving the analysis of South Asian ethnicity, but subgroup analysis of ethnicity by country of birth would add clarity to this assumption. Further research stratifying ethnic populations by country of birth would serve to further confirm findings. Through analysis of the ILSSA study, South Asian maternal country of birth demonstrated similar risk associations to findings of meta-analysis, but measure of Asian ethnicity was not adequately subgrouped by Asian regions to replicate associations demonstrated through systematic review and meta-analysis. African and Somalian maternal country of birth were both shown to be strongly associated with increased stillbirth odds, both through systematic review, and meta-analysis. Interestingly, although South Asian maternal country of birth stillbirth odds increased as gestation approached term, African maternal country of birth demonstrated a decrease in stillbirth odds as gestation approached term (≥37 weeks gestational age (GA)). Both findings implicate alternative mechanistic pathways driving the stillbirth risk within these vulnerable populations.

Indigenous and First Nations populations within high-income countries have been exposed to intergenerational trauma, cultural assimilation, and genocide throughout modern history[572]. Poorer perinatal and health outcomes have commonly been noted repeatedly in research findings associated with Indigenous and First Nations populations, owing to poor access and non-community controlled/culturally inappropriate healthcare[573-575]. The systematic review contained within this thesis supports the current findings that Indigenous populations are at increased risk of stillbirth. American Indian and Australian Aboriginal and/or Torres Strait Islander populations were identified as at higher odds of stillbirth through meta-analysis. Furthermore, this finding was supported as Aboriginal and/or Torres Strait Islander women were also shown to have higher odds of stillbirth through analysis of the ILSSA study, particularly within regional and remote areas. This is the first analysis of regional and remote community stillbirth risk associated with Aboriginal and/or Torres Strait Islander women within levels of remoteness and demonstrates the benefit of stratification by regional or remoteness in Australian studies.

These findings demonstrate the ongoing inequity and disadvantage affecting First Nations women that have yet to be addressed. Recent findings have implicated better continuity of care and cultural medicine practices ingrained into western models of care to assist in achieving health equality for Inuit families in Canada[506], and recent research indicates similar notions emerging in New Zealand[576, 577]. Interestingly Māori (New Zealand), Cree and Inuit (Canada) First People populations did not demonstrate increased stillbirth risk compared to non-First People populations within New Zealand and Canada within systematic review findings. Through subgroup analysis, findings of the ILSSA study suggest that higher Aboriginal and/or Torres Strait Islander stillbirth odds are contributed to by remoteness, therefore it would be expected that this effect is replicated in Canada due to similar remote and rural access issues. Although not stratified by ethnicity, systematic review findings of increased stillbirth odds associated with remote/rural living in Canada are similar to that of Australia, leading to speculation that the contributors at play are possibly different within each country. Further research should seek to identify the difference in care within New Zealand and Canada offered to Māori, Cree and Inuit populations that are not available to American Indian, Aboriginal and/or Torres Strait Islander women.

Systematic review and meta-analysis findings present the only known analysis of environmental pollution and associated stillbirth odds to date. Although air quality is a focus of many national strategies, the impact of chlorination by-products has been largely overlooked. This is despite associations with poorer perinatal outcomes[477, 492, 496], and as confirmed by findings of this analysis, with increased stillbirth odds. The World Health Organization stance that water chlorination risk should be weighed against waterborne infectious microbes[475], understandably, speaks at a national level to all countries globally, particularly lower- and middle-income countries. Given multiple technologies available to provide clean drinking water, as well as to ensure sustainable water use[578], high-income countries need to lead the way in decreasing pollutant exposure and improving population health through use of advanced technologies.

Limitations

This research is not without limitations, and throughout meta-analysis, heterogeneity varied within and between results. Heterogeneity between studies in some instances was attributed to differences between high-income cohorts, but overall stillbirth definitions described in Chapter 2, and Appendix C differed vastly between studies. This was mitigated where possible through subgroup meta-analysis of studies describing comparable stillbirth definitions but was not consistently possible. Furthermore, almost half of the included studies reviewed were assessed to have high bias and low quality attributed mostly to detection bias owing to methodology of exposure measures used. Due to the nature of stillbirth research, large datasets are required to form meaningful conclusions, and therefore national datasets are frequently used for analysis. The inherent limitations associated with use of national datasets results in findings based upon self-reported data at varying gestational age timepoints alongside medical and hospital admission/discharge coding. Neither are preferred methods of exposure measure, and individualised quantitative measures are the gold standard for measure of risk exposure. Examination of risk through the ILSSA study similarly relied upon routinely collected hospital data that varied in exposure measurement methodology.

A further limitation of registry data use for research in Australia is associated with the timeliness of data availability. Data provided for use in the ILSSA study is now six years old, and results in findings that are also out of date with current practice. In Australia, the timeliness of perinatal data availability is of particular concern, and impetus rests on data registry systems to look to registry systems used in other high-income countries that enable real time, or near real time, data for research use.

Although limitations affecting data quality impact the interpretation of results, this research forms the foundation for guiding focus of care for families within high-income countries to mitigate stillbirth risk. The large systematic review and meta-analysis collates findings of 390 studies and populations spanning 30 high-income countries to quantify the association of 32 risk categories concerning individual families, healthcare systems, and global stillbirth rates.

Conclusion

In conclusion, stillbirth rates are shown to vary across high-income countries, and this is indeed, due to complex risk factor distribution and varying environmental factors as demonstrated through findings of this research. The evolving landscape of risk factors demonstrated highlight the need for ongoing quantification and evaluation of stillbirth risk factors across high-income countries. Through systematic review, and analysis, clear areas for improvement and focus of preventative strategies are shown, including domestic assault, consensus of adequate antenatal care guidance, continuity of antenatal care, improving lifelong family health, and investigation of cultural, social and support needs of identified vulnerable populations.

Implications of findings and future research needed

Findings at a global level highlight the need for further research to investigate the characteristics of adequate antenatal care that define adequacy. A focused examination of each facet of care combined with multiple pregnancy outcome analysis would better inform global policy moving forward.

This research examined maternal country of birth, alongside country of birth for associations with stillbirth odds and provided evidence to establish that these measures provide separate risk patterns. Parental (maternal and paternal) ethnicity examined in tandem with country of birth would provide a two-pronged approach to quantifying the best measure to use during risk assessment of stillbirth odds.

Due to the varying nature of stillbirth definition, future research must quantify birth outcomes by gestational age and period of gestation; very preterm (≥20-24+6 weeks GA) preterm (≥25-36+6 weeks GA), third trimester (≥28 weeks GA) and term (≥37week GA) stillbirth. Although tedious, this will render findings not only comparable at a global level, but also comparable between gestational periods.

Although no included studies examine the impact of pre-conception care on stillbirth odds, most analysis demonstrated increased odds of stillbirth regarding factors that may be addressed through preconception care and support. A review expanding on perinatal outcomes and examining the impact of preconception care may better inform these findings.

Implications of findings for policy

Due to the need for large cohort studies to examine stillbirth outcomes, and the consistent reliance on national registry datasets, there exists a need for government policy to support and encourage the best available measures to be used consistently through general healthcare. Only through robust, high-quality datasets can conclusions be made at a national level, and therefore it is in the national interest to ensure data quality across registry systems.

Findings indicate that there is a lack of consensus between antenatal care policy, care provision, and vast differences between recommendations provided by national guidelines. Important timepoints for risk identification and modification are during the antenatal period, and furthermore, during pregnancy planning. To enable healthcare teams and support programs to effectively engage with women and families to prevent stillbirth, global consensus is needed on the best care practices.

Risk factors identified with the strongest associations with stillbirth odds were domestic abuse, inadequate antenatal care, advanced maternal age, remote and rural living, and additionally, within SA, parental occupations such as maternal plant and machine operators, paternal tradespeople, and parental unemployment. Most of these risk factors rely on government support systems, and although awareness is needed at an individual treatment level, mitigation can only be achieved through policy update to address inequality and disadvantage nationally.

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Appendix A - Stillbirth rates for high-income countries (2019)

2019 stillbirth rates per 1000 births (≥28 weeks GA), and annual reduction in rate from 2000-2019 across high-income countries.

Country	2019 stillbirth rate	Annual rate of reduction in stillbirth rate (over previous 20 years)
Monaco	1.42	2.31
Japan	1.52	2.71
San Marino	1.77	3.22
Iceland	1.90	1.83
Singapore	1.98	2.11
Denmark	2.01	2.34
Finland	2.02	1.44
Andorra	2.08	2.79
Estonia	2.18	4.02
Austria	2.19	1.32
Australia	2.22	1.95
Switzerland	2.22	1.11
Spain	2.24	1.97
Netherlands	2.31	4.23
Poland	2.34	3.19
Italy	2.39	0.86
Norway	2.44	2.14
Sweden	2.45	2.22
Portugal	2.48	2.52
Cyprus	2.52	2.92
Slovenia	2.55	1.80
Czechia	2.65	0.38
New Zealand	2.68	1.60
Germany	2.71	0.43
Lithuania	2.75	2.64
Israel	2.77	2.11
Canada	2.77	0.81
Slovakia	2.79	1.87
Ireland	2.83	2.94
Belgium	2.84	0.93
United States	3.00	0.52
Croatia	3.01	2.85
Malta	3.04	1.28
United Kingdom	3.04	2.00
Chile	3.09	1.57
Greece	3.10	2.03

Latvia	3.24	3.22
Hungary	3.30	1.39
Luxembourg	3.35	0.44
France	4.35	0.74
Brunei Darussalam	4.61	0.52
Uruguay	4.71	2.33
United Arab Emirates	4.93	2.82
Saudi Arabia	5.02	3.23
Qatar	5.40	0.84
Antigua and Barbuda	5.47	2.50
Oman	5.56	1.93
Kuwait	5.83	1.02
Bahrain	5.91	1.93
Barbados	7.40	0.67
Saint Kitts and Nevis	7.45	1.85
Palau	7.71	1.65
Democratic People's Republic of Korea	8.49	2.52
Trinidad and Tobago	9.09	1.41
Seychelles	9.47	-0.29
Bahamas	11.57	0.39
Nauru	13.12	0.69
Average	**3.93**	

Data Source: UNICEF data warehouse, https://data.unicef.org/resources/
High-income country status classified as per world bank data, High-income | Data (worldbank.org)

Appendix B – Systematic review search strategy details

Search strategy

Database searched (bibliographic databases)	Search Terms	Date of Search	Years Searched	Filters/limits	Number of records retrieved	Number of records retrieved (top-up searches)*
PubMed	(Fetal Death[MH:noexp] OR Fetal death*[ALL] OR Foetal death*[ALL] OR fetal wast*[ALL] OR foetal wast*[ALL] OR Fetal mortalit*[ALL] OR Foetal mortalit*[ALL] OR perinatal wast*[ALL] OR perinatal mortalit*[ALL] OR perinatal death*[ALL] OR Prenatal death*[ALL] OR Prenatal mortalit*[ALL] OR Antenatal mortalit*[ALL] OR Antenatal Death*[ALL] OR Perinatal Mortality[MH] OR Perinatal Death[MH] OR Stillbirth[MH] OR Stillb*[ALL] OR fetal Loss*[ALL] OR foetal Loss*[ALL] OR perinatal Loss*[ALL] OR Prenatal loss*[ALL]) AND (cohort studies[mh] OR cohort analys*[tw] OR cohort design*[all] OR cohort evaluation*[tw] OR cohort research[all] OR cohort stud*[tw] OR cohort survey*[tw] OR concurrent stud*[tw] OR concurrent survey*[tw] OR incidence analys*[tw] OR incidence research*[all] OR incidence stud*[tw] OR incidence survey*[tw] OR longitudinal analys*[tw] OR longitudinal design*[all] OR longitudinal evaluation*[tw] OR longitudinal research[all] OR longitudinal studies[tw] OR longitudinal study[tw] OR longitudinal survey*[tw] OR follow up evaluation*[tw] OR followup evaluation*[tw] OR followup stud*[tw] OR follow up stud*[tw] OR followup survey*[tw] OR follow up survey*[tw] OR prospective analys*[tw] OR prospective design*[all] OR prospective evaluation*[tw] OR prospective studies[tw] OR prospective study[tw] OR prospective survey*[tw] OR retrospective analys*[tw] OR retrospective design*[all]	18/01/2018 *29/07/2020	1998-2018 *2018-2020	English language	12260	2817

	OR retrospective evaluation*[tw] OR retrospective research[all] OR retrospective stud*[tw] OR retrospective survey*[tw] OR case-control studies[mh] OR case control analys*[all] OR case control design*[all] OR case control cohort*[all] OR case control evaluation*[all] OR case control stud*[all] OR case control survey*[all] OR case comparison analys*[all] OR case comparison stud*[all] OR case referent analys*[all] OR case referent stud*[all] OR case referent survey*[all] OR case base stud*[all] OR case matched analys*[all] OR case matched stud*[all] OR risk[MH] OR risk[ALL] OR risks[ALL])					
CINAHL	TX ((Fetal or Foetal or Perinatal or prenatal or Antenatal) N7 (death or wast* or Mortalit* or Loss*) OR Stillb*) AND TX ((Cohort OR Concurrent OR Incidence OR longitudinal OR "follow up" OR followup OR prospective OR retrospective OR "case-control" OR "case Control" OR "Case Comparison" OR "Case referent" OR "Case Base" OR "Case Matched") W9 (Stud* OR Survey* OR design OR analys* OR Research) OR risk OR risks)	18/01/2018 *29/07/2020	1998-2018 *2018-2020	English language	10404	2125
Embase	(Fetal near/7 death* OR "Fetus Death"/SYN OR Foetal near/7 death* OR "Fetus mortality"/SYN OR fetal near/7 wast* OR foetal near/5 wast* OR Fetal near/10 mortalit* OR Foetal near/3 mortalit* OR perinatal near/2 wast* OR perinatal NEXT/10 mortalit* OR perinatal NEAR/6 death* OR Prenatal NEAR/6 death* OR Prenatal NEAR/5 mortalit* OR Antenatal NEAR/7 mortalit* OR Antenatal NEAR/4 Death* OR "Perinatal Mortality"/SYN OR Stillb* OR fetal NEXT/5 Loss* OR foetal NEXT/2 Loss* OR perinatal NEAR/5 Loss* OR Prenatal NEAR/4 loss*) AND ((Cohort OR Concurrent OR Incidence OR longitudinal OR follow NEAR/2 up OR followup OR prospective OR retrospective OR case NEXT/2 control OR Case NEXT/2 Comparison OR Case NEXT/1 referent OR Case NEXT/1 Base OR Case NEXT/3 Matched) W9 (Stud* OR Survey* OR design OR analys* OR Research) OR risk OR risks)	18/01/2018 *29/07/2020	1998-2018 *2018-2020	English language	29419	5579

Ovid Medline	**1**	fetal death/ OR stillbirth/	22/01/2018 *29/07/2020	1998-2018 *2018-2020	English language	12273	2572
	2	(fetal adj7 death$).mp.					
	3	(Foetal adj3 death$).mp.					
	4	(fetal adj7 wast$).mp.					
	5	(foetal adj2 wast$).mp.					
	6	(Fetal adj6 mortalit$).mp.					
	7	(Foetal adj3 mortalit$).mp.					
	8	(perinatal adj2 wast$).mp.					
	9	(perinatal asj9 mortalit$).mp.					
	10	(perinatal adj6 death$).mp.					
	11	(Prenatal adj6 death$).mp.					
	12	(Prenatal adj5 mortalit$).mp.					
	13	(Antenatal adj7 mortalit$).mp.					
	14	(Antenatal adj6 Death$).mp.					
	15	(fetal adj5 Loss$).mp.					
	16	(foetal adj3 Loss$).mp.					
	17	(perinatal adj5 Loss$).mp.					
	18	(Prenatal adj4 loss$).mp.					
	19	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18					
	20	(((cohort or concurrent or longitudinal or follow up or followup or prospective or retrospective) adj5 (analys$ or design$ or evaluation$ or research or stud$ or survey)) or (incidence adj1 (analys$ or research or stud$ or survey))).mp.					
	21	(risk or risks).mp.					
	22	20 or 21					
	23	19 and 22					

Cochrane	((mh ^"Fetal Death") OR "F*tal death*" OR "f*tal wast*" OR "F*tal mortalit*" OR "perinatal wast*" OR "perinatal mortalit*" OR "perinatal death*" OR "Prenatal death*" OR "Prenatal mortalit*" OR "Antenatal mortalit*" OR "Antenatal Death*" OR (mh "Perinatal Mortality") OR (mh "Perinatal Death") OR (mh Stillbirth) OR Stillb* OR "f*tal loss*" OR "perinatal Loss*" OR "Prenatal loss*") AND ((mh "cohort studies") OR ("cohort analys*"):ti,ab,au,kw OR "cohort design*" OR ("cohort evaluation*"):ti,ab,au,kw OR "cohort research" OR ("cohort stud*"):ti,ab,au,kw OR ("cohort survey*"):ti,ab,au,kw OR ("concurrent stud*"):ti,ab,au,kw OR ("concurrent survey*"):ti,ab,au,kw OR ("incidence analys*"):ti,ab,au,kw OR "incidence research*" OR ("incidence stud*"):ti,ab,au,kw OR ("incidence survey*"):ti,ab,au,kw OR ("longitudinal analys*"):ti,ab,au,kw OR "longitudinal design*" OR ("longitudinal evaluation*"):ti,ab,au,kw OR "longitudinal research" OR ("longitudinal studies"):ti,ab,au,kw OR ("longitudinal study"):ti,ab,au,kw OR ("longitudinal survey*"):ti,ab,au,kw OR ("follow up evaluation*"):ti,ab,au,kw OR ("followup evaluation*"):ti,ab,au,kw OR ("followup stud*"):ti,ab,au,kw OR ("follow up stud*"):ti,ab,au,kw OR (mh "Follow-Up Studies") OR ("followup survey*"):ti,ab,au,kw OR ("follow up survey*"):ti,ab,au,kw OR ("prospective analys*"):ti,ab,au,kw OR "prospective design*" OR ("prospective evaluation*"):ti,ab,au,kw OR ("prospective studies"):ti,ab,au,kw OR ("prospective study"):ti,ab,au,kw OR ("prospective survey*"):ti,ab,au,kw OR ("retrospective analys*"):ti,ab,au,kw OR "retrospective design*" OR ("retrospective evaluation*"):ti,ab,au,kw OR "retrospective research" OR ("retrospective stud*"):ti,ab,au,kw OR ("retrospective survey*"):ti,ab,au,kw OR (mh "case-control studies") OR "case control analys*" OR "case control design*" OR "case control cohort*" OR "case control evaluation*" OR "case control stud*" OR "case control survey*" OR "case comparison analys*" OR "case comparison stud*" OR "case referent analys*" OR	22/01/2018 *29/07/2020	1998-2018 *2018-2020	English language	1428	382

	“case referent stud*” OR “case referent survey*” OR “case base stud*” OR “case matched analys*” OR “case matched stud*” OR (mh risk) OR risk OR risks)

*Top-up searches for review conducted on 29/July/2020

Appendix C – Systematic review - Included study characteristics

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Aagaard-tillery 2006[98]	USA 1992-2002	Case-control study	4306	1586	≥20 wks GA	≥400 grams	Terminations, congenital anomalies.	Chronic hypertension	Y	Y	N	N	N	Y	Anaemia, acute or chronic lung disease, herpes virus, chronic or essential hypertension, gestational hypertension, cervical insufficiency, hydramnios, eclampsia, preterm premature rupture of membranes [PPROM], need for tocolysis, thick meconium, placental abruption, placenta previa, breech/malpresentation, cord prolapse, alcohol, use, SES
Adams 2018[528]	Australia 1998-2013	Retrospective cohort study	60418	852	≥20 wks GA	≥400 grams	Intrapartum hospital transfers and births with missing data	Public/ private hospital care	N	N	N	N	N	N	ART use, congenital abnormalities, method of birth, GA at birth
Ahlenius 1999[99]	Sweden 1984-1991	Retrospective cohort study	281471	845	≥28 wks GA	Not reported	Multiple births	Smoking status, maternal age, Parity	Y	Y	N	N	Y	N	None
Ahmad 2012[579]	Norway 1967-2006	Retrospective cohort study	1051654	11414	≥20 wks GA	Not reported	Multiple births, pregnancies missing GA, <20 or ≥43 weeks GA	Chronic hypertension	Y	N	N	N	N	N	None

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Akobirshoev 2019[507]	USA 2004-2011	Retrospective cohort study	2110	Not reported	None provided	Not reported	Women without IDD of other races (besides White, Black, and Hispanic)	Maternal ethnicity	Y	N	N	NA	N	Y	Type of health insurance, median household income for parent's zip code, co-morbidities, urban vs rural, teaching status of the hospital, bed size of the hospital, region of the hospital.
Alemu 2020[385]	USA 2000-2014	Retrospective cohort study	1937455	Not reported	None provided	Not reported	None	Drug use	Y	Y	Y	N	N	Y	Household income, rural/urban status, alcohol use, chronic renal failure, diabetes mellitus, pre-existing hypertension.
Alio 2012[298]	USA 1989-2005	Retrospective cohort study	755334	2617	≥20 wks GA	Not reported	Multiple births, births less than 20 weeks or over 44 weeks, cases missing information	Maternal age, paternal age	y	Y	N	Y	N	Y	Education, marital status, year of birth, prenatal care, alcohol use, preeclampsia, eclampsia, hypertension, placental abruption, placental previa or anaemia
Aliyu 2005[299]	USA 1989-2000	Retrospective cohort study	27069385	81386	≥20 wks GA	Not reported	Multiple births, birth <20 weeks GA, births missing maternal age, paternal age, birth weight and GA.	Parity	Y	Y	N	Y	NA	Y	Maternal education, year of birth, marital status, adequacy of prenatal care, maternal diabetes, chronic and pregnancy-associated hypertension, eclampsia, cardiac disease, placental abruption, and placenta previa
Aliyu 2007[428]	USA 1978-1997	Retrospective cohort study	1436725	8310	≥20 wks GA	Not reported	Nulliparous women, multiple births	Smoking	Y	NA	N	Y	Y	N	Educational level, marital status, adequacy of prenatal care, fetal gender

