PREDICTION AND SEQUELAE OF SMOKING IN PREGNANCY

By

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Dedication

I would like to dedicate this thesis to my late grandfather, who passed away earlier this year. He always joked that my academic success was thanks to the genes I inherited from him — and he was probably right. I wouldn't be here without you, and I miss you so much.

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First and foremost, I would like to thank my wonderful supervisors, Professor Lawrence Impey and Dr Christina Aye, for their guidance and support throughout this year, from helping with the application process to guiding me through the completion of this thesis. Thank you both for your mentorship, support, and kindness.

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Finally, I would like to thank my parents, sister, and friends for getting me through all the years of medical school - and now this extra intercalated year on top of that. I love you all.

List of publications

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- Galka, K., Shea, M., Aye, C. Y. L., & Impey, L. (2025). *Carbon monoxide levels, smoking, and adverse pregnancy outcomes. Acta Obstetricia et Gynecologica Scandinavica.* (Accepted for publication; in final proofing stage at the time of thesis submission). https://doi.org/10.1111/aogs.70068

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- **Galka, K., Shea, M., Aye, C. Y. L., & Impey, L.** (2025). *Carbon monoxide levels, smoking, and adverse pregnancy outcomes.*
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Abstract

Introduction

Maternal smoking during pregnancy remains a leading modifiable risk factor for adverse fetal outcomes such as low birthweight, preterm birth, and stillbirth. The aim of this thesis was to inform the appropriate method and timing for surveillance in pregnancies of smokers, by assessing how smoking exposure affects pregnancy outcomes and how it can be most accurately identified and managed.

Methods

Three complementary studies were conducted. First, a systematic review and meta-analysis (registered with PROSPERO: CRD42024592194) synthesised evidence from 145 studies on maternal smoking and fetal outcomes. Second and third, retrospective observational studies using data from the Oxford Growth Restriction Identification Programme (OxGRIP) examined how smoking exposure measured by exhaled carbon monoxide (CO) and self-report relates to pregnancy outcomes, and how fetal growth and Doppler findings differ between smokers and non-smokers across gestation.

Results

The meta-analysis showed that smoking during pregnancy significantly increased the risks of small-for-gestational-age birth, preterm delivery, and stillbirth, with risk magnitude rising with higher cigarette consumption and later cessation. Breath carbon monoxide was associated with low birthweight and adverse neonatal outcomes, with a clear dose–response above a threshold of >2 ppm. In the ultrasound analysis, fetal growth and Doppler findings were largely similar between smokers and non-smokers at 20 weeks but showed clear divergence by 36 weeks.

Conclusions

In conclusion, this thesis demonstrates that smoking in pregnancy is an independent risk factor for adverse outcomes, with effects that become more pronounced as pregnancy progresses. Early identification, reliable exposure testing, and cessation support remain central to mitigating these risks. Incorporating smoking status and measured CO levels into antenatal risk prediction models could help guide the need for enhanced fetal surveillance and targeted interventions, particularly in the third trimester when Doppler and growth changes are most evident.

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List of abbreviations

AOR – Adjusted Odds Ratio

ANOVA – Analysis of Variance

BMI – Body Mass Index

BW – Birthweight

CI – Confidence Interval

CO – Carbon Monoxide

CPR – Cerebroplacental Ratio

EPM – Extended Perinatal Mortality

EFW – Estimated Fetal Weight

GA – Gestational Age

IQR – Interquartile Range

IMD – Index of Multiple Deprivation

IV – Inverse Variance

LBW – Low Birthweight

MD – Mean Difference

MCA PI – Middle Cerebral Artery Pulsatility Index

MeSH – Medical Subject Headings

NHS – National Health Service

NICU – Neonatal Intensive Care Unit

NOS – Newcastle–Ottawa Scale

OR – Odds Ratio

OxGRIP – Oxford Growth Restriction Identification Programme

PI – Pulsatility Index

ppm – Parts per million

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

PROSPERO – International Prospective Register of Systematic Reviews

PTB – Preterm Birth

REML – Restricted Maximum Likelihood

SD – Standard Deviation

SE – Standard Error

SGA – Small for Gestational Age

SPSS – Statistical Package for the Social Sciences

UA – Umbilical Artery

UmbA PI – Umbilical Artery Pulsatility Index

utAPI – Uterine Artery Pulsatility Index

Chapter I. Introduction and Aims

1.1 Introduction

1.1.1 Smoking in Pregnancy

Smoking during pregnancy is a well-documented public health concern. In England, despite record-low smoking rates, 7.4% of women were smoking at the end of their pregnancy in 2023–24[1]. Although this represents steady progress compared with previous years, smoking remains one of the most important preventable causes of adverse pregnancy outcomes. Rates are higher among younger women and those with lower educational attainment or living in areas of greater socioeconomic deprivation, reflecting persistent health inequalities[2]. In the United Kingdom, smoking in pregnancy continues to be a major focus of public health policy. The government's *Smokefree 2030*[3] ambition aims to reduce adult smoking prevalence to 5% or less, and NHS England has identified reducing smoking in pregnancy as *Element 1* of the *Saving Babies' Lives* care bundle[4].

Pregnancy offers a unique window for health intervention: women are often highly motivated to modify their behaviour for the health of their child, and health services have repeated opportunities for engagement through antenatal care. It is important to maximise these opportunities, as smoking is a leading modifiable risk factor for adverse pregnancy outcomes, including low birthweight and preterm birth[5]. Beyond perinatal outcomes, in utero exposure to tobacco smoke is associated with long-term adverse effects on child health, including increased risks of sudden infant death syndrome, respiratory infections, wheezing, asthma, obesity, and neurodevelopmental disorders[6]. Importantly, cessation of smoking during pregnancy substantially reduces these risks[7].

1.1.2 Biological Mechanisms Driving Adverse Outcomes

The mechanisms by which smoking adversely affects pregnancy outcomes are complex and not yet fully understood. However, a growing body of evidence implicates placental dysfunction and fetal hypoxia as key processes. Nicotine, the primary pharmacologically active component in cigarette smoke, and its major metabolite, cotinine, readily cross the fetoplacental barrier[8]. Nicotine has been shown to disrupt trophoblast proliferation, migration, and invasion, processes critical for establishing an adequate fetomaternal circulation during early placentation[9]. Impairment of these processes may result in abnormal placental vascularisation and, ultimately, placental insufficiency[9].

Both nicotine and carbon monoxide contribute to reduced oxygen and nutrient delivery to the fetus. Nicotine induces vasoconstriction of uterine and placental vessels, reducing uteroplacental blood flow[10], while carbon monoxide binds to maternal and fetal haemoglobin with a much higher affinity than oxygen, thereby diminishing oxygen transport capacity[10]. Together, these effects lead to chronic placental hypoxia, which in turn limits fetal oxygenation and growth[11].

Structural and functional alterations within the placenta have also been observed among smokers. Histopathological studies describe thickening of placental membranes, reduced capillary volume, and diminished villous vascularisation[12,13], all of which impair efficient nutrient and gas exchange between the mother and fetus.

1.1.3 Current Clinical Practice and Surveillance Approaches

Although the adverse effects of smoking in pregnancy are well established, important gaps remain in understanding when these effects become apparent and how they should influence clinical care. Smoking is widely recognised as a risk factor for adverse pregnancy outcomes and is routinely included in antenatal risk assessment tools. However, approaches to fetal surveillance differ between settings, with no universal standard for the frequency or timing of additional scans in smokers. Some maternity units offer serial ultrasound assessments of fetal growth to women who continue to smoke throughout pregnancy, whereas others rely on clinical assessment or reserve additional scans for those with multiple risk factors. This variation reflects ongoing uncertainty about the extent to which smoking alone warrants enhanced monitoring, and at what stage of pregnancy such surveillance is most informative.

1.1.4 OxGRIP Dataset and Ethical Approval

To examine the predictors and sequelae of smoking in pregnancy, and to inform evidence-based approaches to surveillance, I used data from the Oxford Growth Restriction Identification Programme (OxGRIP)[14]. The OxGRIP dataset routinely collects information on pregnancies managed within Oxford University Hospitals NHS Foundation Trust. The study began in May 2016, offering universal uterine artery Doppler assessment at 20 weeks and a universal growth-restriction screening test at 36 weeks, with the initial aim of predicting impaired placental function. Its scope has since evolved to develop a staged risk-prediction model for adverse pregnancy outcomes, integrating prior risk data with new clinical findings at key gestational time points: 20 weeks, 28–30 weeks, 36 weeks, and immediately before labour. Unlike many current approaches, this model is designed to be quantitative and dynamic, providing more accurate and timely estimates of risk as pregnancy progresses.

A major strength of the OxGRIP dataset is that it includes routinely collected data for all women receiving antenatal care at Oxford, rather than being limited to those already identified as high risk. In most studies, women who undergo additional ultrasound scans are referred because of pre-existing concerns, which introduces an important selection bias. In contrast, OxGRIP captures pregnancies across the full risk spectrum, enabling unbiased assessment of how smoking exposure influences fetal growth and perinatal outcomes. Ethical approval for OxGRIP was granted by the South-Central Hampshire Research Ethics Committee (reference 17/SC/0374) on 26 July 2017, under which this thesis is conducted.

1.2 Aims

The aim of this thesis is to inform the appropriate method and timing for surveillance in pregnancies of smokers, by assessing how smoking exposure affects pregnancy outcomes and how it can be most accurately identified and managed.

In Chapter II, I conduct a systematic review and meta-analysis of the literature on maternal smoking in pregnancy and fetal outcomes, to quantify the effect of smoking on a broad range of perinatal outcomes and explore how timing of cessation and intensity of smoking influence risk.

In Chapter III, I evaluate the use of carbon monoxide (CO) as a biochemical measure of smoking in pregnancy, identify the CO threshold associated with adverse neonatal outcomes, and compare its performance with self-reported smoking as a predictor of risk.

In Chapter IV, I compare ultrasound findings and fetal growth between smokers and non-smokers at different gestations, to investigate when in pregnancy the effects of smoking become most apparent and how these changes might inform surveillance strategies.

In Chapter V, I integrate the findings from these chapters to consider their implications for clinical practice, including how smoking exposure should be incorporated into antenatal risk assessment and surveillance models.

Chapter II. Systematic Review of Maternal Smoking in Pregnancy and Fetal Outcomes

2.1 Introduction

2.1.1 Rationale for the systematic review

The effects of maternal smoking in pregnancy on fetal outcomes have been commonly studied and described in the literature; however, gaps remain in the synthesis of this evidence. No comprehensive systematic review has focused specifically on fetal outcomes of active maternal smoking in pregnancy and included a meta-analysis for each outcome. Existing studies have typically examined individual outcomes, such as fetal biometry[15] or preterm birth[16], but no review has assessed a broad range of fetal outcomes together. Such an approach would enable comparison across outcomes and highlight areas where smoking has a greater or more consistent effect. A few studies have attempted to provide a broader overview of the subject, but these have generally been narrative or descriptive in nature, without quantitative synthesis[17,18].

Moreover, the effects of smoking during specific trimesters and the patterns of quitting have also been understudied. Similarly, while it is likely that a dose–response relationship exists, with greater cigarette consumption associated with higher risk, it remains unclear whether some outcomes are disproportionately affected. Clarifying these aspects could help refine surveillance strategies or guide counselling on the benefits of cessation at different stages of pregnancy.

2.1.2 Objectives

The objective of this review was therefore to investigate the impact of maternal smoking during pregnancy on fetal outcomes. In addition, this review examined how smoking during specific trimesters of pregnancy, the timing of cessation, and the number of cigarettes smoked affect these outcomes.

2.2 Methods

2.2.1 Protocol and Registration

This systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42024592194) on the 1st of October 2024. The review was conducted in accordance with the PRISMA 2020 reporting guidelines[19].

2.2.2 Eligibility Criteria

Studies were eligible for inclusion if they examined the association between maternal smoking during pregnancy and at least one prespecified fetal or neonatal outcomes defined in Table 2. Eligible outcomes were birthweight, gestational age at birth, small-for-gestational age (SGA), low birthweight (<2500 g), preterm birth, stillbirth, neonatal death, and admission to a neonatal intensive care unit (NICU).

The study population comprised pregnant women of any age. The exposure of interest was active maternal smoking, defined as the use of any smoked tobacco product, including cigarettes, cigars, pipes, waterpipe, heated tobacco, or mixed use of these. Studies were included only when the smoking status was based on women's self-report, either through questionnaires administered during the study or from hospital or registry records. Studies in which self-report was validated with biochemical markers were also included, but those relying solely on biochemical markers without self-report were excluded. Pregnant women who had never smoked were classified as the comparator group (non-smokers). Women who had smoked previously but quit before pregnancy were included within the exposure group to allow comparison of cessation timing.

Both observational and interventional studies were eligible for inclusion, although in practice mostly observational studies were identified.

Studies were excluded if they were secondary research (systematic reviews, meta-analyses, or narrative reviews), editorials, or case reports. Studies investigating passive smoking, smokeless tobacco, electronic nicotine delivery systems (e.g., e-cigarettes or vapes), or nicotine replacement therapies were also excluded. In addition, studies were excluded if they contained non-extractable data, if the full text was not retrievable, or if they were otherwise outside the scope of this review.

2.2.3 Information Sources

Two electronic databases, MEDLINE (Ovid) and Embase (Ovid), were searched from inception to 27 September 2024. Only articles published in English were included. No additional databases, grey literature, or trial registries were searched.

2.2.4 Search Strategy

I developed the search strategy, which was then reviewed and approved by an outreach librarian. The strategy combined controlled vocabulary terms (Medical Subject Headings-MeSH) and free-text keywords related to pregnancy, smoking, and fetal outcomes. The full search strategies for both databases are presented in Table 1.

Table 1: Search Strategy

Table 1a: Embase 1974 to present

1	(fetal or fetus* or foetal or foetus* or newborn* or neonat* or infant* or antenatal or prenatal).ti,ab,kf.	1432018
2	exp *"parameters concerning the fetus, newborn and pregnancy"/	120074
3	(pregnancy adj2 outcome*).ti,ab,kf.	62375
4	*smoking/	69729
5	*maternal smoking/	2110
6	*tobacco/	21127
7	1 or 2 or 3	1492636
8	4 or 5 or 6	89669
9	7 and 8	4255
10	limit 9 to english language	3864

Table 1b: Medline (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present

1	(fetal or fetus* or foetal or foetus* or newborn* or neonat* or infant* or antenatal or prenatal).ti,ab,kf.	1204677
2	"Congenital, Hereditary, and Neonatal Diseases and Abnormalities"/	891
3	(pregnancy adj2 outcome*).ti,ab,kf.	41347
4	1 or 2 or 3	1223468
5	*smoking/	71357
6	*Tobacco Smoking/	1339
7	5 or 6	72604
8	4 and 7	3600
9	limit 8 to english language	3255

2.2.5 Selection Process

All titles and abstracts were imported into Rayyan[20] platform for screening. Duplicates and conference abstracts were automatically removed by the system; in cases of uncertainty, I manually reviewed and resolved duplicates. After automated removal, I also manually checked the dataset to ensure that no duplicates were retained that unique records were not incorrectly excluded.

Title and abstract screening was first completed by me, after which inclusion and exclusion decisions were independently completed by two additional reviewers. Discrepancies were resolved through discussion and consensus. Full-text screening was conducted in the same manner.

After the initial search, and following discussion with the review team, the pool of eligible studies was restricted to those published from the year 2000 onwards. This was done in Rayyan using the built-in filtering tools. The rationale for this restriction was the large number of studies retrieved, combined with the aim to focus on more recent research.

2.2.6 Data Collection Process

I extracted all data independently using Covidence systematic review software[21]. Automated extraction tools within Covidence were not used; all data were extracted manually. Extracted information included:

1. Identification: author, year, and country.
2. Methods: study design, outcomes examined, and smoking exposure definition.
3. Population: total sample size.
4. Exposure: number of women in the smoking and non-smoking categories, as well as subcategories.
5. Outcomes: results data

Where studies reported both adjusted and unadjusted effect estimates, I extracted the most fully adjusted estimate available. If only unadjusted results were reported, these were used.

2.2.7 Data Items, Effect Measures, and Synthesis Methods

Data were exported from Covidence into Review Manager (RevMan) Version 5.4[22], which was used for quantitative synthesis. The outcomes for which data were sought, along with the definitions applied in this review, are presented in Table 2.

Table 2: Definitions of Outcomes Included in the Systematic Review

Outcome	Type	Definition
Birthweight	Continuous	Infant's weight at birth, measured in grams
Gestational age at birth	Continuous	Duration of pregnancy from first day of last menstrual period to delivery, extracted in days in this review
Small-for-gestational age	Binary	Birthweight below the 10th percentile[23]
Low birthweight	Binary	Birthweight < 2,500 g[24]
Preterm birth	Binary	Birth before 37 completed weeks (259 days) of gestation[24]. We considered both spontaneous and iatrogenic preterm birth, although in practice, most of the included studies focused on spontaneous cases.
Stillbirth	Binary	Definitions of stillbirth varied across studies, with gestational age thresholds ranging from 20 to 28 weeks and some using a minimum birth weight of 500 g. These definitions were considered together as stillbirth.

Neonatal death	Binary	Death of a liveborn infant within the first 28 days of life[25]
NICU admission	Binary	Admission of the newborn to a neonatal intensive care unit

Smoking exposure was categorised as smokers versus non-smokers for the main analysis. Where available, additional subcategories were extracted according to timing of cessation (quit before pregnancy; quit in the first, second, or third trimester; smoked throughout pregnancy) and number of cigarettes smoked per day (1–5, 6–10, >10, or ≤10 vs >10 depending on reporting granularity). When different definitions or cut-offs were used in included studies, data were mapped to these categories wherever possible. Subanalysis by timing of cessation or number of cigarettes smoked per day were undertaken when more than two studies reported the outcome of interest and provided the data in a format that allowed stratification.

Effect measures were extracted as reported in the original studies. Odds ratios (ORs) were used for binary outcomes, and mean differences (MDs) for continuous outcomes. Where necessary, alternative effect estimates were recalculated in RevMan's built-in calculator to ensure consistency across studies. Where effect estimates were not reported, raw event counts or summary statistics were extracted and used to calculate effect measures. All effect sizes were presented with 95% confidence intervals (CIs), calculated using the Wald-type method, and depicted in forest plots.

A random-effects model was used for meta-analysis. This choice was based on the a priori assumption that true effect sizes were unlikely to be identical across studies, given variation in populations, geographic settings, and definitions of smoking exposure.

Statistical heterogeneity was quantified using the χ^2 test, Higgins' I^2 statistic, and τ^2, with τ^2 estimated using the Restricted Maximum Likelihood (REML) method. A statistical meta-analysis was conducted for each fetal outcome when two or more studies reported the same outcome. Meta-analyses were not excluded based on high statistical heterogeneity alone; instead, analyses were retained when the direction of effect was broadly consistent across studies and the pooled estimates were considered clinically interpretable. The primary aim of these analyses was to identify patterns in the effects of smoking across the body of evidence, rather than to derive a single summary estimate applicable to an individual study population. All analyses were conducted using Review Manager (RevMan).

2.2.8 Risk of Bias Assessment

I independently assessed the risk of bias of all included observational studies using the Newcastle–Ottawa Scale (NOS)[26]. The domains of the NOS were adapted and uploaded into Covidence to facilitate structured assessment. The NOS evaluates study quality across three broad domains:

1. Selection (up to 4 stars): representativeness of the exposed cohort or adequacy of case definition, selection of the non-exposed cohort or controls, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of follow-up.
2. Comparability (up to 2 stars): assessment of whether the study controlled for the most important potential confounders (such as maternal age, socioeconomic status, or parity) and, where possible, for additional confounding factors.

3. Outcome (for cohort studies) or Exposure (for case–control studies) (up to 3 stars): assessment of outcome/exposure ascertainment, adequacy and consistency of follow-up, and whether methods were applied equally across groups.

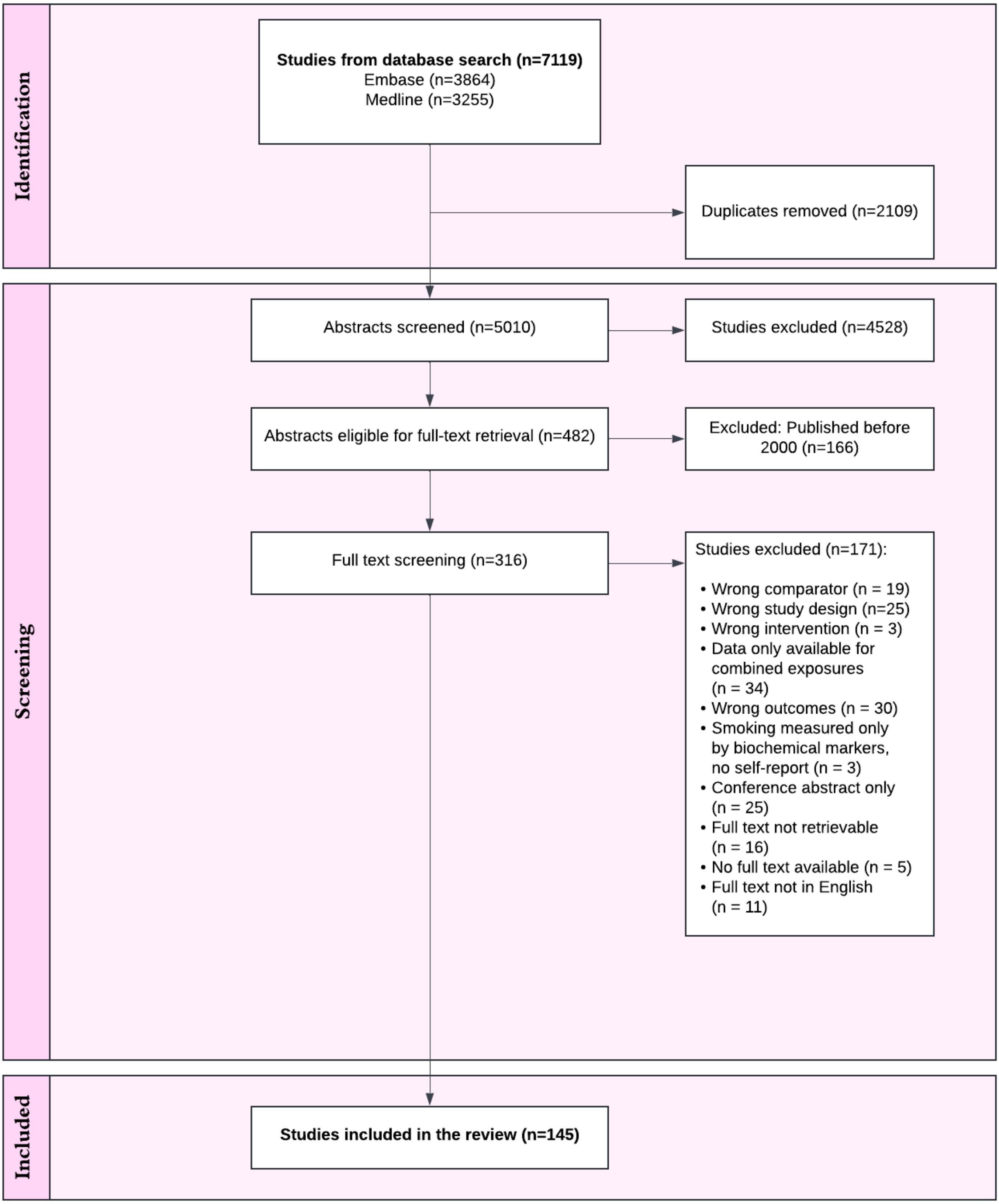
Each study could receive a maximum of nine stars, with higher scores indicating lower risk of bias. For synthesis and interpretation, studies with 7–9 stars were considered low risk of bias (high quality), those with 4–6 stars as moderate risk, and those with 0–3 stars as high risk (low quality).

2.3 Results

2.3.1 Study Selection

The results of the search and study selection are illustrated in the PRISMA flow chart (Figure 1). In total, 7,119 records were identified, and 5,010 abstracts were screened after removal of duplicates. Of these, 482 articles were retrieved for full-text screening, and 145 studies met the eligibility criteria and were included in the quantitative synthesis.

Figure 1: PRISMA flow diagram of selected studies



2.3.2 Study Characteristics

A total of 145 studies were included, published between 2000 and 2024, and spanning 35 countries across all continents except Antarctica (Table 3)

The vast majority of studies were observational, with retrospective cohort studies comprising the largest proportion (n = 87, 60.0%), followed by prospective cohort studies (n = 37, 25.5%), case–control studies (n = 11, 7.6%), and cross-sectional studies (n = 9, 6.2%). One randomized controlled trial was also identified. Sample sizes ranged from fewer than 100 participants to more than 25 million in population-based registry analyses.

The most frequently reported outcomes were related to birthweight, including mean birthweight, low birthweight, and small for gestational age, all of which were assessed in more than half of the included studies. Preterm birth was investigated in 58 studies (40.0%), and gestational age at birth was reported in 33 studies (22.8%). Stillbirth was reported in 23 studies, neonatal death in 6, and NICU admission in 10 studies.

Exposure to smoking was most often assessed by maternal self-report of cigarette use (n = 120, 82.8%), followed by registry-based data (n = 13, 9.0%), and self-report validated with biochemical markers (n = 4, 2.8%). A smaller subset of studies reported on other or mixed tobacco use (n = 8, 5.5%), assessed either by self-report (n = 7) or registry data (n = 1).