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Aliyu 2008[370]	USA 1989-1997	Retrospective cohort study	655979	3508	≥20 wks GA	Not reported	Multiple births, Births < 20 weeks or >44 weeks GA. Congenital anomalies.	Alcohol consumption	Y	Y	N	Y	Y	N	Maternal education, adequacy of prenatal care, fetal gender and year of birth
Aliyu 2010[100]	USA 1978-1997	Retrospective cohort study	205887	2830	≥20 wks GA (antepartum)	Not reported	Birth < 20 weeks GA.	Maternal age combined with smoking status	Y	NA	Y	Y	N	N	Adequacy of prenatal care, fetal gender, and year of birth
Aliyu 2011[425]	USA 1989-2005	Retrospective cohort study	1224133	5821	≥20 wks GA	Not reported	Congenital anomalies, births without GA, birthweight or time of fetal demise indicated.	Smoking status	Y	NA	N	Y	Y	N	Maternal education, marital status, adequacy of prenatal care, gender of infant and year of birth
Allen 2004[300]	Canada 1998-2000	Retrospective cohort study	135466	534	≥20 wks GA	≥500 grams	Higher order multiples, major anomalies	Chronic hypertension	Y	Y	Y	N	N	Y	Diabetes, anaemia, maternal autoantibodies, plurality.
Allen 2005[508]	USA 1999-2000	Retrospective cohort study	100670	944	≥20 wks GA	Not reported	Multiple pregnancies	Maternal race	Y	N	N	NA	N	N	Gestational age, prenatal care initiation
Allen 2018[360]	USA 1997-2006	Retrospective cohort study	38324	Not reported	≥24 wks GA to 41+6 wks GA	Not reported	Women with Type I diabetes or GDM, multiple pregnancy	Prenatal care initiation	Y	N	N	Y	N	Y	Maternal educational level, insurance type, chronic hypertension
Allen 2020[101]	UK 1995-2013	Retrospective cohort study	197792	844	≥24 wks GA	Not reported	Births outside Wales	Maternal age (with T1DM)	NA	Y	N	N	Y	N	Townsend deprivation score, delivery by c-section, baby gender, GA at birth and breastfeeding at 8 weeks.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Amark 2018[231]	Sweden 2006-2015	Retrospective cohort study	145319	158	≥28 wks GA	Not reported	Births with no matching identifiers between the databases, abortions, miscarriages, twins, missing covariate data, fetal anomalies, births prior to 28 weeks GA, pre-gestational diabetes.	Maternal BMI, Smoking status, country of birth	Y	Y	Y	Y	Y	Y	Level of PAPP-A, maternal annual income, educational status, drug abuse, previous SGA, previous pre-eclampsia, previous SB. Antiphospholipid syndrome, diagnosis of SLE, pregnancy induced hypertension, essential hypertension, GDM.
Ananth 1995[47]	USA 1988-1991	Retrospective cohort study	87655	3107	≥20 wks GA	Not reported	Non-residents of north Carolina, multiple births, births with missing or incomplete hypertension data, birth with missing data on gestation.	Chronic hypertension	Y	Y	N	Y	Y	Y	Placental abruption, education, fetal sex.
Andersen 2004[301]	Denmark 1997-1999	Retrospective cohort study	23821	146	≥20 wks GA	Not reported	Pregnancies where the father could not be identified	Paternal age	Y	Y	N	N	Y	N	Number of previous abortions, alcohol and coffee consumption, paternal smoking, parental occupational status
Andersen 2012[367, 580]	Denmark 1996-2003	Retrospective cohort study	91843	444	≥22 wks GA	Not reported	Missing exposure, GA or variable data	Alcohol consumption	Y	Y	N	N	Y	N	Change in weekly alcohol consumption since pregnant, coffee consumption during pregnancy.
Angley 2018[373, 581]	USA 2006-2008	Case-control study	1767	538	20 wks GA (18wks GA for stillbirths where GA was not	Not reported	Multiple births excluded	WIC enrolment, maternal ethnicity	Y	Y	Y	NA	N	Y	Insurance status, GA at birth, pregnancy history, pre-existing diabetes, trimester of entry into prenatal care, chart-documented hospitalizations during pregnancy, marital status,

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
					accurately dated)										receipt of wages (any household member) education, lifetime illicit drug use.
Anthony 2009[582]	Belgium, Estonia, Finland, Germany, Ireland, Latvia, Lithuania, Malta, Netherlands, Poland, Sweden, UK (Scotland), UK (Wales) 2000	Cross-sectional study	1532817	4.7/1000 births	≥24 wks GA (with exceptions: Latvia ≥22wks GA, Germany birthweight ≥500g, Sweden ≥28wks GA)	Not reported	All births <24 weeks GA at birth	Maternal age, parity	Y	N	N	N	N	N	Multiple birth, mode of conception, first trimester visit and antenatal care provider
Arnold 2012[102]	Australia 1998-2008	Retrospective cohort study	62351	73	≥37 wks GA	Not reported	Multiple pregnancy, congenital anomalies, births missing maternal age, or any of the study variables, preterm births	Maternal age, smoking status, BMI, previous caesarean	Y	Y	Y	N	N	Y	Antepartum haemorrhage, prior birth by caesarean section (CS) and SGA
Aschengrau 2018[484]	USA 1968-1995	Case-control study	1079	296	≥20 wks GA	≥350 grams	Multiple births and for cases cause of death not listed as "placental abruption" and/or "placental insufficiency"	Pollution - drinking water	N	N	N	N	N	N	State of birth, birth year, paternal education level, receipt of prenatal care during the first trimester.
Astolfi 2005[103]	Italy 1990-1996	Retrospective cohort study	3616622	15872	≥26 wks GA	Not reported	Babies anomalously large for GA	Maternal age, paternal age	Y	N	N	N	Y	N	Educational level.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Auger 2012[259]	Canada 1981-2006	Retrospective cohort study	2152080	8946	None provided	≥500 grams	Terminations, multiple births	Maternal education	Y	N	N	Y	Y	N	Marital status
Auger 2013[65]	Canada 1981-2009	Retrospective cohort study	2385775	8491	≥24 wks GA	Not reported	Voluntary terminations	Maternal ethnicity	Y	N	N	NA	Y	N	Education level, marital status and period of data collection
Auger 2014[66]	Canada 1981-2010	Retrospective cohort study	2276316	9037	None provided	≥500 grams	Terminations, births with missing data	Maternal ethnicity)	Y	N	N	N	Y	N	Education level, marital status, period of birth
Auger 2020[104]	Canada 1981-2015	Retrospective cohort study	2992901	13452	None provided	≥500 grams	None	Maternal ethnicity, paternal ethnicity, maternal age, parity, maternal education.	N	N	N	N	N	N	Maternal mother tongue.
Baba 2014[423]	Sweden 1999-2010	Retrospective cohort study	857650	2322	≥28 wks GA	Not reported	Births < 28 weeks GA, pregnancies missing maternal age, smoking habits, women who smoked and used snuff.	Maternal smoking and snuff use	Y	N	Y	N	Y	N	Maternal education
Balayla 2011[40]	USA, Hawaii and Alaska 1995-2004	Retrospective cohort study	37504381	130353	≥24 wks GA	Not reported	Any birth prior to 24 weeks GA, congenital anomalies, births with unknown marital status, birth outside of the USA or in Puerto Rico, Guam, and the virgin islands	Age, ethnicity, education, marital status.	Y	N	N	Y	Y	N	Plurality, maternal education, prenatal care

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Balayla 2011 (2)[105]	USA 1995-2004	Retrospective cohort study	37461715	130353	≥24 wks GA	Not reported	Births before 24 weeks, congenital anomalies, unknown marital status, births outside study area.	Maternal ethnicity, marital status, education, Alcohol consumption, smoking, maternal age.	Y	Y	N	N	Y	Y	Alcohol intake, plurality, prenatal care, marital status, maternal education, and maternal medical conditions (unspecified)
Balchin 2007[106]	UK 1988-2000	Prospective cohort study	197016	Not reported	≥24 wks GA	≥500 grams	Preterm births, other racial groups, missing GA	Ethnicity, BMI, maternal age	Y	N	Y	Y	N	Y	Placental abruption, meconium stained liquor, birthweight, birthweight centile, maternal fever, congenital anomaly.
Barona-Vilar 2014[530]	Spain 2005-2008	Retrospective cohort study	203805	928	≥22 wks GA	Not reported	None	Maternal country of origin	Y	N	N	N	N	N	None
Bartsch 2015[42]	Canada 2002-2011	Retrospective cohort study	1167470	1373	≥20 wks GA	Not reported	Births without country of origin for both parents	Country of origin	Y	N	N	NA	Y	N	Infant gender, marital status, residential income quintile
Bateman 2006[107]	USA 1995-2002	Retrospective cohort study	5874203	Not reported	None provided	Not reported	Missing data	Maternal age, maternal ethnicity	Y	Y	N	N	N	Y	Maternal Hypertension, maternal Diabetes, Antepartum Maternal haemorrhage, fetal abnormality, multiple gestation, chronic renal disease, systemic lupus erythematous, illicit drug or alcohol use/abuse, infection of the amniotic cavity, isoimmunisation, placenta previa, umbilical cord

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
															complications, poor fetal growth.
Baum 2015[271]	Finland 2009	Retrospective cohort study	43604	103	≥22 wks GA	Not reported	Pregnancies conceived prior to Feb 2009	H1N1 vaccination	Y	Y	Y	N	Y	Y	History of pregnancy loss, SES, marital status, urbanisation, hospital admissions, drug use in the last 6 months and pandemic influenza.
Bay 2019[302]	Denmark 2003-2013	Retrospective cohort study	425732	572	≥22 wks GA	Not reported	All preterm births, pregnancies to women > 40 years, women with BMI of 35 or more and women with pre-existing or gestational hypertension, pre-eclampsia, eclampsia or GDM, intrahepatic cholestasis or immunisation. All induced births unless the induction was due to antenatal diagnosis of stillbirth	Mode of conception	Y	Y	N	N	Y	N	Child sex, year pf birth
Bech 2005[436]	Denmark 1996-2002	Retrospective cohort study	86282	1102	≥28 wks GA	Not reported	Hydatidiform mole	Coffee consumption	Y	Y	Y	N	Y	N	Alcohol consumption and socio-occupational status

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Berman 2020[531]	Australia 2004-2015	Retrospective cohort study	944457	3221	≥24 wks GA	≥400 grams	Multiple births, homebirths, births to mothers born outside of the country of birth groups, or resident in states other than NSW were excluded. Mothers who were born in Australia and had ever identified as Aboriginal or Torres Strait Islander in the birth data were also excluded	Maternal ethnicity	Y	Y	N	NA	Y	Y	Maternal region of birth, chronic conditions, year of birth, chronic hypertension, antepartum haemorrhage, private hospital/patient, SES, pre-existing diabetes, previous stillbirth, antenatal visit in first trimester.
Best 2019[340]	UK 2014-2015	Retrospective cohort study	1476672	5651	≥24 wks GA	Not reported	Births with inadequate information to allocate deprivation index. Multiple births. Terminations of pregnancy. Northern Ireland births.	Maternal ethnicity and SES	N	N	N	Y	N	N	SES and infant gender
Beyerlein 2010[108]	Germany 1987-2007	Retrospective cohort study	2292053	8280	None provided	Not reported	None	Ethnicity, smoking status, maternal age, maternal BMI, Maternal hypertension, prenatal care utilisation,	Y	Y	Y	Y	N	Y	Hypertension, multiple pregnancy.
Beyerlein 2020[342]	Germany 2009-2016	Retrospective cohort study	827105	2473	None provided	≥500 grams	None mentioned	SES/deprivation	Y	Y	Y	Y	Y	Y	Offspring's sex, multiple birth, diabetes during pregnancy, excessive gestational weight gain, single mother status, substandard use of antenatal

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
															care, living in a city (>100,000 inhabitants) and year of birth
Bilsteen 2018[53]	Denmark 2000-2009	Retrospective cohort study	649905	3076	≥22 wks GA	Not reported	Pregnancies with errors in the mothers and fathers or childrens cpr-number. Births <22 weeks GA. Induced abortions. Births with implausible relations between birthweight and GA Births lacking information on maternal country of origin Births with implausible values of maternal birth year.	Maternal education level	Y	N	N	Y	N	N	Country of origin and year of birth
Bjornholt 2016[418]	Denmark 1997-2010	Retrospective cohort study	844251	3023	≥28 wks GA (prior to 1/4/04) ≥22 wks GA (after 1/4/04)	Not reported	Multiple births	Maternal smoking	Y	N	N	N	N	N	Year of birth, marital status
Borrell 2003[109]	Spain 1994-1997	Case-control study	1555	287	≥22 wks GA	≥500 grams	Birth defects	Maternal age, maternal education level	Y	N	N	N	Y	N	Social class, fetal gender, hospital of birth, gravity, mothers employment
Brisendine 2017[110]	USA 2007-2014	Retrospective	21526830	85404	≥20 wks GA	≥500 grams	Multiple births	Maternal age	Y	N	N	N	Y	Y	Hypertensive disorders, diabetes

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study													
Brown 2007[532]	USA 1994-2004	Retrospective cohort study	10755	93	None provided	Not reported	Non-Medicaid patients, women with missing medical data, women with >1 birth in a calendar year, women <11	Maternal ethnicity, maternal age, substance abuse	Y	N	N	Y	N	Y	Location of residence, medical co-morbidity, substance abuse, psychological abnormality, length of stay in hospital and total hospital charges
Brown 2012[111]	USA 1994-2006	Retrospective cohort study	1419767	12114	≥20 wks GA	Not reported	Hispanic black women	Maternal age, household income, marital status, segregation by ethnicity,	Y	N	N	Y	N	N	Marital status, year of event, country level covariates (residential segregation, % of adults over 25 with a high school degree)
Browne 2019[191]	USA 2006-2014	Retrospective cohort study	3097123	5997	24+0 to 41+6 wks GA	Not reported	Multifetal gestations, pregnancies outside of the gestational age range, and those complicated by severe fetal anomalies. Women with GDM, maternal weight less than 70 pounds, chronic hypertension, gestational hypertension. Births with missing BMI data	Maternal BMI, diabetes	Y	Y	NA	Y	N	N	None
Butler 2019[487]	USA 1968-1995	Case-control study	1079 (783 controls)	296	Cases - ≥20 wks GA Controls - none	≥350 grams	Duplicate records, births with missing residential information. Stillbirths related to maternal fall or vehicular accident were not included.	Air pollution	N	N	N	N	N	N	Year of birth, maternal residence state at birth, maternal educational level, and receipt of prenatal care in the first trimester.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Canterino 2004[112]	USA 1995-2000	Retrospective cohort study	21610873	58580	≥24 wks GA	≥500 grams	Congenital anomalies, missing GA or birthweight, missing maternal age. Maternal age <15 or >=50	Maternal age, chronic hypertension	Y	Y	N	Y	N	Y	Birth year, gravity, maternal race, marital status, prenatal care, maternal education, smoking, and placental abruption.
Carlsen 2014[261]	Norway 1999-2004	Retrospective cohort study	297663	369	≥23 wks GA	Not reported	Women whose parents were not born in Norway, pregnancies missing GA information, missing education information and GA >43 weeks.	Education level							Maternal age, offspring sex, multiple births and year of birth
Carmichael 2015[44]	USA 2007-2010	Retrospective cohort study	1125246	4012	≥20 wks GA	Not reported	Births with unknown GA, congenital anomalies, incalculable BMI, women with BMI <18.5, women who were not white, black or Hispanic. Women with diabetes or hypertension (any).	Maternal BMI	Y	N	N	N	N	N	Maternal education level, height
Carmichael 2019[192]	USA 2007-2011	Retrospective cohort study	2487468	4610	20-25 wks GA (peri viable stillbirths)	Not reported	Missing race - ethnicity, infants who were non-singletons, infants with gestational age<20 or>42 weeks, infants with implausible birthweight for gestational age based on previously published criteria.	Maternal ethnicity, maternal education, health care type, maternal BMI, smoking status, pre-gestational hypertension/diabetes, parity, interpregnancy	Y	Y	Y	Y	Y	Y	Race/ethnicity, maternal education, payer (insurance status), parity, IPI, pre-pregnancy diabetes, prior preterm birth, prior stillbirth, BMI, pre-pregnancy hypertension, smoking status, maternal age, maternal height

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
								interval, country of birth							
Cedergren 2004[193]	Sweden 1992-2001	Retrospective cohort study	610969	1923	≥28 wks GA	Not reported	Women with insulin dependant diabetes	Maternal BMI	Y	Y	NA	N	Y	N	Year of birth
Chughtai 2017[583]	Australia 2007-2009	Retrospective cohort study	407368	3342	≥20 wks GA	≥400 grams	None	ART use	Y	Y	Y	Y	Y	N	Insurance status
Chang 2011[437]	USA 1989-2005	Retrospective cohort study	857435	65	36-44 wks GA	Not reported	Multiple births	Place of birth	Y	Y	Y	Y	Y	Y	Gestational age, Medicaid use, diabetes, hemoglobinopathy, chronic hypertension, preeclampsia/eclampsia, renal disease
Chen 1998[253]	Canada 1990-1991	Retrospective cohort study	192150	859	None provided	≥500 grams	None	Maternal education	Y	N	N	N	Y	N	Marital status, infants sex and birthweight
Chen 2015[538]	Canada 1996-2010	Retrospective cohort study	254410	10321	≥20 wks GA	≥500 grams	Multiple births	Maternal ethnicity	Y	N	N	N	Y	N	Marital status, educational and rural vs. Urban residence

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Choi 2019[509]	Australia 2004-2013	Retrospective cohort study	2337023	Not reported	≥20 to 40 wks GA	≥400 grams	Births with missing birthweight, infant gender, or mothers country of birth. Births with outlier birthweights, maternal country of birth listed as 'other'. Multiple births.	Maternal ethnicity	Y	N	N	NA	Y	Y	Maternal age (<24 years, 25-34 years, 35-44 years, and ≥ 45 years), parity (0, 1, 2, and ≥3), remoteness of mother's dwelling (categorised into major cities, inner regional, outer regional, remote, and very remote), socio-economic disadvantage index (categorised into quintiles, ranging from 1 [most disadvantaged] to 5 [least disadvantaged]), pre-existing diabetes status (yes or no), pre-existing hypertension status (yes or no), infant sex (male or female), and year of birth.
Cnattingius 1998[194]	Sweden 1992-1993	Prospective cohort study	167750	466	≥28 wks GA	Not reported	Multiple births, births missing BMI or to women not born outside the study area	Maternal BMI	Y	Y	N	N	Y	N	Education, height and cohabitation
Cnattingius 2002[195]	Sweden 1992-1997	Retrospective cohort study	453801	1318	≥28 wks GA	Not reported	Multiple births	Maternal BMI, Maternal smoking status	Y	Y	Y	Y	Y	N	Cohabitation with infants father, maternal education, maternal height
Cnattingius 2016[232]	Sweden 1992-2012	Retrospective cohort study	456711	1082	≥28 wks GA	Not reported	Multiple births	BMI change between pregnancies	Y	Y	Y	Y	N	N	BMI during first pregnancy, maternal height, age at second childbirth, education, interpregnancy interval, and year of second childbirth.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Cornman-homonoff 2012[366, 584]	Chile 1995-2000	Case-control study	202	3	≥20 wks GA	Not reported	None	Alcohol consumption	Y	N	N	N	N	N	Maternal education, and years of alcohol consumption prior to pregnancy.
Corsi 2019[388]	Canada 2012-2017	Retrospective cohort study	98512	352	≥20 wks GA	Not reported	Women who were missing cannabis exposure information. Births with missing covariate data. Multiple births	Any cannabis use during pregnancy	N	N	N	N	N	N	Infant sex, age, parity, area-level income quintile, pre-pregnancy BMI, Gestational weight gain, self reported substance use during current pregnancy (tobacco smoking, alcohol use, opioid use, SSRI use, other drug use), mental health conditions, antenatal care (type of provider), Year of birth
Crane 2011[585]	Canada 2001-2009	Retrospective cohort study	14650	49	≥20 wks GA	Not reported	Multiple births, women missing environmental tobacco exposure status, women who didn't report smoking status	Environmental tobacco smoke	Y	NA	Y	N	Y	N	Partnered status, work status, alcohol of illicit drug use, and GA.
Crane 2013[196]	Canada 2002-2011	Retrospective cohort study	5788	12	None provided	Not reported	Births missing maternal BMI data	Maternal BMI	Y	Y	NA	N	Y	N	Partnered status, and gestational age
Cruz 2011[304]	USA 2002-2008	Retrospective cohort study	206969	27	≥23 wks GA	Not reported	None	Chronic hypertension	Y	N	Y	Y	Y	Y	Gestational age, insurance status, order of pregnancy, substance use, gestational diabetes, pre-gestational diabetes, renal disease, heart disease, thromboembolic history, intrauterine growth

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
															restriction in current pregnancy
Cupul-Uicab 2011[424]	Norway 1999-2008	Retrospective cohort study	76357	268	≥20 wks GA	Not reported	Multiple pregnancies, pregnancies with missing data for GA, smoking status and BMI.	Maternal smoking	Y	NA	Y	N	N	N	None
Davies-tuck 2016[197]	Australia 2009-2013	Retrospective cohort study	41041	141	≥24 wks GA	Not reported	Missing data, congenital abnormalities	Maternal BMI	Y	Y	NA	N	Y	N	Previous caesarean, account class, baby gender, gestation at birth
Davies-Tuck 2017[73]	Australia 2000-2011	Retrospective cohort study	685869	2299	≥24 wks GA	Not reported	Indigenous mothers	Maternal country of birth	Y	N	N	N	Y	Y	Socioeconomic status, 1st trimester ultrasound, pre-existing hypertension, gestational hypertension, APH, detection of SGA, previous stillbirth, GDM and PE/HELLP.
de Graaff 2017[67]	Australia 2002-2012	Retrospective cohort study	390	130	≥20 wks GA	≥400 grams	Stillbirths due to chromosomal anomalies or terminations.	Maternal BMI, Maternal ethnicity, mode of conception, social issues	Y	N	Y	Y	N	Y	Pre-gestational DM, DVT/PE, method of conception, gestation at birth, birth weight.
de Jonge 2009[113]	Netherlands 2000-2006	Retrospective cohort study	529688	174	37 - 42 wks GA	Not reported	Women in obstetrician led care, pregnancies that were not low risk, PROM, non-cephalic position, IUFD before the onset of labour, congenital anomalies.	Socioeconomic status, maternal age, parity,	Y	N	N	Y	Y	N	Gestational age, planned place of birth,

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
de Jonge 2015[586]	Netherlands 2000-2009	Retrospective cohort study	743,070	330	37-42 wks GA	Not reported	Women eligible for home birth, with known place of birth. Antepartum fetal deaths, prolonged rupture of membranes, congenital anomalies, unknown place of birth	Place of birth (intended)	Y	N	N	Y	N	N	Gestational age, SES.
de Vienne 2009[114]	France 1994-2001	Retrospective cohort study	8514	109	≥22 wks	Not reported	None	Maternal age	Y	Y	Y	Y	N	N	Marital status, education level, history of previous miscarriage or abortion, prenatal care
DeFranco 2015[333]	USA 2005-2010	Retrospective cohort study	351,036	1,848	≥20 wks GA	≥350 grams	Multiple births, major congenital anomalies, induced terminations.	Pollution, maternal age, maternal ethnicity, education level, prenatal care initiation, tobacco use	Y	Y	N	Y	N	N	Maternal education level, prenatal care initiation, season of conception, pollution.
Delbaere 2007[115]	Belgium 2002-2003	Retrospective cohort study	26891	117	None provided	≥500 grams	None	Maternal age	Y	N	N	N	N	Y	Hypertensive disorders in pregnancy, diabetes in pregnancy, mode of conception, level of education
Delbaere 2008[116]	Belgium 2001-2004	Retrospective cohort study	2312 (twins)	25	None provided	Not reported	Multiparity	Maternal age	Y	N	N	N	N	Y	Mode of conception, hypertension, maternal education, zygosity and chronicity
Dhalwani 2019[417]	UK 2000-2013	Retrospective cohort study	220630	805	≥28 wks GA	Not reported	Women who were using NRT as well as smoking	Smoking and NRT use.	Y	N	Y	N	N	Y	Diabetes, SES.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Dickinson 2002[249]	UK 1966 to 1992	Retrospective cohort study	280757	Not reported	≥28 wks GA	Not reported	Multiple births, Births where the father recorded on the birth registration but social class was unknown.	Rural/remote living, SES	Y	N	N	N	N	N	Birth order, year of birth and deprivation by social class
Dodds 1999[477]	Canada 1988-1995	Retrospective cohort study	50755	197	None provided	≥500 grams	Women who reported using a private well as their dominant water source, or where water source was unknown.	Water pollution	N	Y	N	N	N	N	None
Dodds 2004[587]	Canada 1999-2001	Case-control study	510	112	None provided	≥500 grams	None	Pollution	Y	N	N	N	N	N	Province of residence, household income
Dodds 2006[305]	Canada 1999-2001	Retrospective cohort study	494	105	None provided	≥500 grams	Terminations for fetal anomalies and multiple births	Maternal age, family income, smoking, Maternal occupations, mode of conception,	Y	Y	N	N	N	Y	Fertility treatment, family income, previous pregnancy loss, antiemetic use during 1st trimester, acetaminophen exposure during 2nd trimester, antibiotic exposure during 2nd trimester, occupation.
Donegan 2014[306]	UK 2010-2013	Retrospective cohort study	24708	54	≥24 wks GA	Not reported	None	Vaccination - pertussis	Y	N	N	N	N	N	Gestational age at birth
Dongarwar 2020[118]	USA 2003-2017	Retrospective cohort study	57273305	302522	20-42 wks GA	Not reported	Records with missing information on exposure, outcome, and the covariates were excluded.	Maternal age, maternal ethnicity, chronic hypertension, gestational weight gain.	Y	N	N	Y	N	Y	Sex of fetus, plurality, hypertension, eclampsia, diabetes, chronic and gestational hypertension.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
dos Santos Silva 2009[403]	UK 1989-1999	Non-concurrent cohort study	11682	107	≥23 wks GA	Not reported	Non-consent, developmental disorders and perinatal complications	Paternal occupation - flight crew	Y	N	N	N	N	N	Paternal age and paternal smoking history (ever/never smokers) at the time of the survey and paternal BMI at entry into the study
Doyle 2000[400]	UK 1993-1996	Retrospective cohort study	13600	238	≥24 wks GA	Not reported	Employees whose industrial status was unknown, ectopic pregnancies, hydatidiform moles	Maternal/paternal exposure to radionuclides/radiation	Y	N	N	N	N	N	Pregnancy order, previous fetal loss, year of pregnancy end, and industrial status
Draper 2017[119]	Europe 2011-2012	Prospective cohort study	8888	1470	≥22 and 31+6 wks GA	Not reported	Terminations, congenital anomalies, 3 regions with <150 cases (not specified)	Maternal age, Parity.	Y	N	N	N	Y	Y	Multiple pregnancy and pregnancy complications (defined as hypertensive diseases, admission to hospital for antepartum haemorrhage after 20+0 weeks, preterm premature rupture of membranes) GA at birth, birthweight, sex, multiplicity and small for gestational age.
Drysdale 2012[71]	Australia 2001-2011	Retrospective cohort study	44326	75	Antepartum	Not reported	Congenital anomalies, intrapartum deaths, multiple pregnancies, women whose country of birth was not Australia, South Asia, East Asia, and South-East Asia.	Maternal country of birth	Y	N	Y	N	N	Y	Pre-pregnancy diabetes, babies birthweight
Ebisu 2018[485]	USA 2002-2009	Case-control study	32,262	1377	20-44 wks GA	Not reported	Births that could not be matched adequately to cases/controls within the dataset. Births that were not assigned any exposures	Pollution	N	N	N	N	N	N	Food stamp rate at residential ZCTA, matched exposure to apparent temperature and natural cubic spline of LMP with