Table 3: Characteristics of studies included in the systematic review

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Abdelwahab et al.[27]	2022	USA	325	Retrospective cohort study	SGA	Self-reported cigarette smoking
Abufraijeh et al.[28]	2024	Jordan	410	Retrospective cohort study	Gestational age at birth, Preterm birth	Self-reported cigarette smoking
Agrawal et al.[29]	2010	USA	1,122	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Ahmadi-Montecalvo et al.[30]	2016	USA	886	Retrospective cohort study	SGA	Self-reported cigarette smoking
Akahoshi et al.[31]	2016	Japan	621	Retrospective cohort study	SGA	Registry-based smoking status
Al-sheyab et al.[32]	2016	Jordan; Saudi Arabia	285	Retrospective cohort study	BW	Self-reported other/mixed tobacco use
Aliyu et al.[33]	2007	USA	1,436,725	Retrospective cohort study	Stillbirth	Self-reported cigarette smoking
Aliyu et al.[34]	2010	USA	1,304,557	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Alptekin et al.[35]	2017	Turkey	148	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Andriani et al.[36]	2014	Taiwan	3,789	Retrospective cohort study	BW, Gestational age at birth, Preterm birth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Baba et al.[37]	2013	Sweden	846,411	Retrospective cohort study	SGA	Self-reported other/mixed tobacco use
Baba et al.[38]	2014	Sweden	851,371	Retrospective cohort study	Stillbirth, Neonatal death	Self-reported other/mixed tobacco use
Bailey et al.[39]	2012	USA	121	Retrospective cohort study	BW	Self-reported cigarette smoking
Barbieri et al.[40]	2000	Brazil	5,492	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Berlin et al.[41]	2017	France	374	Retrospective cohort study	BW	Self-reported cigarette smoking
Bickerstaff et al.[42]	2012	Australia	30,525	Retrospective cohort study	BW, Preterm birth	Self-reported cigarette smoking
Bird et al.[43]	2017	New Zealand	6,822	Retrospective cohort study	SGA, PTB, Low birthweight (<2500g)	Self-reported cigarette smoking
Bjornholt et al.[44]	2016	Denmark	841,228	Retrospective cohort study	Stillbirth	Registry-based smoking status
Blatt et al.[45]	2015	USA	927,424	Retrospective cohort study	BW, SGA, NICU admission	Self-reported cigarette smoking
Bramsved et al.[46]	2023	Sweden	1,256	Retrospective cohort study	BW	Self-reported cigarette smoking
Brink et al.[47]	2022	South Africa, USA	4,926	Prospective cohort study	BW, SGA, Gestational age at birth, Preterm birth, Stillbirth	Self-reported cigarette smoking
Burguet et al.[48]	2004	France	1,431	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Campbell et al.[49]	2012	Canada	2,195	Prospective cohort study	SGA	Self-reported cigarette smoking
Cardenas et al.[50]	2020	USA	1,434	Retrospective cohort study	SGA	Self-reported cigarette smoking
Chan et al.[51]	2008	Australia	25,828	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Chelchowska et al.[52]	2013	Poland	150	Case-control study	BW, Gestational age at birth	Self-reported cigarette smoking
Chen et al.[53]	2018	China	202,725	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Chiolero et al.[54]	2005	Switzerland	6,284	Prospective cohort study	SGA, Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Coleman-Cowger et al.[55]	2018	USA	393	Prospective cohort study	Low birthweight (<2500g), Preterm birth, Stillbirth, NICU admission	Self-reported cigarette smoking
Cupul-Uicab et al.[56]	2011	USA, Norway	76,357	Prospective cohort study	Stillbirth	Self-reported cigarette smoking
da Fonseca et al.[57]	2012	Brazil	1,046	Case-control study	Low birthweight (<2500g)	Registry-based smoking status
Dahlin et al.[58]	2016	Sweden	1,301,377	Retrospective cohort study	Preterm birth	Self-reported other/mixed tobacco use
Delcroix-Gomez et al.[59]	2022	France	4,625	Prospective cohort study	BW, Gestational age at birth, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Delpisheh et al.[60]	2006	UK	4,537	Retrospective cohort study	SGA, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Dew et al.[61]	2007	USA	83,685	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Dodds et al.[62]	2006	USA	494	Case-control study	Stillbirth	Self-reported cigarette smoking
El-Shahawy et al.[63]	2021	Egypt	200	Prospective cohort study	BW, Gestational age at birth	Self-reported other/mixed tobacco use
Feferkorn et al.[64]	2022	Canada	9,096,788	Retrospective cohort study	SGA, Preterm birth	Registry-based smoking status
Fenercioglu et al.[65]	2009	Turkey	102	Retrospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Fenercioglu et al.[66]	2009	Turkey	163	Retrospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Flower et al.[67]	2013	UK	18,178	Retrospective cohort study	Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Ganer-Herman et al.[68]	2016	Israel	1,203	Retrospective cohort study	BW, SGA, Gestational age at birth	Self-reported cigarette smoking
Gibberd et al.[69]	2019	Australia	28,119	Retrospective cohort study	SGA, Preterm birth	Self-reported cigarette smoking
Goy et al.[70]	2008	UK	510	Case-control study	Stillbirth	Self-reported cigarette smoking
Grjibovski et al.[71]	2004	Sweden	1,023	Retrospective cohort study	BW	Self-reported cigarette smoking
Hamadneh et al.[72]	2021	Jordan	120	Case-control study	BW, Gestational age at birth, NICU admission	Self-reported cigarette smoking
Harrod et al.[73]	2014	USA; Colombia	916	Retrospective cohort study	BW, SGA, Gestational age at birth	Self-reported cigarette smoking
Himes et al.[74]	2013	USA	119	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Hosokawa et al.[75]	2022	Japan	5,647	Cross-sectional study	SGA	Self-reported other/mixed tobacco use
Huang et al.[76]	2017	Taiwan	165	Prospective cohort study	BW, Low birthweight (<2500g)	Self-reported cigarette smoking
Hviid et al.[77]	2024	Denmark	2,785	Prospective cohort study	Stillbirth	Self-reported cigarette smoking
Hyland et al.[78]	2015	USA	80,762	Retrospective cohort study	Stillbirth	Self-reported cigarette smoking
Ingvarsson et al.[79]	2007	Iceland	–	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Iniguez et al.[80]	2012	Spain	818	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Inoue et al.[81]	2017	USA; Japan	16,396	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Jackson et al.[82]	2007	South Africa	400	Case-control study	Low birthweight (<2500g)	Self-reported cigarette smoking
Jaddoe et al.[83]	2007	Netherlands	7,098	Retrospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Jaddoe et al.[84]	2008	Netherlands	7,098	Retrospective cohort study	Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Jeena et al.[85]	2020	South Africa	1,099	Prospective cohort study	Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Kataoka et al.[86]	2018	Brazil	1,313	Cross-sectional study	BW	Self-reported cigarette smoking
Kayemba-Kay's et al.[87]	2010	France	361	Prospective cohort study	BW	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Kharkova et al.[88]	2017	Russia	44,486	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Kirchengast et al.[89]	2003	Austria	7,803	Retrospective cohort study	BW	Self-reported cigarette smoking
Kleijer et al.[90]	2005	Australia	788	Retrospective cohort study	SGA	Self-reported cigarette smoking
Ko et al.[91]	2014	Taiwan	21,248	Retrospective cohort study	BW, SGA, Gestational age at birth, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Kondracki et al.[92]	2019	USA	2,485,74*	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Kuja-Halkola et al.[93]	2014	Sweden	1,823,697	Retrospective cohort study	BW, SGA, Preterm birth	Registry-based smoking status
Kyrklund-Blomberg et al.[94]	2005	Sweden	590	Case-control study	Preterm birth	Self-reported cigarette smoking
Lamm et al.[95]	2020	USA	3,032,928	Retrospective cohort study	SGA	Self-reported cigarette smoking
Lanting et al.[96]	2009	Netherlands	14,553	Retrospective cohort study	SGA, Preterm birth	Self-reported cigarette smoking
Li et al.[97]	2019	Australia	139,873	Retrospective cohort study	BW, SGA, Gestational age at birth, Preterm birth, NICU, Stillbirth, Neonatal death	Self-reported cigarette smoking
Li et al.[98]	2024	USA	14,713	Cross-sectional study	BW	Self-reported cigarette smoking
Lindley et al.[99]	2000	USA	15,185	Retrospective cohort study	BW	Self-reported cigarette smoking
Liu et al.[100]	2020	USA	25,623,479	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Madley-Dowd et al.[101]	2021	UK; Sweden	1,070,012	Prospective cohort study	SGA	Registry-based other/mixed tobacco use
Matsubara et al.[102]	2000	Japan	8,624	Prospective cohort study	BW, Gestational age at birth, Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
McCowan et al.[103]	2007	New Zealand	69,173	Retrospective cohort study	Stillbirth	Registry-based smoking status
McCowan et al.[104]	2009	New Zealand; Australia	2,504	Prospective cohort study	BW, SGA, Gestational age at birth, Preterm birth	Self-reported cigarette smoking
McDonnell et al.[105]	2019	Ireland	207	Retrospective cohort study	BW	Registry-based smoking status
Meghea et al.[106]	2014	Romania	474	Prospective cohort study	BW, SGA, Gestational age at birth, Preterm birth	Self-reported cigarette smoking
Mei-Dan et al.[107]	2015	Canada	20,938	Retrospective cohort study	BW, Gestational age at birth, Preterm birth, NICU admission, Stillbirth, Neonatal death	Self-reported cigarette smoking
Mercer et al.[108]	2008	USA	4,405	Retrospective cohort study	SGA, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Meyer et al.[109]	2009	Germany	14,593	Retrospective cohort study	BW, SGA	Self-reported cigarette smoking
Miller et al.[110]	2010	USA	308,197	Retrospective cohort study	SGA, Preterm birth, NICU admission, Stillbirth	Self-reported cigarette smoking
Mitchell et al.[111]	2002	New Zealand	1,707	Case-control study	SGA	Self-reported cigarette smoking
Miyake et al.[112]	2013	Japan	1,565	Prospective cohort study	BW, SGA, Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Mohsin et al.[113]	2006	Australia	433,379	Retrospective cohort study	Stillbirth	Registry-based smoking status

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Moore et al.[114]	2000	USA	1,146	Retrospective cohort study	Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Moore et al.[115]	2016	USA	913,757	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Moore et al.[116]	2019	USA	492	Prospective cohort study	BW	Self-report validated by biochemical markers
Murphy et al.[117]	2013	Ireland	907	Retrospective cohort study	BW, Gestational age at birth, Preterm birth, NICU admission	Self-reported cigarette smoking
Nanninga et al.[118]	2023	Netherlands	1,915	Cross-sectional study	SGA, Preterm birth	Self-reported cigarette smoking
O'Donnell et al.[119]	2020	Ireland	3,158	Retrospective cohort study	Gestational age at birth	Self-reported cigarette smoking
Odendaal et al.[120]	2021	South Africa	11,695	Prospective cohort study	Stillbirth	Self-reported cigarette smoking
Oh et al.[121]	2021	Korea	1,675	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Ohmi et al.[122]	2002	Japan	1,194	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Okah et al.[123]	2005	USA	78,397	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Olafsdottir et al.[124]	2006	Iceland	408	Prospective cohort study	BW	Self-reported cigarette smoking
Olbertz et al.[125]	2018	Germany	508,926	Prospective cohort study	SGA	Self-reported cigarette smoking
Olives et al.[126]	2020	France	1,195	Prospective cohort study	BW	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Pietersma et al.[127]	2022	Netherlands	689	Prospective cohort study	BW, SGA, Gestational age at birth	Self-reported cigarette smoking
Pollack et al.[128]	2000	USA	297,841	Retrospective cohort study	Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Raatikainen et al.[129]	2007	Finland	25,591	Randomized controlled trial	SGA, NICU admission, Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Raisanen et al.[117]	2014	Finland	1,164,953	Retrospective cohort study	BW, SGA, Gestational age at birth, NICU admission, Stillbirth, Prematurity, Low birthweight (<2500g)	Self-reported cigarette smoking
Ramadani et al.[131]	2019	Indonesia	128	Prospective cohort study	BW	Self-report validated by biochemical markers
Ratnasiri et al.[132]	2020	USA	4,971,896	Retrospective cohort study	SGA, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Reddy et al.[133]	2010	USA	174,809	Retrospective cohort study	Stillbirth	Self-reported cigarette smoking
Reynolds et al.[134]	2020	Ireland	40,156	Retrospective cohort study	BW, SGA, Gestational age at birth	Registry-based smoking status
Rode et al.[135]	2013	Denmark	1,774	Prospective cohort study	BW, SGA	Self-reported cigarette smoking
Rumrich et al.[136]	2020	Finland	1,376,778	Retrospective cohort study	BW, SGA, Gestational age at birth, Preterm birth, Low birthweight (<2500g)	Registry-based smoking status
Salihu et al.[137]	2003	USA	3,004,616	Retrospective cohort study	Neonatal death	Registry-based smoking status
Salihu et al.[138]	2008	USA	879,700	Case-control study	Stillbirth	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Samper et al.[139]	2012	Spain	1,216	Retrospective cohort study	BW, Preterm birth	Self-reported cigarette smoking
Savitz et al.[140]	2001	USA	2,418	Prospective cohort study	SGA, Preterm birth	Self-reported cigarette smoking
Schultze et al.[141]	2016	Austria	11,142	Retrospective cohort study	BW, SGA, Preterm birth	Self-reported cigarette smoking
Selvaratnam et al.[142]	2023	Australia, UK	807	Case-control study	Preterm birth	Self-report validated by biochemical markers
Silva et al.[143]	2022	Portugal	582	Cross-sectional study	BW, Gestational age at birth	Self-report validated by biochemical markers
Smith et al.[144]	2015	UK	1,890	Retrospective cohort study	Preterm birth	Self-reported cigarette smoking
Steyn et al.[145]	2006	USA	1,593	Prospective cohort study	BW, Gestational age at birth	Self-reported other/mixed tobacco use
Sun et al.[146]	2023	China	13,524,204	Retrospective cohort study	Neonatal death	Self-reported cigarette smoking
Sutan et al.[147]	2010	UK	541,811	Retrospective cohort study	Stillbirth	Registry-based smoking status
Suzuki et al.[148]	2008	Japan	1,329	Prospective cohort study	SGA, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Suzuki et al.[149]	2014	Japan	2,663	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Suzuki et al.[150]	2016	Japan	9,369	Retrospective cohort study	BW	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Tashan et al.[151]	2017	Turkey	664	Cross-sectional study	Low birthweight (<2500g)	Self-reported cigarette smoking
Tatsuta et al.[152]	2023	Japan	73,025	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Tayie et al.[153]	2012	USA	11,560	Cross-sectional study	BW, NICU admission, Low birthweight (<2500g)	Self-reported cigarette smoking
Tong et al.[154]	2017	USA	87,239	Retrospective cohort study	SGA, Preterm birth	Self-reported cigarette smoking
Tsukamoto et al.[155]	2007	Japan	2,972	Retrospective cohort study	BW, SGA	Self-reported cigarette smoking
Tveit et al.[156]	2010	Norway	2,168	Retrospective cohort study	SGA, Preterm birth, Stillbirth	Self-reported cigarette smoking
Vardavas et al.[157]	2010	Greece, Spain	1,400	Prospective cohort study	BW, SGA, Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Veloso et al.[158]	2014	Brazil	5,040	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Vila-Candel et al.[159]	2015	Spain	137	Prospective cohort study	BW, Gestational age at birth	Self-reported cigarette smoking
Villalbi et al.[160]	2007	Spain	2,297	Cross-sectional study	Preterm birth, Low birthweight (<2500g)	Self-reported cigarette smoking
Waldenstrom et al.[161]	2014	Sweden	955,804	Retrospective cohort study	SGA, Preterm birth, Stillbirth, Neonatal death	Self-reported cigarette smoking
Wang et al.[162]	2002	USA	741	Case-control study	Low birthweight (<2500g), Preterm birth	Self-reported cigarette smoking
Wang et al.[163]	2020	China	8,586	Cross-sectional study	BW, Low birthweight (<2500g)	Self-reported cigarette smoking

Author	Year	Country	Number of women	Study design	Examined outcomes	Smoking exposure definition
Wang et al.[164]	2020	USA	31,402	Retrospective cohort study	SGA, Preterm birth	Self-reported cigarette smoking
Wang et al.[165]	2024	China	1,947	Prospective cohort study	BW, Preterm birth	Self-reported cigarette smoking
Ward et al.[166]	2007	UK	14,497	Retrospective cohort study	BW, Prematurity, Low birthweight (<2500g)	Self-reported cigarette smoking
Winbo et al.[167]	2001	Sweden	9,785	Retrospective cohort study	SGA	Registry-based smoking status
Wisborg et al.[168]	2001	Denmark	25,102	Retrospective cohort study	Stillbirth	Self-reported cigarette smoking
Witt et al.[169]	2016	USA	9,350	Retrospective cohort study	Low birthweight (<2500g)	Self-reported cigarette smoking
Wojtyla et al.[170]	2021	Poland	8,625	Prospective cohort study	BW	Self-reported cigarette smoking
Zaren et al.[171]	2000	Sweden	856	Retrospective cohort study	BW	Self-reported cigarette smoking

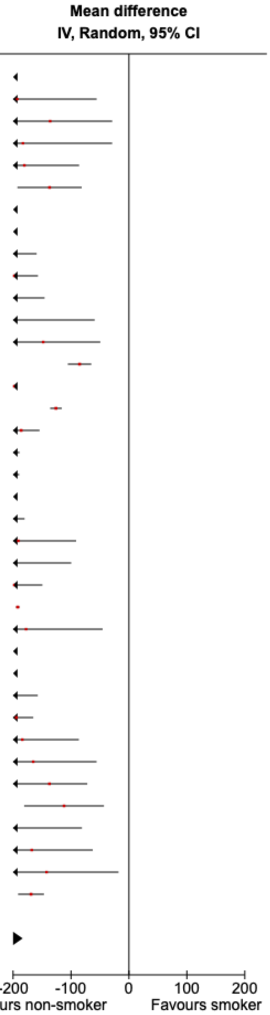
2.3.3 Synthesis of included studies

2.3.3.1 Birthweight

Overall analysis: Smoker vs. Non-smoker

Infants born to mothers who smoked during pregnancy had significantly lower mean birthweight compared with those of non-smokers (mean difference –208 g, 95% CI –233 to –183, $p < 0.00001$) (Figure 2). Heterogeneity across studies was high ($I^2 = 99\%$), but the direction of effect was consistent, with all studies showing reduced birthweight among infants exposed to maternal smoking.

Figure 2: Forest plot of mean birthweight differences between infants born to smokers and non-smokers



Study or Subgroup	MD	SE	Smoker Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
Al-sheyab 2016	-377.391304	74.882849	184	101	1.6%	-377.39 [-524.16 , -230.62]
Alptekin 2017	-192.8	69.947633	59	89	1.7%	-192.80 [-329.89 , -55.71]
Andriani 2014	-136	54.656015	84	796	2.2%	-136.00 [-243.12 , -28.88]
Bailey 2012	-183	78.596106	75	46	1.5%	-183.00 [-337.05 , -28.95]
Bramsved 2023	-180.5	48.22576	185	1071	2.4%	-180.50 [-275.02 , -85.98]
Brink 2022	-137	28.325004	862	877	3.1%	-137.00 [-192.52 , -81.48]
Chelchowska 2013	-377	8.223034	70	80	3.6%	-377.00 [-393.12 , -360.88]
El-Shahawy 2021	-439.357069	46.812465	58	142	2.4%	-439.36 [-531.11 , -347.61]
Grjibovski 2004	-249	45.762715	164	859	2.5%	-249.00 [-338.69 , -159.31]
Hamadneh 2021	-200	21.908902	60	60	3.3%	-200.00 [-242.94 , -157.06]
Harrod 2014	-240	48.171797	85	831	2.4%	-240.00 [-334.41 , -145.59]
Huang 2017	-246.2	95.439559	20	145	1.2%	-246.20 [-433.26 , -59.14]
Kayemba-Kay's 2010	-148	50.286288	129	232	2.3%	-148.00 [-246.56 , -49.44]
Kirchengast 2003	-85.2	10.324411	2629	5174	3.6%	-85.20 [-105.44 , -64.96]
Kuja-Halkola 2014	-200	1.140868	306000	1426000	3.7%	-200.00 [-202.24 , -197.76]
Li 2019	-126	5.086562	20477	119396	3.7%	-126.00 [-135.97 , -116.03]
Li 2024	-186	16.155494	1928	12785	3.5%	-186.00 [-217.66 , -154.34]
McDonnell 2019	-310	61.778686	99	108	1.9%	-310.00 [-431.08 , -188.92]
Mei-Dan 2015	-227	19.206735	1646	19292	3.4%	-227.00 [-264.64 , -189.36]
Meyer 2009	-233	13.169852	1722	12871	3.5%	-233.00 [-258.81 , -207.19]
Moore 2019	-343	83.121478	35	457	1.4%	-343.00 [-505.92 , -180.08]
Murphy 2013	-191	50.97417	110	637	2.3%	-191.00 [-290.91 , -91.09]
Olafsdottir 2006	-243	73.164059	53	270	1.6%	-243.00 [-386.40 , -99.60]
Olives 2020	-200	25.821748	759	741	3.2%	-200.00 [-250.61 , -149.39]
Raisanen 2014	-192	1.589472	145710	958177	3.7%	-192.00 [-195.12 , -188.88]
Ramadani 2019	-177.6	67.438288	35	93	1.8%	-177.60 [-309.78 , -45.42]
Reynolds 2020	-265.8	9.224786	5039	21136	3.6%	-265.80 [-283.88 , -247.72]
Rode 2013	-270	30.810431	321	1104	3.0%	-270.00 [-330.39 , -209.61]
Samper 2012	-215	29.40663	269	947	3.1%	-215.00 [-272.64 , -157.36]
Schultze 2016	-194.31	14.905953	2022	9120	3.5%	-194.31 [-223.53 , -165.09]
Silva 2022	-184	49.784269	89	493	2.3%	-184.00 [-281.58 , -86.42]
Steyn 2006	-165.25	55.822871	97	1376	2.1%	-165.25 [-274.66 , -55.84]
Suzuki 2016	-137.2	33.358807	414	4357	2.9%	-137.20 [-202.58 , -71.82]
Vardavas 2010	-112	35.130639	256	843	2.9%	-112.00 [-180.85 , -43.15]
VilaCandel 2015	-235	78.51545	14	123	1.5%	-235.00 [-388.89 , -81.11]
Wang 2020	-167.72	53.718871	81	8505	2.2%	-167.72 [-273.01 , -62.43]
Wang 2024	-142.2	63.399142	73	1874	1.9%	-142.20 [-266.46 , -17.94]
Ward 2007	-169	11.401754	6397	8100	3.6%	-169.00 [-191.35 , -146.65]
Total (Wald[a])			**498310**	**2619308**	**100.0%**	**-208.00 [-232.57 , -183.42]**

Test for overall effect: Z = 16.59 (P < 0.00001)

Heterogeneity: Tau^2 (REML[b]) = 4270.47; Chi^2 = 945.60, df = 37 (P < 0.00001); I^2 = 99%

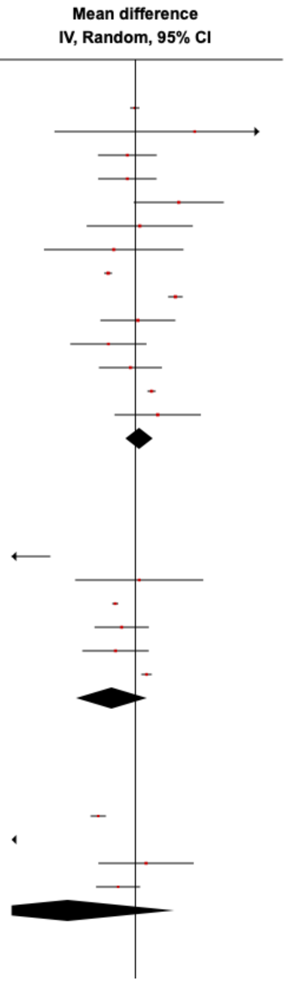
Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: Timing of smoking cessation

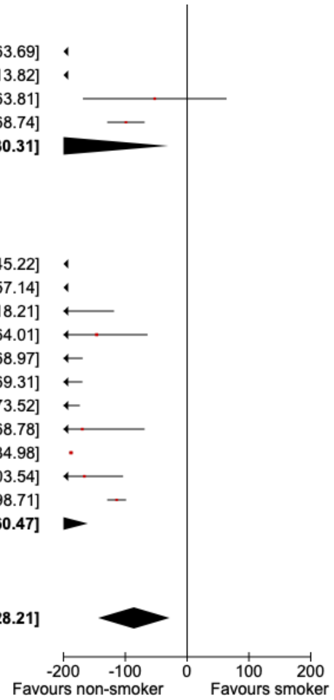
Timing of smoking cessation influenced this effect. There was no difference in mean birthweight between infants of women who quit before pregnancy and never-smokers (MD 5.85 g, 95% CI –16.19 to 27.89, $p = 0.62$; $I^2 = 95\%$) (Figure 3). Quitting in the first or second trimester was associated with small, non-significant reductions in mean birthweight (first trimester: MD –38.71 g, 95% CI –95.98 to 18.56, $p = 0.19$; second trimester: MD –109.67 g, 95% CI –282.01 to 62.68, $p = 0.21$; both $I^2 = 99\%$). Quitting in the third trimester was linked to a significant reduction (MD –234.79 g, 95% CI –439.27 to –30.31, $p = 0.02$; $I^2 = 99\%$), and the lowest mean birthweight was observed among infants of mothers who smoked throughout pregnancy (MD –226.65 g, 95% CI –292.83 to –160.47, $p < 0.0001$; $I^2 = 100\%$). A test for subgroup differences confirmed that the effect of smoking on birthweight varied significantly with timing of cessation ($p < 0.00001$).

Figure 3: Forest plot of mean birthweight differences between infants born to smokers and non-smokers, stratified by timing of smoking cessation

Study or Subgroup	MD	SE	Timing of smoking Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
2.1.1 Quit before pregnancy						
Blatt 2015[a]	-1	3.830911	21803	697266	0.9%	-1.00 [-8.51 , 6.51]
Himes 2013[a]	95.8	115.574933	28	46	1.7%	95.80 [-130.72 , 322.32]
Jaddoe 2007[a]	-13	24.214532	591	5289	2.2%	-13.00 [-60.46 , 34.46]
Jaddoe 2008[a]	-13	24.088413	591	5289	2.2%	-13.00 [-60.21 , 34.21]
McCowan 2009[a]	70	37.11426	261	1992	3.8%	70.00 [-2.74 , 142.74]
Murphy 2013	7	43.743306	160	637	4.3%	7.00 [-78.74 , 92.74]
Olafsdottir 2006	-35	57.485029	85	270	4.0%	-35.00 [-147.67 , 77.67]
Raisanen 2014	-44	3.194468	30136	958177	4.7%	-44.00 [-50.26 , -37.74]
Reynolds 2020	64.6	5.979799	13981	21136	4.7%	64.60 [52.88 , 76.32]
Rode 2013	4	30.91457	349	1104	4.5%	4.00 [-56.59 , 64.59]
Suzuki 2014[a]	-43.6	31.415124	170	1920	1.6%	-43.60 [-105.17 , 17.97]
Suzuki 2016[a]	-8	25.978645	1885	4357	3.3%	-8.00 [-58.92 , 42.92]
Tatsuta 2023[a]	26	3.343523	16461	44198	3.5%	26.00 [19.45 , 32.55]
Vardavas 2010	36	35.587046	216	843	4.4%	36.00 [-33.75 , 105.75]
Subtotal (Wald[b])			**86717**	**1742524**	**45.7%**	**5.85 [-16.19 , 27.89]**
Test for overall effect: Z = 0.52 (P = 0.60)						
Heterogeneity: Tau² (REML[c]) = 1069.98; Chi² = 375.00, df = 13 (P < 0.00001); I² = 95%						
2.1.2 Quit 1st trimester						
Delcroix-Gomez 2022[a]	-269	67.17024	121	3704	0.7%	-269.00 [-400.65 , -137.35]
Iniguez 2012[a]	6.2	52.809072	126	457	2.3%	6.20 [-97.30 , 109.70]
Rumrich 2020[a]	-32.57	2.498241	47819	1163225	1.6%	-32.57 [-37.47 , -27.67]
Suzuki 2014[a]	-22.2	22.363906	396	1920	3.2%	-22.20 [-66.03 , 21.63]
Suzuki 2016[a]	-32.1	27.335874	1078	4357	3.0%	-32.10 [-85.68 , 21.48]
Tatsuta 2023[a]	18	4.284484	8948	44198	2.1%	18.00 [9.60 , 26.40]
Subtotal (Wald[b])			**58488**	**1217861**	**12.9%**	**-38.71 [-95.98 , 18.56]**
Test for overall effect: Z = 1.32 (P = 0.19)						
Heterogeneity: Tau² (REML[c]) = 4100.42; Chi² = 118.17, df = 5 (P < 0.00001); I² = 99%						
2.1.3 Quit 2nd trimester						
Blatt 2015[a]	-60	6.323742	8797	697266	0.3%	-60.00 [-72.39 , -47.61]
Delcroix-Gomez 2022[a]	-381	49.17381	111	3704	1.3%	-381.00 [-477.38 , -284.62]
Miyake 2013[a]	17.2	39.26563	71	1427	3.0%	17.20 [-59.76 , 94.16]
Tatsuta 2023[a]	-28	18.147089	498	44198	0.1%	-28.00 [-63.57 , 7.57]
Subtotal (Wald[b])			**9477**	**746595**	**4.8%**	**-109.67 [-282.01 , 62.68]**
Test for overall effect: Z = 1.25 (P = 0.21)						
Heterogeneity: Tau² (REML[c]) = 29875.74; Chi² = 49.58, df = 3 (P < 0.00001); I² = 99%						



2.1.4 Quit 3rd trimester						
Blatt 2015[a]	-268	2.199458	132536	697266	2.9%	-268.00 [-272.31 , -263.69]
Delcroix-Gomez 2022[a]	-526	57.236013	57	3704	0.9%	-526.00 [-638.18 , -413.82]
Miyake 2013[a]	-52.4	59.293662	28	1427	1.3%	-52.40 [-168.61 , 63.81]
Tatsuta 2023[a]	-99	15.4387	651	44198	0.2%	-99.00 [-129.26 , -68.74]
Subtotal (Wald[b])			**133272**	**746595**	**5.3%**	**-234.79 [-439.27 , -30.31]**
Test for overall effect: Z = 2.25 (P = 0.02)						
Heterogeneity: Tau² (REML[c]) = 41842.39; Chi² = 151.11, df = 3 (P < 0.00001); I² = 99%						
2.1.5 Smoked throughout pregnancy						
Blatt 2015[a]	-250	2.441352	53355	697266	2.3%	-250.00 [-254.78 , -245.22]
Delcroix-Gomez 2022[a]	-516	30.032617	632	3704	3.4%	-516.00 [-574.86 , -457.14]
Himes 2013[a]	-298.6	92.039416	45	46	2.6%	-298.60 [-478.99 , -118.21]
Iniguez 2012[a]	-146.4	42.038661	193	457	3.6%	-146.40 [-228.79 , -64.01]
Jaddoe 2007[a]	-203	17.363	1218	5289	4.2%	-203.00 [-237.03 , -168.97]
Jaddoe 2008[a]	-203	17.186678	1218	5289	4.2%	-203.00 [-236.69 , -169.31]
McCowan 2009[a]	-270	49.223487	251	1992	2.2%	-270.00 [-366.48 , -173.52]
Miyake 2013[a]	-169.6	51.440589	39	1427	1.8%	-169.60 [-270.42 , -68.78]
Rumrich 2020[a]	-187.83	1.453705	165734	1163225	4.8%	-187.83 [-190.68 , -184.98]
Suzuki 2014[a]	-166.2	31.970149	177	1920	1.6%	-166.20 [-228.86 , -103.54]
Tatsuta 2023[a]	-114	7.800666	2269	44198	0.6%	-114.00 [-129.29 , -98.71]
Subtotal (Wald[b])			**225131**	**1924813**	**31.4%**	**-226.65 [-292.83 , -160.47]**
Test for overall effect: Z = 6.71 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 11229.09; Chi² = 724.50, df = 10 (P < 0.00001); I² = 100%						
Total (Wald[b])			**513085**	**2911337**	**100.0%**	**-86.13 [-144.05 , -28.21]**
Test for overall effect: Z = 2.91 (P = 0.004)						
Test for subgroup differences: Chi² = 48.35, df = 4 (P < 0.00001), I² = 91.7%						
Heterogeneity: Tau² (REML[c]) = 14748.03; Chi² = 8219.30, df = 17 (P < 0.00001); I² = 100%						



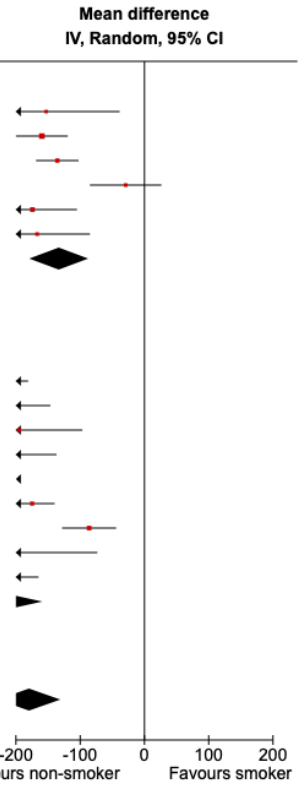
Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: ≤10 vs >10 cigarettes per day

Smoking intensity also had an impact on mean birthweight. Smoking ≤10 cigarettes per day was associated with a significant reduction in mean birthweight (MD –133.44 g, 95% CI –179.38 to –87.50, p < 0.00001; I² = 74%), and the reduction was even greater among mothers who smoked more than 10 cigarettes daily (MD –237.29 g, 95% CI –315.73 to –158.85, p < 0.00001; I² = 84%) (Figure 4). A test for subgroup differences confirmed that the effect varied significantly with the number of cigarettes smoked (p = 0.03).

Figure 4: Forest plot of mean birthweight differences between infants born to mothers smoking ≤10 cigarettes/day vs. >10 cigarettes/day.

Study or Subgroup	MD	SE	Number of cigarettes Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
3.1.1 ≤10 cigarettes/day						
GanerHerman 2016[a]	-153	58.391178	83	1016	5.5%	-153.00 [-267.44 , -38.56]
Ko 2014[a]	-159.6	20.563116	512	20623	15.8%	-159.60 [-199.90 , -119.30]
Lindley 2000[a]	-135.57	16.892253	3070	9802	9.6%	-135.57 [-168.68 , -102.46]
Tsukamoto 2007[a]	-29.2	28.405448	126	2554	6.3%	-29.20 [-84.87 , 26.47]
Wojtyla 2021[a]	-174.25	35.328915	260	8284	11.5%	-174.25 [-243.49 , -105.01]
Zaren 2000[a]	-167	41.964905	242	306	6.4%	-167.00 [-249.25 , -84.75]
Subtotal (Wald[b])			**4293**	**42585**	**55.1%**	**-133.44 [-179.38 , -87.50]**
Test for overall effect: Z = 5.69 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 2228.36; Chi² = 17.19, df = 5 (P = 0.004); I² = 74%						
3.1.2 >10 cigarettes/day						
Berlin 2017	-585	206.164681	37	20	1.3%	-585.00 [-989.08 , -180.92]
Fenercioğlu 2009	-409	133.980857	22	77	2.8%	-409.00 [-671.60 , -146.40]
GanerHerman 2016[a]	-195	50.219085	104	1016	7.4%	-195.00 [-293.43 , -96.57]
Kataoka 2018	-435.01	152.12	44	1137	2.2%	-435.01 [-733.16 , -136.86]
Ko 2014[a]	-388.1	84.697779	88	20623	0.9%	-388.10 [-554.10 , -222.10]
Lindley 2000[a]	-174.78	17.860563	2313	9802	8.6%	-174.78 [-209.79 , -139.77]
Tsukamoto 2007[a]	-86.1	21.483088	292	2554	11.1%	-86.10 [-128.21 , -43.99]
Wojtyla 2021[a]	-204.98	67.176037	80	8284	3.2%	-204.98 [-336.64 , -73.32]
Zaren 2000[a]	-241	38.828667	308	306	7.4%	-241.00 [-317.10 , -164.90]
Subtotal (Wald[b])			**3288**	**43819**	**44.9%**	**-237.29 [-315.73 , -158.85]**
Test for overall effect: Z = 5.93 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 8885.80; Chi² = 35.88, df = 8 (P < 0.0001); I² = 84%						
Total (Wald[b])			**7581**	**43819**	**100.0%**	**-179.73 [-228.53 , -130.92]**
Test for overall effect: Z = 7.22 (P < 0.00001)						
Test for subgroup differences: Chi² = 5.01, df = 1 (P = 0.03), I² = 80.1%						
Heterogeneity: Tau² (REML[c]) = 3247.19; Chi² = 40.45, df = 8 (P < 0.00001); I² = 80%						



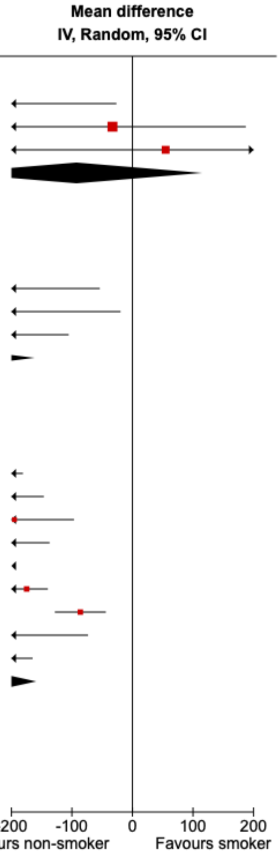
Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: detailed number of cigarettes per day

When examining more detailed categories of daily cigarette use, smoking 1–5 cigarettes per day showed no significant effect (MD –92.55 g, 95% CI –300.36 to 115.25, p = 0.38; I² = 43%) (Figure 5). In contrast, both smoking 6–10 per day (MD –301.57 g, 95% CI –441.49 to –161.65, p < 0.0001; I² = 0%) and more than 10 per day (MD –237.29 g, 95% CI –315.73 to –158.85, p < 0.00001; I² = 84%) were associated with significant reduction in birthweight. However, the test for subgroup differences did not show a statistically significant difference between categories (p = 0.26).

Figure 5: Forest plot of mean birthweight differences between infants born to mothers by detailed categories of daily cigarette consumption (1–5, 6–10, and >10 cigarettes/day)

Study or Subgroup	MD	SE	Detailed number of cigarettes Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
4.1.1 1–5 cigarettes/day						
Berlin 2017[a]	-336	157.92011	192	20	28.4%	-336.00 [-645.52 , -26.48]
Fenercioğlu 2009[a]	-33	112.332733	34	77	41.3%	-33.00 [-253.17 , 187.17]
Kataoka 2018[b]	54.81	150.09	49	1137	30.3%	54.81 [-239.36 , 348.98]
Subtotal (Wald[c])			**275**	**1234**	**100.0%**	**-92.55 [-300.36 , 115.25]**
Test for overall effect: Z = 0.87 (P = 0.38)						
Heterogeneity: Tau² (REML[d]) = 14602.22; Chi² = 3.61, df = 2 (P = 0.16); I² = 43%						
4.1.2 6–10 cigarettes/day						
Berlin 2017[a]	-374	163.284206	122	20	19.1%	-374.00 [-694.03 , -53.97]
Fenercioğlu 2009[a]	-245	114.953365	30	77	38.6%	-245.00 [-470.30 , -19.70]
Kataoka 2018[b]	-320.41	109.74	66	1137	42.3%	-320.41 [-535.50 , -105.32]
Subtotal (Wald[c])			**218**	**1234**	**100.0%**	**-301.57 [-441.49 , -161.65]**
Test for overall effect: Z = 4.22 (P < 0.0001)						
Heterogeneity: Tau² (REML[d]) = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%						
4.1.3 >10 cigarettes/day						
Berlin 2017[a]	-585	206.164681	37	20	3.1%	-585.00 [-989.08 , -180.92]
Fenercioğlu 2009[a]	-409	133.980857	22	77	6.0%	-409.00 [-671.60 , -146.40]
GanerHerman 2016	-195	50.219085	104	1016	14.0%	-195.00 [-293.43 , -96.57]
Kataoka 2018[b]	-435.01	152.12	44	1137	5.0%	-435.01 [-733.16 , -136.86]
Ko 2014	-388.1	84.697779	88	20623	10.0%	-388.10 [-554.10 , -222.10]
Lindley 2000	-174.78	17.860563	2313	9802	17.4%	-174.78 [-209.79 , -139.77]
Tsukamoto 2007	-86.1	21.483088	292	2554	17.1%	-86.10 [-128.21 , -43.99]
Wojtyla 2021	-204.98	67.176037	80	8284	12.0%	-204.98 [-336.64 , -73.32]
Zaren 2000	-241	38.828667	308	306	15.4%	-241.00 [-317.10 , -164.90]
Subtotal (Wald[c])			**3288**	**43819**	**100.0%**	**-237.29 [-315.73 , -158.85]**
Test for overall effect: Z = 5.93 (P < 0.00001)						
Heterogeneity: Tau² (REML[d]) = 8885.80; Chi² = 35.88, df = 8 (P < 0.0001); I² = 84%						
Total			**3781**	**46287**		**Not estimable**
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 2.67, df = 2 (P = 0.26), I² = 25.2%						
Heterogeneity: Not applicable						



Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

2.3.3.2 Low birthweight (<2500g)

Overall analysis: Smoker vs. Non-smoker

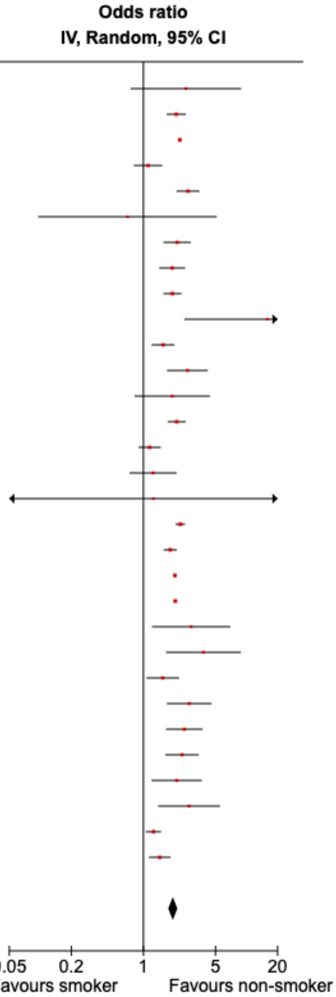
The odds of low birthweight were almost doubled among infants of mothers who smoked compared with non-smokers (OR 1.93, 95% CI 1.74–2.13, p < 0.00001). Heterogeneity was high ($I^2 = 95\%$), though the effect direction was consistent (Figure 6).

Figure 6: Forest plot of odds ratios for low birthweight among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Andriani 2014	0.947789	0.631066	84	796	0.6%	2.58 [0.75 , 8.89]
Barbieri 2000	0.732368	0.110427	1620	4172	4.5%	2.08 [1.68 , 2.58]
Chan 2008	0.81093	0.015878	83208	345005	5.7%	2.25 [2.18 , 2.32]
Chen 2018	0.102557	0.162171	521	147460	3.7%	1.11 [0.81 , 1.52]
Chiolero 2005	0.993252	0.130315	1170	4656	4.2%	2.70 [2.09 , 3.49]
Coleman-Cowger 2018	-0.356675	1.017617	39	354	0.3%	0.70 [0.10 , 5.14]
daFonseca 2012	0.751416	0.155847	196	721	3.8%	2.12 [1.56 , 2.88]
Delpisheh 2006	0.641854	0.147916	4354	183	3.9%	1.90 [1.42 , 2.54]
Flower 2013	0.647103	0.103437	6017	11429	4.7%	1.91 [1.56 , 2.34]
Huang 2017	2.76506	0.945476	20	145	0.3%	15.88 [2.49 , 101.31]
Inoue 2017	0.438255	0.130315	580	15816	4.2%	1.55 [1.20 , 2.00]
Jackson 2007	0.982078	0.232238	200	200	2.7%	2.67 [1.69 , 4.21]
Jeena 2020	0.641854	0.429028	31	1068	1.2%	1.90 [0.82 , 4.40]
Kharkova 2017	0.741937	0.102446	40702	3968	4.7%	2.10 [1.72 , 2.57]
Mercer 2008	0.139762	0.126891	775	3630	4.3%	1.15 [0.90 , 1.47]
Murphy 2013	0.215111	0.26834	110	637	2.3%	1.24 [0.73 , 2.10]
Oh 2021	0.223144	1.923844	19	1656	0.1%	1.25 [0.03 , 54.26]
Okah 2005	0.824175	0.054676	12496	64917	5.4%	2.28 [2.05 , 2.54]
Raatikainen 2007	0.598837	0.075413	6785	18806	5.1%	1.82 [1.57 , 2.11]
Raisanen 2014	0.703098	0.012632	145710	958177	5.7%	2.02 [1.97 , 2.07]
Ratnasiri 2020	0.71295	0.015011	75864	4812411	5.7%	2.04 [1.98 , 2.10]
Suzuki 2008	1.064711	0.446233	72	1028	1.1%	2.90 [1.21 , 6.95]
Tashan 2017	1.34025	0.427043	72	592	1.2%	3.82 [1.65 , 8.82]
Tayie 2012	0.431782	0.184963	1670	9890	3.3%	1.54 [1.07 , 2.21]
Vardavas 2010	1.022451	0.25489	256	843	2.4%	2.78 [1.69 , 4.58]
Veloso 2014	0.912283	0.208073	186	4854	3.0%	2.49 [1.66 , 3.74]
Villalbi 2007	0.86289	0.190537	942	1353	3.2%	2.37 [1.63 , 3.44]
Wang 2002	0.741937	0.287253	124	567	2.1%	2.10 [1.20 , 3.69]
Wang 2020	1.018847	0.352273	81	8505	1.6%	2.77 [1.39 , 5.53]
Ward 2007	0.223144	0.087566	6397	8100	4.9%	1.25 [1.05 , 1.48]
Witt 2016	0.364643	0.122987	2169	7181	4.3%	1.44 [1.13 , 1.83]
Total (Wald[a])			**392470**	**6439120**	**100.0%**	**1.93 [1.74 , 2.13]**

Test for overall effect: Z = 12.56 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.05; Chi² = 145.89, df = 30 (P < 0.00001); I² = 95%



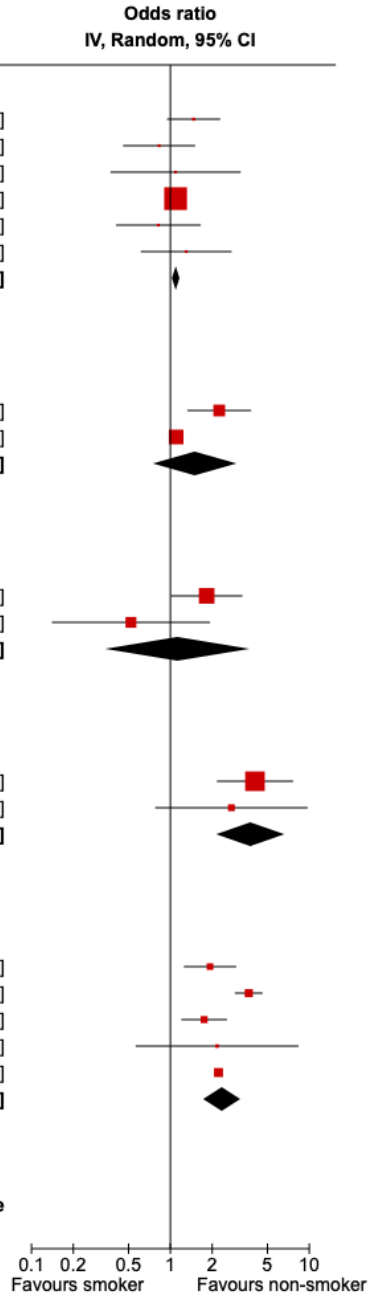
Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: Timing of smoking cessation

Quitting late in pregnancy (third trimester: OR 3.76, 95% CI 2.14 to 6.61, $p < 0.00001$; I^2 = 0%) and smoking throughout (OR 2.34, 95% CI 1.72 to 3.18, $p < 0.00001$; I^2 = 83%) were associated with elevated risk, whereas earlier cessation was not (Figure 7). Subgroup differences were significant ($p < 0.00001$).

Figure 7: Forest plot of odds ratios for low birthweight among infants born to smokers vs. non-smokers, stratified by timing of smoking cessation

Study or Subgroup	log[OR]	SE	Timing of smoking Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
2.4.1 Quit before pregnancy						
Bird 2017[a]	0.385262	0.225387	610	4904	2.0%	1.47 [0.95 , 2.29]
Jaddoe 2008[a]	-0.18633	0.304914	591	5289	1.1%	0.83 [0.46 , 1.51]
Murphy 2013	0.086178	0.551164	160	637	0.3%	1.09 [0.37 , 3.21]
Raisanen 2014	0.086178	0.032811	30136	958177	95.1%	1.09 [1.02 , 1.16]
Vardavas 2010	-0.198451	0.358277	216	843	0.8%	0.82 [0.41 , 1.65]
Wang 2002	0.262364	0.3837	50	567	0.7%	1.30 [0.61 , 2.76]
Subtotal (Wald[b])			**31763**	**970417**	**100.0%**	**1.09 [1.03 , 1.16]**
Test for overall effect: Z = 2.76 (P = 0.006)						
Heterogeneity: Tau^2 (REML[c]) = 0.00; Chi^2 = 3.40, df = 5 (P = 0.64); I^2 = 0%						
2.4.2 Quit 1st trimester						
Delcroix-Gomez 2022[d]	0.810368	0.269653	121	3704	43.0%	2.25 [1.33 , 3.81]
Rumrich 2020[a]	0.09531	0.039325	47819	165734	57.0%	1.10 [1.02 , 1.19]
Subtotal (Wald[b])			**47940**	**169438**	**100.0%**	**1.50 [0.75 , 3.00]**
Test for overall effect: Z = 1.14 (P = 0.25)						
Heterogeneity: Tau^2 (REML[c]) = 0.22; Chi^2 = 6.89, df = 1 (P = 0.009); I^2 = 85%						
2.4.3 Quit 2nd trimester						
Delcroix-Gomez 2022[d]	0.601528	0.302326	111	3704	61.3%	1.82 [1.01 , 3.30]
Miyake 2013[a]	-0.653926	0.668645	71	1427	38.7%	0.52 [0.14 , 1.93]
Subtotal (Wald[b])			**182**	**5131**	**100.0%**	**1.12 [0.34 , 3.72]**
Test for overall effect: Z = 0.19 (P = 0.85)						
Heterogeneity: Tau^2 (REML[c]) = 0.52; Chi^2 = 2.93, df = 1 (P = 0.09); I^2 = 66%						
2.4.4 Quit 3rd trimester						
Delcroix-Gomez 2022[d]	1.402305	0.322372	57	3704	80.0%	4.06 [2.16 , 7.65]
Miyake 2013[a]	1.011601	0.644761	28	1427	20.0%	2.75 [0.78 , 9.73]
Subtotal (Wald[b])			**85**	**5131**	**100.0%**	**3.76 [2.14 , 6.61]**
Test for overall effect: Z = 4.59 (P < 0.00001)						
Heterogeneity: Tau^2 (REML[c]) = 0.00; Chi^2 = 0.29, df = 1 (P = 0.59); I^2 = 0%						
2.4.5 Smoked throughout pregnancy						
Bird 2017[a]	0.65752	0.221099	647	4904	18.9%	1.93 [1.25 , 2.98]
Delcroix-Gomez 2022[d]	1.299289	0.117458	632	3704	25.9%	3.67 [2.91 , 4.62]
Jaddoe 2008[a]	0.559616	0.193291	1218	5289	20.7%	1.75 [1.20 , 2.56]
Miyake 2013[a]	0.774727	0.688707	39	1427	4.4%	2.17 [0.56 , 8.37]
Rumrich 2020[a]	0.797507	0.018394	165734	165734	30.1%	2.22 [2.14 , 2.30]
Subtotal (Wald[b])			**168270**	**181058**	**100.0%**	**2.34 [1.72 , 3.18]**
Test for overall effect: Z = 5.43 (P < 0.00001)						
Heterogeneity: Tau^2 (REML[c]) = 0.08; Chi^2 = 19.93, df = 4 (P = 0.0005); I^2 = 83%						
Total			**248240**	**1331175**		**Not estimable**



Test for overall effect: Not applicable
Test for subgroup differences: Chi^2 = 40.60, df = 4 (P < 0.00001), I^2 = 90.1%
Heterogeneity: Not applicable

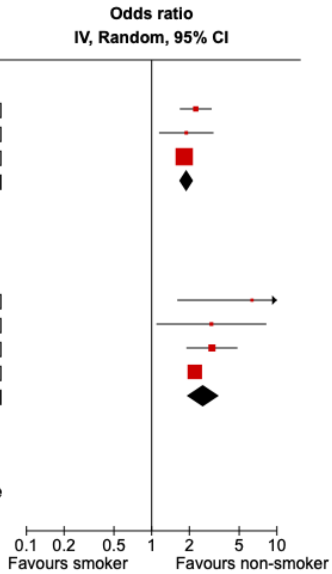
Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: ≤10 vs >10 cigarettes per day

Smoking ≤10 cigarettes per day was associated with an increased risk of low birthweight (OR 1.89, 95% CI 1.66 to 2.14, $p < 0.00001$; $I^2 = 23\%$), and the risk was slightly greater among mothers who smoked more than 10 cigarettes daily (OR 2.56, 95% CI 1.90 to 3.44, $p < 0.00001$; $I^2 = 35\%$) (Figure 8). A test for subgroup differences did not show a statistically significant difference between categories ($p = 0.38$).

Figure 8: Forest plot of odds ratios for low birthweight among infants born to mothers smoking ≤10 cigarettes/day vs. >10 cigarettes/day.

Study or Subgroup	log[OR]	SE	Number of cigarettes Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
3.3.1 ≤10 cigarettes/day						
Ko 2014[a]	0.81093	0.149611	512	20623	15.5%	2.25 [1.68 , 3.02]
Moore 2000[a]	0.636577	0.255431	129	893	6.0%	1.89 [1.15 , 3.12]
Pollack 2000[a]	0.598837	0.020752	25824	258089	78.5%	1.82 [1.75 , 1.90]
Subtotal (Wald[b])			**26465**	**279605**	**100.0%**	**1.89 [1.66 , 2.14]**
Test for overall effect: Z = 9.73 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 1.99, df = 2 (P = 0.37); I² = 23%						
3.3.2 >10 cigarettes/day						
Ko 2014[a]	1.8453	0.701256	88	20623	4.3%	6.33 [1.60 , 25.02]
Matsubara 2000	1.098612	0.515726	63	6335	7.6%	3.00 [1.09 , 8.24]
Moore 2000[a]	1.108563	0.239592	124	893	24.6%	3.03 [1.89 , 4.85]
Pollack 2000[a]	0.792993	0.026513	13928	258089	63.5%	2.21 [2.10 , 2.33]
Subtotal (Wald[b])			**14203**	**285940**	**100.0%**	**2.56 [1.90 , 3.44]**
Test for overall effect: Z = 6.22 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.04; Chi² = 4.28, df = 3 (P = 0.23); I² = 35%						
Total			**40668**	**565545**		**Not estimable**
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 3.45, df = 1 (P = 0.06), I² = 71.0%						
Heterogeneity: Not applicable						



Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

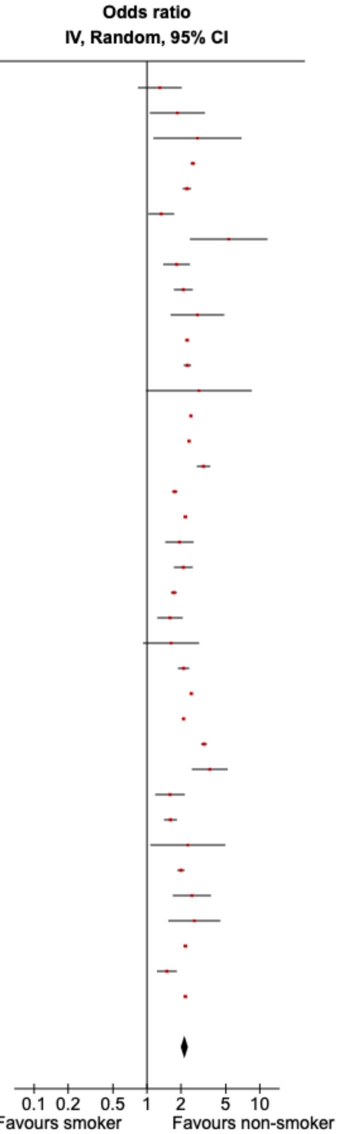
2.3.3.3 Small-for-gestational age

Overall analysis: Smoker vs. Non-smoker

Maternal smoking during pregnancy was associated with a two-fold increase in the odds of SGA (OR 2.14, 95% CI 1.99 to 2.31, $p < 0.00001$) (Figure 9). Heterogeneity was high ($I^2 = 99\%$), but the direction of effect was consistent across studies.