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
															two degrees of freedom per year.
Efkarpidis 2004[121]	UK 1991-1997	Case-control study	38697	161	≥24 wks GA	Not reported	Termination of pregnancy, missing data, multiple pregnancy	Maternal BMI, Maternal age, Parity	Y	N	Y	N	Y	N	Blood group
Efkarpidis 2005[120]	UK 1991-1997	Case-control study	660	161	≥24 wks GA	Not reported	Multiple pregnancy, terminations, <24 weeks GA	Maternal age, Smoking status	Y	N	Y	Y	Y	N	Fetal gender, blood group
Eidem 2011[245]	Norway 1985-2004	Retrospective cohort study	1162399	6817	≥22 wks GA	≥500 grams	None	Type 1 DM	Y	N	N	Y	Y	N	Parity, maternal age, maternal education, ethnic origin, year of birth, fetal gender and marital status
Ekeus 2011[533]	Sweden 1992-2005	Retrospective cohort study	1313978	4359	≥28 wks GA	Not reported	Internationally adopted women, multiple births, records where country of birth was unknown	Maternal country of birth	Y	N	Y	N	Y	N	Year of birth. Income, usual place of residence, height
El-Bastawissi 2007[381]	USA 1999-2000	Retrospective cohort study	39608	195	≥20 wks GA	Not reported	Multiple births, women not on Medicaid, non-matched records	Year of maternal education and access to a special supplement nutritional program during pregnancy	Y	Y	N	Y	N	N	Education, marital status, adequacy of prenatal care, gravity
Elliot 2001[588]	UK 1982-1997	Prospective cohort study	>8.2 million	43471	None provided	Not reported	Sites with inadequate data for analysis	Pollution	N	N	N	N	N	N	Deprivation, year, region, sex.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Eng 2016[43]	Australia 2007-2011	Case-control study	164	64	≥20 wks GA	≥400 grams	None	Maternal BMI, smoking in pregnancy, Haemoglobin levels, previous caesarean, Marital status,	Y	N	N	N	N	N	Previous caesarean section, marital status, high haemoglobin level and reduced foetal movement in the previous weeks to birth
Engel 2008[246]	Australia 1995-1999	Retrospective cohort study	16445	162	20-43 wks GA	Not reported	Multiples, births with absent medical history, births where the gender was not assigned, pregnancy outcome not reported.	Diabetes	N	N	N	N	N	N	Fetal gender, birthweight, GA at birth
Everett 2019[307]	USA 2006-2015	Retrospective cohort study	19955	3959	≥20 wks GA	Not reported	Terminations of pregnancy, reports where the pregnancy was currently ongoing, births to women <14 years, ectopic pregnancies. Multiple births. Births where the woman did not answer the sexual orientation question.	Sexual orientation	Y	Y	N	Y	Y	N	Race/ethnicity, education, maternal age, public assistance, income-to-needs ratio, intrauterine insemination, in vitro fertilization, prenatal care in first trimester, smoked during pregnancy, gravidity, and month of interview
Faber 2019[264]	Denmark 2006-2014	Retrospective cohort study	351878	1139	≥23 wks GA	Not reported	Births not specifically labelled as spontaneous abortions or induced abortions, pregnancies with no information on GA, births with no patent identifier number for the child and linkage. Women who purchased the bivalent	Vaccination - HPV vaccinations	Y	Y	Y	N	N	N	Education

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							version of the HPV vaccine. Multiple births (stillbirth analysis.								
Fabiani 2015[267]	Italy 2009-2010	Retrospective cohort study	100332	103	≥22 wks GA	Not reported	Women giving birth with neither hospital admissions for birth or pregnancy related diseases nor vaccination for pregnancy. Multiple births, age <13 or >55 years. GA at >45 weeks GA, Women delivering with 2 contrary outcomes recorded. Chromosomal malformations.	Vaccination - A/H1N1 pandemic influenza	Y	N	N	N	N	N	Propensity score and region of birth
Facchinetti 2011[198]	Italy 2005-2007	Case-control study	751	254	≥22 wks	≥500 grams	Intrapartum stillbirths	Maternal BMI	Y	N	NA	Y	N	Y	Placenta abruption, multiple pregnancy, previous SB, chronic hypertension and poly/oligohydramnios

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Faiz 2012[122]	USA 1997-2005	Retrospective cohort study	933258	4025	≥20 wks GA	Not reported	None	Maternal age, Maternal race, Maternal education, prenatal care, smoking status, chronic hypertension, diabetes, mellitus	Y	N	N	Y	N	Y	Maternal education, placental abruption, prenatal care, diabetes mellitus
Familiari 2016[510]	UK 2000-2014	Retrospective cohort study	23894	90	≥23 wks +6 days GA	≥500 grams	Fetal anomalies, maternal medical disorders, previous adverse obstetric outcomes, aneuploidy or infection. Referrals from other hospitals	Maternal ethnicity	Y	N	Y	NA	N	N	GA at scan, GA at birth, Head circumference centile, Abdominal circumference centile, Femur length centile, Uterine artery doppler pulsatility index, birthweight, SGA
Fell 2012[589]	Canada 2009-2010	Retrospective cohort study	55570	199	≥20 wks GA	≥500 grams	Terminations of pregnancy, home births, missing birth records.	H1N1 vaccination	Y	Y	N	N	N	N	Income and education
Frederiksen 2018[123]	Denmark 2008-2014	Retrospective cohort study	369516	1045	≥22 wks GA	Not reported	Congenital anomalies detected antenatally. Multiple pregnancies	Maternal age	NA	Y	Y	Y	Y	Y	Use of assisted reproductive therapy.
Froen 2001[124]	Norway 1986-1995	Retrospective cohort study	873	291	≥22 wks GA	≥500 grams	Multiple pregnancy, neonatal deaths, induced abortions, fetal age <22 weeks GA, Birth weight <500g and stillbirths with unknown time of death.	Maternal age, smoking status, maternal education, BMI	Y	Y	Y	N	N	N	Maternal education

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Fuchs 2017[199]	France 2009-2011	Retrospective cohort study	26973	165	≥24 wks GA	Not reported	None	Maternal BMI	Y	N	NA	Y	N	Y	Ethnicity, maternal age, gestational diabetes, type 1 and type 2 diabetes, history of hypertensive disorders of pregnancy and inherited thrombophilia
Gallicchio 2009[258]	USA (NR)	Cross-sectional study	747	23	≥20 wks GA	Not reported	Hysterectomy or oophorectomy, unemployed women, women >55 years, non-consenting women, women who completed less than 50% of the survey	Maternal occupation, maternal education, maternal race, smoking status	Y	Y	N	Y	N	N	Adjusted to account for the lack of independence among multiple pregnancies per mother, maternal education, alcohol use.
Gardosi 2013[200]	England 2009-2011	Retrospective cohort study	92218	389	≥24 wks GA	Not reported	Multiple births, congenital anomalies	Parity, maternal ethnicity, BMI, maternal employment, partner employment, Mental health problems, Pre-existing hypertension, Pre-existing diabetes, Smoking status, Antenatal folic acid use, Initiation of antenatal care,	Y	Y	Y	Y	Y	Y	Maternal age, parity, body mass index, history of mental health problems, pre-existing hypertension, pre-existing diabetes, cardiac disease, previous stillbirths, smoking in pregnancy, alcohol consumption, antenatal folic acid intake, late booking (≥13 weeks), gestational diabetes, pregnancy induced hypertension, pre-eclampsia, antepartum haemorrhage, and fetal growth restriction. Maternal and paternal employment status, ethnic origin

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Gaskins 2014[379]/Gaskins 2014[364]	USA 1989-2009	Prospective cohort study	15950	120	≥20 wks GA	Not reported	History of pregnancy loss in 1989 Missing data on diet; implausible or missing GA; missing year of pregnancy; diagnosis of type 2 diabetes; cardiovascular disease or cancer prior to pregnancy	Maternal diet	Y	Y	Y	Y	N	N	Total energy intake, physical activity, history of infertility, year, marital status.
Gaskins 2016[202]/Gaskins 2014[201]	USA 1989-2011	Prospective cohort study	29860	205	≥20 wks GA	Not reported	History of pregnancy loss in 1991	Maternal BMI, Alcohol consumption	Y	Y	Y	Y	N	N	Physical activity, year of pregnancy, history of infertility, current multivitamin use, marital status
Germain 2016[308]	Canada 2001-2011	Retrospective cohort study	14556	42	None provided	Not reported	Women who left the region permanently	Blood donation	Y	N	N	N	Y	N	Maternal education level, region of residence, year of birth, marital status.
Getahun 2005[511]	USA 1995-2001	Retrospective cohort study	25668302	Not reported	≥20 wks GA	≥500 grams	Births <20 weeks GA or <500g birthweight. Women aged < 15 years, births with missing parental races or implausible GA/birthweight combinations.	Parental race.	Y	Y	N	NA	Y	N	Paternal age, maternal education, trimester at which prenatal care began, marital status.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Getahun 2007[309]	USA 1989-1997	Cross-sectional study	626883	3465	≥20 wks GA	Not reported	Sequential multiple births, pregnancies that ended <20 weeks and ≥43 weeks GA, births to races other than white or African American women, births with missing data on timing of fetal death	Diabetes, chronic hypertension	Y	Y	Y	N	Y	Y	Maternal education, marital status, late/no prenatal care, excess weight gain, male gender, prior preterm birth of SGA, current SGA birth, congenital anomaly, chronic hypertension, PIH, PROM/Maternal fever, placental abruption, placenta previa, excessive bleeding, renal disease, fetal distress, cord complications.
Getahun 2019[268]	USA 2008-2016	Retrospective cohort study	247036	710	≥22 wks and <45 wks GA	Not reported	Multiple births, non-KPSC patient during the entire pregnancy, gestational age at birth <22 weeks GA or >45 weeks GA. Women without documented prenatal care, women who had vaccination not in the flu season.	Vaccination	Y	Y	Y	Y	Y	N	Maternal education, prenatal care, median family household income, year of vaccination
Ghosh 2019[488]	UK 2003-2010	Retrospective cohort study	1025064	5659	≥24 wks GA	Not reported	One (mass waste incinerator)MWI in the Isle of Man was excluded due to lack of health and emissions data, and 3 other incinerators were excluded as they were not solely MWIs. Births with missing health data, area-level confounder data,	Pollution (air)	Y	N	N	Y	N	N	Adjusted for year of birth, sex, season of birth, maternal age, area-level deprivation, area-level ethnicity, population density, road density, incinerator road density, other potential sources of emissions, random effect for incinerator area and random slope for the exposure.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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							emissions data or where >=5% of the exposure period had invalid values or where the dispersion models were unable to estimate a concentration.								
Gibson-helm 2015[512]	Australia 2002-2011	Retrospective cohort study	13319	87	≥20 wks GA	Not reported	Women not born in a HSC/non-HSC.	Women from Humanitarian source countries	Y	N	N	N	Y	N	None
Gilbreath 2006[590]	Alaska 1997-2001	Retrospective cohort study	10327	47	≥20 wks GA	Not reported	Multiple births	Pollution	Y	Y	N	N	Y	N	Fetal gender, IPI adequacy of prenatal care, alcohol intake, education, healthcare options, piped water and missing values.
Gold 2010[539]	USA 1998-2002	Retrospective cohort study	1601749	1749	≥20 wks GA	≥500 grams	Multiple births were excluded as well as birth where race was not clear for either parent, or when more than one race was recorded for parents.	Parental race	Y	Y	N	N	Y	N	Prenatal care initiation, education, insurance, social biological and genetic congenital risk factors.
Gordon 2013[125]	Australia 2002-2006	Retrospective cohort study	327690	1127	≥20 wks GA	≥400 grams	Fetal anomalies, births with missing data for study variables.	Maternal ethnicity, maternal age, Parity, pre-existing diabetes, pre-existing	Y	Y	N	Y	Y	Y	Pre-existing hypertension, pre-existing diabetes, area health service of residence

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
								hypertension, smoking status,							
Gordon 2015[92]	Australia 2006-2011	Case-control study	295	103	≥32 wks GA	Not reported	Aboriginal and Torres strait islander women, women with lethal chromosomal abnormalities and terminations of pregnancy	Maternal age, BMI, Employment, maternal smoking, maternal education, Sleep position,	Y	Y	Y	N	Y	N	Maternal age, maternal BMI, primiparous, not in paid work, sleep apnoea symptoms, smoking, suspected fetal growth restriction, education to high school or less, sleep position
Gottvall 2011[529]	Sweden 2004-2008	Retrospective cohort study	12446	79	None provided	Not reported	Multiple pregnancy, women with a history or diabetes, hypertension, perinatal mortality, smoking, women >40 years of nulliparous.	Care type used	Y	Y	N	Y	N	N	Education, income, smoking before pregnancy, elective caesarean section and gestational age.
Goy 2008[126]	Canada 1999-2001	Case-control study	510	112	None provided	≥500 grams	Multiple birth (for stillbirths)	Obesity, smoking, income, maternal age, mode of conception, physical activity,	Y	Y	N	Y	N	N	Inactivity during pregnancy, previous stillbirth, use of fertility treatment to achieve conception
Graham 2007[62]	Australia 2001-2004	Retrospective cohort study	35658	315	≥20 wks GA	≥400 grams	Non-indigenous women where the category of remoteness was unknown	Remote/regional living (Aboriginal women)	Y	Y	N	N	Y	Y	Diabetes, hypertension

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Gray 2009[338]	Scotland 1994-2003	Retrospective cohort study	532016	2699	≥24 wks GA	Not reported	Multiple births, births outside of hospital, mothers < 10 years of age, records with missing deprivation score, infant fender, age or parity.	Smoking status, deprivation score	Y	Y	N	N	Y	Y	Year of birth, infant sex, primary obstetric intervention
Green 2015[34]	USA 1999-2009	Retrospective cohort study	3026269	13999	≥20 wks GA	Not reported	Multiple births, births with missing data on ZIP codes, reasonable Gas/birthweight, missing covariate data, Mothers living outside of the air basins.	Pollution	Y	N	N	Y	N	N	Ozone, PM 2.5, maternal education (high school or less, some college, or college graduate or beyond), maternal race/ethnicity (non-Hispanic white; non-Hispanic black; Hispanic; non-Hispanic Asian; or other non- Hispanic, which included American Indian, Hawaiian, and other Pacific Islander),maternal age (<25, 25–34, or≥35 years), and sex of the infant or fetus.
Grunebaum 2016[410]	USA 2012-2013	Retrospective cohort study	79727	99	≥37 wks GA	Not reported	Home births that were unplanned, births whose status regarding to intended place was unknown, and births that occurred in other locations recorded on the birth certificate	Unplanned place of birth	Y	N	N	Y	Y	Y	utilization of prenatal care, education, prior cesarean birth, a composite of chronic hypertension, gestational hypertension, preeclampsia, eclampsia, prepregnancy diabetes, or gestational diabetes
Gulliver 2015[392]	New Zealand 1991-1999	Retrospective cohort study	54980	536	≥20 wks GA	Not reported	Women >25 years of age	Assault	N	N	N	N	N	N	Deprivation, number of live births in the 5 years since the index pregnancy

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Gulliver 2014[95]	New Zealand 2001-2006	Retrospective cohort study	254282	Not reported	≥20 wks GA	Not reported	Home births	Assault	Y	N	N	Y	N	N	None
Gunnarsson 2014[411]	Norway 1999-2013	Retrospective cohort study	892137	3177	≥22 wks	≥500 grams	None	Place of birth	Y	N	N	N	Y	N	Civil status, remoteness, period.
Gupta 2019[310]	USA 2006-2008	Retrospective cohort study	1276	291	≥20 wks GA	Not reported	Women who refused to take part in the study. Cases with missing maternal interview and medical chart abstraction. Multiple pregnancies, women with a previous therapeutic abortion or fetal reduction and women with incomplete data on the estimated date of LMP and/or date the pregnancy before the index ended.	Interpregnancy interval	Y	Y	Y	Y	Y	Y	Insurance status, alcohol use, marital status, ART and prior pregnancy outcome.
Ha 2017[591]	USA 2002-2008	Prospective cohort study	223375	992	≥23 wks GA	Not reported	Multiple births, births with missing data	Air temperature	Y	N	Y	Y	Y	Y	Study site, infant sex, marital status, hypertensive disorders of pregnancy, insurance status, humidity, and season of conception, exposure to particulate matter with diameter < 2.5um and ozone.
Haavaldsen 2010[128]	Norway 1967-2006	Retrospective	2182756	22754	≥16 wks GA	Not reported	Births with missing study data, births >43 weeks GA	Maternal age	Y	N	N	N	Y	Y	Period of birth, plurality, paternal age, preeclampsia

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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		cohort study													
Halliday-bell 2010[394, 397]	Finland 1990-2006	Retrospective cohort study	946392	Not reported	≥22 wks	≥500 grams	Multiple births	Maternal occupation	Y	Y	N	N	Y	N	Marital status
Harrison 2018[592]	USA 2006-2008	Case-control study	1911	497	≥20 wks GA	Not reported	Women who were underweight multiple births Incarcerated women Women who were unable to give informed consent.	Maternal BMI	N	N	N	N	N	N	Controls and cases were matched. Adjustments were made for various biomarkers including Maternal serum ferritin, C-reactive protein, White cell count and histologic chorioamnionitis
Haruyama 2018[129]	Japan 2013-2014	Retrospective cohort study	379211	2133	≥22 wks GA	Not reported	Congenital anomalies, multiple births, births with missing gestational age, or cause of death. Births with missing or implausible data for the following variables: maternal age, parity, pre-pregnancy weight, height, smoking status, infant sex and birth weight. Maternal weight below 30kg or over 150kg, and height below 130cm or over 200cm were considered implausible.	Maternal age, maternal BMI, smoking status, parity.	Y	Y	Y	N	Y	Y	Pregnancy induced hypertension, amniotic fluid volume, infant size.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Healy 2006[514]	USA 1999-2002	Retrospective cohort study	35529	Not reported	≥24 wks GA	Not reported	Terminations (elective) congenital anomalies and women with incomplete demographic information	Maternal ethnicity	Y	Y	Y	NA	Y	Y	Education, marital status, illicit drug use during pregnancy, alcohol use during pregnancy, medication use during pregnancy, pre-gestational diabetes, obstetric history (history of previous live birth, miscarriage, and preterm birth), use of assisted reproductive technologies, antihypertensive medication uses prior to pregnancy, and site of enrolment.
Heaman 2019[87]	Canada 2005, 2008-09	Retrospective cohort study	67076	Not reported	≥20 wks GA	≥500 grams	Multiple births	Adequacy of prenatal care, area of residence and rural/remoteness, income, maternal age, parity.	N	N	N	N	N	N	Region of residence, income quintile, maternal age, parity, maternal health conditions, parity.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Heazell 2018[91]	UK 2014-2016	Case-control study	1024	291	≥28 wks GA	Not reported	Infants with congenital anomalies Multiple pregnancies maternal age <16 years Women who were unable to give informed consent, also women with stillbirths or congenital anomalies were excluded from the control group.	Maternal age, Ethnicity, Parity, Level of Education, Sleep duration last night prior to stillbirth, Number of times up to toilet last night, Maternal daytime naps in the last 4 weeks, Maternal going-to-sleep position in the last night	Y	N	Y	Y	Y	N	Last night going to sleep position, level of education, birthweight centile, gestation, duration of daytime nap and study site.
Heggland 2011[393]	Norway 1967-2006	Case-control study	1130251	24007	None provided	Not reported	None	Maternal occupation	Y	N	N	N	Y	N	Educational level
Helgadottir 2011[130]	Norway 1990-2003	Case-control study	87772	377	≥23 wks GA	≥500 grams	Wrongly diagnosed cases of IUFD, births with missing age, parity, women with venous thrombosis in the previous pregnancy, Women <16 or >44yrs	Maternal age, civil status, hypertension, diabetes, smoking	Y	N	N	N	N	Y	Multiple pregnancy, hypertensive disorders, diabetes, placental abruption and placenta previa

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Henningsen 2014[131]	Denmark: 1995-2007 Sweden: 1982-2007 Norway: 1988-2007 Finland: 1990-2007	Retrospective cohort study	587257	1582	Until April 2004 28+0 to 22+0. From July 2008 22+0	Not reported	Birth with plurality > 2	Method of conception, maternal age	Y	N	N	N	Y	N	Years of birth, fetal gender, country
Herbert 2012[311]	Australia 2006-2009	Retrospective cohort study	7280	17	None provided	Not reported	Women who had not reported they child's birth date	Mode of conception	Y	N	Y	N	N	N	Area of residence
Hesselman 2019[341]	Sweden 2013-2017	Retrospective cohort study	218030	524	≥22 wks GA	Not reported	Multiple pregnancies. Women residing in areas not included in the study, or women attending their first visit in areas not participating in the Maternal health care Register.	Deprivation/SES	N	N	N	N	Y	Y	Pre-gestational hypertension, pre-gestational diabetes.
Hilden 2019[204]	Sweden 1998-2012	Retrospective cohort study	1455667	4910	≥22 wks GA	Not reported	Women with type 1 and type 2 diabetes. Multiple pregnancies Women with data on early pregnancy BMI	Maternal BMI	Y	Y	NA	Y	Y	Y	GDM maternal age, non-Nordic origin, parity, smoking and chronic hypertension
Hodyl 2014[68]	Australia 1999-2008	Retrospective cohort study	178029	1004	≥20 wks GA	≥400 grams	Multiple pregnancy	Maternal ethnicity, smoking status	Y	NA	N	NA	Y	Y	SIEFA, year of birth, pre-existing hypertension, pre-existing diabetes, asthma

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Hogberg 2007[132]	Sweden 1983-2001	Retrospective cohort study	526691	1420	≥28 wks GA	Not reported	Multiple births, women who didn't have a second pregnancy during the study period	Smoking status, country of birth, maternal education, interpregnancy interval, maternal age,	Y	N	N	Y	N	N	Maternal education, interpregnancy interval, stillbirth in the first pregnancy, and year of second birth.
Hogue 2013[97]	USA 2006-2008	Case-control study	2430	614	≥20 wks GA (≥17 wks GA if poor dating)	Not reported	Terminations, women incarcerated, women unable to give consent	Significant life event	Y	N	N	N	N	N	SLE + Marital Status, Health Insurance, and Income
Homer 2019[408]	Australia 2000-2012	Retrospective cohort study	1251420	399	37 - 41 wks GA	Not reported	Multiparous women high risk of complicated pregnancies Received no antenatal care, had a previous caesarean section, a breech or non-vertex presentation, labour was induced for any reason, they had an elective caesarean section prior to labour, pre-existing and/or pregnancy related hypertension or diabetes. Antepartum haemorrhage or any other relevant pregnancy complications. Babies born before 37 or after 41 weeks GA, babies born prior to the arrival	Place of birth	Y	N	N	Y	Y	N	Gestational age

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							for a planned hospital or birth centre birth. Babies with congenital anomalies								
Huang 2000[134]	USA 1961-1996	Retrospective cohort study	84294	196	None provided	≥500 grams	If maternal, fetal or placental conditions were recognised as causes of death	Maternal age, SES, maternal weight, Antenatal visits	Y	N	Y	N	N	N	Gestational age, SES, number of antenatal visits, birth weight, cord loops.
Hyland 2015[51]	USA 1993-1998	Case-control study	80762	3552	≥20 wks GA	Not reported	Women with no history of pregnancy, birth with incomplete data for smoking	Smoking status	Y	NA	Y	Y	Y	N	Maternal education, alcohol intake, oral contraceptive use.
Iacobelli 2012[135]	La reunion 2001-2011	Retrospective cohort study	13284	150	≥21 wks GA	Not reported	None	Maternal age	Y	Y	Y	Y	N	N	Marital status. Alcohol consumption, poor prenatal care.