Figure 9: Forest plot of odds ratios for SGA among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Abdelwahab 2022	0.262364	0.227604	325	259	1.6%	1.30 [0.83 , 2.03]
Ahmadi-Montecalvo 2016	0.620576	0.287383	620	266	1.2%	1.86 [1.06 , 3.27]
Akahoshi 2016	1.029619	0.459687	45	576	0.6%	2.80 [1.14 , 6.89]
Baba 2013	0.936093	0.024028	74359	663649	3.7%	2.55 [2.43 , 2.67]
Bickerstaff 2012	0.815365	0.04384	4710	25814	3.6%	2.26 [2.07 , 2.46]
Brink 2022	0.29097	0.134836	862	877	2.5%	1.34 [1.03 , 1.74]
Campbell 2012	1.667707	0.40412	223	1956	0.7%	5.30 [2.40 , 11.70]
Cardenas 2020	0.604316	0.13933	372	1062	2.5%	1.83 [1.39 , 2.40]
Chiolero 2005	0.741937	0.098385	1170	4656	3.0%	2.10 [1.73 , 2.55]
Delpisheh 2006	1.029619	0.280263	4354	183	1.2%	2.80 [1.62 , 4.85]
Feferkorn 2022	0.81978	0.017989	443590	8653198	3.8%	2.27 [2.19 , 2.35]
Gibberd 2019	0.824175	0.038113	13292	14827	3.7%	2.28 [2.12 , 2.46]
Kleijer 2005	1.061257	0.55	394	394	0.4%	2.89 [0.98 , 8.49]
Kuja-Halkola 2014	0.896088	0.007304	306000	1426000	3.8%	2.45 [2.42 , 2.49]
Lamm 2020	0.858662	0.004324	545008	2487920	3.8%	2.36 [2.34 , 2.38]
Lanting 2009	1.153732	0.070602	1416	13137	3.3%	3.17 [2.76 , 3.64]
Li 2019	0.565314	0.029021	20477	119396	3.7%	1.76 [1.66 , 1.86]
Madley-Dowd 2021	0.783902	0.018646	93978	976035	3.8%	2.19 [2.11 , 2.27]
Mercer 2008	0.662688	0.147986	775	3630	2.4%	1.94 [1.45 , 2.59]
Meyer 2009	0.741937	0.098385	1722	12871	3.0%	2.10 [1.73 , 2.55]
Miller 2010	0.548121	0.030915	34508	273689	3.7%	1.73 [1.63 , 1.84]
Mitchell 2002	0.470004	0.132792	718	989	2.6%	1.60 [1.23 , 2.08]
Nanninga 2023	0.492108	0.292271	209	1706	1.1%	1.64 [0.92 , 2.90]
Raatikainen 2007	0.746688	0.059087	6785	18806	3.5%	2.11 [1.88 , 2.37]
Raisanen 2014	0.904218	0.012396	145710	958177	3.8%	2.47 [2.41 , 2.53]
Ratnasiri 2020	0.746688	0.014512	75864	4812411	3.8%	2.11 [2.05 , 2.17]
Reynolds 2020	1.163151	0.03096	5039	21136	3.7%	3.20 [3.01 , 3.40]
Rode 2013	1.280934	0.186832	321	1104	2.0%	3.60 [2.50 , 5.19]
Savitz 2001	0.470004	0.154629	472	696	2.3%	1.60 [1.18 , 2.17]
Schultze 2016	0.479187	0.067579	2022	9120	3.4%	1.61 [1.41 , 1.84]
Suzuki 2008	0.832909	0.391316	72	1028	0.7%	2.30 [1.07 , 4.95]
Tong 2017	0.693147	0.0374	10683	64860	3.7%	2.00 [1.86 , 2.15]
Tveit 2010	0.916291	0.198398	259	1909	1.8%	2.50 [1.69 , 3.69]
Vardavas 2010	0.966984	0.271331	256	843	1.3%	2.63 [1.55 , 4.48]
Waldenstrom 2014	0.783902	0.019858	56663	548848	3.8%	2.19 [2.11 , 2.28]
Wang 2020a	0.405465	0.103437	2632	28770	2.9%	1.50 [1.22 , 1.84]
Winbo 2001	0.783902	0.01744	2631	6017	3.8%	2.19 [2.12 , 2.27]
Total (Wald[a])			**1858536**	**21156815**	**100.0%**	**2.14 [1.99 , 2.31]**



Test for overall effect: Z = 20.37 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.04; Chi² = 607.78, df = 36 (P < 0.00001); I² = 99%

Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

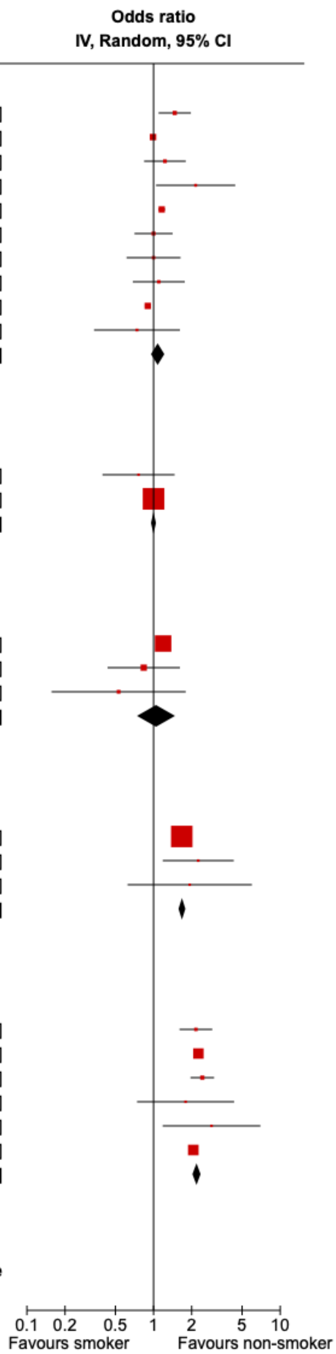
Subgroup analysis: Timing of smoking cessation

Quitting before or during early pregnancy was not associated with a difference in SGA risk compared with non-smokers. Quitting in the third trimester (OR 1.68, 95% CI 1.57 to 1.78, $p < 0.00001$; $I^2 = 0\%$) and smoking throughout (OR 2.18, 95% CI 2.03 to 2.35, $p < 0.00001$; $I^2 = 90\%$) were linked to a higher risk (Figure 10). A test for subgroup differences showed that the effect varied significantly with timing of cessation ($p < 0.00001$).

Figure 10: Forest plot of odds ratios for SGA among infants born to smokers and non-smokers, stratified by timing of smoking cessation

Study or Subgroup	log[OR]	SE	Timing of smoking Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
2.3.1 Quit before pregnancy						
Bird 2017[a]	0.385262	0.149688	610	4904	9.5%	1.47 [1.10 , 1.97]
Blatt 2015[a]	-0.01005	0.018137	21803	697266	20.9%	0.99 [0.96 , 1.03]
Hosokawa 2022	0.207014	0.193006	1274	4114	6.9%	1.23 [0.84 , 1.80]
Meghea 2014[a]	0.765468	0.367254	112	290	2.5%	2.15 [1.05 , 4.42]
Raisanen 2014	0.14842	0.030826	30136	958177	20.2%	1.16 [1.09 , 1.23]
Reynolds 2020	0	0.176827	13981	21136	7.8%	1.00 [0.71 , 1.41]
Rode 2013	0	0.250216	349	1104	4.7%	1.00 [0.61 , 1.63]
Savitz 2001	0.09531	0.240939	192	696	5.0%	1.10 [0.69 , 1.76]
Tong 2017	-0.105361	0.026878	11696	64860	20.4%	0.90 [0.85 , 0.95]
Vardavas 2010	-0.301105	0.398282	216	843	2.2%	0.74 [0.34 , 1.62]
Subtotal (Wald[b])			**80369**	**1753390**	**100.0%**	**1.08 [0.95 , 1.22]**
Test for overall effect: Z = 1.21 (P = 0.23)						
Heterogeneity: Tau² (REML[c]) = 0.02; Chi² = 51.69, df = 9 (P < 0.00001); I² = 87%						
2.3.2 Quit 1st trimester						
Delcroix-Gomez 2022[d]	-0.272899	0.334458	121	3704	0.5%	0.76 [0.40 , 1.47]
Rumrich 2020[a]	0	0.023091	47819	165734	99.5%	1.00 [0.96 , 1.05]
Subtotal (Wald[b])			**47940**	**169438**	**100.0%**	**1.00 [0.95 , 1.04]**
Test for overall effect: Z = 0.06 (P = 0.96)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%						
2.3.3 Quit 2nd trimester						
Blatt 2015[a]	0.173953	0.023698	8797	697266	72.7%	1.19 [1.14 , 1.25]
Delcroix-Gomez 2022[d]	-0.17849	0.335789	111	3704	20.1%	0.84 [0.43 , 1.62]
Miyake 2013[a]	-0.634878	0.622205	71	1427	7.3%	0.53 [0.16 , 1.79]
Subtotal (Wald[b])			**8979**	**702397**	**100.0%**	**1.05 [0.74 , 1.48]**
Test for overall effect: Z = 0.25 (P = 0.80)						
Heterogeneity: Tau² (REML[c]) = 0.04; Chi² = 2.78, df = 2 (P = 0.25); I² = 33%						
2.3.4 Quit 3rd trimester						
Blatt 2015[a]	0.512824	0.032026	132536	697266	98.8%	1.67 [1.57 , 1.78]
Delcroix-Gomez 2022[d]	0.81229	0.329254	57	3704	0.9%	2.25 [1.18 , 4.30]
Miyake 2013[a]	0.65752	0.576507	28	1427	0.3%	1.93 [0.62 , 5.97]
Subtotal (Wald[b])			**132621**	**702397**	**100.0%**	**1.68 [1.57 , 1.78]**
Test for overall effect: Z = 16.21 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 0.88, df = 2 (P = 0.64); I² = 0%						
2.3.5 Smoked throughout pregnancy						
Bird 2017[a]	0.770108	0.151714	647	4904	5.4%	2.16 [1.60 , 2.91]
Blatt 2015[a]	0.815365	0.010138	53355	697266	41.6%	2.26 [2.22 , 2.31]
Delcroix-Gomez 2022[d]	0.886361	0.109461	632	3704	9.3%	2.43 [1.96 , 3.01]
Meghea 2014[a]	0.582216	0.4501	72	290	0.7%	1.79 [0.74 , 4.32]
Miyake 2013[a]	1.054312	0.45323	39	1427	0.7%	2.87 [1.18 , 6.98]
Rumrich 2020[a]	0.722706	0.007431	165734	165734	42.2%	2.06 [2.03 , 2.09]
Subtotal (Wald[b])			**220479**	**873325**	**100.0%**	**2.18 [2.03 , 2.35]**
Test for overall effect: Z = 20.65 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 56.37, df = 5 (P < 0.00001); I² = 90%						
Total			**490388**	**4200947**		**Not estimable**

Test for overall effect: Not applicable
Test for subgroup differences: Chi² = 392.27, df = 4 (P < 0.00001), I² = 99.0%
Heterogeneity: Not applicable



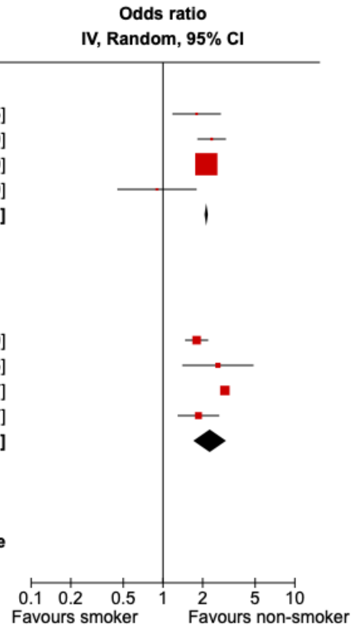
Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: ≤10 vs >10 cigarettes per day

Smoking ≤10 cigarettes per day was associated with a significantly increased risk of SGA compared with non-smokers (OR 2.13, 95% CI 2.07 to 2.19, $p < 0.00001$; $I^2 = 0\%$) (Figure 11). A slightly higher risk was observed among women who smoked more than 10 cigarettes per day (OR 2.26, 95% CI 1.70 to 3.01, $p < 0.00001$; $I^2 = 84\%$). A test for subgroup differences did not show a statistically significant difference between categories ($p = 0.68$).

Figure 11: Forest plot of odds ratios for SGA among infants born to mothers smoking ≤10 cigarettes/day vs. >10 cigarettes/day

Study or Subgroup	log[OR]	SE	Number of cigarettes Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
3.2.1 ≤10 cigarettes/day						
GanerHerman 2016[a]	0.587787	0.216151	83	1016	0.5%	1.80 [1.18 , 2.75]
Ko 2014[a]	0.850151	0.127496	512	20623	1.3%	2.34 [1.82 , 3.00]
Olbertz 2018[a]	0.756591	0.014958	0	0	98.0%	2.13 [2.07 , 2.19]
Tsukamoto 2007[b]	-0.104808	0.353636	126	2554	0.2%	0.90 [0.45 , 1.80]
Subtotal (Wald[c])			**721**	**24193**	**100.0%**	**2.13 [2.07 , 2.19]**
Test for overall effect: Z = 51.02 (P < 0.00001)						
Heterogeneity: Tau² (REML[d]) = 0.00; Chi² = 7.08, df = 3 (P = 0.07); I² = 0%						
3.2.2 >10 cigarettes/day						
GanerHerman 2016[a]	0.587787	0.103437	104	1016	29.8%	1.80 [1.47 , 2.20]
Ko 2014[a]	0.95935	0.317497	88	20623	13.2%	2.61 [1.40 , 4.86]
Olbertz 2018[a]	1.080788	0.021376	0	0	34.7%	2.95 [2.83 , 3.07]
Tsukamoto 2007[b]	0.619592	0.185387	292	2554	22.3%	1.86 [1.29 , 2.67]
Subtotal (Wald[c])			**484**	**24193**	**100.0%**	**2.26 [1.70 , 3.01]**
Test for overall effect: Z = 5.59 (P < 0.00001)						
Heterogeneity: Tau² (REML[d]) = 0.06; Chi² = 27.46, df = 3 (P < 0.00001); I² = 84%						
Total			**1205**	**48386**		**Not estimable**
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.68), I² = 0%						
Heterogeneity: Not applicable						



Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

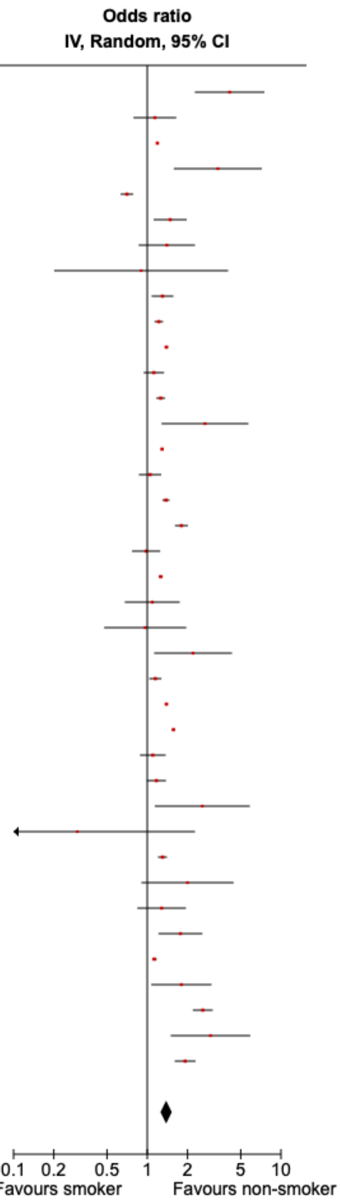
2.3.3.4 Preterm birth

Overall analysis: Smoker vs. Non-smoker

Maternal smoking during pregnancy was associated with an increased risk of preterm birth compared with non-smokers (OR 1.38, 95% CI 1.25 to 1.53, $p < 0.00001$), with high heterogeneity across studies ($I^2 = 99\%$) (Figure 12).

Figure 12: Forest plot of odds ratios for preterm birth among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Abufraijeh 2024	1.418277	0.305563	114	296	1.5%	4.13 [2.27 , 7.52]
Agrawal 2010	0.131028	0.187885	159	963	2.4%	1.14 [0.79 , 1.65]
Aliyu 2010	0.173953	0.006459	238962	980197	3.6%	1.19 [1.18 , 1.21]
Andriani 2014	1.214913	0.386555	84	796	1.1%	3.37 [1.58 , 7.19]
Bickerstaff 2012	-0.350657	0.055326	25814	4710	3.4%	0.70 [0.63 , 0.78]
Brink 2022	0.394476	0.145411	862	877	2.7%	1.48 [1.12 , 1.97]
Chiolero 2005	0.336472	0.247301	1170	4656	1.9%	1.40 [0.86 , 2.27]
Coleman-Cowger 2018	-0.105361	0.764231	39	354	0.4%	0.90 [0.20 , 4.02]
Delpisheh 2006	0.262364	0.095587	4354	183	3.2%	1.30 [1.08 , 1.57]
Dew 2007	0.198851	0.037707	15122	67778	3.5%	1.22 [1.13 , 1.31]
Feferkorn 2022	0.329304	0.014686	443590	8653198	3.6%	1.39 [1.35 , 1.43]
Flower 2013	0.113329	0.089644	6017	11429	3.2%	1.12 [0.94 , 1.34]
Gibberd 2019	0.231112	0.038389	13292	14827	3.5%	1.26 [1.17 , 1.36]
Jeena 2020	0.993252	0.38151	31	1068	1.2%	2.70 [1.28 , 5.70]
Kuja-Halkola 2014	0.254642	0.009851	306000	1426000	3.6%	1.29 [1.27 , 1.32]
Lanting 2009	0.04879	0.098262	1416	13137	3.1%	1.05 [0.87 , 1.27]
Li 2019	0.322083	0.031352	20477	119396	3.5%	1.38 [1.30 , 1.47]
Mei-Dan 2015	0.587787	0.056925	1646	19292	3.4%	1.80 [1.61 , 2.01]
Mercer 2008	-0.020203	0.123601	775	3630	2.9%	0.98 [0.77 , 1.25]
Miller 2010	0.231112	0.018158	34508	273689	3.6%	1.26 [1.22 , 1.31]
Murphy 2013	0.086178	0.241147	110	637	1.9%	1.09 [0.68 , 1.75]
Nanninga 2023	-0.035491	0.360392	209	1706	1.2%	0.97 [0.48 , 1.96]
Ohmi 2002	0.788457	0.341785	183	716	1.3%	2.20 [1.13 , 4.30]
Raatikainen 2007	0.139762	0.05297	6785	18806	3.4%	1.15 [1.04 , 1.28]
Raisanen 2014	0.329304	0.012804	145710	958177	3.6%	1.39 [1.36 , 1.43]
Ratnasiri 2020	0.451076	0.014581	75864	4812411	3.6%	1.57 [1.53 , 1.62]
Savitz 2001	0.09531	0.112715	472	696	3.0%	1.10 [0.88 , 1.37]
Schultze 2016	0.15765	0.084502	2022	9120	3.2%	1.17 [0.99 , 1.38]
Selvaratnam 2023	0.947789	0.417205	89	718	1.0%	2.58 [1.14 , 5.84]
Suzuki 2008	-1.203973	1.033638	72	1028	0.2%	0.30 [0.04 , 2.27]
Tong 2017	0.262364	0.039325	10683	64860	3.5%	1.30 [1.20 , 1.40]
Tveit 2010	0.693147	0.404845	259	1909	1.1%	2.00 [0.90 , 4.42]
Vardavas 2010	0.24686	0.213535	256	843	2.2%	1.28 [0.84 , 1.95]
Villalbi 2007	0.57098	0.193159	942	1353	2.3%	1.77 [1.21 , 2.58]
Waldenstrom 2014	0.122218	0.020239	56663	548848	3.6%	1.13 [1.09 , 1.18]
Wang 2002	0.587787	0.264314	124	567	1.8%	1.80 [1.07 , 3.02]
Wang 2020a	0.955511	0.087488	2632	28770	3.2%	2.60 [2.19 , 3.09]
Wang 2024	1.088562	0.349365	73	1874	1.3%	2.97 [1.50 , 5.89]
Ward 2007	0.652325	0.091468	6397	8100	3.2%	1.92 [1.60 , 2.30]
Total (Wald[a])			**1423977**	**18057615**	**100.0%**	**1.38 [1.25 , 1.53]**



Test for overall effect: Z = 6.52 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.07; Chi² = 745.38, df = 38 (P < 0.00001); I² = 99%

Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

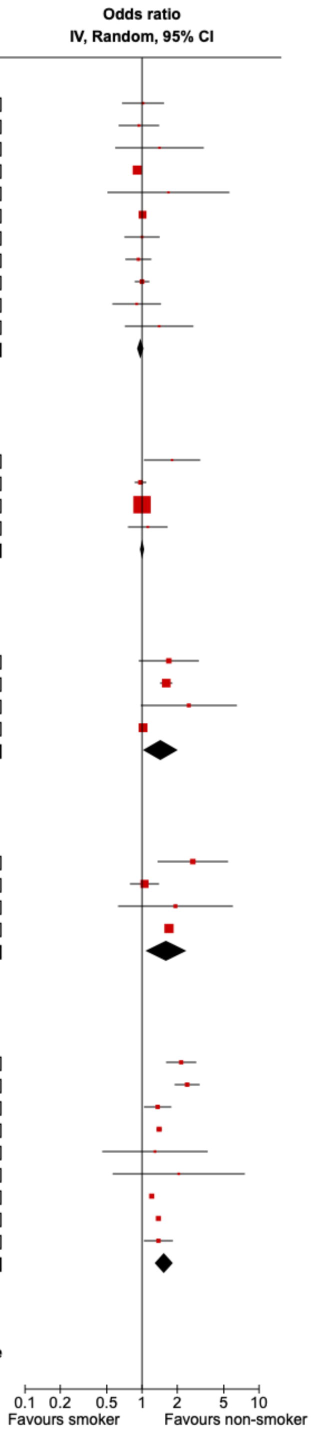
Subgroup analysis: Timing of smoking cessation

Subgroup analysis showed no significant difference in risk for women who quit before pregnancy (OR 0.97, 95% CI 0.91–1.03; $I^2 = 36\%$) or during the first trimester (OR 1.00, 95% CI 0.96–1.04; $I^2 = 0\%$) (Figure 13). In contrast, quitting in the second trimester (OR 1.43, 95% CI 1.02–2.02; $I^2 = 93\%$), quitting in the third trimester (OR 1.60, 95% CI 1.07–2.39; $I^2 = 80\%$), and smoking throughout pregnancy (OR 1.53, 95% CI 1.28–1.83; $I^2 = 98\%$) were all associated with significantly increased odds of preterm birth. The test for subgroup differences confirmed that timing of cessation significantly modified the association (p < 0.00001).

Figure 13: Forest plot of odds ratios for preterm birth among infants born to smokers and non-smokers, stratified by timing of smoking cessation

Study or Subgroup	log[OR]	SE	Timing of smoking Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
2.5.1 Quit before pregnancy						
Bird 2017[a]	0.019803	0.211133	610	4904	2.3%	1.02 [0.67 , 1.54]
Jaddoe 2008[a]	-0.061875	0.203705	591	5289	2.4%	0.94 [0.63 , 1.40]
Meghea 2014[a]	0.34359	0.444535	112	290	0.5%	1.41 [0.59 , 3.37]
Moore 2016[a]	-0.094311	0.016826	53355	697266	38.5%	0.91 [0.88 , 0.94]
Murphy 2013	0.518794	0.612627	160	637	0.3%	1.68 [0.51 , 5.58]
Raisanen 2014	0.00995	0.030345	30136	958177	31.3%	1.01 [0.95 , 1.07]
Savitz 2001	0	0.176827	192	696	3.2%	1.00 [0.71 , 1.41]
Smith 2015[a]	-0.072571	0.130315	341	1096	5.5%	0.93 [0.72 , 1.20]
Tong 2017	0	0.07339	11696	64860	13.5%	1.00 [0.87 , 1.15]
Vardavas 2010	-0.105361	0.244457	216	843	1.7%	0.90 [0.56 , 1.45]
Wang 2002	0.336472	0.344375	50	567	0.9%	1.40 [0.71 , 2.75]
Subtotal (Wald[b])			**97459**	**1734625**	**100.0%**	**0.97 [0.91 , 1.03]**
Test for overall effect: Z = 1.03 (P = 0.30)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 13.36, df = 10 (P = 0.20); I² = 36%						
2.5.2 Quit 1st trimester						
Delcroix-Gomez 2022[d]	0.591672	0.283036	121	3704	0.6%	1.81 [1.04 , 3.15]
Kondracki 2019[a]	-0.030459	0.058109	33469	2253887	13.4%	0.97 [0.87 , 1.09]
Rumrich 2020[a]	0	0.023091	47819	165734	84.9%	1.00 [0.96 , 1.05]
Smith 2015[a]	0.113329	0.199303	114	1096	1.1%	1.12 [0.76 , 1.66]
Subtotal (Wald[b])			**81523**	**2424421**	**100.0%**	**1.00 [0.96 , 1.04]**
Test for overall effect: Z = 0.03 (P = 0.98)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 4.97, df = 3 (P = 0.17); I² = 0%						
2.5.3 Quit 2nd trimester						
Delcroix-Gomez 2022[d]	0.527043	0.301887	111	3704	17.7%	1.69 [0.94 , 3.06]
Kondracki 2019[a]	0.476234	0.061522	14454	2253887	35.6%	1.61 [1.43 , 1.82]
Miyake 2013[a]	0.920283	0.483116	71	1427	9.7%	2.51 [0.97 , 6.47]
Moore 2016[a]	0.019803	0.022414	21803	697266	37.0%	1.02 [0.98 , 1.07]
Subtotal (Wald[b])			**36439**	**2956284**	**100.0%**	**1.43 [1.02 , 2.02]**
Test for overall effect: Z = 2.05 (P = 0.04)						
Heterogeneity: Tau² (REML[c]) = 0.08; Chi² = 53.89, df = 3 (P < 0.00001); I² = 93%						
2.5.4 Quit 3rd trimester						
Delcroix-Gomez 2022[d]	0.999498	0.353956	57	3704	18.2%	2.72 [1.36 , 5.44]
Kondracki 2019[a]	0.04879	0.145971	6343	2253887	33.0%	1.05 [0.79 , 1.40]
Miyake 2013[a]	0.65752	0.576507	28	1427	9.6%	1.93 [0.62 , 5.97]
Moore 2016[a]	0.530628	0.030047	8797	697266	39.2%	1.70 [1.60 , 1.80]
Subtotal (Wald[b])			**15225**	**2956284**	**100.0%**	**1.60 [1.07 , 2.39]**
Test for overall effect: Z = 2.28 (P = 0.02)						
Heterogeneity: Tau² (REML[c]) = 0.11; Chi² = 12.41, df = 3 (P = 0.006); I² = 80%						
2.5.5 Smoked throughout pregnancy						
Bird 2017[a]	0.770108	0.151714	647	4904	11.2%	2.16 [1.60 , 2.91]
Delcroix-Gomez 2022[d]	0.887419	0.125669	632	3704	12.5%	2.43 [1.90 , 3.11]
Jaddoe 2008[a]	0.307485	0.137092	1218	5289	11.9%	1.36 [1.04 , 1.78]
Kondracki 2019[a]	0.336472	0.027262	177590	2253887	16.1%	1.40 [1.33 , 1.48]
Meghea 2014[a]	0.254642	0.529785	72	290	2.5%	1.29 [0.46 , 3.64]
Miyake 2013[a]	0.722706	0.663763	39	1427	1.7%	2.06 [0.56 , 7.57]
Moore 2016[a]	0.19062	0.0105	132536	697266	16.3%	1.21 [1.19 , 1.24]
Rumrich 2020[a]	0.322083	0.012896	165734	165734	16.3%	1.38 [1.35 , 1.42]
Smith 2015[a]	0.322083	0.14555	339	1096	11.5%	1.38 [1.04 , 1.84]
Subtotal (Wald[b])			**478807**	**3133597**	**100.0%**	**1.53 [1.28 , 1.83]**
Test for overall effect: Z = 4.69 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.05; Chi² = 111.29, df = 8 (P < 0.00001); I² = 98%						
Total			**709453**	**13205211**		**Not estimable**

Test for overall effect: Not applicable
Test for subgroup differences: Chi² = 31.93, df = 4 (P < 0.00001), I² = 87.5%
Heterogeneity: Not applicable



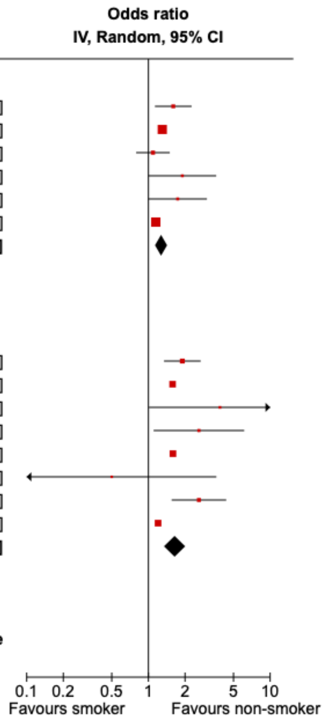
Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: ≤10 vs >10 cigarettes per day

Smoking ≤10 cigarettes per day was associated with a significantly increased risk of preterm birth compared with non-smokers (OR 1.27, 95% CI 1.13 to 1.42, $p < 0.00001$; $I^2 = 85\%$) (Figure 14). The risk was higher among women who smoked more than 10 cigarettes per day (OR 1.64, 95% CI 1.34 to 2.00, $p < 0.00001$; $I^2 = 98\%$). A test for subgroup differences indicated that the effect on preterm birth varied significantly according to the number of cigarettes smoked per day ($p = 0.03$).

Figure 14: Forest plot of odds ratios for preterm birth among infants born to mothers smoking ≤10 cigarettes/day vs. >10 cigarettes/day

Study or Subgroup	log[OR]	SE	Number of cigarettes Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
3.4.1 ≤10 cigarettes/day						
Burguet 2004[a]	0.470004	0.176827	227	951	8.5%	1.60 [1.13 , 2.26]
Dahlin 2016[a]	0.262364	0.019633	79783	1177464	37.2%	1.30 [1.25 , 1.35]
Ko 2014[a]	0.086178	0.162057	512	20623	9.7%	1.09 [0.79 , 1.50]
Kyrklund-Blomberg 2005[a]	0.641854	0.326775	106	394	2.9%	1.90 [1.00 , 3.60]
Moore 2000[a]	0.553885	0.281958	129	893	3.8%	1.74 [1.00 , 3.02]
Pollack 2000[a]	0.139762	0.015466	25824	258089	37.8%	1.15 [1.12 , 1.19]
Subtotal (Wald[b])			**106581**	**1458414**	**100.0%**	**1.27 [1.13 , 1.42]**
Test for overall effect: Z = 4.10 (P < 0.0001)						
Heterogeneity: Tau² (REML[c]) = 0.01; Chi² = 30.62, df = 5 (P < 0.0001); I² = 85%						
3.4.2 >10 cigarettes/day						
Burguet 2004[a]	0.641854	0.176827	253	951	13.8%	1.90 [1.34 , 2.69]
Dahlin 2016[a]	0.457425	0.027562	28459	1177464	23.0%	1.58 [1.50 , 1.67]
Ko 2014[a]	1.353255	0.685224	88	20623	2.0%	3.87 [1.01 , 14.82]
Kyrklund-Blomberg 2005[a]	0.955511	0.436992	60	394	4.4%	2.60 [1.10 , 6.12]
Liu 2020	0.463734	0.004798	876153	23983690	23.4%	1.59 [1.58 , 1.61]
Matsubara 2000	-0.693147	1.009387	63	6335	1.0%	0.50 [0.07 , 3.62]
Moore 2000[a]	0.955511	0.26325	124	893	9.2%	2.60 [1.55 , 4.36]
Pollack 2000[a]	0.182322	0.019222	13928	258089	23.2%	1.20 [1.16 , 1.25]
Subtotal (Wald[b])			**919128**	**25448439**	**100.0%**	**1.64 [1.34 , 2.00]**
Test for overall effect: Z = 4.84 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.04; Chi² = 211.20, df = 7 (P < 0.00001); I² = 98%						
Total			**1025709**	**26906853**		**Not estimable**
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 4.74, df = 1 (P = 0.03), I² = 78.9%						
Heterogeneity: Not applicable						



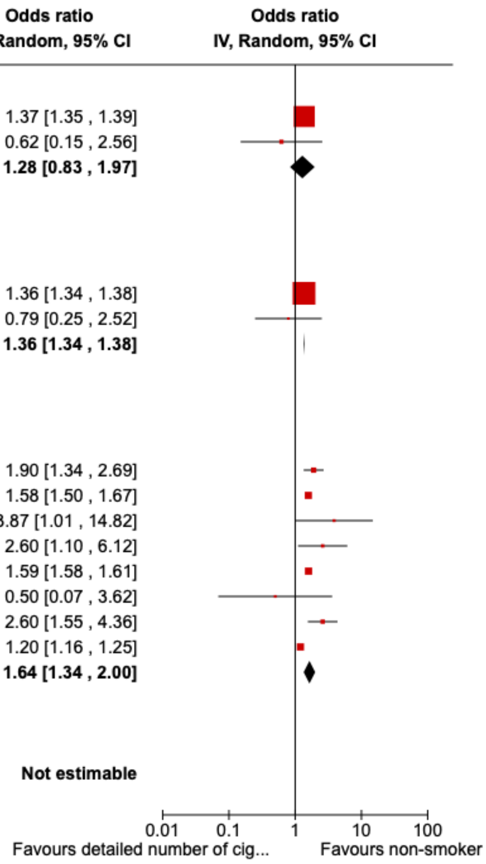
Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: detailed number of cigarettes per day

The risk of preterm birth increased with the number of cigarettes smoked (Figure 15). For light smokers (1–5 per day), the increase was not significant (OR 1.28, 95% CI 0.83 to 1.97, p = 0.26; I² = 17%). In contrast, risk was higher and significant for those smoking 6–10 per day (OR 1.36, 95% CI 1.34 to 1.38, p < 0.00001; I² = 0%) and was highest among those smoking more than 10 per day (OR 1.64, 95% CI 1.34 to 2.00, p < 0.00001; I² = 98%). A test for subgroup differences did not show statistically significant variation between categories (p = 0.18).

Figure 15: Forest plot of odds ratios for preterm birth among infants born to mothers by detailed categories of daily cigarette consumption (1–5, 6–10, and >10 cigarettes/day)

Study or Subgroup	log[OR]	SE	Detailed number of cigarettes Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
4.2.1 1–5 cigarettes/day						
Liu 2020[a]	0.314811	0.007449	611370	23983690	91.7%	1.37 [1.35 , 1.39]
Matsubara 2000[a]	-0.478036	0.72377	91	6335	8.3%	0.62 [0.15 , 2.56]
Subtotal (Wald[b])			**611461**	**23990025**	**100.0%**	**1.28 [0.83 , 1.97]**
Test for overall effect: Z = 1.13 (P = 0.26)						
Heterogeneity: Tau² (REML[c]) = 0.05; Chi² = 1.20, df = 1 (P = 0.27); I² = 17%						
4.2.2 6–10 cigarettes/day						
Liu 2020[a]	0.307485	0.007504	152266	23983690	100.0%	1.36 [1.34 , 1.38]
Matsubara 2000[a]	-0.235722	0.591454	126	6335	0.0%	0.79 [0.25 , 2.52]
Subtotal (Wald[b])			**152392**	**23990025**	**100.0%**	**1.36 [1.34 , 1.38]**
Test for overall effect: Z = 40.97 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.00; Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
4.2.3 >10 cigarettes/day						
Burguet 2004	0.641854	0.176827	253	951	13.8%	1.90 [1.34 , 2.69]
Dahlin 2016	0.457425	0.027562	28459	1177464	23.0%	1.58 [1.50 , 1.67]
Ko 2014	1.353255	0.685224	88	20623	2.0%	3.87 [1.01 , 14.82]
Kyrklund-Blomberg 2005	0.955511	0.436992	60	394	4.4%	2.60 [1.10 , 6.12]
Liu 2020[a]	0.463734	0.004798	876153	23983690	23.4%	1.59 [1.58 , 1.61]
Matsubara 2000[a]	-0.693147	1.009387	63	6335	1.0%	0.50 [0.07 , 3.62]
Moore 2000	0.955511	0.26325	124	893	9.2%	2.60 [1.55 , 4.36]
Pollack 2000	0.182322	0.019222	13928	258089	23.2%	1.20 [1.16 , 1.25]
Subtotal (Wald[b])			**919128**	**25448439**	**100.0%**	**1.64 [1.34 , 2.00]**
Test for overall effect: Z = 4.84 (P < 0.00001)						
Heterogeneity: Tau² (REML[c]) = 0.04; Chi² = 211.20, df = 7 (P < 0.00001); I² = 98%						
Total			**1682981**	**73428489**		**Not estimable**
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 3.43, df = 2 (P = 0.18), I² = 41.7%						
Heterogeneity: Not applicable						



Abbreviations: OR = Odds Ratio, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

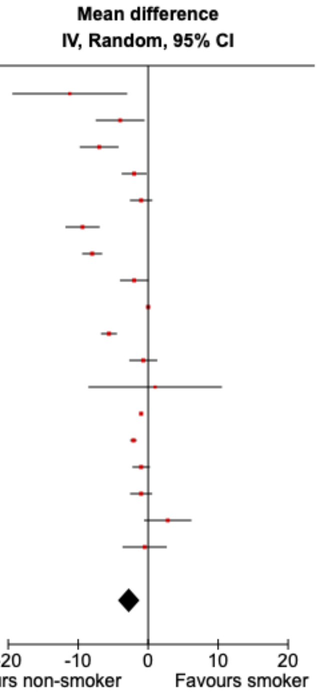
2.3.3.5 Gestational age

Overall analysis: Smoker vs. Non-smoker

Infants of mothers who smoked during pregnancy had a lower mean gestational age compared with those of non-smokers (MD –2.78 days, 95% CI –4.32 to –1.24, p = 0.0004). Heterogeneity across studies was high (I^2 = 99%), but the direction of effect was consistent, with most studies showing shorter gestation among smokers.

Figure 16: Forest plot of mean gestational age (days) differences between infants born to smokers and non-smokers

Study or Subgroup	MD	SE	Smoker Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
Abufraijeh 2024	-11.2	4.188232	114	296	2.3%	-11.20 [-19.41 , -2.99]
Alptekin 2017	-4	1.781697	59	89	5.0%	-4.00 [-7.49 , -0.51]
Andriani 2014	-7	1.414214	84	796	5.5%	-7.00 [-9.77 , -4.23]
Brink 2022	-2	0.912124	862	877	6.1%	-2.00 [-3.79 , -0.21]
Chelchowska 2013	-1	0.818317	70	80	6.2%	-1.00 [-2.60 , 0.60]
El-Shahawy 2021	-9.37931	1.249634	58	142	5.7%	-9.38 [-11.83 , -6.93]
Hamadneh 2021	-8	0.730297	60	60	6.3%	-8.00 [-9.43 , -6.57]
Harrod 2014	-2	1.037486	85	831	6.0%	-2.00 [-4.03 , 0.03]
Li 2019	0	0.075638	20477	119396	6.6%	0.00 [-0.15 , 0.15]
Mei-Dan 2015	-5.6	0.581053	1646	19292	6.4%	-5.60 [-6.74 , -4.46]
Murphy 2013	-0.7	1.022823	110	637	6.0%	-0.70 [-2.70 , 1.30]
O'donnell 2020	1	4.868596	697	2461	1.9%	1.00 [-8.54 , 10.54]
Raisanen 2014	-1	0.038671	145710	958177	6.7%	-1.00 [-1.08 , -0.92]
Reynolds 2020	-2.1	0.235444	5039	21136	6.6%	-2.10 [-2.56 , -1.64]
Samper 2012	-1	0.63774	269	947	6.4%	-1.00 [-2.25 , 0.25]
Silva 2022	-1	0.806197	89	493	6.2%	-1.00 [-2.58 , 0.58]
Steyn 2006	2.8	1.729108	97	1376	5.0%	2.80 [-0.59 , 6.19]
VilaCandel 2015	-0.5	1.613096	14	123	5.2%	-0.50 [-3.66 , 2.66]
Total (Wald[a])			**175540**	**1127209**	**100.0%**	**-2.78 [-4.32 , -1.24]**



Test for overall effect: Z = 3.53 (P = 0.0004)

Heterogeneity: Tau^2 (REML[b]) = 9.29; Chi^2 = 414.33, df = 17 (P < 0.00001); I^2 = 99%

Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

Subgroup analysis: Timing of smoking cessation

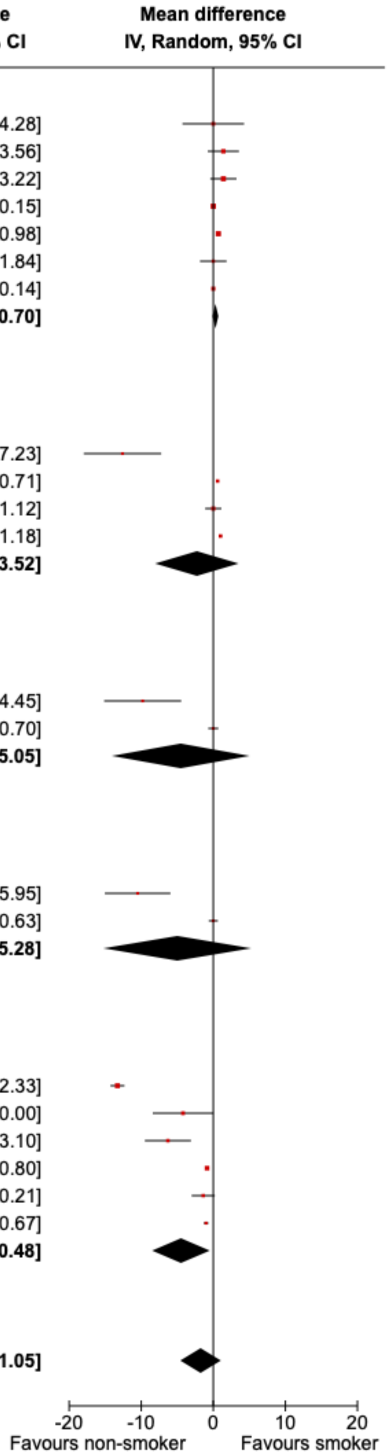
Quitting before or during pregnancy was not associated with a significant difference in mean gestational age compared with non-smokers. The greatest reduction was observed among mothers who smoked throughout pregnancy (MD –4.49 days, 95% CI –8.50 to –0.48, p = 0.03;

I² = 100%). A test for subgroup differences did not show significant variation between subcategories (p = 0.09).

Figure 17: Forest plot of mean gestational age (days) differences between infants born to smokers and non-smokers, stratified by timing of smoking cessation

Study or Subgroup	MD	SE	Timing of smoking Total	Non-smoker Total	Weight	Mean difference IV, Random, 95% CI
2.2.1 Quit before pregnancy						
Himes 2013[a]	0	2.181219	28	46	4.8%	0.00 [-4.28 , 4.28]
McCowan 2009[a]	1.4	1.100684	261	1992	7.6%	1.40 [-0.76 , 3.56]
Murphy 2013	1.4	0.928515	160	637	10.7%	1.40 [-0.42 , 3.22]
Raisanen 2014	0	0.075883	30136	958177	11.2%	0.00 [-0.15 , 0.15]
Reynolds 2020	0.7	0.140444	13981	21136	11.2%	0.70 [0.42 , 0.98]
Suzuki 2014[a]	0	0.939692	170	1920	2.3%	0.00 [-1.84 , 1.84]
Tatsuta 2023[a]	0	0.071888	16461	44198	6.2%	0.00 [-0.14 , 0.14]
Subtotal (Wald[b])			**61197**	**1028106**	**53.9%**	**0.30 [-0.11 , 0.70]**
Test for overall effect: Z = 1.43 (P = 0.15)						
Heterogeneity: Tau² (REML[c]) = 0.14; Chi² = 25.26, df = 6 (P = 0.0003); I² = 85%						
2.2.2 Quit 1st trimester						
Delcroix-Gomez 2022[a]	-12.6	2.740446	121	3704	0.3%	-12.60 [-17.97 , -7.23]
Rumrich 2020[a]	0.6	0.056458	47819	1163225	3.2%	0.60 [0.49 , 0.71]
Suzuki 2014[a]	0	0.573088	396	1920	6.2%	0.00 [-1.12 , 1.12]
Tatsuta 2023[a]	1	0.092352	8948	44198	3.8%	1.00 [0.82 , 1.18]
Subtotal (Wald[b])			**57284**	**1213047**	**13.4%**	**-2.28 [-8.09 , 3.52]**
Test for overall effect: Z = 0.77 (P = 0.44)						
Heterogeneity: Tau² (REML[c]) = 33.40; Chi² = 38.74, df = 3 (P < 0.00001); I² = 100%						
2.2.3 Quit 2nd trimester						
Delcroix-Gomez 2022[a]	-9.8	2.728184	111	3704	0.3%	-9.80 [-15.15 , -4.45]
Tatsuta 2023[a]	0	0.355946	498	44198	0.3%	0.00 [-0.70 , 0.70]
Subtotal (Wald[b])			**609**	**47902**	**0.6%**	**-4.53 [-14.10 , 5.05]**
Test for overall effect: Z = 0.93 (P = 0.35)						
Heterogeneity: Tau² (REML[c]) = 44.24; Chi² = 12.69, df = 1 (P = 0.0004); I² = 92%						
2.2.4 Quit 3rd trimester						
Delcroix-Gomez 2022[a]	-10.5	2.322749	57	3704	0.5%	-10.50 [-15.05 , -5.95]
Tatsuta 2023[a]	0	0.323518	651	44198	0.3%	0.00 [-0.63 , 0.63]
Subtotal (Wald[b])			**708**	**47902**	**0.8%**	**-5.00 [-15.28 , 5.28]**
Test for overall effect: Z = 0.95 (P = 0.34)						
Heterogeneity: Tau² (REML[c]) = 52.38; Chi² = 20.05, df = 1 (P < 0.00001); I² = 95%						
2.2.5 Smoked throughout pregnancy						
Delcroix-Gomez 2022[a]	-13.3	0.49641	632	3704	10.3%	-13.30 [-14.27 , -12.33]
Himes 2013[a]	-4.2	2.141909	45	46	5.0%	-4.20 [-8.40 , -0.00]
McCowan 2009[a]	-6.3	1.631001	251	1992	3.4%	-6.30 [-9.50 , -3.10]
Rumrich 2020[a]	-0.87	0.034445	165734	1163225	8.5%	-0.87 [-0.94 , -0.80]
Suzuki 2014[a]	-1.4	0.820306	177	1920	3.0%	-1.40 [-3.01 , 0.21]
Tatsuta 2023[a]	-1	0.169947	2269	44198	1.1%	-1.00 [-1.33 , -0.67]
Subtotal (Wald[b])			**169108**	**1215085**	**31.3%**	**-4.49 [-8.50 , -0.48]**
Test for overall effect: Z = 2.20 (P = 0.03)						
Heterogeneity: Tau² (REML[c]) = 23.82; Chi² = 637.62, df = 5 (P < 0.00001); I² = 100%						
Total (Wald[b])			**288906**	**2195035**	**100.0%**	**-1.77 [-4.58 , 1.05]**

Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Chi² = 8.09, df = 4 (P = 0.09), I² = 50.5%
Heterogeneity: Tau² (REML[c]) = 18.01; Chi² = 610.37, df = 8 (P < 0.00001); I² = 100%



Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

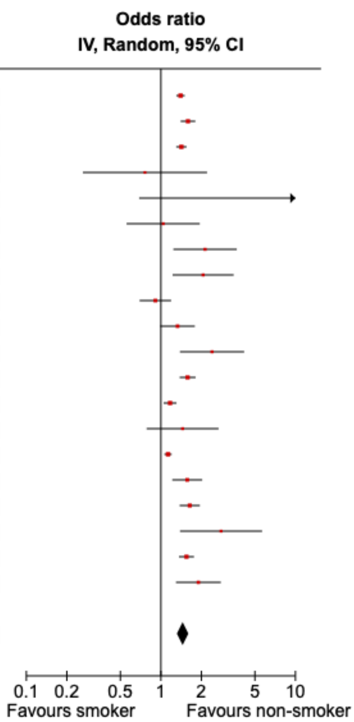
2.3.3.6 Stillbirth

Overall analysis: Smoker vs. Non-smoker

Smoking was associated with an increased risk of stillbirth compared with non-smokers (OR 1.45, 95% CI 1.31 to 1.60, $p < 0.00001$) (Figure 18). Heterogeneity across studies was high ($I^2 = 81\%$; $\tau^2 = 0.03$; $\chi^2 = 91.40$, $p < 0.00001$), but the direction of effect was consistent, with the majority of studies reporting an increased risk of stillbirth for smokers.

Figure 18: Forest plot of odds ratios for stillbirth among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Aliyu 2007	0.336472	0.036506	36889	1067834	8.9%	1.40 [1.30 , 1.50]
Baba 2014	0.463734	0.064112	74998	667301	8.1%	1.59 [1.40 , 1.80]
Bjornholt 2016	0.350657	0.044871	156964	684264	8.7%	1.42 [1.30 , 1.55]
Brink 2022	-0.272609	0.542204	862	877	0.8%	0.76 [0.26 , 2.20]
Coleman-Cowger 2018	2.415914	1.422186	39	354	0.1%	11.20 [0.69 , 181.88]
Cupul-Uicab 2011	0.039221	0.319588	21276	55081	1.9%	1.04 [0.56 , 1.95]
Dodds 2006	0.756122	0.276783	92	402	2.4%	2.13 [1.24 , 3.66]
Goy 2008	0.722706	0.266664	89	421	2.6%	2.06 [1.22 , 3.47]
Li 2019	-0.094311	0.137502	20477	119396	5.5%	0.91 [0.70 , 1.19]
McCowan 2007	0.285179	0.151091	10072	49903	5.0%	1.33 [0.99 , 1.79]
Mei-Dan 2015	0.875469	0.280263	1646	19292	2.4%	2.40 [1.39 , 4.16]
Miller 2010	0.457425	0.069196	34508	273689	7.9%	1.58 [1.38 , 1.81]
Mohsin 2006	0.157004	0.056439	77401	355826	8.3%	1.17 [1.05 , 1.31]
Odendaal 2021	0.371564	0.313919	4593	6810	2.0%	1.45 [0.78 , 2.68]
Raisanen 2014	0.122218	0.031647	145710	958177	9.0%	1.13 [1.06 , 1.20]
Reddy 2010	0.451076	0.130736	11045	163764	5.7%	1.57 [1.22 , 2.03]
Sutan 2010	0.494086	0.088199	141360	309485	7.2%	1.64 [1.38 , 1.95]
Tveit 2010	1.029619	0.358168	259	1909	1.6%	2.80 [1.39 , 5.65]
Waldenstrom 2014	0.438255	0.06535	56663	548848	8.0%	1.55 [1.36 , 1.76]
Wisborg 2001	0.641854	0.195732	7503	17599	3.8%	1.90 [1.29 , 2.79]
Total (Wald[a])			**802446**	**5301232**	**100.0%**	**1.45 [1.31 , 1.60]**



Test for overall effect: Z = 7.42 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.03; Chi² = 91.40, df = 19 (P < 0.00001); I² = 81%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

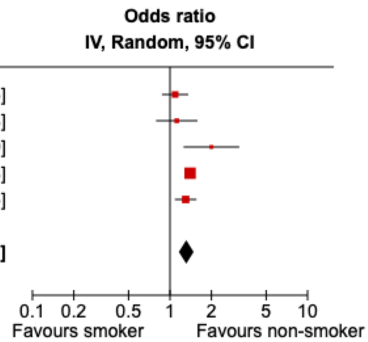
2.3.3.7 Neonatal death

Overall analysis: Smoker vs. Non-smoker

The risk of neonatal death was higher among infants of smokers compared with non-smokers (OR 1.31, 95% CI 1.16 to 1.48, $p < 0.0001$). Heterogeneity was moderate ($I^2 = 48\%$; $\tau^2 = 0.01$; $\chi^2 = 8.87$, $p = 0.06$), and the direction of effect was consistent across studies.

Figure 19: Forest plot of odds ratios for neonatal death among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Baba 2014	0.086178	0.112085	74998	667301	18.8%	1.09 [0.88 , 1.36]
Li 2019	0.113329	0.176827	20477	119396	10.0%	1.12 [0.79 , 1.58]
Mei-Dan 2015	0.693147	0.237647	1646	19292	6.1%	2.00 [1.26 , 3.19]
Salihu 2003	0.336472	0.029187	396609	2608007	42.0%	1.40 [1.32 , 1.48]
Waldenstrom 2014	0.262364	0.092169	56663	548848	23.2%	1.30 [1.09 , 1.56]
Total (Wald[a])			**550393**	**3962844**	**100.0%**	**1.31 [1.16 , 1.48]**



Test for overall effect: Z = 4.32 (P < 0.0001)

Heterogeneity: Tau² (REML[b]) = 0.01; Chi² = 8.87, df = 4 (P = 0.06); I² = 48%

Footnotes

[a]CI calculated by Wald-type method.

[b]Tau² calculated by Restricted Maximum-Likelihood method.

Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

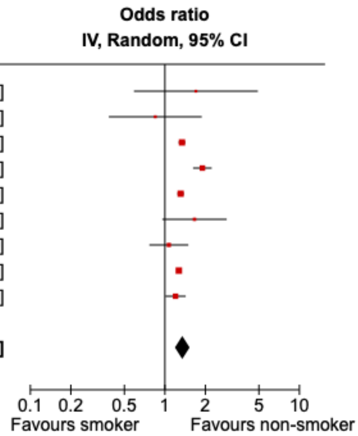
2.3.3.8 NICU admission

Overall analysis: Smoker vs. Non-smoker

Infants exposed to maternal smoking were more likely to require NICU admission (OR 1.35, 95% CI 1.19 to 1.53, $p < 0.00001$). Heterogeneity was high ($I^2 = 92\%$; $\tau^2 = 0.02$; $\chi^2 = 30.80$, $p = 0.0002$), although the direction of effect remained consistent.

Figure 20: Forest plot of odds ratios for NICU admission among infants born to smokers vs. non-smokers

Study or Subgroup	log[OR]	SE	Smoker Total	Non-smoker Total	Weight	Odds ratio IV, Random, 95% CI
Coleman-Cowger 2018	0.530628	0.540893	39	354	1.3%	1.70 [0.59 , 4.91]
Hamadneh 2021	-0.164303	0.4057	60	60	2.2%	0.85 [0.38 , 1.88]
Li 2019	0.29267	0.03027	20477	119396	18.3%	1.34 [1.26 , 1.42]
Mei-Dan 2015	0.641854	0.08124	1646	19292	14.6%	1.90 [1.62 , 2.23]
Miller 2010	0.270027	0.029131	34508	273689	18.4%	1.31 [1.24 , 1.39]
Murphy 2013	0.506818	0.281166	110	637	4.1%	1.66 [0.96 , 2.88]
Raatikainen 2007	0.067659	0.170113	6785	18806	8.1%	1.07 [0.77 , 1.49]
Raisanen 2014	0.239017	0.010005	145710	958177	19.0%	1.27 [1.25 , 1.30]
Tayie 2012	0.182322	0.088707	1670	9890	14.0%	1.20 [1.01 , 1.43]
Total (Wald[a])			**211005**	**1400301**	**100.0%**	**1.35 [1.19 , 1.53]**



Test for overall effect: Z = 4.64 (P < 0.00001)

Heterogeneity: Tau² (REML[b]) = 0.02; Chi² = 30.80, df = 8 (P = 0.0002); I² = 92%

Abbreviations: MD = Mean Difference, SE = Standard Error; IV = Inverse Variance method; CI = 95% Confidence Interval

2.3.4 Risk of bias assessment

The summary of risk of bias results is presented in Table 4. The meta-analyses were not restricted based on risk of bias.