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Ibiebele 2016[593]	Australia 2005-2011	Retrospective cohort study	360987	1552	≥20 wks GA	≥400 grams	Births <20 weeks GA or 400g, unknown indigenous status or GA, congenital anomalies	Diabetes, chronic hypertension.	Y	Y	N	NA	Y	Y	Remoteness, substance use, gender, hospital accommodation status, ART, marital status, number of ANC visits, pre-existing diabetes, pre-existing hypertension
Ihrig 1998[35]	USA 1983-1993	Case-control study	416	119	≥20 wks GA with Apgar's of 0 at 1 and 5 mins.	Not reported	Births without detailed medical records	Maternal age, arsenic exposure, annual income, maternal ethnicity	Y	N	N	Y	Y	N	Annual income,
Ikedionwu 2020[205]	USA 2014-2017	Retrospective cohort study	10043398	48799	≥20 wks GA	Not reported	Multiple births	Maternal BMI	Y	N	N	Y	Y	N	Educational qualification
Irgens 2016[402]	Norway 1980-2012	Retrospective cohort study	Unknown	Not reported	Death before or during birth	Not reported	Female divers	Maternal occupation	Y	Y	N	N	N	N	Year of birth, birth order
Islam 2015[136]	Oman 2000	Retrospective cohort study	1345	31	≥24 wks GA	Not reported	Unmarried women, twin births, women aged less than 20 years, pregnancies with missing obstetric outcomes.	Maternal age	Y	N	N	N	Y	N	Maternal education, previous history of pregnancy loss, marital status
Jacob 2016[206]	UK 1994-2013	Retrospective cohort study	44060	257	≥20 wks GA	Not reported	Multiple births	BMI	Y	Y	NA	N	N	Y	Chronic hypertension, pre-gestational diabetes.
Jacobsson 2004[137]	Sweden 1987-2001	Retrospective	909228	3002	≥28 wks GA	Not reported	None explicitly stated	Maternal age	Y	Y	N	N	Y	N	Significant malformations, maternal disease, multiple pregnancy

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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		cohort study													
Johansson 2017[207]	Sweden 2008-2014	Retrospective cohort study	1514	303	≥22 wks	Not reported	Terminations, women with missing early pregnancy weight, women missing pregnancy weight measures, underweight women.	Gestational weight gain	Y	Y	Y	N	N	Y	Height, living with partner, pre-existing diabetes or hypertension
Jolly 2000[138, 139]	UK 1988-1997	Retrospective cohort study	390366	3700	None provided	Not reported	Births to women ≥ 35 years	Maternal age	Y	N	Y	Y	Y	Y	Pre-existing hypertension, or diabetes, gestational diabetes, preeclampsia
Jonas 2015[273]	Sweden main analysis 2009-2010, sibling analysis 1980 to 2012	Retrospective cohort study	121979 (main analysis) 3801 (sibling analysis)	Not reported	≥28 wks GA(<2009), ≥22 wks GA (≥2009)	Not reported	Births without data in the medical Birth Register	Vaccination -	Y	Y	Y	Y	Y	N	GA and fetal gender, disposable income.
Juhl 2013[58]	Denmark 1996-2002	Retrospective cohort study	71500	854	≥22 wks GA	Not reported	Mole hydatids, ectopic pregnancies. Women who completed the first study interview after fetal loss.	Occupational heavy lifting	Y	Y	Y	N	Y	N	Occupational status, alcohol consumption, physical activity, leisure time lifting, predominant work posture.
El Kady 2005[94]	USA 1990-1999	Retrospective cohort study	4833286	24018	≥20 wks GA	Not reported	Births < 20 weeks GA	Assault	Y	N	N	Y	Y	N	Maternal education, prenatal care and insurance type.
Kallen 2001[431]	Sweden 1983-1996	Retrospective cohort study	1413811	4820	None provided	Not reported	None	Smoking status	Y	NA	N	N	Y	N	Year of birth, educational level

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Kallen 2012[269]	Sweden 2009-2010	Retrospective cohort study	242259	585	None provided	Not reported	Pregnancies where vaccination was administered after 37 weeks GA	Vaccination - H1N1 influenza	Y	Y	Y	N	Y	N	Year of birth
Kang 2001[594]	USA 1990-1991	Cross-sectional study	5996	70	≥20 wks GA	Not reported	Multiple births	Gulf veteran status	Y	Y	N	Y	Y	N	Ground vs non-ground troops, active military ns national guard or reserves, history of prior pregnancy and year of pregnancy outcome.
Kapurubandara 2016[334]	Australia 2004-2013	Retrospective cohort study	44004	273	≥20 wks GA	Not reported	Multiple births, birth missing exposure data	Hypertension	Y	Y	Y	Y	Y	Y	Previous endocrine disease, previous hypertension, heart disease, mental health problems, illicit drug use, alcohol and drug use, IVF, consanguinity
Kennare 2007[595]	Australia 1998-2003	Retrospective cohort study	36038	137	≥20 wks GA	≥400 grams	Multiple pregnancies	Previous method of birth	N	Y	N	N	N	Y	Hypertension, gestation, antepartum haemorrhage (stillbirths)
Kennare 2005[391]	Australia 1998-2002	Retrospective cohort study	89080	585	≥20 wks GA	≥400 grams	Births <20 weeks GA or < 400 g birthweight	Substance abuse	Y	Y	N	Y	N	Y	Mother psychiatric condition
Kennare 2009[413]	Australia 1991-2006	Retrospective cohort study	298333	251	≥20 wks GA	≥400 grams	Terminations or births with no antenatal care	Place of birth	Y	Y	N	N	Y	Y	Occupational status, plurality, medical and obstetric complications (e.g. Antepartum haemorrhage, diabetes, hypertension), gestational age, small for gestational age, congenital anomalies, city or country hospital, and mode of birth.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Kenny 2013[140]	UK 2004-2008	Retrospective cohort study	225710	1109	≥24 wks GA	Not reported	Women less than 20 years of age, women with missing data on social deprivation, missing birthweight, infant sex, or maternal age	Maternal age	Y	N	Y	Y	Y	N	Social deprivation
Kesmodel 2002[371]	Denmark 1989-1996	Prospective cohort study	24768	116	≥28 wks GA	Not reported	Spontaneous abortions, questionnaires completed following pregnancy, and births with missing data on alcohol intake.	Alcohol consumption, caffeine intake	Y	Y	Y	Y	Y	N	Caffeine intake, marital status, occupational status, maternal education, fetal gender, supplement use.
Khalil 2013[345]	UK not reported	Retrospective cohort study	76158	290	≥24 wks GA	Not reported	Congenital anomalies, terminations for psychological reasons, births with incomplete data, fetal deaths caused by maternal deaths.	Maternal ethnicity, Conception mode, cigarette smoking, chronic hypertension, pre-existing diabetes.	Y	Y	N	N	N	Y	Mode of conception, history of chronic hypertension, type 1 or 2 diabetes, outcome of previous pregnancy,
Kharrazi 2004[429]	USA 1992	Prospective cohort study	2796	19	≥20 wks GA	Not reported	Women with missing data, women whose cotinine levels were I the active smoking range.	Environmental tobacco smoke	Y	NA	N	Y	Y	N	Source of payment for prenatal care (private or public) and infant gender
Khashan 2009[343]	UK 2004-2006	Retrospective cohort study	99,403	433	≥24 wks GA	Not reported	Multiple births, missing birthweight, missing infant sex, missing maternal BMI	Maternal BMI	Y	N	NA	Y	Y	N	Infant sex, social deprivation score.
King 2000[596]	Canada 1988-1995	Retrospective cohort study	49756	214	None provided	≥500 grams	Multiple births, women with missing GA at birth	Pollution (water)	Y	Y	N	N	N	N	None

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
King 2005[480]	Canada 1999-2001	Case-control study	510	112	None provided	≥500 grams	Pregnancy terminations, fetal anomalies	Trihalomethane exposure	Y	Y	N	N	N	N	Province, income, occupation, total THM exposure
Kinzler 2002[141]	USA 1995-1997	Retrospective cohort study	8995274	Not reported	≥20 wks GA	Not reported	Multiple pregnancies, pregnancies < 20 weeks GA or < 500g birthweight, missing maternal age or maternal age <12 or >49, missing paternal age or paternal age >69 and congenital anomalies.	Parental age difference	Y	N	N	N	N	N	Gravity, maternal education, adequacy of prenatal care, marital status
Knight-Agarwal 2015[208]	Australia 2008-2013	Retrospective cohort study	14857	162	None provided	Not reported	Women missing BMI data, multiple pregnancies	Maternal BMI, Interpregnancy BMI change	Y	Y	NA	Y	Y	N	Baseline BMI, interpregnancy interval
Kortekaas 2020[142]	Netherlands 1999-2010	Retrospective cohort study	1648992	2952	≥22 wks GA	Not reported	Women with high blood pressure, diabetes mellitus, women <18 years of age. Multiple births	Maternal age	NA	N	N	N	Y	N	Onset of labor, gestational age.
Kristensen 2005[597]	Denmark 1989-1996	Prospective cohort study	24505	112	≥28 wks GA	Not reported	Miscarriages, births with missing weight data, women who were enrolled after birth had occurred.	Maternal BMI	Y	Y	NA	N	Y	N	Alcohol intake, caffeine intake, living with partner, education, working status
Lai 2016[243]	Canada 2005-2011	Retrospective cohort study	332864	2109	≥20 wks GA	≥500 grams	Births to non-Alberta residents, births with missing personal identifiers	Pre-existing diabetes	Y	N	N	Y	Y	Y	Pre-existing hypertension, mode of birth

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Lamminpaa 2016[143]	Finland 2004-2008	Retrospective cohort study	249648	4127	None provided	Not reported	Congenital anomalies and multiple pregnancies	Maternal age and BMI	Y	Y	NA	N	N	Y	Placenta previa, IVF, fertility treatment other than IVF, smoking, anaemia, previous Caesarean section, insulin-treated gestational diabetes, gestational diabetes, hospitalisation because of late pregnancy bleeding or because of hypertension.
Lauria 2003[144]	Italy 1989-1993	Retrospective cohort study	2824080	14425	None provided	Not reported	Infants who were born abroad or for whom the district was missing	Maternal age, parity, education level	Y	N	N	N	Y	N	Birthweight, mother education, districts unemployment rate.
Laws 2010[412]	Australia 2001-2005	Retrospective cohort study	836919	5442	≥20 wks GA	≥400 grams	Missing data on intended place of births, women with pre-existing hypertension and/or pregnancy induced hypertension	Place of birth	Y	N	N	Y	N	N	Gestational age, public or private patient.
Lawton 2018[265]	New Zealand 2008-2014	Retrospective cohort study	34994	140	≥20 wks GA	≥400 grams	Multiple births, women who were vaccinated for HPV elsewhere, Women who were vaccinated during pregnancy, inappropriate HPV vaccination dosage, missing scheduled dose of HPV vaccine.	HPV vaccination exposure	Y	Y	Y	Y	N	N	Area of residence, SES
Lewis 2009[145]	Australia 2004-2006	Retrospective cohort study	4896	94	≥22 wks GA	Not reported	None	Maternal age, maternal ethnicity	Y	Y	N	Y	N	Y	SES, pregnancy induces hypertension, urinary tract infection

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Li 2019[416]	Australia 2000-2007	Retrospective cohort study	139873	667	None provided	Not reported	Genetic or congenital fetal malformation (known). Multiple births.	Maternal smoking	Y	NA	Y	Y	Y	N	Diabetes, hypertension, SEIFA score, gestation at birth, birth weight.
Lindam 2016[210]	Sweden 1992-2011	Case-control study	202070	242	≥28 wks GA	Not reported	Women not born in Sweden	Maternal BMI	Y	Y	NA	N	N	N	Maternal height, education, period
Lisonkova 2010[146]	Canada 1999-2003	Retrospective cohort study	29698	168	≥20 wks GA	Not reported	Women with missing postcodes	Remote/rural living	Y	Y	N	Y	Y	N	Single parent status, low income neighbourhood, alcohol/drug use during pregnancy, congenital anomalies, previous spontaneous birth, induced abortions, male fetal gender, suboptimal prenatal care.
Lisonkova 2011[598])	Canada 1999-2003	Retrospective cohort study	98897	464	≥20 wks GA with Apgar's of 0 at 1 and 5 mins.	Not reported	None	Maternal age	Y	Y	N	N	Y	N	Marital status, low-income neighbourhood, rural residence, alcohol and drug use during pregnancy, suboptimal prenatal care, infants sex, aboriginal status, previous induced abortion, previous spontaneous abortion.
Lisonkova 2013[147]	USA 2003-2005	Retrospective cohort study	6846695	22228	22-43 wks GA	≥500 grams	Births < 500g birthweight and states that did not report gestational age	Maternal age	Y	Y	N	Y	Y	N	Maternal education, marital status, infants gender and congenital anomalies
Lisonkova 2013 (2)[147]	UK 1998-2007	Retrospective cohort study	9034 twins	97	≥24 wks GA	Not reported	None	Maternal age	Y	Y	N	N	Y	N	SES, infant sex, major congenital anomalies, chronicity

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Lisonkova 2017[149]	USA 2003-2013	Retrospective cohort study	82869	Not reported	≥20 wks GA	Not reported	Multiple pregnancies, mothers aged <15 or >60, births occurring outside of hospital, births with missing data.	Maternal age	Y	Y	Y	N	Y	N	Marital status, drug use, maternal education, type of health insurance, year of childbirth, fetal sex.
Liu 2010[312]	Canada 2004-2006	Retrospective cohort study	334231	1798	≥20 wks GA	Not reported	Multiple births, births with missing information on GA, infant sex, birth weight	Neighbourhood income quintile	Y	Y	N	N	Y	Y	Maternal health problems, initiating prenatal care in the first trimester.
Liu 2019[534]	Sweden 2014-2017	Retrospective cohort study	286870	Not reported	None provided	Not reported	Births without manual data entry in antenatal care. Multiple births Births missing maternal country of birth data Births or foreign-born women who were not from Syria, Iraq, Somalia, Eritrea or Afghanistan	Maternal country of birth, refugee status.	Y	N	N	NA	Y	N	Parity in quadratic forms, calendar year of birth and mothers country of origin, maternal education.
Lorch 2012[150]	USA 1995-2005	Retrospective cohort study	7104674	23471	23-44 wks GA	≥400 grams	Unmatched records and births less than 400g or over 8000g	Maternal age	Y	N	N	N	N	Y	Insurance status, trimester of first prenatal visit, maternal education, pre-existing comorbid conditions (chronic hypertension and or diabetes, cord or placental anomalies, placentation anomalies.)
Lou 2013[315]	USA 1995-2000	Retrospective cohort study	561157 (twins)	5975	≥20 wks GA	Not reported	Birth under 20 weeks or over 42 weeks, under 200g or over 6000g, implausible birth weights and births with	Diabetes	Y	Y	N	Y	Y	Y	Maternal education, marital status, fetal sex, mode of birth, twin cluster level, other maternal major illnesses (chronic hypertension, heart disease,

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							missing information on diabetes.								acute or chronic lung disease, genital herpes, renal disease and Rh sensitization)
Lucovnik 2018[211]	Slovenia 2002-2015	Retrospective cohort study	271913	1336	≥22 wks GA	≥500 grams	Pregnancies following controlled hyper-ovulation and intrauterine insemination were excluded.	Maternal BMI	N	N	NA	N	Y	Y	Chronic hypertension, maternal height.
Luke 2019[387]	Canada 2008-2016	Retrospective cohort study	243140	663	≥20 wks GA	≥500 grams	Births less than 20 weeks GA or >44 weeks GA Congenital anomalies late terminations, multiple births	Cannabis use	Y	Y	Y	Y	N	N	Tobacco use, alcohol use, other substance use, SES and race/ethnicity.
Luo 2004[540]	Canada 1990-1997	Retrospective cohort study	720,586	3107	None provided	≥500 grams	None	Marital status,	Y	N	N	Y	Y	N	Infant gender, plurality, maternal education, community size as well as community level random effects.
Luo 2004 (2)[313]	Canada 1985-1997	Retrospective cohort study	112462	4554	None provided	≥500 grams	None	Maternal ethnicity	Y	N	N	N	Y	N	Infant gender, maternal education, marital status, community size, community level random effects.
Luo 2006[314]	Canada 1991-2000	Retrospective cohort study	825349	Not reported	≥22 wks GA	Not reported	Births with missing weight, sex or GA. GA <22 weeks	Neighbourhood income quintile	Y	N	N	Y	Y	N	Plurality, education level, marital status.
Luo 2008[250]	Canada 1991-2000	Retrospective	828161	Not reported	≥20 wks GA	≥500 grams	Births with missing birth weight, GA, sex,	Degree of rurality	Y	N	N	Y	Y	N	Maternal education, marital status, plurality

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study					birthweight < 500g or GA < 20 weeks								
Luo 2010[515]	Canada 1990-2000	Retrospective cohort study	4068131	17939	≥20 wks GA	≥500 grams	Births with missing birth weight, GA, birthweight < 500g or GA < 20 weeks	Place of birth	Y	N	N	N	Y	N	Marital status, infant sex, plurality.
Luo 2012[516]	Canada 1991-2000	Retrospective cohort study	823216	2981	≥20 wks GA with Apgar's of 0 at 1 and 5 mins.	≥500 grams	Births with insufficient data to determine northern vs southern residence, women who are Southern Inuit women	Area of residency	Y	N	N	Y	Y	N	Maternal education, marital status, infant gender, plurality, rural/remote living.
Luque-Fernandez 2019[153]	Spain 2007-2015	Retrospective cohort study	4179402	11323	≥28 wks GA	Not reported	Births < 28 weeks GA Births that could not be linked to the 2015 HDI	SES, maternal age, education level attained, parity.	Y	N	N	N	Y	N	Maternal education
Luque-Fernandez 2011[152]	Spain 2007-2008	Retrospective cohort study	973204	2464	≥28 wks GA	Not reported	Multiple births and births before the 28th week of pregnancy	Maternal age, Country of origin, maternal education, parity.	Y	N	N	Y	Y	N	Maternal education, GA at birth
Luque-Fernandez 2013[151]	Spain 2007-2010	Retrospective cohort study	1920235	5560	≥22 wks GA	≥500 grams	Terminations, multiple births and infants born before 22 weeks GA and infants weighing <500g	Maternal education	Y	N	N	Y	Y	N	Maternal education level, maternal region of residence, unemployment level of the region of residence, unemployment level.
Lygre 2016[444]	Norway 1999-2008	Prospective cohort study	69474	298	None provided	Not reported	Multiple pregnancies	Amalgam fillings	Y	Y	Y	N	Y	N	Education, alcohol consumption

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Macintosh 2006[241]	UK 2002-2003	Retrospective cohort study	623197	Not reported	≥24 wks GA	Not reported	Miscarriages < 20 weeks GA, terminations of pregnancy for reasons other than congenital anomaly, women diagnosed with type 2 DM after pregnancy	Pre-existing diabetes	Y	N	N	N	N	N	None
Malabarey 2012[154]	USA 1995-2004	Retrospective cohort study	37504230	131896	≥24 wks GA	Not reported	Births prior to 24 weeks GA, births with congenital or chromosomal anomalies.	Maternal age, prenatal visits, maternal ethnicity	Y	N	N	Y	Y	N	Plurality, prenatal visits.
Maleckiene 2001[317]	Lithuania 1996-1998	Case-control study	174	58	≥26 wks GA (with intact fetal membranes)	Not reported	Fetal malformations, placental separation, hypertensive disorders, renal diseases, diabetes	Maternal BMI	Y	N	N	N	N	N	Low educational, level, threatened abortion during first trimester, and maternal white blood cell count ≥16,000/mm3
Matijasevich 2006[257]	Uruguay 2002-2003	Case-control study	1174	382	≥20 wks GA	≥350 grams	Multiple births, congenital anomalies	Caffeine consumption	Y	N	N	N	N	N	Parental education level, history of abortions, fetal deaths, vomiting/nausea (1st trimester) and attendance of prenatal care
Mayo 2019[155]	USA 2007-2011	Retrospective cohort study	9931407	48534	≥20 wks GA	Not reported	Maternal age less than 13 or greater than 55 or missing. Paternal age less than 13 or greater than 70 or missing. Multiple births.	Maternal age and paternal age	NA	Y	Y	Y	Y	N	Education, paternal race/ethnicity, maternal race/ethnicity.
McClure 2011[434]	USA 2002-2004	Retrospective cohort study	2215920	<10	20-42 wks GA	Not reported	None	Intentional self inflicted poisoning	Y	N	N	Y	N	N	Maternal education and insurance level

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
McCowan 2007[156]	New Zealand 1993-2002	Case-control study	69610	437	≥20 wks GA	≥400 grams	Congenital anomalies, pregnant women transferred to hospital following stillbirth diagnosis, births missing clinical records.	Maternal ethnicity, Parity, Smoking status, Marital status, maternal age, previous caesareans	Y	Y	N	N	Y	N	Infant gender, marital status, history of previous miscarriage or induced abortion, previous low birth weight infant, multiple pregnancy.
McCowan 2017[32]	New Zealand 2012-2015	Case-control study	733	164	≥28 wks GA	Not reported	Multiple pregnancy, major congenital anomalies	Sleep position, BMI, Ethnicity	Y	Y	Y	Y	Y	N	Gestational age, SGA status, social deprivation
McDonald 2007[390]	Canada 1995-2001	Retrospective cohort study	1854463	8813	None provided	Not reported	None	Maternal drug dependence	Y	N	N	N	N	Y	Preeclampsia or hypertension, diabetes mellitus, thrombophilia, poor fetal growth, antenatal haemorrhage, placenta previa, instrumental birth or Caesarean section, and placental abruption.
McInerney 2019[415]	Australia 2010-2014	Retrospective cohort study	487388	162	≥20 wks GA	≥400 grams	Multiple births non-Aboriginal women births with missing data for outcome Mothers who were not residents of NSW	Maternal smoking	Y	NA	N	N	Y	Y	Any hypertension, any diabetes, SES.
Mei-dan 2015[599]	Canada 2001-2007	Retrospective cohort study	1646	80	None provided	Not reported	None	Smoking during pregnancy	Y	NA	N	N	N	Y	Hypertension, GA at birth, previous abortion, hospital of origin for high risk pregnancies, diabetes, alcohol use during pregnancy
Melchor 2019[212]	Spain 2013-2017	Retrospective	16609	53	≥23 wks GA	Not reported	Multiple births	Maternal BMI	Y	N	NA	N	Y	Y	Gestational age and chronic hypertension

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study													
Mendola 2017[600]	USA 2002-2008	Retrospective cohort study	223375	992	≥23 wks GA	Not reported	Multiple births	Pollution	Y	Y	N	Y	Y	Y	Alcohol use, insurance status, marital status, pre-existing hypertension, pre-existing diabetes, season of birth
Merc 2019[213]	Slovenia 2002-2014	Retrospective cohort study	248151	385	≥34 wks GA	≥500 grams	Fetal deaths due to fetal anomalies intrapartum fetal deaths	Maternal BMI	Y	N	NA	N	Y	Y	Hypertensive disorders of pregnancy (gestational hypertension and/or preeclampsia), gestational diabetes, pre-pregnancy diabetes, previous caesarean section, previous myomectomy, pregnancy following in vitro fertilization (IVF), oligohydramnios (as recorded with the diagnosis of fetal death), polyhydramnios, bleeding in any trimester of pregnancy and small for gestational age (SGA) (defined as neonatal weight <5th percentile for gestation) neonates.
Mjøen 2006[404]	Norway 1976-1995	Retrospective cohort study	1106665	2529	≥28 wks GA	Not reported	Births where occupation data is missing or occupation cannot be categorised	Paternal occupation	Y	N	N	N	N	N	Calendar year, place of birth and level of education

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Mocevic 2014[56]	Denmark 1996-2002	Retrospective cohort study	65886	341	≥22 wks GA	Not reported	Women working < 15 hours per week in the previous 3 month period, Mola hydatids, extrauterine pregnancy, multiple pregnancies, pregnancies with invalid date of last menstrual period, pregnancies with missing GA at recruitment or event. Women with unknown occupational status, second of more pregnancies included in the dataset.	Occupational heavy lifting	Y	Y	Y	N	Y	N	Alcohol use during pregnancy.
Mogos 2016[96]	USA 2002-2009	Retrospective cohort study	32658259	Not reported	None provided	Not reported	Pregnancy admissions not related to birth	Intimate partner violence	Y	Y	Y	Y	N	Y	CHD, hyperlipidaemia, hypothyroidism, adrenal disorders, hypertension, diabetes, depression) and pregnancy related conditions (preeclampsia, eclampsia, placenta abruption, placenta accrete, placenta previa, gestational diabetes and gestational hypertension, household income, alcohol use, Medicare status, rural/urban living.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Mohsin 2006[157]	Australia 1998-2002	Retrospective cohort study	433379	2776	≥20 wks GA	≥400 grams	None	Maternal age, antenatal care initiation, country of birth, ethnicity, smoking status, pre-existing diabetes, parity, SES, place of birth.	Y	Y	Y	Y	Y	Y	Country of birth, SES, diabetes mellitus, hypertension, 1st antenatal care visit, mothers discharge status, fetal gender, plurality, place of birth, birth type and birthweight
Moraitis 2015[601]	UK 1999-2008	Retrospective cohort study	128585	359	24-43 wks GA	≥500 grams	Multiple births, congenital anomalies, deaths due to rhesus isoimmunisation, births <24 weeks or over 43 weeks GA or under 500g birthweight, records with missing data	Previous mode of birth	Y	Y	N	N	N	N	Maternal height, social deprecation, interpregnancy interval, birthweight percentile and perinatal death.
Morales 2017[374]	Denmark 1997-2002	Prospective cohort study	90086	285	≥28 wks GA	Not reported	None	Coffee consumption, smoking	Y	NA	Y	N	Y	N	SES, physical exercise, alcohol consumption
Morales-Suarez-Varela 2018[372]	Denmark 1997-2002	Retrospective cohort study	90086	285	≥28 wks GA	Not reported	Spontaneous abortion before the first interview, pregnant without the first questionnaire completed. Births with no information on exposures, mola pregnancies, extrauterine pregnancies, unknown outcome.	Smoking status and diet	Y	NA	Y	N	Y	N	SES, physical activity, alcohol consumption.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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Morisaki 2018[602]	Japan 2003-2011	Retrospective cohort study	14726	6614	22-24 wks GA	Not reported	Births at home or birthing centres	Annual income, Maternal age, marital status, parity	Y	N	N	N	Y	N	Annual income, previous stillbirth, GA in weeks, infant gender, year of birth and marital status, parity, maternal age, SGA.
Morris 2003[479]	UK 1982-1997	Retrospective cohort study	368007	1849	None provided	Not reported	None	Proximity to special waste landfill site	Y	N	N	N	N	N	Year of birth, fetal gender, deprivation.
Mozooni 2018[518]	Australia 2005-2013	Retrospective cohort study	259684	1313	≥20 wks GA	Not reported	Australia Aboriginal and Torres Strait Islander women. Terminations of pregnancy.	Maternal ethnicity	Y	Y	Y	NA	Y	Y	Previous stillbirth, year of birth, sex of baby, marital status, pregnancy complication, medical conditions, plurality, index of relative SES.
Mozooni 2020[158]	Australia 2005-2013	Retrospective cohort study	260997	1313	≥20 wks GA	≥500 grams	Terminations Indigenous women	Maternal country of birth stratified by ethnicity, maternal age, parity, pre-existing diabetes, essential hypertension, smoking, accessibility/remoteness, antenatal care type.	Y	Y	N	Y	Y	Y	SES, year of birth, plurality, marital status, previous SB, sex of baby, essential hypertension, pre-existing diabetes health insurance, interpreter use, accessibility/remoteness.
Mozooni 2020(2)[252]	Australia 2005-2013	Retrospective cohort study	260997	1313	≥20 wks GA	≥400 grams	Terminations, births to indigenous women	Acculturation - length of residence	N	Y	N	N	Y	Y	Marital status, SES, plurality, previous SB, medical conditions,

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
								stratified by country of birth							pregnancy complications, sex of baby.
Mueller 2007[603]	USA 1987-2001	Case-control study	66757	5302	≥20 wks GA	Not reported	Missing geocodes	Pollution	Y	Y	N	N	Y	N	None
Nabukera 2006[159]	USA 1995-2000	Retrospective cohort study	7112322	Not reported	≥20 wks GA	Not reported	Women < 20 years of age, multiple births	Maternal age	Y	N	N	Y	N	N	Education, marital status, prenatal care, GA at birth, SGA
Nabukera 2008[160]	USA 1978-1997	Retrospective cohort study	242559	Not reported	≥20 wks GA	≥500 grams	None	Maternal age, interpregnancy interval	Y	Y	Y	Y	N	Y	Education, marital status, prenatal care, chronic hypertension, pre-eclampsia, adverse pregnancy outcome (previous fetal death, low birthweight, preterm birth, SGA), year of birth
Nabukera 2009[318]	USA 1978-1997	Retrospective cohort study	239930	Not reported	≥20 wks GA	≥500 grams	Births with missing data	Maternal ethnicity	Y	Y	Y	NA	N	Y	Marital status, education level, chronic hypertension, diabetes, pregnancy induced hypertension, past adverse pregnancy outcome, year at first birth.
Nair 2017[604]	UK 2013-2015	Retrospective cohort study	14001	76	≥24 wks GA	Not reported	Multiple births, births < 24 weeks GA	Maternal haemoglobin	Y	Y	Y	Y	Y	Y	GDM, Antepartum haemorrhage, pregnancy induced hypertension, pre-existing diabetes, haemoglobinopathies, other medical co-morbidities
Nohr 2005[214]	Denmark 1998-2001	Prospective	54505	679	≥28 wks GA	Not reported	Births with missing data, terminations of	Maternal BMI	Y	Y	NA	N	Y	N	Height, socio-occupational status, physical exercise,

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study					pregnancy, and GA <28 days								alcohol and coffee consumption
Nohr 2014[378]	Denmark 1996-2002	Prospective cohort study	35914	206	≥20 wks GA	Not reported	Women of unknown recruitment date, unknown pregnancy outcome, supplement use, women who only used a single supplement, abortions	Folate and, multivitamin use	Y	Y	Y	N	Y	N	Socio-occupational status, waiting time to pregnancy, mode of conception, previous miscarriage
O'Leary 2007[161]	Australia 1984-2003	Retrospective cohort study	499595	Not reported	≥20 wks GA	≥400 grams	None	Maternal age	Y	N	N	Y	Y	N	Marital status, multiple birth, disadvantage and region.
O'Leary 2012[365]	Australia 1983-2007	Retrospective cohort study	85083	825	≥20 wks GA	≥400 grams	For the comparison group (no heavy prenatal alcohol exposure), "women with an ICD-8 diagnostic code for alcoholic psychosis (291.0–291.3; 291.9), alcoholism (303.0–303.2; 303.9), or 'accidental' poisoning (E860) occurring in the Hospital Morbidity data set from 1970 to 1982 and the Mental Health Outpatient data set from 1966 to 1982" (pg. 946).	Alcohol consumption	Y	N	N	N	Y	Y	Year of birth, marital status, illicit drugs, any mental health
Oakley 2016[162]	UK 2004-2012	Retrospective cohort study	51225	312	≥22 wks GA	Not reported	None	Maternal age	Y	Y	Y	Y	Y	Y	Deprivation, marital status, year of birth, hypertension and diabetes.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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O'Brien 2018[90]	Web based survey in Minneapolis from United Kingdom, Canada, Australia, New Zealand, Germany, Greece, India, Philippines, South Africa, Finland, Italy, Sweden, Switzerland, Israel, Bahrain. 2012-2014	Case-control study	633	153	≥28 wks GA	None	Women less than 18 years old, those with a multifetal gestation, a fetus with known congenital anomaly, and those who were not fluent in reading or writing English	Sleep position, awakenings during the last month, getting up in the last month, restlessness in the last month, wake up position in the last month, naps in the last month, excessive daytime sleepiness, sleep quality last month.	Y	N	Y	Y	Y	N	Educational level, country of respondent (USA vs non-USA)
Olausson 1999[163]	Sweden 1973-1989	Retrospective cohort study	320174	1489	≥28 wks GA	Not reported	Multiparous women, women ≥25	Maternal age	Y	N	N	N	N	N	Education level, year of birth
Olsen 1999[254]	Denmark 1991-1992	Retrospective cohort study	113814	518	≥28 wks GA	Not reported	Multiple births, second births to the same women in the study period.	Smoking, education level							Maternal age, parity and smoking
Ombelet 2016[605]	Belgium 1993-2010	Retrospective cohort study	1079814	Not reported	None provided	≥500 grams	None	Mode of conception	Y	N	N	N	Y	N	Year of birth, fetal gender

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
O'Neill 2014[606]	Denmark 1982-2010	Retrospective cohort study	832996	1996	≥28 wks GA (≤2004), ≥22 wks GA (>2004)	Not reported	None	Previous method of birth	Y	N	N	Y	N	Y	Previous stillbirth, miscarriage or ectopic pregnancy, marital status, birth year, SES, income, medical complications in the first live birth, GDM, placenta previa, hypertensive disorders, GA and birthweight
Ovesen 2011[215]	Denmark 2004-2010	Retrospective cohort study	369347	1113	≥22 wks GA	Not reported	Missing BMI, women who were entered in the dataset twice	Maternal BMI	Y	Y	NA	N	Y	Y	GA at birth, birth weight, GDM, fetal gender, and calendar year
Panaitescu 2017[607]	UK 2007-2015	Prospective cohort study	109932	449	≥24 wks GA	Not reported	Pregnancies with fetal aneuploidies or major defects, pregnancies ending in miscarriage and those ending in termination for psychological reason. Pregnancies ending in spontaneous PTB.	Chronic hypertension	N	Y	Y	Y	N	Y	History of diabetes, previous SB
Paranjothy 2014[384]	UK 1995-2009	Retrospective cohort study	412827	132	≥24 wks GA	Not reported	Antepartum stillbirths, congenital anomalies, multiple pregnancy, missing data	Distance to hospital	Y	N	N	N	Y	N	Gestational age, gender, social deprivation quintile, urban/rural index
Parker 1999[60, 405, 406]	UK 1950-1989	Case-control study	9208	130	≥28 wks GA (≥1 Oct 1992), ≥24 wks GA (>1 Oct 1992)	Not reported	None stated	Paternal exposure to ionising radiation	Y	N	N	N	N	N	Year of birth, social class, birth order, paternal age

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Parker 2016[344]	USA 2012	Retrospective cohort study	186705	1125	None provided	Not reported	Hospitalisations for conditions other than child birth	Gastric bypass surgery	Y	Y	N	Y	N	Y	Pre-existing diabetes, gestational diabetes, hypertension
Partridge 2012[88]	USA 1995-2002	Retrospective cohort study	28729765	Not reported	≥22 wks GA	Not reported	Births in Puerto Rico, Guam and the Virgin Islands, congenital anomalies	Adequacy of care	Y	Y	N	Y	Y	N	Marital status, maternal education, alcohol in pregnancy
Pasternak 2012[270]	Denmark 2009-2010	Retrospective cohort study	50677	138	≥22 wks GA	Not reported	Abortion diagnosis during the first 6 weeks, women with no follow-up information, pregnancies with implausible Gas, H1N1 vaccination prior to the onset of pregnancy, pregnancy onset before 1-2-09 or after 6-12-09	Vaccination - H1N1 vaccine	Y	N	Y	Y	Y	Y	Country of residence, degree of urbanisation, history of fetal death in siblings, number of hospital admissions and outpatient hospital contacts within the 3 years preceding pregnancy, selected drugs and number of drugs used within the last 6 months, comorbidities (Pulmonary disease, cardiovascular disease, haematological disease, diabetes, liver and kidney disease, rheumatic disease, inflammatory bowel disease, obesity, immunodeficiency, disorders of the female pelvic organs, hospital contact for injury/poisoning.).

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Patel 2015[320]	USA 2008-2010	Case-control study	12524119	51075	≥20 wks GA	≥350 grams	Not report, but study implies non-hospital births were excluded)	Alcohol consumption, smoking, drug use, chronic hypertension	Y	Y	N	Y	N	Y	Insurance status, multiple gestation, diabetes, chronic hypertension, cardiomyopathy, congenital heart disease, cardiac conduction disorders, chronic renal disease, SLA, collagen vascular disease, HIV, thrombophilia, sickle cell disease, alcohol use, GDM, preeclampsia/eclampsia, FGR, placental abruption.
Pearce 2010[482]	England 1961-2992	Retrospective cohort study	90537	812	≥28 wks GA	≥500 grams	Home births, stillbirths of unknown gestational age, and birthweight less than 500g	Maternal black smoke exposure	Y	N	N	N	Y	N	Fetal gender, Townsend deprivation score.
Penn 2014[164]	England 2004-2012	Prospective cohort study	53293	329	≥24 wks GA	Not reported	Multiple pregnancies	Parity, BMI, ethnicity	Y	N	Y	Y	N	Y	Hypertensive disorders
Peticca 2009[248]	Canada 2005-2006	Retrospective cohort study	120604	Not reported	≥20 wks GA	Not reported	None stated	Diabetes	Y	Y	N	N	Y	N	Multiple birth, mode of conception, first trimester visit and antenatal care provider
Petrangelo 2019[386]	USA 1999-2013	Retrospective cohort study	12578557	78766	None provided	Not reported	Home births	Drug use	N	Y	N	N	N	Y	Hypertension, alcohol and other illicit drug use.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Pickens 2019[217]	USA 2006-2008	Case-control study	2080	479	≥20 wks GA	Not reported	Births < 20 weeks GA, missing or implausible GWG (weight loss >50 pounds of gain >150 pounds), or missing pre-pregnancy BMI or covariates. Monochromic twins, triplets or missing data on twin type. Dichorionic/diamniotic twins to women with underweight BMIs. Births with missing data on covariates or implausible GWGs.	Gestational weight gain	Y	Y	NA	Y	N	Y	Maternal age at birth, maternal race and ethnicity, study site, maternal education, marital status/cohabitating, health insurance type, trimester prenatal care began, family income in the last 12 months, WIC enrolment, smoking or alcohol consumption during the 3 months prior to pregnancy, lifetime drug use, pregnancy history, history of hypertension, history of pre-existing diabetes, and history of thyroid disorder.
Pilkington 2014[383]	France 2002-2005	Retrospective cohort study	3086128	26860	≥22 wks GA	≥500 grams	None	Distance to maternity unit	Y	N	N	N	N	N	Unemployment, % single parent household, % foreign born, multiplicity
Po 2019[218]	Italy 2014-2016	Retrospective cohort study	107528	332	≥22 wks GA	≥500 grams	None	Maternal BMI, Maternal nationality	N	Y	Y	Y	N	N	Educational level
Quansah 2009[396]	Finland 1990-2006	Retrospective cohort study	132248	395	≥22 wks	Not reported	None	Maternal occupation	Y	Y	N	N	Y	N	Marital status
Raatikainen 2007[608]	Finland 1989-2001	Retrospective cohort study	23614	Not reported	≥22 wks GA	≥500 grams	Multiple pregnancies, congenital anomalies, missing data, >19 ANC visits.	Antenatal care engagement	Y	Y	N	N	Y	Y	Marital status, alcohol use during pregnancy, educational level, multiparity, prolonged

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
															gravity, chronic illness and diabetes.
Raisanen 2013[609]	Finland 2006-2010	Retrospective cohort study	291004	894	≥22 wks GA	≥500 grams	Multiple pregnancies	IVF/ICSI use	Y	Y	N	N	Y	Y	Gestational diabetes, pre-existing diabetes, pre-eclampsia and SES
Raisanen 2018[165]	Finland 2000-2010	Retrospective cohort study	604047	1917	≥22 wks GA	≥500 grams	Multiple births Women < 20 years of age Births with minimal information on pregnancy history.	Maternal age, parity, Smoking, IVF, Diabetes	Y	Y	N	N	Y	Y	Maternal age, pregnancy history, prior SGA, prior preterm birth, smoking status, gestational diabetes, in vitro fertilization, pre-eclampsia, placenta previa, placental abruption, and major congenital anomaly, pre-existing diabetes
Raisanen 2014[422]	Finland 1991-2010	Retrospective cohort study	1164953	9260	≥22 wks GA	≥500 grams	Multiple births	Smoking status	Y	N	N	N	Y	N	Fetal gender, SES.
Rammah 2019[491]	USA 2008-2013	Retrospective cohort study	358366	1599	≥20 wks GA	≥350 grams	Births with missing GA estimateBirths with implausible combinations of birth weight and GA for livebirths.GA <20 or >44 weeksBirths that would cause fixed-cohort biasMultiple births	Air pollution	Y	Y	N	Y	N	N	Apparent temperature, education level, number of prenatal care visits.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Rammah 2019 (2) [489]	USA 2008-2013	Case-control study	8204	1172	≥20 wks GA	Not reported	Births with missing GA data and birthweight. Live births with implausible gas and birth weight combinations were excluded. Women with conception dates more than 20 weeks GA before Jan 1, 2008, or less than 44 weeks before dec 31, 2013.	Air pollution	Y	Y	Y	Y	N	N	Education level, number of prenatal visits, apparent temperature
Ramö isgren 2017[219]	Sweden 1992-2013	Retrospective cohort study	31386	102	1992 until June 2008 included fetal deaths after 28 wks GA, and from July 2008 until 2013 included fetal deaths after 22 wks GA.	Not reported	Multiple pregnancies, multiparous women	Maternal BMI	Y	N	NA	N	N	Y	Calendar year of birth, maternal comorbidities.
Rasmussen 2003[166]	Norway 1967-1998	Retrospective cohort study	1676160	3126	≥28 wks GA	Not reported	Multiple births, births missing data, births delivered at < 28 weeks GA	Maternal age, marital status, maternal education.	Y	N	N	N	N	N	Birth order

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Ravelli 2011[69]	Netherlands 2000-2006	Retrospective cohort study	554234	3135	≥24 wks GA	≥500 grams	Births less than 24 weeks GA or 500g, women who conceived after ART	Ethnicity, SES, maternal age, urbanisation, income, booking visit, smoking status, pre-existing diabetes, pre-existing hypertension	Y	Y	N	N	N	Y	Urbanisation, income, SES, trimester of booking visit, pre-existing disease
Ravelli 2013[610]	Netherlands 1999-2007	Retrospective cohort study	1092255	995	39 wks - 42 wks +6 days GA	Not reported	Births >43 weeks GA or with congenital anomalies	Maternal ethnicity	Y	N	N	N	Y	N	SES
Reddy 2010[535]	USA 2002-2008	Retrospective cohort study	174809	712	≥23 wks GA	Not reported	2 institutes had a large component of maternal medical history missing and so were excluded from the study	Maternal ethnicity, maternal age, marital status, public/private status, parity, previous CS, re-existing diabetes, Chronic hypertension, smoking status, alcohol consumption, Maternal BMI	Y	Y	Y	Y	Y	Y	Preterm birth, pre-existing diabetes, HIV/aids, marital status, maternal insurance status, Prior CS, Pre-existing diabetes, chronic hypertension.
Regan 2016[52]	Australia 2012-2013	Retrospective cohort study	58008	377	None provided	Not reported	Women with a date of influenza vaccination administered at or before 14 days prior to	H1N1 vaccination	N	Y	N	Y	N	N	Indigenous status and propensity for vaccination

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							conception, missing data.								
Regan 2019[321]	Finland 1987-2016 Norway 1980-2015 Western Australia 1980-2015	Retrospective cohort study	84452	184	≥22 wks GA	Not reported	Births with missing data for gestational age, birthweight, sex, date of birth, parity, or maternal age at birth multiple births	Interpregnancy interval	Y	N	N	N	Y	N	Birth decade of birth, gestational length of the previous pregnancy.
Reime 2009[395]	Germany 1990-1999	Retrospective cohort study	297880	Not reported	None provided	until march 1994 > 999g and after march 1999 > 499g	Multiple births, students/trainees, blue collar workers, white collar workers, and births out of hospital.	Maternal employment, Paternal employment, couple employment	Y	Y	N	Y	Y	Y	Psychological stress and chronic conditions.
Reime 2009 (2)[86]	Germany 1990, 1995, 1999	Retrospective cohort study	182444	789	None provided	≥999 grams (until March 1994), ≥499 grams (from 1 April 1994)	Multiple pregnancy	Prenatal care adequacy, immigration status	Y	Y	N	N	N	N	Interpregnancy interval, employment status, stillbirth definition