Table 4: Risk of bias assessment

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Abdelwahab 2022	4	1	3	8	High
Abufraijeh 2024	1	0	1	2	Low
Agrawal 2010	4	1	2	7	High
Ahmadi-Montecalvo 2016	3	1	1	5	Moderate
Akahoshi 2016	3	1	2	6	Moderate
Al-sheyab 2016	3	1	3	7	High
Aliyu 2007	4	1	3	8	High
Aliyu 2010	3	1	3	7	High
Alptekin 2017	4	1	3	8	High
Andriani 2014	4	1	3	8	High
Baba 2013	4	1	3	8	High
Baba 2014	4	1	3	8	High
Bailey 2012	4	1	3	8	High
Barbieri 2000	4	1	3	8	High
Berlin 2017	3	1	3	7	High
Bickerstaff 2012	3	1	3	7	High
Bird 2017	4	1	3	8	High
Bjornholt 2016	4	1	3	8	High
Blatt 2015	2	1	3	6	Moderate
Bramsved 2023	2	1	3	6	Moderate
Brink 2022	2	1	3	6	Moderate
Burguet 2004	4	1	3	8	High
Campbell 2012	4	1	3	8	High
Cardenas 2020	3	1	3	7	High

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Chan 2008	4	1	3	8	High
Chelchowska 2013	3	0	3	6	Moderate
Chen 2018	4	1	3	8	High
Chiolero 2005	4	1	3	8	High
Coleman-Cowger 2018	4	1	3	8	High
Cupul-Uicab 2011	4	1	3	8	High
da Fonseca 2012	4	1	3	8	High
Dahlin 2016	3	1	3	7	High
Delcroix-Gomez 2022	3	0	2	5	Moderate
Delpisheh 2006	3	1	3	7	High
Dew 2007	4	1	3	8	High
Dodds 2006	4	1	3	8	High
El-Shahawy 2021	3	0	3	6	Moderate
Feferkorn 2022	4	1	3	8	High
Fenercioglu 2009	3	0	3	6	Moderate
Fenercioglu 2009	2	0	3	5	Moderate
Flower 2013	4	1	3	8	High
GanerHerman 2016	4	1	3	8	High
Gibberd 2019	4	1	3	8	High
Goy 2008	3	1	3	7	High
Grjibovski 2004	4	1	3	8	High
Hamadneh 2021	2	0	2	4	Moderate
Harrod 2014	3	1	3	7	High
Himes 2013	3	0	3	6	Moderate
Hosokawa 2022	4	1	3	8	High

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Huang 2017	3	1	3	7	High
Hviid 2024	3	1	3	7	High
Hyland 2015	4	1	3	8	High
Ingvarsson 2007	2	0	2	4	Moderate
Iniguez 2012	4	1	3	8	High
Inoue 2017	3	1	3	7	High
Jackson 2007	4	1	3	8	High
Jaddoe 2007	4	1	3	8	High
Jaddoe 2008	4	1	3	8	High
Jeena 2020	3	1	3	7	High
Kataoka 2018	3	1	3	7	High
Kayemba-Kay's 2010	4	1	3	8	High
Kharkova 2017	3	1	3	7	High
Kirchengast 2003	2	0	3	5	Moderate
Kleijer 2005	3	1	3	7	High
Ko 2014	4	1	3	8	High
Kondracki 2019	4	1	3	8	High
Kuja-Halkola 2014	3	1	3	7	High
Kyrklund-Blomberg 2005	3	1	3	7	High
Lamm 2020	3	1	3	7	High
Lanting 2009	3	1	3	7	High
Li 2019	4	1	3	8	High
Li 2024	3	1	3	7	High
Lindley 2000	3	1	3	7	High
Liu 2020	4	1	3	8	High

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Madley-Dowd 2021	3	1	3	7	High
Matsubara 2000	3	1	3	7	High
McCowan 2007	4	1	3	8	High
McCowan 2009	4	1	3	8	High
McDonnell 2019	2	0	3	5	Moderate
Meghea 2014	3	1	3	7	High
Mei-Dan 2015	3	1	3	7	High
Mercer 2008	4	1	3	8	High
Meyer 2009	3	1	3	7	High
Miller 2010	3	1	3	7	High
Mitchell 2002	3	1	3	7	High
Miyake 2013	4	1	3	8	High
Mohsin 2006	4	1	3	8	High
Moore 2000	4	1	3	8	High
Moore 2016	4	1	3	8	High
Moore 2019	4	1	3	8	High
Murphy 2013	4	1	3	8	High
Nanninga 2023	1	0	3	4	Moderate
O'donnell 2020	4	1	3	8	High
Odendaal 2021	3	1	3	7	High
Oh 2021	2	0	3	5	Moderate
Ohmi 2002	2	0	3	5	Moderate
Okah 2005	3	1	3	7	High
Olafsdottir 2006	4	1	3	8	High
Olbertz 2018	3	1	3	7	High

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Olives 2020	2	0	3	5	Moderate
Pietersma 2022	3	1	3	7	High
Pollack 2000	3	1	3	7	High
Raatikainen 2007	4	1	3	8	High
Raisanen 2014	4	1	3	8	High
Ramadani 2019	3	1	3	7	High
Ratnasiri 2020	4	1	3	8	High
Reddy 2010	4	1	3	8	High
Reynolds 2020	3	0	3	6	Moderate
Rode 2013	4	1	3	8	High
Rumrich 2020	4	1	3	8	High
Samper 2012	2	0	3	5	Moderate
Salihu 2003	4	1	3	8	High
Salihu 2008	4	1	3	8	High
Savitz 2001	4	1	3	8	High
Schultze 2016	2	0	3	5	Moderate
Selvaratnam 2023	4	1	3	8	High
Silva 2022	4	1	3	8	High
Smith 2015	4	1	2	7	High
Steyn 2006	4	1	3	8	High
Sun 2023	4	1	3	8	High
Sutan 2010	4	1	3	8	High
Suzuki 2008	3	1	3	7	High
Suzuki 2014	4	1	3	8	High
Suzuki 2016	3	1	3	7	High

Study ID	Selection (max 4)	Comparability (max 2)	Outcome/Exposure (max 3)	Total NOS (0–9)	Quality
Tashan 2017	3	0	3	6	Moderate
Tatsuta 2023	4	1	3	8	High
Tayie 2012	4	1	3	8	High
Tong 2017	4	1	3	8	High
Tsukamoto 2007	3	1	3	7	High
Tveit 2010	4	1	3	8	High
Vardavas 2010	3	1	3	7	High
Veloso 2014	4	1	3	8	High
VilaCandel 2015	3	0	3	6	Moderate
Villalbi 2007	3	1	3	7	High
Waldenstrom 2014	4	1	3	8	High
Wang 2002	4	1	3	8	High
Wang 2020	3	1	3	7	High
Wang 2020	4	1	3	8	High
Wang 2024	4	1	3	8	High
Ward 2007	4	1	3	8	High
Winbo 2001	4	1	3	8	High
Wisborg 2001	4	1	3	8	High
Witt 2016	4	1	3	8	High
Wojtyla 2021	2	0	3	5	Moderate
Zaren 2000	2	0	3	5	Moderate

2.4 Discussion

2.4.1 Summary of main findings

Active maternal smoking during pregnancy was consistently associated with an increased risk of adverse fetal outcomes. A summary of the key findings is presented in Table 5. The most pronounced and consistent associations were identified for fetal growth measures, but significant effects were also observed for preterm birth, shorter gestational length, stillbirth, neonatal death, and admission to a neonatal intensive care unit.

Table 5: Summary of key findings from the systematic review of maternal smoking in pregnancy

Outcome	Overall smoking vs non-smokers	Quit 1st trimester vs non-smokers	Quit 3rd trimester vs non-smokers
Birthweight (g)	MD −208 g (95% CI −233 to −183)	MD −38.7 g (95% CI −95.98 to 18.56)	MD −234.8 g (95% CI −439.27 to −30.31)
Low birthweight (<2500 g)	OR 1.93 (95% CI 1.74–2.13)	OR 1.50 (95% CI 0.75-3.00)	OR 3.76 (95% CI 2.14–6.61)
Small-for-gestational age	OR 2.14 (95% CI 1.99–2.31)	OR 1.00 (95% CI 0.95-1.04)	OR 1.68 (95% CI 1.57–1.78)
Preterm birth	OR 1.38 (95% CI 1.25–1.53)	OR 1.00 (95% CI 0.96–1.04)	OR 1.60 (95% CI 1.07–2.39)
Gestational age (days)	MD −2.78 (95% CI −4.32 to −1.24)	Not reported	Not reported
Stillbirth	OR 1.45 (95% CI 1.31–1.60)	Not reported	Not reported

Abbreviations: CI, confidence interval, MD, mean difference, OR, odds ratio

The timing of smoking cessation influenced risk. Women who quit before conception or in the first trimester appeared to have risks similar to never-smokers. Those who smoked until the second trimester and then quit had a higher risk of preterm birth, while those who quit only in the third trimester had lower mean birthweights and higher risks of small-for-gestational-age birth, low birthweight, and preterm birth. Late cessation and continued smoking were both associated with persistently increased risk across outcomes, with differences between these groups generally small.

Smoking intensity also modified outcomes in a dose–response pattern. Risks were higher with >10 cigarettes per day, although adverse effects were already evident at ≤10 cigarettes per day for birthweight, low birthweight, and small-for-gestational age. More detailed categorisation showed little effect at 1–5 cigarettes per day but significant increases at 6–10 and >10 cigarettes per day. Although subgroup tests were not always statistically significant, the overall pattern indicates that both smoking intensity and duration of exposure contribute to risk.

2.4.2 Comparison with literature

The present results are in line with conclusions from previous narrative reviews. Lassandro et al.[18] provided a descriptive overview of parental smoking during pregnancy and lactation. Like our findings, they reported that SGA and low birthweight were most consistently affected. Diago-Almela et al.[17] reviewed 12 studies in the specific context of twin pregnancies and concluded that smoking during pregnancy increased the risk of preterm birth and impaired fetal growth. Both reviews were narrative in nature, included fewer studies, and did not conduct a meta-analysis.

Findings from this chapter are also consistent with results from previous meta-analyses that focused on individual outcomes. Quelhas et al.[172] found significantly higher rates of SGA (OR 1.95, 95% CI 1.76–2.16) and also demonstrated a dose–response relationship. Shah and Bracken[173] reported an increased risk of preterm birth (OR 1.27, 95% CI 1.21–1.33) based on studies published before 2000, with subgroup analyses also suggesting a dose–response relationship. The present review, which included studies from 2000 onwards, confirmed this association with a very similar pooled effect (OR 1.38, 95% CI 1.25–1.53) and likewise identified dose–response effects. Another review[174] focused on mortality outcomes and reported risks of stillbirth and neonatal death (stillbirth: sRR 1.46, 95% CI 1.38–1.54; neonatal death: sRR 1.22, 95% CI 1.14–1.30) that were very similar to those observed here (stillbirth: OR 1.45, 95% CI 1.31–1.60; neonatal death: OR 1.31, 95% CI 1.16–1.48).

Several observational studies have examined trimester-specific effects. Blatt et al.[175] reported that smoking in any trimester increased the risk of fetal growth restriction, with the highest risks observed among women who continued smoking throughout pregnancy. Harrod et al.[176] similarly demonstrated a dose–response association for neonatal body composition, with more pronounced effects when smoking continued into late pregnancy. Moore et al.[177] reported that women who quit smoking early had similar risks of preterm birth to non-smokers, whereas quitting late in pregnancy was associated with the highest risks. These findings are consistent with our subgroup analyses, which showed that cessation early in pregnancy attenuated risk, while smoking through the second or third trimester was associated with adverse outcomes. Thus, our review not only confirms earlier observations but also extends them by integrating multiple outcomes within a single framework and quantifying how risks vary with cessation timing and smoking intensity.

2.4.3 Strengths

This systematic review with meta-analysis has several important strengths. First, it was conducted in accordance with a pre-registered protocol and followed PRISMA 2020 guidelines, with established tools used throughout the process to ensure transparency and reproducibility.

Second, the review synthesised evidence from 145 studies across 35 countries, encompassing very large sample sizes and providing strong statistical power.

Another strength of this review is the broad scope of outcomes considered. Unlike earlier reviews that focused on a single endpoint, this work examined a wide range of fetal and neonatal outcomes. This allowed comparisons across outcomes and provided a more complete picture of the effects of maternal smoking in pregnancy. Subgroup analyses were possible for the most affected outcomes, such as small-for-gestational age and preterm birth, assessing both the timing of smoking cessation and the number of cigarettes smoked per day. Finally, the overall consistency of associations strengthens the conclusions. Despite high heterogeneity, the direction of effect was uniform, with maternal smoking consistently linked to adverse fetal outcomes.

2.4.4. Limitations

This review has several limitations that should be acknowledged. Although screening was carried out by multiple reviewers, data extraction was completed by a single reviewer, which may introduce errors. Additionally, the review was limited to studies published in English, which may have introduced a language bias.

Another limitation is the variability in smoking reporting methods among the included studies. While over 90% of studies focused on traditional cigarettes, a small number examined other smoked tobacco products such as cigars, pipes, or waterpipes. These exposures are likely to contribute to adverse fetal outcomes through similar biological mechanisms, especially carbon monoxide–mediated fetal hypoxia. However, differences in exposure classification may have contributed to heterogeneity. Studies also often used different categories for the number of cigarettes smoked, for example, 1–2, increments of 5, or broader thresholds such as 20. This meant that the dose–response categories could not always be harmonised or mapped. As a result, some analyses were restricted to broader groupings, such as ≤10 versus >10 cigarettes per day, and relatively few studies contributed to the finer subcategories. In addition, not all outcomes could be examined according to cessation timing or cigarette dose, because too few studies reported these subgroup data in a comparable format. This limited the ability to fully assess how the timing of cessation and smoking intensity influence the full range of outcomes.

Although the direction of effect was generally consistent, high heterogeneity was present in almost all analyses. As the aim was to provide a broad summary to inform practice, the subgroups were not analysed in a way that adjusted for this heterogeneity. Further approaches, such as meta-regression, may help to clarify the sources of heterogeneity in future work. Lastly, most of the included studies were observational and differed in the extent of adjustment for confounders, meaning that residual confounding cannot be excluded.

2.4.4 Conclusions

In conclusion, this systematic review demonstrates that maternal smoking during pregnancy is consistently associated with adverse fetal outcomes, particularly reduced birthweight, small-for-gestational age, and preterm birth, with risks increasing alongside smoking intensity and duration. Early cessation, especially before or during the first trimester, appears to mitigate these risks. Identifying pregnant women who continue to smoke and examining when and what kind of enhanced surveillance should be offered will be discussed in the subsequent chapters of this thesis.

Chapter III. Carbon Monoxide, Smoking, and Pregnancy Outcomes

3.1 Introduction

3.1.1 Rationale

The previous chapter identified that maternal smoking in pregnancy is associated with a number of adverse fetal outcomes. It also showed that quitting significantly reduces these risks, consistent with findings from earlier studies. Identifying pregnant smokers is therefore essential in order to provide appropriate cessation advice and increase fetal surveillance.

However, only 2% of studies in the systematic review validated self-reported smoking status with the use of biochemical markers. Enquiring about smoking is an important part of the clinical history, but relying solely on self-report is insufficient to identify all women who may require additional support and care. It is well recognised that not all women disclose their smoking, or the extent of their smoking, during antenatal visits[178]. Biomarkers can therefore provide a more objective measure of exposure. Accordingly, this chapter focuses on evaluating approaches to predict smoking in pregnancy and to better identify women at risk.

3.1.2 Non-disclosure

The extent of non-disclosure varies widely across studies, with reported rates ranging from around 3% to 75%[49,117,178–180]. Non-disclosure may occur for a variety of reasons, including stigma, fear of judgment by healthcare professionals, and underestimation of the harm associated with smoking[181]. Some women may also understate the intensity of their smoking or describe themselves as non-smokers if they have reduced their intake or only smoke intermittently[181]. Unsurprisingly, women who perceive negative or judgmental attitudes from healthcare providers are less likely to disclose[182]. The phrasing of the question also matters: using multiple-choice formats that allow women to indicate, for example, that they have "cut down," rather than responding yes or no, has been shown to increase reporting[183]. Non-disclosure has significant implications, as it limits access to cessation support, reduces opportunities for additional fetal monitoring, and affects the accuracy of prevalence estimates and intervention evaluations.

3.1.3 Biochemical markers

Biochemical markers can be used to address that issue as they offer a more objective measure of smoking status. A range of markers has been developed and applied in pregnancy research.

The most widely used and validated marker is cotinine, the primary metabolite of nicotine. Cotinine can be measured in serum, urine, or saliva, and reflects nicotine exposure over the preceding 48–72 hours[184]. It is considered particularly useful because of its specificity and relatively long half-life[185]. However, cotinine testing is costly, requires laboratory infrastructure, and does not provide immediate results[186], which limits its application in routine antenatal care.

An alternative is carbon monoxide (CO), measured in exhaled breath. Following inhalation of tobacco smoke, CO binds to haemoglobin to form carboxyhaemoglobin (COHb), which has a half-life of approximately 4–6 hours[187]. Exhaled CO levels reflect COHb concentration[188], supporting the wider use of handheld monitors in both research and clinical settings to assess CO exposure[32,189]. Low levels of CO may also be detected in non-smokers due to environmental sources such as air pollution, passive smoke, or, more rarely, faulty household appliances. However, active smoking remains the most common cause of elevated breath CO[190].

Measurement of exhaled CO is a quick, cost-effective, and non-invasive method of assessing smoking status at the point of care[191,192]. In the UK, CO monitoring is now offered to all pregnant women at booking and again at 36 weeks, in line with recommendations from the *Saving Babies' Lives Care Bundle (Version 3)* issued by NHS England[4].

3.1.4 Research gaps

Although the use of CO testing to determine smoking status has been widely investigated[191–194], much less is known about the threshold at which CO levels are associated with adverse pregnancy outcomes. Previous studies have examined the optimal CO threshold for identifying smokers and suggested values such as 3 ppm or 5 ppm. These studies reported that birthweight was lower, and the risk of adverse pregnancy outcomes higher, in those with CO levels indicative of smoking[195–197].

However, the optimal CO threshold for predicting smoking-related adverse outcomes remains uncertain, including whether there is a dose–response relationship between CO levels and outcomes. It is also unclear whether CO provides a more reliable predictor of adverse outcomes than self-reported smoking status. This has important clinical implications: a practical threshold could, for example, be incorporated into clinical pathways to guide risk stratification and referral for increased fetal surveillance.

3.1.5 Aims

This chapter aims to identify the CO threshold and relationship with adverse neonatal outcomes and compare the use of CO with self-reported smoking as risk indicators.

3.2 Methods

3.2.1 Study design, setting, and population

This was a retrospective cohort study of one year of pregnancies (2023) using the OxGRIP dataset, which has been described previously in more detail in Chapter 1.1.4. Briefly, the dataset comprises routinely collected data on women receiving antenatal care and giving birth at Oxford University Hospitals. Pregnancies from 2023 were selected for analysis because CO data were only available for that year. Women with singleton, non-anomalous pregnancies were included; exclusion criteria comprised multiple pregnancies, any fetal congenital abnormalities, pregnancies ending before 22 weeks, and those without CO measurements.

A woman was classified as a smoker if she self-reported smoking at the booking appointment (median gestation 10 weeks) or any time during pregnancy. Carbon monoxide levels were measured at the booking visit using the Bedfont piCO™ Smokerlyzer® breath CO monitor (Bedfont Scientific Ltd., UK) and only ad hoc at other gestations: the highest CO level at any test was used.

3.2.2 Outcomes

Outcome measures were birthweight (BW) and BW centile, small for gestational age (SGA: <10th centile[23]), preterm birth (PTB: 22 to <37 weeks), and extended perinatal mortality (EPM, intrauterine death or neonatal death within 28 days of birth). Analyses were conducted across groups stratified by CO thresholds, and outcomes were additionally compared between smokers and non-smokers and between CO $\leq$ 2 ppm and CO > 2 ppm. The threshold of 2 ppm was selected following changepoint analysis, which demonstrated a significant reduction in mean BW at this level. To further investigate unreported smoking or exposure, four groups were examined: non-smokers with CO ≤ 2 ppm, non-smokers with CO > 2 ppm, smokers with CO ≤ 2 ppm, and smokers with CO > 2 ppm.

3.2.3. Statistical analysis

Most statistical analyses were conducted using IBM SPSS Statistics version 29.0.2.0. The Chi-square test for trend (Cochran-Armitage test) and changepoint analysis were performed in R version 4.2.2. Demographic data were presented as mean (SD) for normally distributed variables, as median (interquartile range) for non-normally distributed variables, and as n (%) for categorical variables.

Changepoint analysis was used to identify the CO exposure threshold associated with changes in birthweight. It was implemented using a segmented regression model via the *'segmented'* package in R[198]. Birthweight was chosen as the potentially most sensitive outcome to CO, because it is a function of both growth and preterm birth. A one-way analysis of variance (ANOVA) was applied to compare mean birthweight across different, approximately equal-sized, CO exposure categories and self-reported smoking groups.

To assess the association between CO exposure and SGA, PTB, and EPM, a chi-square test for trend (Cochran-Armitage test) was conducted. Binary logistic regression was applied to examine the association between CO exposure categories and smoking with SGA, PTB, and EPM, analysing smoking and CO exposure both combined and as separate predictors. No covariate adjustment was undertaken, as this analysis aimed to evaluate carbon monoxide (CO) as a risk stratification and screening marker rather than to estimate a causal effect. The level of significance was set at $p < 0.05$ for all analyses, and 95% confidence intervals were calculated.

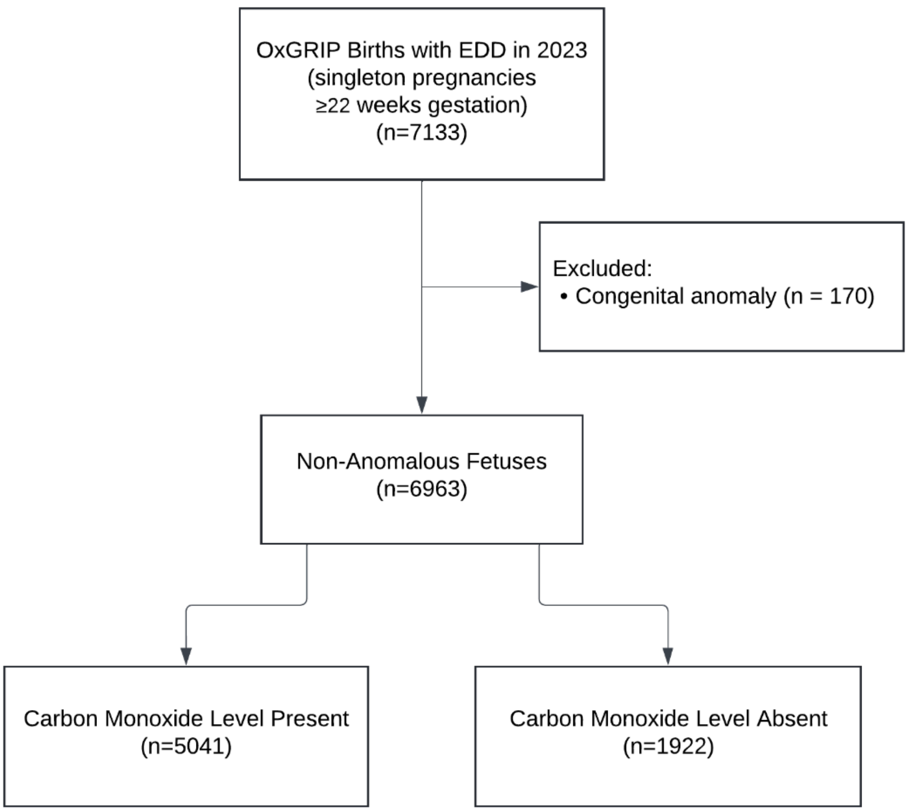
Potential sources of bias were evaluated through additional analyses. To assess whether CO data were missing at random, analyses were repeated on all deliveries with an EDD in 2023, including those with and without recorded CO levels. To determine whether the number of CO tests performed influenced results, mean CO level was compared according to the number of CO tests completed, and linear regression was used to assess whether that relationship was independent of self-reported smoking status. Finally, a chi-square test for trend was conducted to determine whether self-reported smokers were more likely than non-smokers to undergo repeat CO testing.

3.3 Results

3.3.1 Cohort characteristics

Of 6963 eligible pregnancies, 5041 (72.4%) women had CO levels recorded and were included in the final analysis (Figure 21.)

Figure 21: Flowchart summarizing population selection in Chapter III



Demographic characteristics are shown in Table 6. The mean birthweight of the cohort was 3439 (560); the mean birthweight centile was 54.25 (28.00). The prevalence of SGA, PTB, and EPM was 6.7%, 5.0%, and 0.6%, respectively. The incidence of self-reported smoking was 9.2% and CO levels were > 2 ppm in 11.7%; 5.0% of the cohort were self-identified non-smokers with CO levels above 2 ppm. The majority of women (71.8%) had only one CO test during pregnancy, 25.9% had two tests, and just 2.2% had more than two.

Table 6: Demographic characteristics of study III participants (n=5041)

Characteristic	Value
Maternal age (years) mean (SD)	31.4 (5.3)
≥40	266 (5.3%)
Parity	
Nulliparous	2470 (49%)
Parous	2571 (51%)
Smoking in pregnancy	
Yes	466 (9.2%)
No	4575 (90.8%)
CO Level	
≤ 2	4449 (88.3%)
3	184 (3.7%)
4-5	126 (2.5%)
6-10	129 (2.6%)
>10	153 (3.0%)
Ethnicity	
White	3853 (76.4%)
Asian	535 (8.8%)
Black	195 (3.9%)
Mixed	122 (2.4%)
Other	74 (1.5%)
Missing	262 (5.2%)
Index of Multiple Deprivation Decile	
1-2 (most)	245 (4.9%)
3-4	428 (8.5%)
5-6	751 (14.9%)
7-8	1241 (24.6%)
9-10 (least)	1993 (39.5%)
Missing	383 (7.6%)
Body mass index	
Underweight (< 18.5 kg/m^2)	156 (3.1%)
Normal weight (18.5–24.9 kg/m^2)	2465 (48.9%)
Overweight (25.0–29.9 kg/m^2)	1406 (27.9%)
Class-1 obesity (30.0–34.9 kg/m^2)	622 (12.3%)
Class-2–3 obesity (≥ 35.0 kg/m^2)	386 (7.7%)
Missing	6 (0.1%)
Neonatal sex	

Female	2439 (48.4%)
Male	2602 (51.6%)
GA at birth (weeks)	39 + 6 (1 + 6)
Birth weight (g) mean (SD)	3439 (560)
Birth weight (centile), mean (SD)	54.25 (28.00)
SGA (<10th centile)	338 (6.7%)
PTB (<37+0 weeks)	251 (5.0%)
EPM (intrauterine death or neonatal death within 28 days of birth)	28 (0.6%)

Data are given as n (%), or mean (SD). CO, carbon monoxide, GA, gestational age, SGA, small for gestational age, PTB, EPM, extended perinatal mortality

3.3.2 Carbon monoxide threshold for predicting birthweight

Figure 22 presents the results of the changepoint analysis, illustrating the estimated CO exposure threshold of 2 ppm. Based on this threshold, CO levels above 2 ppm were subdivided into approximately equal groups for use in subsequent analyses.