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Richter 2007[519]	Germany 1993-1999	Retrospective cohort study	62698	231	≥24 wks GA	Not reported	Multiple pregnancy, birth before 24 weeks GA	Previous CS, Nationality	Y	Y	N	Y	N	Y	Weight, citizenship, medical, obstetric and antenatal history, fetal presentation
Rivera-Nunez 2018[486]	USA 1998-2004	Case-control study	27092	2460	20 wks GA	≥350 grams	Cases where the cause of death was not one of the 5 causes of interest.	Pollution: THM4, Chloroform, BDCN, DBCM, Bromoform, HAA5, DCAA, TCAA, MCAA.	N	N	N	Y	N	N	Maternal education, marital status, source of water, THM4 or HAA5
Robson 2006[168]	Australia 1998-2003	Retrospective cohort study	21880	183	≥20 wks GA	≥400 grams	Multiple pregnancies, women ≥20 years, births <20 weeks GA	ARIA classification	Y	Y	N	N	Y	Y	Age, parity, smoking status, obstetric complication, medical complications.
Rockhill 2019[414]	USA 2009-2013	Retrospective cohort study	749977	1041	≥20 wks GA	Not reported	ART births where gestational carriers were used. Births where embryo banking was performed. Births missing the following: data on cycle type missing outcome data Ectopic or heterotopic pregnancies, ART cycles that resulted in no clinical pregnancy.	Smoking status in separate modalities of ART	Y	N	N	N	Y	Y	Year of treatment, maternal age, gravidity, number of prior ART procedures, cycle type, oocyte/embryo source, tubal factor, endometriosis, uterine factor, ovulatory dysfunction, diminished ovarian reserve, male factor infertility, and unexplained infertility as fixed effects and accounting for clustering by patient, clinic, and state using random effect

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Roman 2007[220]	La Reunion 2001-2005	Case-control study	2162	38	≥22 wks GA	Not reported	None	Maternal BMI	Y	Y	NA	N	N	Y	Alcohol use, previous voluntary abortions, prenatal visits, pregnancy induced hypertension, chronic hypertension, pre-eclampsia, GDM, chronic DM, Insulin dependent DM.
Rozdarz 2017[322]	Australia 2007-2013	Retrospective cohort study	64010	389	≥20 wks GA	Not reported	Multiple pregnancies	Mode of conception	Y	N	Y	N	N	Y	Gestational age, mode of birth, thyroid disease.
Rukuni 2016[611]	Scotland 1995-2012	Retrospective cohort study	80422	462	None provided	Not reported	Abortions, multiple birth, pregnancies occurring after 2012	Maternal anaemia	Y	Y	Y	Y	Y	N	SES
Russell 2010[221]	USA 1989-1997	Retrospective cohort study	667 (triplets)	24	≥20 wks GA	Not reported	None stated	Maternal obesity	Y	Y	NA	Y	N	Y	Education, adequacy of prenatal care, fetal gender, year of birth, placental abruption, placenta previa, insulin and noninsulin dependent diabetes, anaemia, SGA.
Salihu 2003[612]	USA 1997-1999	Retrospective cohort study	12066854	62238	≥20 wks GA	Not reported	None	Maternal age	Y	Y	N	N	Y	N	Marital status, maternal education level, drinking during pregnancy, prenatal care utilization and year of birth
Salihu 2004(4)[175]	USA 1995-1997	Retrospective cohort study	7792990	42823	≥20 wks GA	Not reported	Multiple births	Maternal smoking	Y	NA	N	Y	Y	N	Marital status, education, adequacy of prenatal care, drinking during pregnancy, fetal gender.
Salihu 2004(2)[171])	USA 1995-1997	Retrospective	1628 (quin/quadruplets)	73	≥20 wks GA	Not reported	Singletons, twins, and triplet births	Maternal age	Y	Y	N	Y	Y	N	Maternal education, level of prenatal care, alcohol intake during pregnancy

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study													
Salihu 2004(3)[520]	USA 1995-1998	Retrospective cohort study	14348318	85916	≥24 wks GA	Not reported	Plurality above triplets	Maternal ethnicity	Y	Y	N	NA	Y	N	Maternal education, prenatal care
Salihu 2005[597]	USA 1995-2000	Retrospective cohort study	37498600	281542	≥20 wks GA	Not reported	Births less than 20 weeks GA or over 44 weeks GA	Maternal ethnicity	Y	N	N	NA	N	N	Marital status, maternal education, prenatal care, fetal gender
Salihu 2005(2)[169]	USA 1995-1997	Retrospective cohort study	2349	774	≥20 wks GA	Not reported	None reported	Maternal age	Y	Y	N	Y	Y	N	Maternal education, level of prenatal care, alcohol use during pregnancy
Salihu 2006(3)[613]	USA 1978-1997	Retrospective cohort study	396441	1612	≥20 wks GA	Not reported	Congenital anomalies	Previous caesarean section	Y	Y	Y	N	Y	N	Marital status, maternal education, SGA, adequacy of prenatal care and preterm birth in first pregnancy
Salihu 2006(4)[174, 614]	USA 1989-2000	Retrospective cohort study	18180371	Not reported	≥20 wks GA	Not reported	None	Maternal age	Y	Y	N	Y	Y	N	Marital status, year of birth, prenatal care received, fetal gender
Salihu 2007[223]	USA 1978-1997	Retrospective cohort study	1577082	8240	≥20 wks GA	Not reported	Births missing BMI data or with implausible values	Maternal BMI	Y	Y	NA	Y	N	N	Educational achievement, marital status, adequacy of prenatal care, fetal gender, year of birth
Salihu 2008[615]	USA 1978-1997	Case-control study (nested)	879700	7965	≥20 wks GA	Not reported	Multiple births, congenital anomalies, chromosomal anomalies	Maternal smoking	Y	N	Y	Y	Y	N	Maternal education level, prenatal care adequacy, year of birth.
Salihu 2008(2)[176]	USA 1978-1997	Retrospective	1235307	5405	≥20 wks GA	Not reported	Congenital or chromosomal abnormalities, invalid	Maternal age	Y	Y	N	Y	Y	N	Maternal education, marital status, adequacy of prenatal

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study					time of deaths, multiple births								care, fetal gender, year of birth
Salihu 2009[70]	USA 1989-1997	Retrospective cohort study	430130	1808	≥20 wks GA	Not reported	Records with BMI missing.	Maternal BMI	Y	Y	NA	N	Y	Y	Maternal education, marital status. Adequacy of prenatal care, fetal gender, year of birth, pregnancy complications, preterm birth, SGA
Salihu 2010[222]	USA 1989-2005	Retrospective cohort study	27257 (twins)	423	≥20 wks GA	Not reported	Underweight and overweight women, women with implausible height and weight, twins were excluded where details of one of the twins was missing.	Maternal BMI	Y	Y	NA	Y	N	N	Adequacy of prenatal care, fetal gender, year of birth
Salihu 2011[173]	USA 1989-2005	Retrospective cohort study	152151	520	≥20 wks GA	Not reported	Multiple pregnancies, women without 2 consecutive pregnancies during the study period.	Maternal age	Y	Y	Y	Y	N	N	Maternal education, marital status, adequacy of prenatal care and interpregnancy interval.
Savard 2013[260]	Canada 1981-2009	Retrospective cohort study	2454845	11233	None provided	≥500 grams	Multiple births and terminations	Maternal education level	Y	N	N	Y	Y	N	Marital status
Savitz 2012[483]	USA 1990-2004	Case-control study	1950	106	≥20 wks GA	Not reported	Non-white births, term births over 2500g birthweight	Pollution - perfluorooctanoic acid exposure	Y	Y	N	N	Y	N	Maternal education, exposure year, state of residence.
Scheller 2017[266]	Denmark 2006-2013	Case-control study	2505	6	≥22 wks GA	Not reported	Births with missing data, women vaccinated with the bivalent HPV vaccination before or during Pregnancy	Vaccination - HPV	Y	N	N	N	N	N	Calendar year of pregnancy onset, GA at birth

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Schneuer 2014[377]	Australia 2006-2007	Case-control study	5109	26	≥20 wks GA	≥400 grams	Serum collected prior to 10 weeks GA or after 14 weeks GA, women with vitamin D levels outside limits, medical abortion, major congenital anomalies	Vitamin D status	Y	Y	N	Y	Y	Y	Maternal weight, pre-existing diabetes or hypertension, season at sampling, SES.
Scott-Pillai 2013[224]	Ireland 2004-2011	Retrospective cohort study	30298	126	≥24 wks GA	Not reported	Births less than 24 weeks GA, multiple births, women booking into antenatal care >16 weeks GA or with no recorded BMI	Maternal BMI	Y	Y	N	N	Y	N	Social deprivation, year of birth
Sebire 2001[225, 616]	UK 1988-1997	Retrospective cohort study	325395	1356	None provided	Not reported	Births with missing maternal BMI data	Maternal BMI	Y	Y	NA	Y	Y	Y	Pre-existing hypertension, gestational diabetes, pre-eclampsia, pre-existing diabetes
Shapiro 2018[63]	Canada 2004-2006	Retrospective cohort study	42831	Not reported	None provided	Not reported	Births to Non-first nations women in Canada. Multiple births.	Place of residence	N	N	N	N	N	N	Status (unsure what status is)
Shapiro 2018 (2)[323]	Canada 2004-2006	Retrospective cohort study	130931	Not reported	≥20 wks GA	≥500 grams	Multiple births	Marital status	Y	N	N	N	N	N	Education level
Shapiro 2017[54]	Canada 2004-2006, 1994-1996	Retrospective cohort study	131285	753	None provided	Not reported	Multiple births	Paternal education	Y	N	N	Y	Y	N	Maternal education, marital status, parental age discrepancy, nativity.
Shumpert 2004[617]	USA 1995-1997	Retrospective cohort study	80495	3144	≥20 wks GA	Not reported	None	Maternal anaemia	Y	Y	N	Y	Y	Y	Marital status, education level, alcohol use, prenatal care adequacy, fetal gender, antenatal maternal complications (chronic

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
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															hypertension, pre-eclampsia, eclampsia, abruptio placenta and placenta previa).
Siahanidou 2020[177]	Greece 2004-2015	Retrospective cohort study	1276816	5023	≥26 wks GA	Not reported	None - the study mentions that maternal nationality was unknown in 12 neonates	Birth order (2nd - 3rd, 1st, 4th) Maternal education Marital status Place of residence maternal and paternal age	N	N	N	N	N	N	Child's sex (female, male), multiplicity (yes, no), birth order (as a categorical variable: 1st, 2nd, 3rd, 4th,maternal education (low, intermediate, high), marital status (unmarried, married), place of residence (rural versus urban or semi urban), study period [2009–2015 (crisis) versus 2004–2008 (pre-crisis).
Silver 2019[89]	USA 2010-2014	Prospective cohort study	8178	18	≥20 wks GA	Not reported	Multiple pregnancies Pregnancy outcome data unavailable, elective terminations, indicated terminations, fetal death prior to 20 weeks GA, sleep data unavailable.	Sleep position: Left lateral sleep Non-left lateral sleep	Y	N	Y	N	N	Y	Chronic hypertension, rate of weight gain from early pregnancy to mid pregnancy
Simonet 2009[438]	Canada 1989-2000	Retrospective cohort study	2726	16	≥20 wks GA	≥500 grams	Missing data, low GA or birthweight, Non-Inui mother tongue	Place of birth and birth attendant	Y	N	N	N	Y	N	Education, marital status, plurality, community size, community level random effects
Sloggett 1998[335]	UK 1981-1992	Retrospective cohort study	Unknown	80835	None provided	Not reported	Residents of any institutions and those classified as permanently sick or disabled in 1981, deaths in 1981 and 1982.	Deprivation score	Y	N	N	N	N	N	North/South zone of residency

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Smith 2001[618]	UK 1992-1998	Retrospective cohort study	180238	423	≥24 wks GA	≥500 grams	None explicitly stated	Maternal age	Y	N	N	N	N	N	Maternal height, SES, previous spontaneous and therapeutic abortions, year.
Smith 2003 (2)[619]	UK 1992-1998	Retrospective cohort study	69055	168	≥24 wks GA	Not reported	Multiple pregnancies, cases with missing or implausible gas, Missing or implausible data.	Interpregnancy interval	Y	Y	N	N	N	N	Marital status, height, SES, previous birthweight vigesimal, previous caesarean section
Smith 2020[490]	UK 2006-2010	Retrospective cohort study	580500	2889	≥24 wks GA	Not reported	Multiple births Births with GA <24 weeks Births with missing data for GA, noise, or ethnicity	Pollution	Y	Y	N	Y	N	N	Sex, Maternal age, Birth registration type, Tobacco expenditure (COA-level), Carstairs quintile (COA-level), Individual-level ethnicity, Season of conception, Year (linear term) and random intercept for MSOA, night-time noise as continuous per IQR.
Smith 2003[620]	UK 1992-1998	Retrospective cohort study	103790	312	≥34 wks GA	Not reported	Multiple pregnancy, births outside 24-43 weeks GA, birthweight less than 500g. Congenital anomalies causing death, records with missing values, implausible interpregnancy interval discrepancies between method of birth	Previous caesarean section	Y	Y	N	N	N	N	Height, SES
Smith 2007[178]	UK 1992-2001	Prospective cohort study	84769	406	24 to 43 wks GA	Not reported	Multiple births, births outside of the study GA range (24-43 weeks), therapeutic abortions,	Maternal age, deprivation score, smoking status, BMI, marital status	Y	Y	Y	N	N	N	Marital status, maternal height

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							chromosomal anomalies causing fetal death.								
Smulian 2002[238]	USA 1995-1997	Retrospective cohort study	10614679	14785	≥24 wks GA	≥500 grams	Multiple births, chromosomal anomalies, birthweight less than 500g, GA < 24 weeks, pregnancies with placenta previa/unexplained uterine bleeding.	Pre-existing diabetes, Chronic hypertension	Y	N	N	Y	N	Y	GA at birth, anaemia, intrapartum fever, gravity, marital status
Snowden 2015[433]	USA 2012-2013	Retrospective cohort study	79727	Not reported	≥37 wks GA	Not reported	Home births that were unplanned, births whose status regarding intended place of birth was unknown, and births that occurred in other locations.	Place of birth	Y	N	N	Y	Y	Y	Utilization of prenatal care, education, prior caesarean birth, and a composite of maternal conditions associated with an increased medical risk (a composite of chronic hypertension, gestational hypertension, preeclampsia, eclampsia, pre-pregnancy diabetes, or gestational diabetes).
Sorbye 2014[536]	Norway 1995-2010	Retrospective cohort study	723045	2624	≥22 wks GA	≥500 grams	Births to parents where only on parent was foreign born, Births missing generational information or birthweight or GA at birth. Terminations of pregnancy.	Country of birth	Y	N	N	N	Y	N	Year of birth, residence.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Stacey 2011[179, 362, 442]	New Zealand 2006-2009	Case-control study	465	155	≥28 wks GA	Not reported	Multiple pregnancy, congenital anomalies, pregnancies not booked to deliver in the Auckland region.	Maternal BMI, antenatal care adequacy, deprivation score.	Y	Y	Y	Y	Y	N	SES
Stephansson 2001/Stephansson 2000[336, 337]	Sweden 1987-1996	Case-control study (nested)	1404	707	≥28 wks GA	Not reported	Multiple births	Maternal SES	Y	Y	Y	Y	N	N	Maternal height
Stephansson 2003[326]	Sweden 1983-1997	Retrospective cohort study	410021	1062	≥28 wks GA	Not reported	Multiple births, women without 2 consecutive pregnancies within the study period	Interpregnancy interval	Y	Y	N	Y	N	N	Maternal education, cohabitation, diabetes, hypertensive disease, year of second birth, previous birth outcome (stillbirth, early neonatal death, preterm or SGA)
Strand 2012[327]	Australia 2005-2009	Retrospective cohort study	101870	653	≥20 wks GA	≥400 grams	Multiple births	Smoking status, marital status, Ethnicity, Month of birth,	Y	N	N	N	N	N	Temperature, humidity, sulphur dioxide levels in the last 4 weeks, secular trends of livebirth and stillbirth
Strandberg-Larsen 2008[427]	Denmark 1996-2002	Prospective cohort study	87032	495	≥20 wks GA	Not reported	Missing data, multiple pregnancies, terminations, <20 weeks GA	Nicotine replacement therapy use during pregnancy	Y	N	N	N	N	N	SES
Strandberg-larsen 2008(2)[369]	Denmark 1996-2002	Prospective cohort study	92717	444	≥22 wks GA	Not reported	Missing data	Alcohol consumption	Y	Y	Y	N	Y	N	Previous spontaneous abortions, coffee consumption, time to conceive, occupational status.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Sutan 2010[180]	UK 1994-2003	Case-control study (nested)	541811	2822	≥20 wks GA	≥200 grams	Non-NHS births, Multiple births, Births < 20 weeks GA	Maternal age, marital status, smoking status, Parity,	Y	Y	N	N	Y	Y	Previous stillbirth, deprivation score, previous spontaneous abortion, diabetes, maternal height, remote/rural living.
Syngelaki 2011[227]	UK not reported	Prospective cohort study	41577	Not reported	≥24 wks GA <42 wks	Not reported	Pregnancies conceived by IUI, terminations for psychosocial reasons, pregnancies with incomplete outcome data or diagnosis of a major defect.	Maternal BMI	Y	Y	NA	Y	N	Y	Mode of conception, chronic hypertension or diabetes, history of adverse pregnancy outcome, family history of pe
Tennant 2011[228]	UK 2003-2005	Retrospective cohort study	29856	200	≥24 wks GA	Not reported	Multiple pregnancies, congenital anomalies, maternal pre-gestational diabetes and unknown maternal BMI	Maternal BMI	Y	Y	NA	Y	N	N	Deprivation score, Standardised birthweight and/or GA
The Stillbirth Collaborative Research Network Writing group[127]	USA 2006-2008	Case-control study	2595	663	≥20 wks GA	Not reported	Terminations and cases/controls where the interview or prenatal chart abstraction were missing	Maternal age, paternal age, Maternal ethnicity, marital status, maternal education, maternal health insurance status, family income, smoking status, alcohol consumption, illicit drug use, maternal BMI,	Y	Y	N	Y	N	N	Paternal age, maternal education, paternal education, marital status, insurance method, family income, smoking, illicit drug use.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Toledano 2005[36]	UK 1993-1998	Retrospective cohort study	920571	60641	≥24 wks GA	Not reported	Multiple births, births where exposure data were missing	Pollution - Trihalomethane exposure	Y	N	N	N	N	N	Carstairs quintile and based on total births for United utilities 1993-1997
Tomashek 2006[621]	USA 1988	Retrospective cohort study	5896	1375	≥28 wks GA	Not reported	Women whose first haemoglobin measure was after 28 weeks GA	Anaemia status	Y	N	Y	N	Y	Y	Marital status, maternal education, alcohol use, prenatal iron supplement, iron/multivitamin use during pregnancy, preeclampsia/eclampsia, cocaine use, marijuana use.
Tracy 2007[435]	Australia 1999-2002	Retrospective cohort study	994464	6800	≥20 wks GA	≥400 grams	Women delivering outside of hospitals or birthing centres	Place of birth	Y	N	N	Y	N	N	Private or public health care sector
Tran 2014[622]	Australia 2000-2010	Retrospective cohort study	846039	5038	≥20 wks GA	≥400 grams	Births < 20 weeks GA, births not linked to a birth admission records.	Maternal smoking	Y	NA	N	Y	Y	Y	Year of birth, marital status, private health insurance, residential remoteness, SIEFA, diabetes, hypertensive disorders.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Trotta 2014[274]	Italy 2009-2010	Retrospective cohort study	86171	74	≥180 days	Not reported	Chromosomal anomalies or congenital viral infections, women with the pandemic vaccinations administered before the start of her pregnancy, voluntary abortions, miscarriages, multiple births, women residing outside the study area.	Vaccination	Y	N	N	Y	Y	Y	Hospital size, maternal age, nationality, study degree, maternal occupational status, civil status, paternal occupational status, consanguinity between parents, low income allowance, previous conceptions, previous birth, live birth (previous), previous stillbirth, spontaneous abortion, voluntary abortion, caesarean birth, pulmonary diseases, cardiovascular diseases, haematological diseases, diabetes, psychiatric disorders, IBD, immunosuppressive therapy, prescription drug use, thyroid disorders, folic acid use prior to conception and first trimester, iron supplementation, autoimmune diseases, other maternal disease, ART use.
Trudell 2017[181]	USA 1999-2009	Retrospective cohort study	64173	464	≥32 wks GA	Not reported	Women with missing data	Maternal smoking	Y	NA	N	Y	Y	Y	Year of birth, marital status, private health insurance, residential remoteness, SIEFA, diabetes and hypertensive disorders.
Tudehope 2018[528]	Australia 1998-2013	Retrospective	60418	359	≥20 wks GA	≥400 grams	Intrapartum inter-hospital transfers, births with missing data	Public/private hospital care	N	N	N	N	N	N	ART use, congenital abnormalities, method of birth, GA at birth

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
		cohort study													
Urhoj 2017[329]	Denmark 1994-2010	Retrospective cohort study	944031	3746	Birth showing no signs of life at 22+ completed wks or more	Not reported	Pregnancies where the assigned father was a woman, ectopic pregnancies, registration errors in the id number of the mother	Paternal age	Y	N	N	N	N	N	Year of outcome, paternal education level, maternal education level
Valanis 1999[478]	USA, Canada, Puerto Rico, Australia and Ireland 1992	Cross-sectional study	6041	65	≥20 wks GA	Not reported	Participants who had not parented a baby, participants treated with antineoplastic drugs, abortions.	Occupation	Y	Y	N	N	N	N	Gravity, outcome of all prior pregnancies
Vangen 2002[543]	Norway 1986-1998	Retrospective cohort study	703924	4368	≥22 wks GA	≥500 grams	None	Maternal country of birth	Y	N	N	N	Y	N	None
Varner 2014[420]	USA 2006-2008	Case-control study	1980	614	≥20 wks GA	Not reported	Incarcerated women, non-consenting women	Cotinine concentration and drug use	Y	Y	Y	Y	Y	Y	Marital status, maternal education, paternal age, pregnancy history, alcohol use, illicit drug use, diabetes, seizure disorder, blood type, Rh factor, multiple gestation, family income, insurance status and clinical site.
Villadsen 2009[522]	Denmark 1981-2003	Retrospective cohort study	1333452	5811	≥28 wks GA	Not reported	None	Maternal country of birth	N	N	N	N	N	N	Calendar year, household income, maternal education

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Villadsen 2010[523]	Austria, Flemish park of Belgium, Denmark, England, Wales, north Rhine west Phalia (Germany), the Netherlands, Norway, Sweden and Switzerland 1990-2005	Retrospective cohort study	239287	Not reported	**	See to the left	None	Maternal country of birth	N	N	N	N	N	N	Year of birth
Villamor 2006[234]	Sweden 1992-2001	Retrospective cohort study	207534	666	≥28 wks GA	None	Women without height and weight	Maternal BMI	Y	Y	Y	Y	N	N	Height, interpregnancy interval, country of origin, years of education, year of birth
Vintzileos 2002[276]	USA 1995-1997	Retrospective cohort study	10560077	29469	≥24 wks GA	≥500 grams	Multiple births, congenital anomalies, births with missing GA or birth weight below 500g, births with	Antenatal care attendance	Y	N	N	N	N	N	Gravity, marital status, maternal education

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							missing or absent prenatal care								
Wahabi 2017[239]	Saudi Arabia 2013-2015	Prospective cohort study	9723	94	≥24 wks GA	None	Non-Saudi women, multiple pregnancies, and women with unknown glycaemic index status	Maternal diabetes	Y	N	Y	N	Y	N	None
Waldenstrom 2014[182]	Norway, Sweden 1990-2010	Retrospective cohort study	955804	3869	≥22 wks GA	None	None	Maternal age, Smoking status, Maternal BMI,	N	Y (Swedish data)	N	N	N	Y	Year of birth, civil status, chronic hypertension, diabetes, Swedish dataset also adjusted for Country of birth and smoking status
Waldenstrom 2015[183]	Sweden 1990-2011	Retrospective cohort study	1804442	1810	≥28 wks GA	None	Women who were < 25 years, births less than 28 weeks GA and births with missing data on parity	Maternal age,	NA	Y	Y	Y	N	Y	Year of birth, family situation (living with baby's father compared with not), maternal height, history of stillbirth in previous pregnancy, and number of years from previous to present birth; maternal morbidity (pre gestational diabetes, gestational diabetes, pre gestational hypertension, preeclampsia) and intrauterine growth restriction (small for gestational age).

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Walfisch 2016[262]	Canada 2001-2007	Retrospective cohort study	19164	50	None provided	≥500 grams	Congenital anomalies (for final analysis only)	Maternal age, parity, smoking status, alcohol consumption, maternal education	Y	Y	N	N	N	N	Alcohol consumption, maternal education and congenital anomalies.
Warland 2008[330]	Australia 1997-2002	Case-control study	367	124	≥20 wks GA	≥1000 grams	Cases: multiple births, cases where the last 3 antenatal visits were not attended, no U/S, <1000g birthweight, absent data, cases where no controls could be found. Controls: neonatal deaths excluded	Chronic Hypertension	N	N	N	Y	Y	N	Parity, SGA
Warshak 2013[184]	USA 1998-2005	Retrospective cohort study	529445	2258	≥20 wks GA	≥350 grams	Incomplete medical records, major congenital anomalies, multiple births, 35+ years, <20 weeks GA or <350 grams birth weight	Maternal age	NA	N	N	Y	N	Y	Prenatal care, pregestational diabetes, chronic hypertension, SES.
Warshak 2015[389]	USA 2008-2011	Retrospective cohort study	6468	79	≥20 wks GA	None	Multiple birth, illicit drug use	Marijuana use in pregnancy	Y	N	Y	Y	Y	N	Prenatal care use
Wassimi 2010[64]	Canada 1991-2000	Retrospective cohort study	11033	Not reported	≥20 wks GA	None	Births with missing values for included variables.	Remote/rural living	Y	N	N	N	Y	N	Maternal education, marital status, plurality, infant gender

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Webster 2019[185]	UK 2000-2014	Retrospective cohort study	4481	139	≥20 wks GA	None	Multiple pregnancies, pregnancies where the participants could not be linked to deprivation index as they were recorded incorrectly. Births where there were missing variables.	Ethnicity, maternal age, smoking, parity, deprivation score.	N	Y	N	Y	N	N	Deprivation index.
Wernham 2016[623]	New Zealand 2008-2012	Retrospective cohort study	244047		≥37 wks GA	None	Multiple births, congenital anomalies, pregnancies with unknown maternity carer	Care type		Y	Y	Y	N	Y	NZ department, trimester of registration, pre-existing diabetes or hypertension.
Whiteman 2011[235]	USA 1978-2005	Retrospective cohort study	218389	831	≥20 wks GA	None	First pregnancies that resulted in a stillbirth and data were also excluded where sib-ships could not be identified and where the BMI values were missing	Maternal BMI	Y	Y	NA	Y	N	Y	Maternal education, marital status, prenatal smoking, alcohol abuse, prenatal care, interpregnancy interval, obstetric complications (pre-eclampsia and diabetes), year of birth and infant gender.
Wikstrom 2010[426]	Sweden 1999-2006	Prospective cohort study	610879	1926	≥28 wks GA	None	Multiple births, non-Nordic born mothers, births < 28 weeks GA	Maternal tobacco use	Y	NA	Y	N	Y	Y	Maternal education, Maternal hypertension, pregestational diabetes.
Wikstrom 2016[624]	Sweden 2008-2014	Prospective cohort study	167695	194	≥37 wks GA	None	Pregnancies with pregnancy related hypertensive disorders, multiple pregnancies, births missing data on blood pressure.	Chronic hypertension	Y	Y	Y	N	Y	Y	Maternal height, cohabitation, pregestational diabetes or GDM

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Williams 2018[275]	USA 2002-2008	Retrospective cohort study	121754	545	≥23 wks GA	None	Multiple pregnancies, pregnancies with missing exposure data, pregnancies from Utah due to the small number of black of white mothers.		Y	Y	Y	NA	N	Y	Birth year, insurance status, marital status, smoking in pregnancy, alcohol use in pregnancy, pre-pregnancy BMI, prior stillbirth, stillbirth risks in prior pregnancy (previous c-section, prior preterm birth), current risks (small for gestational age, preterm birth, placental abruption), preconception chronic disease (asthma, hypertension, diabetes), plus current area-level percent poverty, exposure to ozone, and temperature
Wilson 2008[187]	USA 1978-1997	Retrospective cohort study	633849	2830	≥20 wks GA	None	Congenital anomalies and malformations	Maternal age	NA	Y	Y	Y	N	N	Adequacy of prenatal care, fetal gender, year of birth
Wingate 2006[525]	USA 1995-1999	Retrospective cohort study	17879923	107664	≥20 wks GA	None	None	Maternal ethnicity	Y	Y	N	N	Y	Y	Marital status, education level, prenatal care utilisation, diabetes, hypertension, and birthweight
Wingate 2012[242]	USA 2001-2002	Retrospective cohort study	5598197	23836	≥20 wks GA	≥500 grams	Hispanic ethnicities, multiple births, births under 20 weeks GA or <500g	Maternal ethnicity.	Y	Y	N	N	Y	Y	Marital status, maternal education, diabetes, hypertension, prenatal care.
Wingate 2015[524]	USA 2005-2008	Retrospective cohort study	29786071	Not reported	≥20 wks GA	≥500 grams	Records with unknown or missing Hispanic origin. Women who	Maternal ethnicity	Y	N	N	N	Y	Y	Marital status, diabetes, hypertension.

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
							were not in study specific racial groups								
Wingate 2017[526]	USA 2009-2013	Retrospective cohort study	17787576	Not reported	≥20 wks GA	≥500 grams	Births where the GA was inconsistent with the birthweight, births out of the study period and births with missing data.	Maternal ethnicity	Y	N	N	N	N	Y	Birth year, diabetes, hypertensive disorders
Wisborg 2003[382]	Denmark 1989-1996	Prospective cohort study	25444	82	≥28 wks GA	None	Multiple pregnancies, women unable to speak Danish, births prior to 28 weeks GA	Coffee consumption	Y	Y	Y	N	Y	N	Alcohol intake, marital status, years of education, employment status.
Wisborg 2010[625]	Denmark 1989-2006	Prospective cohort study	20166	86	<April 2004, ≥28 wks GA >April 2004, ≥22 wks GA	None	Women with chronic diseases, births with missing data	ART use	Y	Y	Y	N	N	N	Education, marital status, alcohol and coffee use during pregnancy.
Wisborg 2001[430]	Denmark 1989-1996	Prospective cohort study	25444	116	≥28 wks GA	None	Multiple pregnancies, women unable to speak Danish, births prior to 28 weeks GA	Maternal smoking	Y	NA	N	N	Y	N	Fetal gender, marital status, maternal education, employment status, caffeine and alcohol intake during pregnancy, maternal weight and height

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Wolfe 2005[188]	USA 1991-1998	Retrospective cohort study	4536701	28011	≥22 wks GA	≥400 grams	None	Amphetamine use, cocaine use, polydrug use, maternal age, maternal ethnicity, tobacco use, prenatal care use,	Y	Y	N	Y	N	N	Maternal education, drug/alcohol use, no prenatal care, low birth weight.
Wood 2003[331]	UK 1987-1999	Case-control study	10913	98	≥20 wks GA	≥500 grams	Women with GDM or hyperglycaemia alone	Pregestational diabetes	Y	N	N	N	N	N	Year of birth
Wood 2012[339]	UK 1992-2008	Retrospective cohort study	1386967	3259	≥28 wks GA	None	Multiple births, births < 28 weeks GA	Deprivation	Y	N	Y	N	N	N	Maternal height, marital status, and hospital throughout.
Wu 2019[189]	Canada 2012-2015	Retrospective cohort study	386023	1134	≥20 wks GA	≥500 grams	Multiple births, women <20 years	Maternal age	NA	N	Y	N	Y	Y	Neighbourhood income, educational level, pre-pregnancy body mass index, drug/alcohol/tobacco use, type of conception, maternal pre-existing health problems, gestational diabetes mellitus, and preeclampsia
Xiao 2016[527]	Canada 1996-2010	Retrospective cohort study	246110	9980	≥20 wks GA	≥2500 grams	Births from Inuit communities, Aboriginal births in non-aboriginal communities	Maternal ethnicity	Y	N	N	NA	Y	N	Marital status, maternal education, year of birth, fetal gender, GA at birth, birthweight for GA

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Ya-Hui 2020[229]	USA 2006-2013	Retrospective cohort study	212889	636	≥20 wks GA	None	Women with questionable data or prior twin pregnancies were excluded from the study.	Maternal BMI	Y	Y	NA	Y	Y	Y	Maternal race–ethnicity, height, parity, interpregnancy interval between current and previous pregnancy; variables of prior and current pregnancies: maternal age, education, urban residence, percentage of black residents, pre-pregnancy diabetes, pre-pregnancy hypertension, smoking status, marital status and insurance of current and prior pregnancy; variables of prior pregnancy: gestational diabetes, gestational hypertension, smoking status during pregnancy, gestational age, birth weight, birth facility level of neonatal care, neonatal intensive care unit admission, Women, Infants, and Children program usage, breast feeding, mode of birth, Apgar score, stillbirth, and infant death.
Yang 2020[537]	Canada 1996, 2006	Retrospective cohort study	226167	795	None provided	None	Multiple births births with missing data on maternal place of birth	Maternal place of birth and number of years since	Y	N	N	Y	Y	N	Maternal education, marital status

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
								immigration to Canada							
Yao 2017[236]	USA 2006-2011	Retrospective cohort study	192165	Not reported	34-42 wks GA	below the 10th percentile birthweight	Missing height, weight or GA, pregnancies to underweight women, fetal anomalies	Maternal BMI	N	Y	NA	Y	N	Y	Gestational age, fetal gender, diabetes and hypertensive disorders
Yao 2017 (2)[237]	USA 2006-2011	Retrospective cohort study	2230310	5502	≥24 wks GA <42 wks	None	Multiple pregnancies, maternal height >74 inches or < 54 inches. Women with diabetes.	Maternal gestational weight gain	Y	y	N	Y	N	Y	Fetal gender, hypertensive disorders
Yerlikaya 2016[240]	UK 2006-2011	Retrospective cohort study	113019	396	≥24 wks GA (antepartum)	None	Congenital anomalies, miscarriages, terminations, intrapartum stillbirths.	Maternal ethnicity, mode of conception, smoking status, chronic hypertension, pre-existing diabetes.	Y	Y	N	Y	Y	Y	Maternal weight, height, mode of conception, chronic hypertension, interpregnancy interval, APS/SLE, diabetes mellitus.
Youngstrom 2018[626]	UK 2000-2014	Case-control study	1306	28	None provided	None	Women who reported a history of "prehypertension" or who reported resolution of chronic hypertension after lifestyle modification or weight loss were excluded. Multiple births	Chronic hypertension	N	N	N	N	Y	N	Prior preterm birth

Cohort studies	Country/study period	Study design and source	Cohort size	SBs in cohort	Stillbirth definition		Exclusion	Factors assessed	Key factors controlled for in analysis						Specific medical and other factors
					SB GA parameter	SB weight parameter			Age	Smoking	BMI	Race	Parity	Medical condition	
Zetterstrom 2008[332]	Sweden 1992-2004	Retrospective cohort study	866188	2597	≥28 wks GA	None	Multiple pregnancies, mother born outside Nordic countries, births with missing data on BMI and smoking	Chronic hypertension	Y	Y	Y	N	Y	N	None
Zhu 2004[398]	Denmark 1998-2001	Retrospective cohort study	42687	134	≥28 wks GA	None	2nd and 3rd pregnancies in the study period, pregnancies where the outcomes were known at the time of interview, women who died before birth, pregnancies with no outcome data	Shift work rotation and job strain	Y	Y	Y	N	N	N	Gravity, history of spontaneous abortion, occupation, working posture, working hours per week, heavy lifting, perceived strenuous work, support from co-workers, job strain, work schedule.
Zile 2019[244]	Latvia 2001-2014	Retrospective cohort study	294355	1822	≥22 wks GA	≥500 grams	Not listed	Chronic hypertension and diabetes mellitus.	Y	N	N	N	Y	N	Gestational age

**Austria: ≥500g at birth, Belgium (Flanders): ≥500g at birth, Denmark: ≥ 28 wks GA, England and Wales: ≥ 24 wks GA, Germany: ≥500g at birth (prior to 1-Apr-94, ≥1000g), Netherlands: ≥ 24 wks GA, Norway: ≥ 22 wks GA, Sweden: ≥ 28 wks GA, Switzerland: ≥500g at birth or 22 wks GA.

Appendix D – Results of Quality and Bias assessment

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
1	Aagaard-Tillery 2006[98]	+	=	=	=	=	+	+	Unclear
2	Adams 2018[528]	=	+	=	=	=	+	+	Unclear
3	Ahlenius 1999[99]	+	=	=	+	+	=	-	High
4	Ahmad 2012[579]	+	+	=	+	+	=	-	High
5	Akobirshoev 2019[507]	+	+	+	+	=	+	+	Low
6	Alemu 2020[385]	+	+	+	+	=	+	+	Low
7	Alio 2012[298]	+	+	=	+	+	+	+	Low
8	Aliyu 2008[370]	+	=	=	=	+	+	-	High
9	Aliyu 2010[100]	+	=	-	=	+	+	+	High
10	Aliyu 2011[425]	+	=	+	+	=	+	+	Low
11	Aliyu 2005[299]	=	+	=	=	=	+	+	Unclear
12	Aliyu 2007[428]	+	=	-	=	+	+	-	High
13	Allen 2020[101]	+	=	=	+	+	+	+	Low
14	Allen 2004[300]	+	=	+	+	+	+	+	Low
15	Allen 2005[508]	+	+	=	=	+	+	+	Low
16	Allen 2018[360]	+	+	=	+	=	+	+	Low
17	Amark 2018[231]	+	+	+	+	+	=	+	Low
18	Ananth 1995[47]	+	+	+	+	+	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
19	Andersen 2012[367, 580]	+	+	-	=	+	+	+	Unclear
20	Andersen 2004[301]	+	=	=	+	+	=	-	Unclear
21	Angley 2018[373, 581]	+	+	+	+	+	+	+	Low
22	Anthony 2009[582]	=	+	=	=	+	+	+	Unclear
23	Arnold 2012[102]	+	=	-	=	+	+	+	Unclear
24	Aschengrau 2018[484]	-	+	=	=	+	=	-	High
25	Astolfi 2005[103]	+	+	=	=	=	=	-	High
26	Auger 2020[104]	+	=	=	+	+	+	+	Low
27	Auger 2012[259]	+	+	=	+	=	+	+	Low
28	Auger 2013[65]	+	=	=	+	+	+	+	Low
29	Auger 2014[66]	+	=	=	+	+	+	+	Low
30	Baba 2014[423]	+	=	=	+	=	+	+	Unclear
31	Balayla 2011[40]	+	=	=	+	=	+	+	Unclear (Low for age, ethnicity and education)
32	Balayla 2011 (2)[105]	=	=	-	=	=	+	-	High
33	Balchin 2007[106]	+	=	=	+	=	+	+	Unclear
34	Barona-Vilar 2014[530]	=	=	-	=	=	-	-	High
35	Bartsch 2015[42]	+	=	=	+	+	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
36	Bateman 2006[107]	+	=	=	=	=	+	-	High
37	Baum 2015[271]	+	+	=	+	+	+	+	Low
38	Bay 2019[302]	+	=	=	+	+	+	+	Low
39	Bech 2005[436]	+	+	=	+	=	+	-	High
40	Berman 2020[531]	+	+	+	+	=	+	+	Low
41	Best 2019[340]	+	+	+	+	=	+	-	Unclear
42	Beyerlein 2010[108]	+	+	=	+	+	+	+	Low
43	Beyerlein 2020[342]	+	+	+	+	+	+	+	Low
44	Bilsteen 2018[53]	+	+	+	+	+	+	+	Low
45	Bjornholt 2016[418]	+	=	-	=	=	+	+	Unclear
46	Borrell 2003[109]	=	+	+	=	+	+	+	Low
47	Brisendine 2017[110]	+	=	-	=	=	+	+	Unclear
48	Brown 2007[532]	+	+	=	=	=	+	-	High
49	Brown 2012[111]	+	+	-	+	=	+	+	Unclear
50	Browne 2019[191]	+	+	+	+	=	+	+	Low
51	Butler 2019[487]	+	+	=	=	+	=	-	High
52	Canterino 2004[112]	+	=	-	=	+	+	+	Unclear
53	Carlsen 2014[261]	+	+	=	+	+	=	+	Low
54	Carmichael 2015[44]	+	+	=	=	=	=	-	High
55	Carmichael 2019[192]	=	=	=	=	=	+	-	High
56	Cedergren 2004[193]	+	+	=	+	+	=	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
57	Chughtai 2017[583]	+	+	=	+	=	+	+	Low
58	Chang 2011[437]	=	+	=	=	+	+	-	High
59	Chen 1998[253]	+	+	=	=	=	+	+	Unclear
60	Chen 2015[538]	+	=	=	+	=	+	+	Unclear
61	Choi 2019[509]	+	+	+	+	=	+	+	Low
62	Cnattingius 1998[194]	=	=	=	=	+	=	-	High
63	Cnattingius 2002[195]	+	=	-	=	+	=	+	Unclear
64	Cnattingius 2016[232]	+	=	=	+	+	+	+	Low
65	Cornman-homonoff 2012[366, 584]	+	+	=	+	+	+	+	Low
66	Corsi 2019[388]	+	+	=	=	=	+	-	High
67	Crane 2011[585]	+	+	+	+	+	+	+	High
68	Crane 2013[196]	+	+	=	=	=	+	-	High
69	Cruz 2011[304]	+	=	=	+	+	+	+	Low
70	Cupul-Uicab 2011[424]	+	=	=	+	+	-	+	Unclear
71	Davies-tuck 2016[197]	+	=	=	+	=	+	+	Unclear
72	Davie s-Tuck 2017[73]	+	=	=	+	+	+	+	Low
73	DeFranco 2015[333]	+	+	=	+	=	=	+	Unclear
74	de Graaff 2017[67]	+	+	=	+	+	+	-	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
75	de Jonge 2015[586]	+	+	-	=	=	+	+	Unclear
76	de Jonge 2009[113]	+	+	=	+	+	+	+	Low
77	de Vienne 2009[114]	=	+	=	=	=	=	-	High
78	Delbaere 2008[116]	+	=	=	+	+	+	+	Low
79	Delbaere 2007[115]	+	+	=	+	=	+	+	Low
80	Dhalwani 2019[417]	+	+	+	+	+	=	+	Low
81	Dickinson 2002[249]	+	+	=	=	+	+	-	High
82	Dodds 1999[477]	+	+	=	+	=	+	-	High
83	Dodds 2004[587]	=	+	+	+	+	+	+	Low
84	Dodds 2006[305]	=	=	-	=	=	+	+	Unclear
85	Donegan 2014[306]	=	=	=	+	=	+	+	Unclear
86	Dongarwar 2020[118]	+	+	+	+	=	+	+	Low
87	dos Santos Silva 2009[403]	+	=	=	=	=	=	-	High
88	Doyle 2000[400]	+	+	+	=	+	+	+	Low
89	Draper 2017[119]	+	=	=	+	=	+	+	Unclear
90	Drysdale 2012[71]	+	=	=	+	=	+	+	Unclear
91	Ebisu 2018[485]	+	+	+	+	+	+	+	Low
92	Efkarpidis 2005[120]	+	+	=	+	+	+	-	Unclear
93	Efkarpidis 2004[121]	+	=	=	=	+	-	+	Unclear
94	Eidem 2011[245]	+	=	=	+	+	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
95	Ekeus 2011[533]	+	+	=	+	+	=	+	Low
96	El-Bastawissi 2007[381]	=	+	=	-	+	+	+	Unclear
97	Elliot 2001[588]	-	+	-	-	=	+	-	High
98	Eng 2016[43]	=	=	=	=	=	+	+	Unclear
99	Engel 2008[246]	+	=	=	=	=	+	-	High
100	Everett 2019[307]	+	+	+	+	=	+	+	Low
101	Faber 2019[264]	+	+	+	+	=	+	+	Low
102	Fabiani 2015[267]	+	+	+	+	=	=	+	Low
103	Facchinetti 2011[198]	=	+	=	=	+	+	-	High
104	Faiz 2012[122]	+	=	=	+	=	+	+	Unclear
105	Familiari 2016[510]	+	=	=	+	=	=	-	High
106	Fell 2012[589]	+	+	=	+	=	+	+	Low
107	Frederiksen 2018[123]	+	+	+	+	=	+	+	Low
108	Froen 2001[124]	=	=	=	=	=	+	+	Unclear
109	Fuchs 2017[199]	+	+	=	+	+	=	+	Low
110	Gallicchio 2009[258]	+	=	=	-	=	+	+	Unclear
111	Gardosi 2013[200]	+	=	+	=	=	=	+	Unclear
112	Gaskins 2014[379]/Gaskins 2014[364]	+	+	=	=	=	+	+	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
113	Gaskins 2016[202]/Gaskins 2014[201]	+	=	-	=	-	+	+	Unclear
114	Germain 2016[308]	+	+	+	+	=	=	-	High
115	Getahun 2007[309]	+	+	=	+	=	+	+	Low
116	Getahun 2019[268]	+	+	+	+	=	+	+	Low
117	Getahun 2005[511]	=	+	=	=	=	=	-	High
118	Ghosh 2019[488]	+	+	+	+	=	+	+	Low
119	Gibson-helm 2015[512]	+	+	=	+	=	+	+	Low
120	Gilbreath 2006[590]	+	+	=	+	=	+	+	Low
121	Gold 2010[539]	+	=	=	+	+	+	+	Low
122	Gordon 2015[92]	=	=	=	=	+	+	+	Unclear
123	Gordon 2013[125]	+	+	=	+	+	=	+	Low
124	Gottvall 2011[529]	+	+	=	+	=	+	-	Unclear
125	Goy 2008[126]	+	+	=	=	=	+	+	Unclear
126	Graham 2007[62]	+	+	=	+	=	=	+	Unclear
127	Gray 2009[338]	+	+	=	+	=	=	+	Unclear
128	Green 2015[34]	+	+	=	+	+	+	+	Low
129	Grunebaum 2016[410]	+	+	=	+	=	+	+	Low
130	Gulliver 2015[392]	+	+	=	+	=	=	-	High
131	Gulliver 2014[95]	+	=	=	+	=	=	-	High