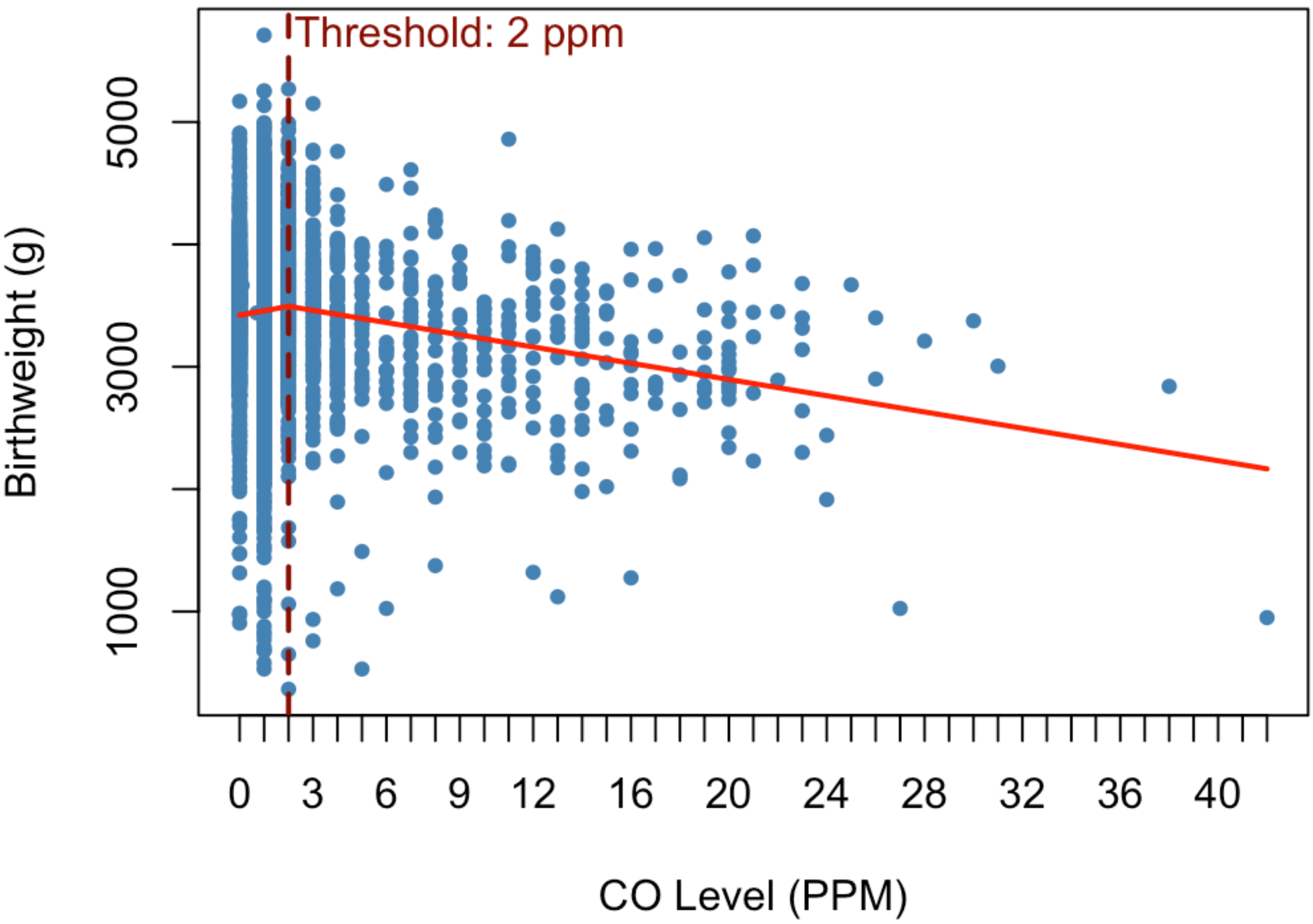


Figure 22: Changepoint analysis of breath carbon monoxide (CO) level and birthweight

3.3.3 Dose-response relationship and adverse outcomes according to CO level

As a continuous variable, CO level was significantly associated with both birthweight and birthweight centile. Above the threshold of 2 ppm, each 1 ppm increase in CO was associated with a 69.35 g decrease in birthweight (SE = 14.53, $p < 0.001$) and a 3.15-point decrease in birthweight centile (SE = 0.73, $p < 0.001$). The Chi-square test for trend demonstrated significant associations between higher CO levels and increased risk of both SGA ($p < 0.001$) and PTB ($p = 0.001$), consistent with a dose–response relationship. No clear dose–response association with EPM was observed, likely due to small numbers.

Table 7 presents mean birthweight, mean birthweight centile, and neonatal outcomes stratified by CO levels. The increasing risks of adverse outcomes with higher CO levels are evident. Above 2ppm, the OR of all adverse outcomes is significantly increased. At very high CO levels (> 10 ppm), the odds ratios (ORs) were 4.22 (1.24–14.29) for EPM, 3.21 (1.99–5.19) for PTB, and 2.75 (1.74–4.36) for SGA.

Table 7: Mean Birthweight and Adverse Outcomes Across CO Exposure Groups

	CO ≤ 2 n=4449	CO> 2 n =592	p-value	CO 3 n=184	CO 4-5 n=126	CO 6-10 n=129	CO >10 n=153	p-value
BW (g), mean (SD) (95% CI)	3461 (548) (3445–3477)	3275 (615) (3225–3324)	< 0.001	3510 (552) (3430–3590)	3297 (594) (3192–3402)	3172 (587) (3070–3275)	3060 (633) (2959–3161)	< 0.001
BW (centile), mean (SD) (95% CI)	55 (28) (54–56)	48 (29) (46–50)	< 0.001	59 (27) (55–63)	48 (28) (43–53)	42 (29) (37–47)	41 (27) (37–45)	< 0.001
SGA n (%)	269 (6.0%)	69 (11.7%)	< 0.001	8 (4.3%)	15 (11.9%)	23 (17.8%)	23 (15.0%)	< 0.001
SGA OR (95% CI)	1.00 (ref)	2.05 (1.55 – 2.71)	< 0.001	0.71 (0.34 – 1.45)	2.10 (1.21 – 3.65)	3.37 (2.11 – 5.38)	2.75 (1.74 – 4.36)	< 0.001
PTB n (%)	210 (4.7%)	41 (6.9%)	0.020	6 (3.3%)	7 (5.6%)	7 (5.4%)	21 (13.7%)	< 0.001
PTB OR (95% CI)	1.00 (ref)	1.50 (1.06 – 2.12)	0.021	0.68 (0.30 – 1.55)	1.19 (0.55 – 2.58)	1.16 (0.53 – 2.51)	3.21 (1.99 – 5.19)	0.001
EPM n (%)	21 (0.5%)	7 (1.2%)	0.029	2 (1.1%)	1 (0.8%)	1 (0.8%)	3 (2.0%)	0.122
EPM OR (95% CI)	1.00 (ref)	2.52 (1.07 – 5.96)	0.035	2.32 (0.54 – 9.96)	1.69 (0.23 – 12.64)	1.65 (0.22 – 12.34)	4.22 (1.24 – 14.29)	0.017

Abbreviations: BW, birthweight, CO, carbon monoxide, GA, gestational age, SGA, small for gestational age, PTB, EPM, extended perinatal mortality, OR, odds ratio

3.3.4 Smoking status versus CO level as predictors

Table 8 presents mean birthweight, mean birthweight centile, and neonatal outcomes stratified according to self-reported smoking status and CO level > 2 ppm. Compared with non-smokers with a low CO level, smokers with a high CO level had increased risk for all outcomes. The risk of adverse outcomes in self-reported non-smokers with a high CO level was increased but not significantly. The risk of preterm birth remained in smokers even if they had a CO level ≤2 ppm; the risk of other adverse outcomes was increased but not significantly.

Table 8: Mean Birthweight And Neonatal Outcomes by Combined Smoking Status and CO Level

	Nonsmoker CO ≤ 2 N=4324	Nonsmoker CO> 2 N=251	Smoker CO ≤ 2 N=125	Smoker CO> 2 N=341	p-value
BW (g), mean (SD) (95% CI)	3464 (547) (3448–3481)	3460 (578) (3388–3532)	3345 (590) (3241–3450)	3138 (606) (3074–3203)	< 0.001
BW (centile), mean (SD) (95% CI)	55 (28) (54–56)	56 (28) (52–59)	51 (28) (46–56)	42 (28) (40–45)	< 0.001
SGA n (%)	257 (5.9%)	21 (8.4%)	12 (9.6%)	48 (14.1%)	< 0.001
SGA OR (95% CI)	1.00	1.45 (0.91 to 2.30)	1.68 (0.92 to 3.09)	2.59 (1.86 to 3.61)	< 0.001
PTB n (%)	193 (4.5%)	9 (3.6%)	17 (13.6%)	32 (9.4%)	< 0.001
PTB OR (95% CI)	1.00	0.80 (0.40 to 1.57)	3.37 (1.98 to 5.73)	2.22 (1.50 to 3.28)	< 0.001
EPM n (%)	20 (0.5%)	2 (0.8%)	1 (0.8%)	5 (1.5%)	0.101
EPM OR (95% CI)	1.00	1.73 (0.40 to 7.44)	1.74 (0.23 to 13.03)	3.20 (1.19 to 8.59)	0.014
Median CO (ppm)	1.00	3.00	1.00	9.00	< 0.001

Abbreviations: BW, birthweight, CO, carbon monoxide, GA, gestational age, SGA, small for gestational age, PTB, EPM, extended perinatal mortality, OR, odds ratio

3.3.5 Analyses to Assess Potential Bias

3.3.5.1 The Relationship Between Test Frequency, CO Levels, and Smoking

To further explore the observed effect of smoking among women with CO levels ≤ 2 ppm, the relationship between the number of CO tests, CO levels, and smoking status was examined. Table 9 presents the number of CO tests completed and the corresponding mean CO levels.

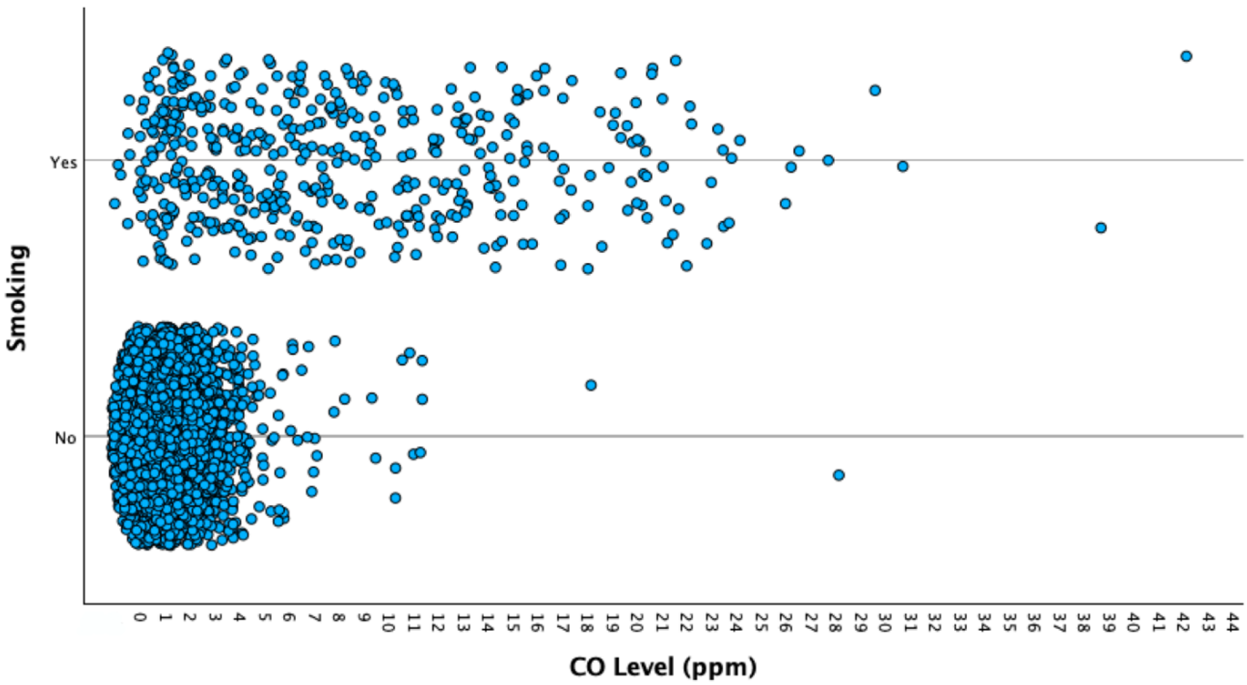
Table 9: Number of CO tests and mean CO levels

Number of CO tests	n	% of cohort	CO ppm mean (SD) (95% CI)
1	3619	71.8 %	1.57 (2.84) (1.48 to 1.66)
2	1304	25.9 %	1.83 (4.18) (1.60 to 2.05)
3	108	2.1%	2.06 (2.54) (1.57 to 2.54)
4	8	0.2%	5.19 (4.40) (1.51 to 8.86)
5	2	0.04%	15.00 (4.24) (23.12 to 53.12)

Abbreviations: CO, carbon monoxide

A one-way ANOVA indicated that mean CO level differed significantly according to the number of tests completed, $F(4, 5036) = 12.80$, $p < 0.001$. Linear regression showed that the association between the number of CO tests and mean CO level remained statistically significant after adjusting for smoking status ($p = 0.005$); however, the effect size was small, with mean CO increasing by only 0.2 ppm for each additional test. A chi-square test showed no significant difference in the proportion of women with more than one CO test between smokers and non-smokers, $\chi^2(1) = 1.84$, $p = 0.175$. To illustrate smoking-related differences more directly, Figure 23 presents the distribution of CO levels for self-reported smokers and non-smokers, based on their highest recorded test result.

Figure 23: Dot plot of CO level by reported smoking



3.3.5.2 Missing carbon monoxide data

To assess whether missing CO data were missing at random, pregnancy outcomes were compared between women with and without CO measurements (Table 10). Women who reported smoking during pregnancy were more likely to undergo CO testing than non-smokers (76.5% vs. 72.0%, OR 1.27; 95% CI: 1.04–1.54, p = 0.018).

Table 10: Mean Birthweight And Neonatal Outcomes compared between women with and without CO measurements

Outcome	CO Level Present (N=5041)	CO Level Missing (N=1922)	OR (95% CI)	p-value
Birth Weight (BW) (mean ± SD, 95% CI)	3439.23 (± 559.71) (3423.78–3454.69)	3368.21 (± 682.65) (3337.67–3398.74)	-	<0.001
BW (centile), mean (SD) (95% CI)	54.25 (±28.00) (53.47 to 55.02)	54.11 (±28.24) (52.84 to 55.37)	-	0.857
Small for Gestational Age (SGA)	338 (6.7%)	141 (7.4%)	1.11 (0.90–1.36)	0.32
Preterm Birth (PTB)	251 (5.0%)	153 (8.0%)	1.65 (1.34–2.03)	<0.001
Extended perinatal mortality (EPM)	28 (0.6%)	18 (0.9%)	1.69 (0.93–3.07)	0.08

Abbreviations: BW, birthweight, CO, carbon monoxide, GA, gestational age, SGA, small for gestational age, PTB, EPM, extended perinatal mortality, OR, odds ratio

3.4 Discussion

3.4.1 Key Findings

In this study, we show that at a threshold of > 2 ppm, CO was associated with lower mean birthweight. A dose-response relationship exists and increasing CO level is associated with lower birthweight centile, and higher rates of SGA and PTB.

3.4.2 Smokers with CO ≤2 and the Role of Measurement Frequency

Smokers with a CO level ≤ 2 had a significantly higher risk of preterm birth, although the associations with size were not significant. It seems likely, given that the more frequently CO was measured, the higher the level, that had more measurements been done in each pregnancy the association would disappear. This is more biologically plausible than smoking being an independent risk factor and suggests that CO testing should be performed more than once: infrequent CO monitoring may be inadequate to detect clinically significant smoking.

3.4.3 Non-Smokers with CO >2 and Threshold Interpretation

Surprisingly, non-smokers with a CO> 2 ppm did not have a higher risk of adverse outcomes. Reynolds et al.[197] found that 'non-disclosers' (CO≥3 but self-reported nonsmokers), who comprised 43% of women with levels ≥3, had lower birthweights than non-smokers with a low CO level. Our rate of CO>2 in non-smokers was 5.0%. That using CO>2 does not apparently 'detect' possible smokers is likely to be because this group had much lower CO levels (3 ppm) than smokers (9 ppm): a level of 2 should still probably be considered abnormal.

3.4.4 Comparison with Other Studies

The two earliest studies that examined CO and smoking used an arbitrary 5 ppm CO cutoff [195,196]. Gómez et al. found a significant reduction in birthweight above this threshold [196]. Secker-Walker et al. observed the same relationship but only when CO was measured at the first visit; at 36 weeks, a significant reduction in birthweight was seen only at CO levels 10 ppm [195]. Reynolds et al.[197] suggested a threshold of 3ppm but only 53 women had this level, and comparison was with 3ppm and above. Our larger numbers suggest >2 is the actual threshold, corresponding to 11.7% of pregnancies, although our data suggest that more frequent testing might mean this is percentage is higher. However, it is the actual CO level is what is most important. The cut off for increased surveillance could vary according to resource, but the actual level should be used when risk is modelled.

Three studies found that mean birthweight decreased in a dose-dependent manner with higher CO levels [195–197]. Secker-Walker et al. reported that CO levels measured at 36 weeks of gestation had a stronger negative association with birthweight than those recorded at the first prenatal visit [195]. In contrast, Reynolds et al. showed that this relationship was similar at both time points. Gómez et al. found that mean birthweight in the 6–10 ppm group was 450 g lower than in the 0–5 ppm group, with this trend continuing at higher exposure levels (11–20 ppm and >20 ppm) [197]. We observed this effect across narrower CO ranges demonstrating that each 1 ppm increase in CO was associated with a reduction in mean birthweight and showed this dose response extends to SGA and PTB.

3.4.4 Limitations

The main limitations of this study include its retrospective design and the relatively small number of adverse pregnancy outcomes. We also did not have information on the number of cigarettes smoked, although this latter measure is likely to be imprecise. Although likely, it remains uncertain whether more frequent CO testing would overcome the apparent independence of smoking. Finally, CO data were not missing at random: women who reported smoking were more likely to undergo CO testing. This limits comparison with smokers but does not alter our findings regarding the relationship between CO levels and adverse outcomes.

3.4.4 Conclusions

Breath carbon monoxide predicts low birthweight and adverse neonatal outcomes with a clear dose response above a threshold of > 2 ppm. Implementing universal CO testing could help to identify at-risk pregnancies and this would need to be performed several times.

Chapter IV. Comparison of Ultrasounds Findings between Smokers and Non-smokers

4.1 Introduction

4.1.1 Rationale

The findings from the previous chapter supported the role of biochemical verification in identifying women at higher risk of adverse pregnancy outcomes and suggested that smoking-related effects may begin to influence fetal development before birth.

Building on this, the present chapter focuses on the in-utero manifestations of these effects by comparing ultrasound findings between smokers and non-smokers. While earlier chapters established the overall impact of maternal smoking on neonatal outcomes, it remains unclear when during pregnancy measurable changes in fetal growth and placental blood flow first appear. Understanding the timing and pattern of these changes can help determine when additional fetal surveillance may be most beneficial, and what form such monitoring should take to optimise early detection and intervention.

4.1.2 Doppler and biometry in pregnancy

Doppler ultrasound is the primary diagnostic tool for assessing blood flow within the maternal–fetal circulation[199]. It measures blood flow velocity throughout the cardiac cycle, allowing calculation of indices such as the Pulsatility Index (PI), Resistance Index (RI), and Systolic/Diastolic (S/D) ratio, which reflect downstream vascular resistance; higher values indicate greater impedance to flow[200].

In normal pregnancy, vascular resistance within the uteroplacental and fetoplacental circulations decreases as gestation advances. As pregnancy progresses, the uterine arteries and their branches undergo extensive remodelling, including dilation and loss of smooth muscle within the spiral arteries[201]. The diameter of the spiral arteries increases from 15–20 to 300–500 mm, converting the uteroplacental circulation into a low-resistance, high-flow system[202].

On the fetal side, the umbilical arteries branch into a dense capillary network within the placental villi. As gestation advances, angiogenesis increases. It further reduces fetoplacental vascular resistance and enhances nutrient and oxygen exchange[203]. Understanding these physiological changes provides a framework for interpreting deviations that may reflect placental dysfunction or fetal hypoxia.

The uterine artery (UtA) Doppler reflects maternal blood flow to the placenta, with elevated resistance or persistent notching suggesting impaired trophoblastic invasion and an increased risk of pre-eclampsia or fetal growth restriction[204]. The umbilical artery (UmbA) Doppler represents placental resistance on the fetal side; raised impedance or absent/reversed end-diastolic flow indicates compromised placental perfusion and is associated with hypoxia and adverse perinatal outcomes[205]. The middle cerebral artery (MCA) Doppler provides insight into fetal circulatory adaptation. A reduction in MCA resistance, known as the "brain-sparing effect," reflects redistribution of blood flow to vital organs in response to hypoxic stress[206]. The cerebroplacental ratio (CPR), derived by dividing the MCA PI by the UmbA PI, combines these measures to assess the balance between fetal adaptation and placental function. A low CPR is associated with increased perinatal morbidity and mortality, even when individual indices are within normal limits[207].

Clinically, Doppler assessment has become a key component of fetal surveillance. In the second trimester, uterine artery Doppler is widely used for risk stratification, identifying women at increased risk of pre-eclampsia, fetal growth restriction, and placental abruption[208]. When abnormal, it can prompt closer surveillance or early preventive measures. In the third trimester, umbilical and middle cerebral artery Dopplers form the basis of monitoring fetoplacental function in pregnancies complicated by suspected growth restriction or other placental disorders[209]. Absent or reversed end-diastolic flow in the umbilical artery signifies critical placental compromise and may necessitate expedited delivery, while a low MCA resistance or CPR reflects redistribution and fetal adaptation to hypoxia, helping to determine the urgency and timing of intervention[209]. Establishing whether smoking is associated with characteristic or earlier Doppler changes could therefore help inform whether additional ultrasound monitoring would be beneficial for this group.

Estimated fetal weight (EFW) is a calculated prediction of a foetus's weight before birth, most commonly determined by ultrasound. It is calculated using established regression formulas that incorporate measurements of the head circumference (HC), abdominal circumference (AC), and femur length (FL). In this study, EFW was derived using the Hadlock formula, the most widely validated and clinically accepted method, which applies logarithmic transformations of these biometric dimensions to estimate fetal mass with high accuracy throughout pregnancy[210].

4.1.3 Research gaps

Several studies have investigated the relationship between smoking and Doppler indices, but the findings have been inconsistent, and there is ongoing uncertainty about where within the maternal-fetal circulation these effects occur. While some studies have reported increased resistance in the uterine arteries of smokers[211,212], others have found no significant differences[35,213–218]. Although there is greater consensus concerning the umbilical artery, with many studies demonstrating elevated resistance in smokers[35,212–214,216,218,219], these findings have not been consistently observed across all papers[215]. Middle cerebral artery had been infrequently assessed in the context of maternal smoking. Most of these studies have performed scans at a single point in pregnancy, limiting the ability to determine when these changes first arise, how they progress over time, and whether there are critical periods when smoking may be most harmful to the pregnancy.

Similarly, studies on fetal biometry differ in the gestational age at which differences between smokers and non-smokers become evident. Some report effects as early as the second trimester[80,84,220], while others detect changes only later in pregnancy[221,222].

Very few studies have examined Doppler findings and estimated fetal weight together. As a result, it remains difficult to determine the optimal time in pregnancy to assess the impact of smoking, and to identify which ultrasound markers are most informative.

4.1.4 Aims

This chapter aims to assess the impact of maternal smoking on estimated fetal weight and Doppler indices across different gestational ages.

4.2 Methods

4.2.1 Study design, setting, and population

This was a retrospective cohort study of singleton pregnancies included in the OxGRIP dataset, with estimated delivery dates between 1 October 2016 and 31 December 2023. The OxGRIP dataset contains routinely collected clinical and ultrasound information from women who received antenatal care and delivered at Oxford University Hospitals. Detailed descriptions of the dataset are provided in Chapter 1.1.4.

During the study period, all women were routinely offered a 12-week dating scan, a 20-week anomaly scan, and a 36-week universal growth scan. Ultrasound scans were undertaken by trained sonographers, obstetricians, and research fellows adhering to uniform clinical protocols. The first-trimester scan included measurement of crown–rump length (CRL) for dating, performed according to the method described by Robinson and Fleming[223]. The anomaly scan included complete fetal biometry comprising head circumference (HC)[224], abdominal circumference (AC)[225], and femur length (FL)[226], with centiles calculated using the Chitty reference charts. This scan also included uterine artery Doppler assessment, with the mean pulsatility index (PI) calculated from measurements of the left and right uterine arteries; if only one side was recorded, that single value was used. The 36-week growth scan included complete fetal biometry, umbilical artery (UA) and middle cerebral artery (MCA) Doppler, and calculation of the cerebroplacental ratio (CPR). Estimated fetal weight (EFW) was derived using the Hadlock equation[210]. Centiles for UtA PI, UmA PI, MCA PI, and CPR were calculated according to the Fetal Medicine Foundation reference charts[227].

Women with singleton, non-anomalous pregnancies were included. Exclusion criteria comprised multiple pregnancies, any fetal congenital abnormalities, and those without an anomaly scan or missing data for estimated fetal weight or Doppler indices. Smoking status was recorded based on self-report at the booking appointment (median gestation approximately 10 weeks) or at any time during pregnancy.

4.2.2 Outcomes

The primary outcomes were EFW and Doppler indices at ultrasound examinations conducted at approximately 17 + 0 to 23 + 6 weeks' gestation (median 20 weeks) and 35 + 0 to 36 + 6 weeks' gestation (median 36 weeks), compared between smokers and non-smokers.

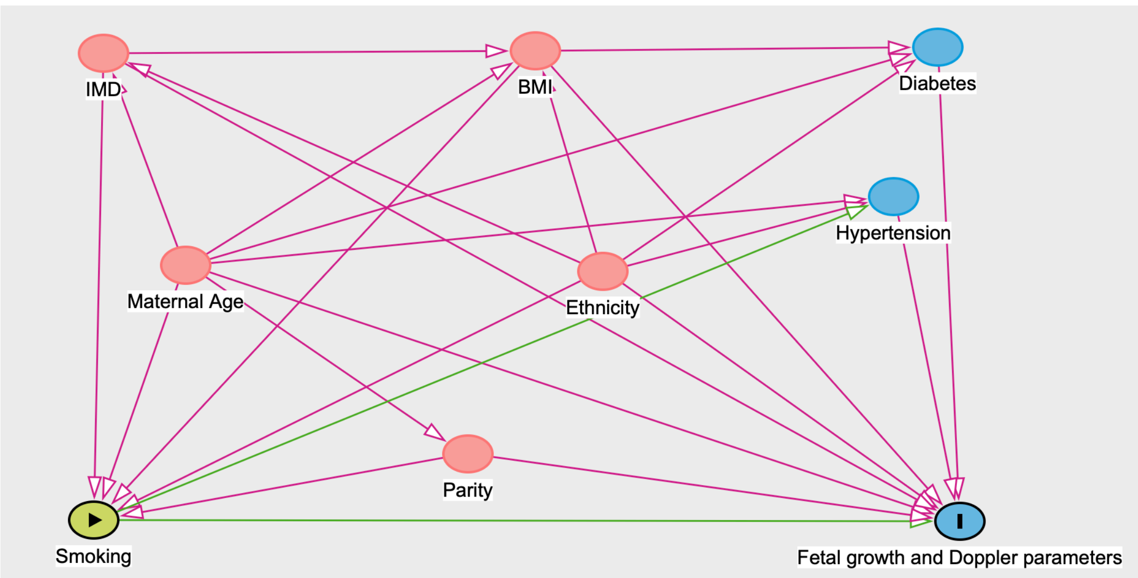
At 20 weeks, outcomes included mean EFW, EFW below the 10th and 3rd centiles, and UtA PI values above the 90th, 95th, and 99th centiles.

At 36 weeks, outcomes included mean EFW, EFW below the 10th and 3rd centiles, and Doppler indicies. Doppler outcomes comprised mean UmbA PI, MCA PI, and CPR, as well as the proportions of UmbA PI above the 90th, 95th, and 99th centiles; MCA PI below the 5th centile; and CPR below the 5th centile.