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
132	Gunnarsson 2014[411]	+	+	=	+	+	+	+	Low
133	Gupta 2019[310]	=	+	=	=	-	+	-	High
134	Ha 2017[591]	+	+	=	+	+	=	+	Low
135	Haavaldsen 2010[128]	+	+	=	+	+	+	+	Low
136	Halliday-bell 2010[394, 397]	+	+	+	+	+	+	-	Unclear
137	Harrison 2018[592]	=	+	=	=	=	+	-	High
138	Haruyama 2018[129]	+	+	=	=	+	=	-	High
139	Healy 2006[514]	+	=	-	=	=	+	+	Unclear
140	Heaman 2019[87]	+	+	+	+	=	+	+	Low
141	Heazell 2018[91]	+	+	+	+	+	+	+	Low
142	Heggland 2011[393]	+	=	=	=	+	+	+	Low
143	Helgadottir 2011[130]	+	=	-	+	+	+	+	Unclear
144	Henningsen 2014[131]	+	+	+	+	=	+	+	Low
145	Herbert 2012[311]	+	+	=	=	=	=	-	High
146	Hesselman 2019[341]	+	+	+	+	+	+	+	Low
147	Hilden 2019[204]	+	+	+	+	=	+	+	Low
148	Hodyl 2014[68]	+	=	=	+	=	+	+	Unclear
149	Hogberg 2007[132]	+	=	=	+	+	+	+	Low
150	Hogue 2013[97]	+	+	=	=	+	+	+	Low
151	Homer 2019[408]	+	+	+	+	+	=	-	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
152	Huang 2000[134]	+	+	=	+	=	=	-	High
153	Hyland 2015[51]	+	+	=	=	=	+	-	High
154	Iacobelli 2012[135]	+	+	=	+	=	+	+	Low
155	Ibiebele 2016[593]	+	+	=	+	=	+	+	Low
156	Ihrig 1998[35]	+	+	=	-	=	+	-	Unclear
157	Ikedionwu 2020[205]	+	+	=	=	=	+	-	High
158	Irgens 2016[402]	+	=	+	+	+	+	+	Low
159	Islam 2015[136]	+	+	=	=	=	+	-	High
160	Jacob 2016[206]	+	=	=	+	+	+	+	Low
161	Jacobsson 2004[137]	+	+	=	+	+	=	+	Low
162	Johansson 2017[207]	=	+	+	+	+	+	+	Low
163	Jolly 2000[138, 139]	+	+	=	+	=	=	+	High
164	Jonas 2015[273]	+	+	=	=	=	+	+	Unclear
165	Juhl 2013[58]	+	=	=	+	=	+	+	Unclear
166	El Kady 2005[94]	+	+	=	+	+	+	+	Low
167	Kallen 2001[431]	+	+	=	=	+	+	+	Low
168	Kallen 2012[269]	+	+	=	=	=	+	+	Unclear
169	Kang 2001[594]	+	+	+	=	+	=	+	Low
170	Kapurubandara 2016[334]	+	+	-	=	=	+	+	Unclear
171	Kennare 2007[595]	+	+	=	+	=	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
172	Kennare 2005[391]	+	=	-	=	+	=	+	Unclear
173	Kennare 2009[413]	+	+	=	+	+	+	-	Unclear
174	Kenny 2013[140]	+	+	=	+	+	+	+	Low
175	Kesmodel 2002[371]	+	=	=	+	=	+	+	Unclear
176	Khalil 2013[345]	+	=	=	+	=	+	+	Unclear
177	Kharrazi 2004[429]	+	=	=	+	=	+	+	Unclear
178	Khashan 2009[343]	+	+	+	+	=	+	+	High
179	King 2000[596]	+	+	=	+	+	+	+	Low
180	King 2005[480]	+	=	=	+	+	+	+	Low
181	Kinzler 2002[141]	+	+	=	+	=	+	+	Low
182	Knight-Agarwal 2015[208]	+	+	=	=	=	+	-	High
183	Kortekaas 2020[142]	+	+	=	=	=	+	-	High
184	Kristensen 2005[597]	=	=	-	-	=	+	+	High
185	Lai 2016[243]	+	+	=	+	=	+	+	Unclear
186	Lamminpaa 2016[143]	+	+	=	=	=	+	+	Unclear
187	Lauria 2003[144]	=	+	=	=	=	=	-	High
188	Laws 2010[412]	+	+	=	+	+	+	+	Low
189	Lawton 2018[265]	+	=	=	=	=	+	+	Unclear
190	Lewis 2009[145]	+	+	=	+	+	+	+	Low
191	Li 2019[416]	+	+	=	=	=	+	-	High

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
192	Lindam 2016[210]	+	+	=	+	=	=	+	Unclear
193	Lisonkova 2017[149]	+	+	=	=	+	+	+	Low
194	Lisonkova 2011[598]	+	+	=	+	+	+	+	Low
195	Lisonkova 2010[146]	+	+	=	+	+	=	+	Low
196	Lisonkova 2013[147]	+	+	=	+	=	+	+	Low
197	Lisonkova 2013 (2)[147]	+	+	=	=	+	=	+	Unclear
198	Liu 2019[534]	+	+	+	+	+	+	+	Low
199	Liu 2010[312]	+	+	=	+	=	+	+	Low
200	Lorch 2012[150]	+	=	=	+	+	+	+	Low
201	Lou 2013[315]	+	+	=	=	=	+	-	High
202	Lucovnik 2018[211]	+	+	+	+	=	+	+	Low
203	Luke 2019[387]	+	+	+	+	=	+	+	Low
204	Luo 2004[540]	+	=	=	+	=	+	+	Unclear
205	Luo 2004 (2)[313]	=	+	=	=	+	+	-	High
206	Luo 2006[314]	+	+	=	+	=	=	+	Unclear
207	Luo 2008[250]	+	+	=	+	+	+	+	Low
208	Luo 2010[515]	+	+	=	+	=	+	-	Unclear
209	Luo 2012[516]	+	+	=	+	=	+	-	Unclear
210	Luque-Fernandez 2019[153]	+	+	+	+	+	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
211	Luque-Fernandez 2011[152]	+	+	=	=	+	=	+	Unclear
212	Luque-Fernandez 2013[151]	+	=	=	+	=	+	+	Unclear
213	Lygre 2016[444]	+	+	+	+	=	+	+	Low
214	Macintosh 2006[241]	=	+	=	=	=	+	-	High
215	Malabarey 2012[154]	+	+	+	+	=	+	+	Low
216	Maleckiene 2001[317]	-	=	=	-	+	+	-	High
217	Matijasevich 2006[257]	=	=	-	=	=	+	+	Unclear
218	Mayo 2019[155]	+	+	+	+	+	=	+	Low
219	McCowan 2007[156]	+	=	=	+	+	+	+	Low
220	McCowan 2017[32]	=	+	=	=	+	+	+	Unclear
221	McClure 2011[434]	+	+	=	=	+	+	-	Unclear
222	McDonald 2007[390]	+	=	-	=	=	+	-	High
223	McInerney 2019[415]	+	+	+	+	=	+	+	Low
224	Mei-dan 2015[599]	+	=	-	=	=	=	-	High
225	Melchor 2019[212]	+	+	=	=	=	+	-	High
226	Mendola 2017[600]	+	+	-	=	=	=	-	High
227	Merc 2019[213]	=	+	=	=	=	+	-	High
228	Mjøen 2006[404]	+	=	=	=	+	+	+	Unclear
229	Mocevic 2014[56]	=	+	=	=	+	+	+	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
230	Mogos 2016[96]	+	+	=	+	=	+	+	Low
231	Mohsin 2006[157]	+	=	-	=	=	=	+	Unclear
232	Moraitis 2015[601]	+	+	=	+	+	+	+	Low
233	Morales 2017[374]	+	=	+	+	=	+	+	Low
234	Morales-Suarez-Varela 2018[372]	+	=	=	+	=	+	+	Unclear
235	Morisaki 2018[602]	+	+	+	+	=	+	+	Low
236	Morris 2003[479]	+	+	=	+	+	+	-	Unclear
237	Mozooni 2018[518]	+	+	+	+	=	+	+	Low
238	Mozooni 2020[158]	+	+	+	+	=	+	+	Low
239	Mozooni 2020(2)[252]	+	+	+	+	=	=	+	Low
240	Mueller 2007[603]	+	+	+	+	+	+	+	Low
241	Nabukera 2006[159]	+	+	=	=	=	+	-	High
242	Nabukera 2008[160]	+	+	=	=	=	=	+	Unclear
243	Nabukera 2009[318]	+	+	=	+	+	+	+	Low
244	Nair 2017[604]	+	=	=	+	=	+	+	Unclear
245	Nohr 2005[214]	+	=	=	=	+	+	+	Unclear
246	Nohr 2014[378]	+	+	=	+	=	=	+	Unclear
247	O'Leary 2007[161]	+	+	=	+	=	+	+	Unclear
248	O'Leary 2012[365]	+	=	-	=	=	+	-	High
249	Oakley 2016[162]	+	+	=	=	=	+	+	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
250	O'Brien 2018[90]	+	+	-	=	-	=	-	High
251	Olausson 1999[163]	+	+	=	+	=	+	+	Unclear
252	Olsen 1999[254]	+	=	-	=	+	+	+	Unclear
253	Ombelet 2016[605]	+	+	-	=	=	+	+	Unclear
254	O'Neill 2014[606]	+	+	=	+	=	=	+	Unclear
255	Ovesen 2011[215]	+	+	=	+	=	+	+	Low
256	Panaitescu 2017[607]	+	=	=	+	=	+	+	Unclear
257	Paranjothy 2014[384]	+	+	=	+	+	+	+	Low
258	Parker 1999[60, 405, 406]	=	+	+	=	+	+	+	Low
259	Parker 2016[344]	+	+	=	+	=	+	-	Unclear
260	Partridge 2012[88]	=	+	=	=	+	=	+	Unclear
261	Pasternak 2012[270]	+	+	+	+	=	+	+	Low
262	Patel 2015[320]	+	=	=	=	+	=	-	High
263	Pearce 2010[482]	+	+	=	=	=	+	+	Unclear
264	Penn 2014[164]	+	=	-	=	+	+	+	Unclear
265	Peticca 2009[248]	+	+	=	+	=	+	+	Unclear
266	Petrangelo 2019[386]	+	+	+	+	=	+	+	Low
267	Pickens 2019[217]	+	+	+	+	=	+	+	Low
268	Pilkington 2014[383]	+	+	-	=	-	=	-	High
269	Po 2019[218]	+	+	+	+	=	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
270	Quansah 2009[396]	+	=	+	+	+	+	-	Unclear
271	Raatikainen 2007[608]	=	+	=	+	=	+	+	Unclear
272	Raisanen 2013[609]	+	+	=	+	+	+	+	Low
273	Raisanen 2018[165]	+	+	+	+	+	+	+	Low
274	Raisanen 2014[422]	+	=	=	+	+	=	+	Unclear
275	Rammah 2019[491]	+	+	+	+	=	+	+	Low
276	Rammah 2019 (2) [489]	+	+	=	=	+	+	+	Low
277	Ramö isgren 2017[219]	+	=	=	=	=	+	+	Unclear
278	Rasmussen 2003[166]	+	+	=	+	+	+	+	Low
279	Ravelli 2011[69]	+	+	=	+	+	+	+	Low
280	Ravelli 2013[610]	+	+	=	+	=	+	-	Unclear
281	Reddy 2010[535]	+	+	=	+	+	=	+	Low
282	Regan 2016[52]	+	+	=	+	=	+	+	Low
283	Regan 2019[321]	+	+	+	+	=	+	+	Low
284	Reime 2009[395]	+	=	-	=	+	=	-	High
285	Reime 2009 (2)[86]	+	=	+	+	+	+	+	Low
286	Richter 2007[519]	+	+	=	+	=	+	+	Low
287	Rivera-Nunez 2018[486]	+	+	+	+	+	+	+	Low
288	Robson 2006[168]	+	=	-	-	=	=	+	High

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
289	Rockhill 2019[414]	+	+	=	=	=	+	+	Unclear
290	Roman 2007[220]	+	+	=	+	=	+	+	Low
291	Rozdarz 2017[322]	+	+	+	+	+	+	+	Low
292	Rukuni 2016[611]	+	=	=	+	+	+	+	Low
293	Russell 2010[221]	+	+	=	+	+	+	+	Low
294	Salihu 2008[615]	=	=	=	+	+	+	+	Unclear
295	Salihu 2003[612]	=	=	=	=	+	+	+	Unclear
296	Salihu 2004(2)[171]	+	=	=	+	+	+	+	Low
297	Salihu 2004(3)[520]	+	=	-	=	+	+	+	Unclear
298	Salihu 2004(4)[175]	+	=	=	+	=	+	+	Unclear
299	Salihu 2005[597]	=	=	=	=	+	+	+	Unclear
300	Salihu 2005(2)[169]	+	=	=	+	+	+	+	Low
301	Salihu 2006(3)[613]	+	=	=	+	+	=	+	Unclear
302	Salihu 2006(4)[174, 614]	+	=	=	+	=	=	+	Unclear
303	Salihu 2007[223]	=	=	=	=	+	=	-	High
304	Salihu 2008(2)[176]	=	=	=	+	=	=	+	Unclear
305	Salihu 2009[70]	+	=	-	=	=	+	-	High
306	Salihu 2010[222]	+	=	=	+	+	+	+	Low
307	Salihu 2011[173]	+	=	=	+	+	+	+	Low
308	Savard 2013[260]	+	+	=	+	+	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
309	Savitz 2012[483]	=	=	=	=	=	+	+	Unclear
310	Scheller 2017[266]	+	+	=	+	=	+	-	Unclear
311	Schneuer 2014[377]	+	+	+	+	+	+	+	Low
312	Scott-Pillai 2013[224]	+	+	=	+	+	=	+	Low
313	Sebire 2001[225, 616]	+	+	=	=	=	+	-	High
314	Shapiro 2018[63]	+	+	=	=	=	=	-	High
315	Shapiro 2018 (2)[323]	+	+	+	+	=	+	-	Unclear
316	Shapiro 2017[54]	+	+	=	+	+	+	+	Low
317	Shumpert 2004[617]	+	=	=	+	+	+	+	Low
318	Siahanidou 2020[177]	+	+	=	=	+	+	+	Low
319	Silver 2019[89]	+	+	+	+	+	+	+	Low
320	Simonet 2009[438]	+	+	-	=	=	=	-	High
321	Sloggett 1998[335]	+	=	-	=	+	+	-	Unclear
322	Smith 2001[618]	+	+	=	+	=	=	+	Unclear
323	Smith 2003 (2)[619]	+	+	=	+	+	+	+	Low
324	Smith 2020[490]	+	+	=	=	=	+	+	Unclear
325	Smith 2003[620]	+	+	+	+	=	=	+	Low
326	Smith 2007[178]	+	=	=	+	+	+	+	Low
327	Smulian 2002[238]	+	+	=	+	=	+	+	Low
328	Snowden 2015[433]	+	+	=	+	=	+	+	Low
329	Sorbye 2014[536]	+	+	=	+	=	+	+	Low

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
330	Stacey 2011[179, 362, 442]	-	+	+	=	+	+	+	Unclear
331	Stephansson 2001/Stephansson 2000[336, 337]	+	=	+	=	=	+	+	Unclear
332	Stephansson 2003[326]	+	=	+	+	+	+	+	Low
333	Strand 2012[327]	=	=	-	=	+	+	+	Unclear
334	Strandberg-Larsen 2008[427]	+	=	-	=	=	=	+	Unclear
335	Strandberg-larsen 2008(2)[369]	+	-	=	=	-	+	+	Unclear
336	Sutan 2010[180]	+	=	-	=	=	=	+	Unclear
337	Syngelaki 2011[227]	+	+	=	+	+	+	+	Low
338	Tennant 2011[228]	+	-	=	+	=	+	+	Unclear
339	The Stillbirth Collaborative Research Network Writing group[127]	+	=	=	+	+	+	+	Low
340	Toledano 2005[36]	+	+	=	+	+	=	+	Low
341	Tomashek 2006[621]	=	=	=	=	+	=	+	Unclear
342	Tracy 2007[435]	+	+	=	+	+	+	-	Unclear

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
343	Tran 2014[622]	+	=	=	=	+	=	+	Unclear
344	Trotta 2014[274]	+	+	=	+	=	+	+	Low
345	Trudell 2017[181]	+	+	=	=	+	+	+	Low
346	Tudehope 2018[528]	+	+	=	+	=	+	+	Low
347	Urhoj 2017[329]	+	+	=	+	=	+	+	Low
348	Valanis 1999[478]	+	=	-	=	=	+	-	High
349	Vangen 2002[543]	=	+	=	=	=	+	-	High
350	Varner 2014[420]	+	+	=	+	+	+	+	Low
351	Villadsen 2009[522]	=	+	=	=	=	+	+	Unclear
352	Villadsen 2010[523]	=	+	=	=	=	=	-	High
353	Villamor 2006[234]	+	+	=	=	=	=	+	Unclear
354	Vintzileos 2002[276]	+	+	=	+	+	+	+	Low
355	Wahabi 2017[239]	+	+	=	+	=	+	+	Low
356	Waldenstrom 2014[182]	+	+	=	+	+	+	+	Low
357	Waldenstrom 2015[183]	+	+	=	+	+	+	+	Low
358	Walfisch 2016[262]	+	=	-	=	+	+	+	Unclear
359	Warland 2008[330]	=	+	=	+	+	=	+	Unclear
360	Warshak 2013[184]	=	+	=	=	+	+	+	Low
361	Warshak 2015[389]	=	=	-	=	+	+	-	High

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
362	Wassimi 2010[64]	+	+	=	=	=	+	-	High
363	Webster 2019[185]	+	+	+	+	=	+	+	Low
364	Wernham 2016[623]	+	+	=	+	=	+	+	Low
365	Whiteman 2011[235]	+	+	=	+	+	=	+	Low
366	Wikstrom 2010[426]	+	=	=	+	=	=	+	Unclear
367	Wikstrom 2016[624]	+	=	=	+	=	+	+	Unclear
368	Williams 2018[275]	+	+	=	=	=	+	+	Unclear
369	Wilson 2008[187]	+	+	=	+	+	+	+	Low
370	Wingate 2012[242]	+	=	=	+	=	+	-	High
371	Wingate 2006[525]	+	+	=	=	=	+	+	Unclear
372	Wingate 2015[524]	+	+	=	+	=	+	+	Low
373	Wingate 2017[526]	+	+	=	+	+	+	-	Unclear
374	Wisborg 2001[430]	=	=	=	=	+	+	+	Unclear
375	Wisborg 2003[382]	=	=	=	=	+	+	+	Unclear
376	Wisborg 2010[625]	+	+	-	=	-	=	-	High
377	Wolfe 2005[188]	=	=	=	=	-	=	+	High
378	Wood 2003[331]	+	+	=	=	=	+	-	High
379	Wood 2012[339]	+	+	=	+	=	+	+	Low
380	Wu 2019[189]	+	+	+	+	=	+	+	Low
381	Xiao 2016[527]	+	+	+	+	+	+	+	Low
382	Ya-Hui 2020[229]	+	+	=	=	=	+	-	High

RTI-item bank assessment by study	**Study ID**	Selection Bias	Performance Bias	Detection Bias	Confounding	Attrition bias	Selective outcome reporting	Overall assessment	**Risk of bias**
383	Yang 2020[537]	+	+	+	+	=	+	-	Unclear
384	Yao 2017[236]	+	+	=	=	+	+	+	Low
385	Yao 2017 (2)[237]	+	+	=	=	=	+	+	Unclear
386	Yerlikaya 2016[240]	+	=	=	+	+	+	+	Low
387	Youngstrom 2018[626]	+	+	+	+	=	+	-	Unclear
388	Zetterstrom 2008[332]	+	=	=	=	=	+	+	Unclear
389	Zhu 2004[398]	+	=	=	+	+	=	+	Unclear
390	Zile 2019[244]	+	+	+	+	=	+	+	Unclear

Appendix E – Systematic review study extraction form

Lifestyle risk factors and social determinates of stillbirth risk.
Data extraction form - v1.6_30May2019

Study ID:	
Paper Title: Additional references of secondary papers (if relevant):	
Data extraction date: Person extracting data: 2nd reviewer/extractor: 2nd review/extraction date:	
Study design (refer to taxonomy on study design sheet):	
Study Setting (e.g. Nationwide/state/hospital/institute/birth centre, also please list the name): Study Country/ies: Study Year(s):	
Conflicts of interest:	
Study Funding:	
Study name (if reported):	
Inclusion criteria:	
Exclusion criteria:	
Are congenital anomalies included in analysis?	
Are terminations included in analysis?	
Definition of stillbirth:	
Factors assessed:	
Data Sources (list each exposure/outcome, and the source)	*Factors/exposure and birth outcomes:*
Total number of participants:	Total included:
Important characteristics of participants noted by study:	

Other factors included in the article that have not been extracted:

Factor	Data type available (crudeOR/raw)

Assessment of Quality (RTI tool)		
1. Do the inclusion/exclusion criteria vary across the comparison groups of the study?	☐ Yes, varies ☐ Partially: some but not all criteria, applied to all groups of not clearly stated if some criteria are applied to all groups ☐ no, does not vary ☐ Cannot determine: article does not specify ☐ Not applicable: study has only one group, no comparison group	If so please explain:
2. Does the strategy for recruiting participants into the study differ across groups?	☐ Yes, differs ☐ No, does not differ ☐ Cannot determine ☐ Not applicable: one study group	How does the study recruit
3. Is the selection of the comparison group inappropriate, after taking into account feasibility and ethical considerations?	☐ Yes, inappropriate ☐ No, not inappropriate ☐ Cannot determine or no description of the derivation of the comparison group ☐ Not applicable: Study does not include a comparison group	If unsure or yes, please explain: (please note here if the study was at 1 hospital and if they used a population comparison group, or a hospital patient comparison group from the same regional area)
4. Does the study fail to account for important variations in the execution of the study from the proposed protocol?	☐ Yes fails to account ☐ Partially, fails to account ☐ No, does not fail to account ☐ Cannot determine ☐ Not applicable: not an intervention study or no variations	
5. Was the outcome assessor not blinded to the intervention or exposure status of participants?	☐ Yes not blinded ☐ No, blinded ☐ Not applicable: assessor cannot be blinded	

6. Were valid and reliable measures, implemented consistently across all study participants used to assess inclusion/exclusion criteria, intervention/exposure outcomes, participant health benefits and harms, and confounding?	☐ Yes, valid and reliable measure used ☐ No, valid and reliable measure not used ☐ Cannot determine or measurement approach not reported	
7. Was the length of follow-up different across the study groups?	☐ Yes different or cannot determine ☐ No, not different or remedied through analysis ☐ not applicable: cross-sectional or only one group followed over time	
8. In cases of high loss to follow-up (or differential loss to follow-up) was the impact assessed (e.g. Through sensitivity analysis or other adjustment method)?	☐ Yes Impact assessed ☐ No, impact not assessed ☐ Cannot determine ☐ Not applicable: no loss to follow-up or loss to follow-up not considered to be high, cross-sectional study, or case control study selected outcome.	
9. Are any important primary outcomes missing from the results?	☐ Yes, important outcome(s) missing ☐ No important outcome(s) missing ☐ Cannot determine	
10. Are any important harms or adverse events that may be a consequence of the exposure missing from the results?	☐ Yes, Important outcome(s) missing ☐ No important outcomes missing ☐ Assessment of harms not applicable to this study	
11. Are the results believable taking study limitations into consideration?	☐ Yes, believable ☐ No, not believable	Please detail any concerns or limitations of the study.
12. Any attempt to balance the allocation between the groups or match groups (e.g., through stratification, matching, propensity scores).	☐ Yes Study accounts for imbalance between groups through a post hoc approach such as multivariate analysis ☐ No or cannot determine ☐ Not applicable: study does not include a comparison group	

13. Were important confounding variables not taken into account in the design and/or analysis (e.g. Through matching, stratification, interaction terms, multivariate analysis, or other statistical adjustment such as instrumental variables)?	☐ Yes, not accounted for or not identified ☐ Partially: some variables taken into account or adjustment achieved to some extent ☐ No: taken into account ☐ Cannot determine	List confounders adjusted for; How many models of adjustment were included in the study results?

Exposure 1

(population characteristic data/study results) ←highlight one

	Exposure type:						
	Specific exposure analysis confounders controlled in adjusted effect measure:						
Comparison definition: *referent, add rows as needed for different categories of exposure)	Descriptor – (e.g. Smoking prior to pregnancy, 20 cigarettes per day in 1st trimester)	Time points of exposure data collection (eg – 1st antenatal visit, at birth, multiple collections (give time points)	Total Participants	Stillbirth	Non-stillbirth	Crude effect measure:	Adjusted effect measure
	Descriptor	Quantitative/Qualitative (highlight one)		Events	Events	OR (95% CI)	AOR (95% CI)
Referent (non-expose)*		Definition: Timepoint:				referent	referent
Exposure		Definition: Timepoint:					