4.2.3 Statistical analysis

All statistical analyses were conducted using IBM SPSS Statistics version 29.0.2.0. Demographic data were presented as mean (SD) for normally distributed variables, median (IQR) for non-normally distributed variables, and as n (%) for categorical variables. Comparisons between smokers and non-smokers were made using one-way analysis of variance (ANOVA) for continuous variables and chi-square (χ^2) tests for categorical variables. Logistic regression was used to estimate odds ratios (OR) and adjusted odds ratios (AOR), adjusting for maternal age, parity, ethnicity, body mass index (BMI), and Index of Multiple Deprivation (IMD). Covariates were selected using a directed acyclic graph (DAG), constructed in DAGitty, based on established clinical associations between maternal smoking and fetal outcomes. They were entered simultaneously into the same multivariable logistic regression model for each outcome to adjust for confounding (Figure 24). The level of significance was set at $p < 0.05$ for all analyses, and 95% confidence intervals were calculated.

Figure 24: Directed acyclic graph used to select minimal sufficient adjustment sets of covariates

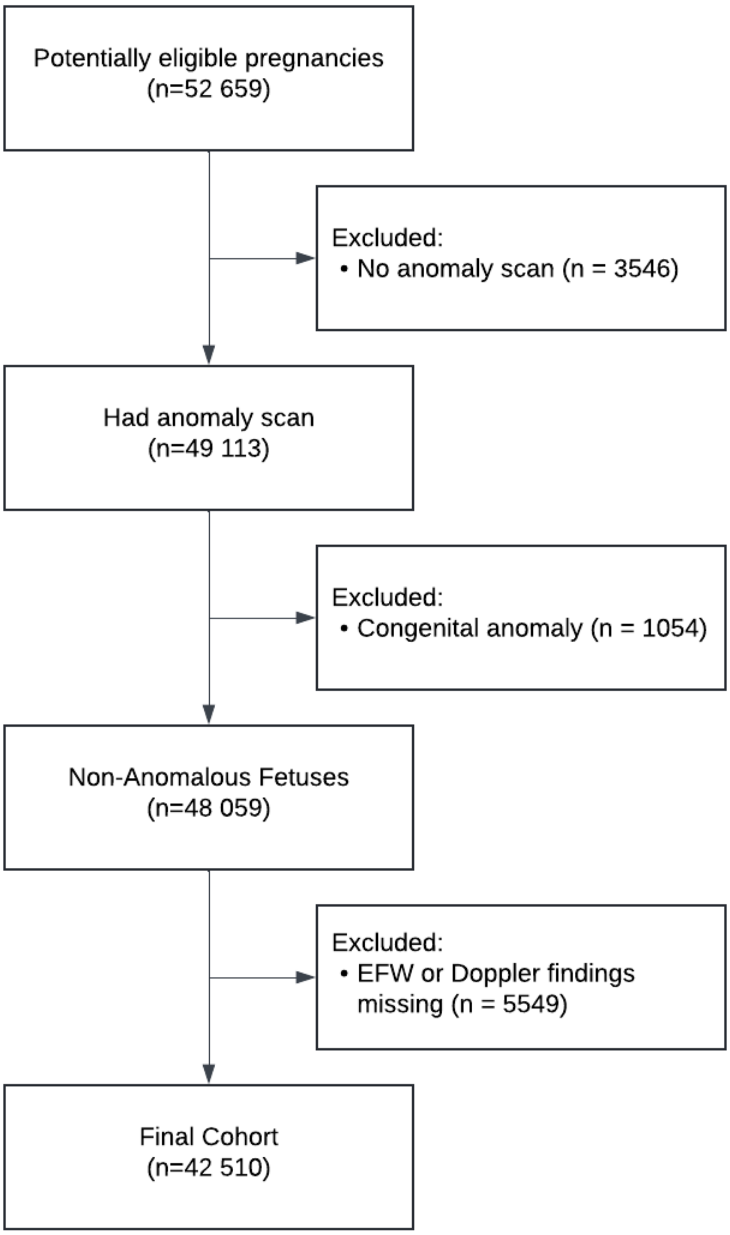


4.3 Results

4.3.1 Cohort characteristics

Of 52,669 potentially eligible pregnancies, 42,510 with complete ultrasound data were included in the final analysis (Figure 25).

Figure 25: Flowchart summarizing population selection in Chapter IV



Demographic characteristics are shown in Table 11. The median maternal age was 32.0 (28–35) years. Over half of participants were parous (54.8%), and 8.0% reported smoking during pregnancy.

The mean gestational age at delivery was 39 + 6 (1 + 2) weeks. The mean birthweight was 3501.05 (496.74) g, with a mean birthweight centile of 54.48 (28.10). The mean estimated fetal weight (EFW) at 20 weeks was 349.98 (46.33) g, corresponding to a mean centile of 46.48 (19.54). At 36 weeks, the mean EFW was 2838.49 (296.15) g, with a mean centile of 49.38 (24.14).

The mean uterine artery pulsatility index (utAPI) at 20 weeks was 1.42 (0.38), with a mean centile of 49.88 (28.41). At 36 weeks, the mean umbilical artery PI was 0.88 (0.14) with a mean centile of 47.32 (28.30), the mean middle cerebral artery PI was 1.72 (0.33) with a mean centile of 45.90 (30.85), and the mean cerebroplacental ratio (CPR) was 2.00 (0.47) with a mean centile of 49.66 (29.83).

Table 11: Demographic characteristics of study IV participants (n=42 510)

Characteristic	Value
Maternal age (years) mean (SD)	31.4 (5.3)
Parity	
Nulliparous	19 206 (45.2%)
Parous	23 304 (54.8%)
Smoking in pregnancy	
Yes	3391 (8.0%)
No	39119 (92.0%)
Ethnicity	
White	35 224 (82.9%)
Asian	3969 (9.3%)
Black	1062 (2.5%)
Mixed	945 (2.2%)
Other	429 (1.0%)
Missing	881 (2.1%)
Index of Multiple Deprivation Decile	
1-2 (most)	2059 (4.8%)
3-4	3768 (8.8%)
5-6	6771 (16.0%)
7-8	11449 (26.9%)
9-10 (least)	17202 (40.5%)
Missing	1261 (3.0%)
Body mass index	

Underweight (< 18.5 kg/m^2)	1191 (2.8%)
Normal weight (18.5–24.9 kg/m^2)	21 533 (50.7%)
Overweight (25.0–29.9 kg/m^2)	11 255 (26.5%)
Class-1 obesity (30.0–34.9 kg/m^2)	4827 (11.4%)
Class-2–3 obesity (≥ 35.0 kg/m^2)	2926 (6.9%)
Missing	778 (1.8%)
GA at delivery (weeks)	39 + 6 (1 + 2)
Birth weight (g) mean (SD)	3501.05 (496.74)
Birth weight (centile), mean (SD)	54.48 (28.10)
EFW at 20 weeks (g) mean (SD)	349.98 (46.33)
EFW at 20 weeks (centile) mean (SD)	46.48 (19.54)
EFW at 36 weeks (g) mean (SD)	2838.49 (296.15)
EFW at 36 weeks (centile) mean (SD)	49.38 (24.14)
Mean utAPI at 20 weeks mean (SD)	1.42 (0.38)
Mean utAPI centile at 20 weeks mean (SD)	49.88 (28.41)
Mean UmbA PI at 36 weeks mean (SD)	0.88 (0.14)
Mean UmbA PI centile at 36 weeks mean (SD)	47.32 (28.30)
Mean MCA at 36 weeks mean (SD)	1.72 (0.33)
Mean MCA centile at 36 weeks mean (SD)	45.90 (30.85)
Mean CPR at 36 weeks mean (SD)	2.00 (0.47)
Mean CPR centile at 36 weeks mean (SD)	49.66 (29.83)

Data are given as n (%), mean (SD) or median (IQR). Abbreviations: GA, gestational age; BW, birth weight; EFW, estimated fetal weight; BMI, body mass index; utAPI, uterine artery pulsatility index; UmbA PI, umbilical artery pulsatility index; MCA PI, middle cerebral artery pulsatility index; CPR, cerebroplacental ratio; IMD, Index of Multiple Deprivation

4.3.2 Ultrasound findings at 20 weeks

Table 12 presents ultrasound findings at 20 weeks stratified by smoking status. There was no meaningful difference in mean gestational age at the second-trimester scan between smokers and non-smokers (20 + 2 weeks [142.26 days] vs 20 + 3 weeks [142.57 days], p= 0.195). At the 20-week anomaly scan, mean estimated fetal weight was slightly higher among smokers compared with non-smokers (352.85 g vs 349.73 g; $F(1, 42{,}508) = 14.17$, $p < 0.001$). The proportions of fetuses with EFW below the 10th or 3rd centiles did not differ significantly between groups (1.8% vs 1.5%, p = 0.203; 0.1% vs 0.1%, p = 0.976). The odds of EFW <10th centile were not significantly increased among smokers (OR 1.19, 95% CI 0.91–1.55; AOR 1.13, 95% CI 0.84–1.51), and no difference was observed for EFW <3rd centile (AOR 1.11, 95% CI 0.31–3.97).

Mean uterine artery pulsatility index was higher in smokers than in non-smokers (0.93 vs 0.91; $F(1, 42,508) = 19.36$, $p < 0.001$). The proportion of women with utA PI >90th centile was 10.1% among smokers and 8.9% among non-smokers ($p = 0.024$), and utA PI >99th centile was observed in 1.6% and 1.1%, respectively ($p = 0.012$). There was no significant difference for utA PI >95th centile ($p = 0.208$). The odds of utA PI >90th centile were modestly increased in smokers (OR 1.14, 95% CI 1.02–1.29; AOR 1.17, 95% CI 1.03–1.32), with a similar pattern for utA PI >99th centile (AOR 1.38, 95% CI 1.01–1.89).

Table 12: Ultrasound findings at 20 Weeks in Smokers and Non-Smokers

	Non-Smokers	Smokers	p-value†	OR (95% CI)	AOR* (95% CI)
Mean EFW (g)	349.73 (45.96) (349.28 to 350.19)	352.85 (50.35) (351.16 to 354.55)	<0.001	-	-
EFW <10th centile	594 (1.5%)	61 (1.8%)	0.203	1.19 (0.91 to 1.55)	1.13 (0.84 to 1.51)
EFW <3rd centile	34 (0.1%)	3 (0.1%)	0.976	1.02 (0.31 to 3.32)	1.11 (0.31 to 3.97)
Mean utA PI	0.91 (0.27) (0.91 to 0.92)	0.93 (0.28) (0.93 to 0.94)	<0.001	-	-
utA PI>90th centile	3,492 (8.9%)	342 (10.1%)	0.024	1.14 (1.02 to 1.29)	1.17 (1.03 to 1.32)
utA PI>95th centile	1,898 (4.9%)	181 (5.3%)	0.208	1.11 (0.95 to 1.29)	1.15 (0.97 to 1.36)
utA PI>99th centile	435 (1.1%)	54 (1.6%)	0.012	1.44 (1.08 to 1.91)	1.38 (1.01 to 1.89)

† *p-values derived from one-way ANOVA for continuous variables and chi-square (χ^2) tests for categorical variables.*
**Adjusted for maternal age, parity, ethnicity, Index of Multiple Deprivation (IMD), and BMI.*

4.3.3 Ultrasound findings at 36 weeks

Table 13 summarises ultrasound findings at 36 weeks by smoking status. There was also no difference in mean gestational age at the 36-week scan between smokers and non-smokers (36 + 0 weeks [252.52 days] vs 36 + 0 weeks [252.56 days], $p = 0.195$). Mean estimated fetal weight at 36 weeks was significantly lower in smokers compared with non-smokers (2744.71 g vs 2846.62 g; $F(1, 42\,508) = 372.74$, $p < 0.001$). The adjusted odds of EFW below the 10th centile were nearly threefold higher in smokers (AOR 2.94, 95% CI 2.56–3.37), and those below the 3rd centile were even more increased (AOR 3.41, 95% CI 2.69–4.33).

Mean umbilical artery pulsatility index was higher among smokers (0.91 vs 0.88; $F(1, 42\ 508) = 191.80$, $p < 0.001$). The odds of UmbA PI above the 90th centile were doubled in smokers (AOR 1.99, 95% CI 1.74–2.29), with progressively higher odds at more extreme thresholds (AOR 2.27, 95% CI 1.80–2.87 for >95th centile; AOR 3.76, 95% CI 2.50–5.66 for >99th centile).

Mean cerebroplacental ratio (CPR) was lower among smokers (1.94 vs 2.00; $F(1, 42\ 014) = 52.01$, $p < 0.001$). The adjusted odds of CPR below the 5th centile were higher in smokers (AOR 1.45, 95% CI 1.26–1.67).

There was no significant difference in mean middle cerebral artery PI (MCA PI) between groups (1.72 vs 1.71; $F(1, 42\ 020) = 2.07$, $p = 0.151$), and the adjusted odds of MCA PI below the 5th centile were not increased (AOR 1.05, 95% CI 0.92–1.19)

Table 13: Ultrasound findings at 36 Weeks in Smokers and Non-Smokers

	Non-Smokers	Smokers	p-value†	OR (95% CI)	AOR* (95% CI)
Mean EFW (g)	2846.62 (294.03) (2843.71 to 2849.54)	2744.71 (304.41) (2734.46 to 2754.96)	<0.001	-	-
EFW <10th centile	1,667 (4.3%)	360 (10.6%)	<0.001	2.67 (2.37 to 3.01)	2.94 (2.56 to 3.37)
EFW <3rd centile	450 (1.2%)	122 (3.6%)	<0.001	3.21 (2.62 to 3.93)	3.41 (2.69 to 4.33)
Mean UmbA PI	0.88 (0.14) (0.88 to 0.88)	0.91 (0.16) (0.91 to 0.92)	<0.001	-	-
UmbA PI >90th centile	1,861 (4.8%)	307 (9.1%)	<0.001	1.99 (1.76 to 2.26)	1.99 (1.74 to 2.29)
UmbA PI >95th centile	568 (1.5%)	108 (3.2%)	<0.001	2.23 (1.81 to 2.75)	2.27 (1.80 to 2.87)
UmbA PI >99th centile	130 (0.3%)	38 (1.1%)	<0.001	3.40 (2.36 to 4.89)	3.76 (2.50 to 5.66)

Mean MCA PI	1.71 (0.33) (1.71 to 1.72)	1.72 (0.34) (1.71 to 1.73)	0.151	-	-
MCA PI <5th centile	4,089 (10.5%)	327 (9.6%)	0.138	0.91 (0.81 to 1.03)	1.05 (0.92 to 1.19)
Mean CPR	2.00 (0.47) (2.00 to 2.01)	1.94 (0.48) (1.92 to 1.96)	<0.001	-	-
CPR <5th centile	2,424 (6.2%)	265 (7.8%)	<0.001	1.28 (1.13 to 1.46)	1.45 (1.26 to 1.67)

† *p-values derived from one-way ANOVA for continuous variables and chi-square (χ^2) tests for categorical variables.*
**Adjusted for maternal age, parity, ethnicity, Index of Multiple Deprivation (IMD), and BMI.*

4.4 Discussion

4.4.1 Key Findings

In this study, maternal smoking was associated with lower estimated fetal weight and a higher risk of abnormal Doppler findings in the third trimester, but not earlier in pregnancy. At 36 weeks, smokers had significantly lower mean EFW, greater odds of fetal size below the 10th and 3rd centiles, higher umbilical artery pulsatility index, and increased risk of cerebroplacental ratio below the 5th centile. At 20 weeks, uterine artery pulsatility index was slightly higher among smokers, but fetal size did not differ significantly.

4.4.2 Strengths and Limitations

The main strengths of this study include the large sample size and the use of routinely collected ultrasound data from women receiving standardized antenatal care. All participants underwent universal scans at 20 and 36 weeks as part of routine practice, rather than scans performed because of clinical concern or perceived risk. This reduces bias related to selective inclusion of higher-risk pregnancies and allows findings to reflect the general obstetric population. In addition, we were able to adjust for major confounding factors, including maternal age, parity, ethnicity, body mass index, and socioeconomic deprivation. Most previous studies assessed ultrasound findings at a single point in pregnancy, whereas this analysis included scans at two stages, allowing a clearer comparison of when smoking-related effects begin to appear. It also examined both Doppler indices and estimated fetal weight within the same cohort, which made it possible to assess which parameters were more affected and at what stage of pregnancy.

The main limitations of this study are similar to those seen in Chapter III. These include its retrospective design and the small number of cases in some outcome categories, such as estimated fetal weight below the 3rd centile. Detailed information on smoking behaviour, including the number of cigarettes smoked, timing, and cessation during pregnancy, was not available, limiting the ability to assess dose–response relationships or the impact of quitting. As shown in Chapter III, self-reported smoking data may not always be reliable; however, we relied on self-report in this analysis because more objective CO measurements were only available for 2023, and we aimed to include a larger sample size without date restrictions. Finally, some ultrasound data were incomplete, as not all pregnancies had full Doppler information recorded.

4.4.3 Comparison with literature

Uterine and Umbilical Doppler

At 20 weeks, smoking was associated with a modest increase in uterine artery resistance but no difference in fetal size. This pattern suggests that vascular changes may occur before measurable effects on fetal growth become evident and supports a cumulative effect of smoking as pregnancy progresses. Previous studies have reported mixed results, with some identifying increased uterine artery resistance among smokers in the second trimester[211,228,229], while others found no significant differences[35,213–218]. However, larger population-based studies have generally demonstrated modest elevations in mean UtA PI, consistent with these findings. In addition to mean values, this analysis also examined the risk of UtA PI within the highest centiles and showed significantly increased odds among smokers. Moreover, this was the largest sample to date and the only study using data from universal clinical screening, rather than targeted high-risk or research-based scans, reducing selection bias**.**

There appears to be greater agreement in the literature regarding the effect of smoking on the umbilical artery[35,212–214,216,218,219]. Most studies report significantly higher umbilical artery pulsatility index among smokers, and the findings in this cohort are consistent with that.

Middle Cerebral Artery

Only a limited number of studies have investigated the effect of maternal smoking on the MCA. Consistent with the findings in this chapter, none have reported significant differences in MCA Doppler indices between smokers and non-smokers. Studies by Albuquerque et al.[213] and Alptekin et al.[35], based on much smaller cohorts that this one (n = 149 and 148, respectively), also found no associations. Another study incorporating biochemical verification of smoking status similarly reported no significant differences in MCA indices[229]. Mean MCA values in this cohort were comparable with those described in previous studies. However, earlier studies did not report the proportion of foetuses with MCA PI below the 5th centile, limiting direct comparison. Nevertheless, the 10% rate observed among smokers in our cohort appears relatively high.

CPR

To the best of current knowledge, this is the first study to report cerebroplacental ratio values and examine centile-based differences in relation to maternal smoking. The adjusted odds of CPR <5th centile were 1.45 (95% CI 1.26–1.67). Using reference data from two studies that provided both MCA and umbilical artery indices, the calculated mean CPR in those populations was above 1 and did not differ markedly between smokers and non-smokers[35,213].

EFW

Differences in EFW between smokers and non-smokers were only evident in the third trimester. At 36 weeks, smokers had significantly lower mean EFW and higher odds of fetal size below the 10th and 3rd centiles. The population attributable fraction of smoking for EFW <10th centile was 13.4%, and for <3rd centile 16.2%. These findings suggest that the impact of smoking on fetal growth becomes apparent later in pregnancy. Although no significant differences were observed at 20 weeks, several previous studies, including a systematic review, reported smaller fetal size among smokers as early as the second trimester[15,80,84,220]. Others, however, detected effects only in late pregnancy[216,221,222,230,231], aligning with results in this chapter. The variation is likely due to differences in the timing and duration of exposure, with the observed pattern supporting a cumulative effect of smoking on placental function and emphasising the importance of early cessation to reduce risk.

4.4.4 Conclusions

In conclusion, maternal smoking in pregnancy was associated with lower estimated fetal weight and a higher risk of abnormal Doppler findings in the third trimester. Although there was no difference in fetal size at 20 weeks, modest increases in uterine artery resistance were observed, suggesting early vascular changes before measurable effects on growth. Taken together, these findings highlight the potential value of enhanced third-trimester surveillance for ongoing smokers.

Chapter V. Discussion and Conclusions

5.1 Discussion

5.1.1 Chapter summary

This thesis aimed to inform the appropriate method and timing for surveillance in pregnancies of smokers by reviewing the existing literature (Chapter II), evaluating the prediction of smoking in pregnancy using biochemical measures (Chapter III), and comparing fetal outcomes and ultrasound markers between smokers and non-smokers at different gestations (Chapter IV). Together, these chapters provide a comprehensive assessment of how smoking in pregnancy affects fetal outcomes, how exposure can be most accurately identified, and at what stages of pregnancy these effects become most evident.

The systematic review presented in Chapter II confirmed that maternal smoking during pregnancy is consistently associated with a wide range of adverse fetal outcomes. Infants of smokers had lower mean birthweight, higher odds of being small for gestational age (SGA), and an increased risk of preterm birth, stillbirth, and neonatal death. Importantly, the review highlighted both dose–response and timing effects: heavier smoking was associated with greater risk, and cessation early in pregnancy largely mitigated adverse outcomes, while quitting later or continuing to smoke increased risk as pregnancy progressed. These findings indicate that the harmful effects of smoking accumulate over time and that the benefits of cessation diminish with later intervention. In this review, I was also able to examine a broad range of fetal and neonatal outcomes and compare the degree to which each was affected. Although outcomes related to fetal size and weight showed the largest and most consistent effects, smoking was also associated with higher rates of preterm birth, stillbirth, and neonatal morbidity, indicating a wider impact on fetal development and perinatal outcomes.

Building on these findings, Chapter III investigated the relationship between maternal carbon monoxide (CO) levels, smoking behaviour, and pregnancy outcomes. This chapter aimed to identify the CO threshold and its relationship with adverse neonatal outcomes, and to compare the use of CO with self-reported smoking as risk indicators. A changepoint analysis identified a threshold of 2 ppm, above which adverse outcomes became more frequent, indicating that even low levels of exposure carry measurable risk. Higher CO levels were associated with lower mean birthweight and increased rates of adverse outcomes, supporting a dose–response relationship. Importantly, these associations persisted even without information on the number of cigarettes smoked, suggesting that CO captures a wider range of exposure, including light or intermittent smoking. While smokers with low CO values still showed some increased risk, this likely reflects limitations of infrequent testing rather than an effect independent of CO. These findings highlight that CO is a more sensitive and objective measure of risk than self-report. Implementing universal, repeated CO testing could improve the identification of at-risk pregnancies, and using the actual CO value rather than a fixed threshold would strengthen its role in risk prediction models and antenatal surveillance.

Chapter IV examined fetal growth and ultrasound findings between smokers and non-smokers at different stages of pregnancy. The results showed that smoking had the greatest effect in the third trimester, when differences in estimated fetal weight and Doppler parameters became most apparent. In earlier pregnancy, including at the 20-week scan, there was no difference in fetal size, although modest differences in uterine artery Doppler indices had already started to emerge. This pattern suggests that the effects of smoking develop gradually and become more pronounced as pregnancy advances, which is consistent with the results of the systematic review. Together, these results demonstrate that early pregnancy exposure may initiate subtle changes that manifest as measurable fetal compromise later in gestation, highlighting the need for early identification and ongoing monitoring of women who continue to smoke.

5.1.2 Integration of Findings and Clinical Implications

Taken together, the findings from this thesis reinforce that smoking in pregnancy should be treated as an independent risk factor for adverse outcomes. Across all chapters, smoking was consistently associated with adverse outcomes, even without detailed information on smoking intensity or precise timing of measurement.

The results also show that the effects of smoking are cumulative and become more pronounced as pregnancy advances. This pattern was evident both in the systematic review and in the ultrasound analyses, where differences were greatest in the third trimester. These findings align with the broader evidence that the risk of many poor pregnancy outcomes can be reduced to that of a non-smoker if cessation is achieved early in pregnancy. This highlights the importance of identifying smokers as early as possible and ensuring referral to cessation services at the first opportunity.

Carbon monoxide testing offers a practical way to achieve this. In the UK, the *Saving Babies' Lives* care bundle from NHS England recommends CO testing at the booking and 36-week appointments. The results from this thesis emphasise that performing CO screening reliably, rather than omitting it, is crucial for accurate identification of ongoing exposure. Given that CO testing is non-invasive, inexpensive, and quick to perform, it could reasonably be done even more frequently than twice to improve detection and monitoring. Repeated testing would allow clinicians to identify women who continue to smoke after their initial visit and provide additional opportunities for intervention. In the future, risk prediction models could also incorporate the actual CO value rather than a binary threshold, offering a more nuanced and quantitative measure of exposure when estimating individual risk.

Finally, the ultrasound findings in this thesis show that fetal growth differences between smokers and non-smokers become evident later in pregnancy, with changes in fetal size and Doppler parameters most apparent in the third trimester. This supports the case for enhanced surveillance of pregnancies with confirmed exposure, to detect early signs of growth restriction or placental dysfunction. Together, these findings support an integrated approach: early identification and cessation support, regular biochemical monitoring, and tailored surveillance later in pregnancy to mitigate the cumulative effects of smoking on fetal development.

5.1.3 Key novelties and directions for future research

5.1.3.1 What was already known

As presented in the systematic review presented in this thesis, the effects of smoking in pregnancy have been extensively investigated. Maternal smoking is an established modifiable risk factor associated with adverse fetal and neonatal outcomes, such as low birthweight and preterm birth. Smoking status has therefore been routinely incorporated into antenatal risk assessment, and smoking cessation during pregnancy is widely promoted as an effective intervention to reduce risk. Assessment of smoking exposure in pregnancy has traditionally relied on self-reported smoking status. However, biochemical markers such as exhaled carbon monoxide have also been adopted in clinical practice as reliable indicators of smoking exposure, particularly for identifying recent smoking.

5.1.3.2 What this thesis adds

This thesis makes several novel contributions to the existing literature. First, the systematic review and meta-analysis provides an up-to-date quantitative synthesis across a broad range of fetal and neonatal outcomes. It demonstrates that cessation before or early in pregnancy is associated with outcomes comparable to those of non-smokers, whereas cessation later in pregnancy appears to confer more limited benefit.

Chapter III utilises changepoint analysis as one of the first studies to evaluate exhaled carbon monoxide as a continuous measure of risk in pregnancy. It identifies a CO threshold above which birthweight and neonatal outcomes are adversely affected, supporting the potential use of CO not only for identifying smoking exposure but also for stratifying risk. The findings also demonstrate a dose–response relationship and indicate that more than one carbon monoxide measurement may be required to fully identify smoking in pregnancy.

Chapter IV uses routinely collected data to examine, as one of the first studies, smoking-related effects on fetal growth and Doppler parameters at two gestational time points. Differences were minimal at 20 weeks but evident by 36 weeks, indicating that the adverse effects of smoking become more apparent later in pregnancy.

5.1.3.3 Future research

These findings highlight several priorities for future research. External validation of the identified carbon monoxide threshold in independent populations and healthcare settings would be beneficial, alongside evaluation of how biochemical measures of smoking exposure can be most effectively integrated into routine antenatal care.

In addition, incorporating smoking exposure, carbon monoxide levels, and gestation-specific ultrasound findings into dynamic risk prediction models may improve identification of pregnancies at highest risk of adverse outcomes.

5.2 Conclusions

In conclusion, this thesis demonstrates that smoking in pregnancy is an independent risk factor for adverse outcomes, with effects that accumulate and become more pronounced as pregnancy progresses. Early identification, reliable exposure testing, and cessation support remain key to reducing these risks. Incorporating smoking status and actual carbon monoxide levels into risk prediction models could guide the need for increased surveillance and other targeted interventions, particularly in the third trimester when Doppler changes and fetal growth differences are most evident.

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