Grandmaternal smoking during pregnancy and grandchild health: A systematic review and meta-analysis

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Abstract

Background

Maternal smoking during pregnancy is associated with a host of detrimental effects on the exposed child. However, emerging evidence suggests that the adverse effects of smoking during pregnancy may be transmitted across generations. We conducted a systematic review to comprehensively summarize evidence on the association between grandmaternal smoking during pregnancy and health outcomes in the grandchild.

Methods

We searched MEDLINE, EMBASE, and 10 other databases from inception to March 02, 2021, updated on October 18, 2021, to identify analytic epidemiologic studies (prospective or retrospective cohort and case-control design) investigating the association between grandmaternal smoking during pregnancy and multiple health outcomes in the grandchild in all countries and settings. Three investigators independently screened records, extracted data, and assessed study quality using the Effective Public Health Practice Project (EPHPP) tool. Random-effects robust variance estimation was used to combine effect estimates whenever possible, separately for maternal and paternal line.

Results

Twenty-four reports from 15 unique studies with 23 health outcomes and 231,478 grandchildren were included. The overall study quality was moderate. In maternal line, grandmaternal smoking during pregnancy was associated with an increased risk of asthma (seven studies, 148,527 grandchildren, risk ratio (RR) 1.10, 95% CI 1.02 to 1.18) and higher birth weight (four studies, 19,478 grandchildren, mean difference (g) 40.04, 95% CI 22.60 to 57.49) in the grandchild. There was suggestive evidence that maternal grandmaternal smoking was associated with increased risks of acute lymphoblastic leukaemia, any cancer, autism, and attention deficit hyperactivity disorder, decreased risks of early-onset myopia and small birth weight for gestational age, and higher birth length and body mass index at birth. In paternal line, grandmaternal smoking during pregnancy was not associated with asthma (four studies, 41,069 grandchildren, RR 1.01, 95% CI 0.85 to 1.19), but there was suggestive evidence for lower intelligence quotient scores and decreased risks of early-onset myopia and intolerance to loud sound.

Conclusions

The effects of maternal smoking during pregnancy may not be limited to the exposed child, but be transmitted to the grandchild, possibly through germline epigenetic inheritance. Further public health efforts are warranted to strengthen smoking cessation programs for pregnant women.

Background

Globally, the prevalence of maternal smoking during pregnancy is estimated to be around 2% [1]. However, in many countries, smoking during pregnancy is still common. More than 10% of pregnant women smoked during pregnancy in 29 (17%) of 174 countries and more than 20% in 12 (7%) countries [1]. Specifically, the prevalence of smoking during pregnancy was on average 8% in Europe (ranging from 0.5–38%) and 17% in the USA [1]. Notably, more than 70% of pregnant women who smoked during pregnancy smoked daily rather than occasionally [1]. With decades of research, smoking during pregnancy has been linked to a host of detrimental effects on the exposed child. For example, smoking

during pregnancy is associated perinatally with low birth weight [2], preterm birth [3, 4], various birth defects [5], still birth [6], and neonatal death [7]; and postnatally with sudden infant death syndrome [8], asthma [9], obesity [10], high blood pressure [11], low intelligence quotient (IQ) scores [12], conduct problems [13], and attention deficit hyperactivity disorder (ADHD) [14]. These findings suggest that smoking during pregnancy may affect offspring's health already *in utero*, with potentially life-long negative health consequences.

The biologic mechanisms by which maternal smoking may lead to diverse adverse health in the offspring are complex. Extensive human and laboratory studies have shown that cigarette smoke contains more than 7,000 chemicals, many of which (e.g., nicotine, carbon monoxide) can cross the placental barrier to influence fetal programming or have a direct toxicologic effect on the fetus [15, 16]. In recent years, it is increasingly recognized that many of the mechanisms are mediated epigenetically [17, 18]. The epigenome refers to the biochemical information that lies 'over and above' the DNA sequence and regulates the expression of genes through mechanisms such as DNA methylation (DNAm), histone modifications and non-coding RNAs [19, 20]. There is a growing body of literature that smoking during pregnancy is associated with numerous epigenetic alterations in the exposed child, which may in turn affect health outcomes [17, 18]. For example, many studies consistently found that DNAm at specific gene loci mediated in part the relationship between maternal smoking and offspring low birth weight [21–26]. An increasing number of human epigenome-wide association studies showed that DNAm marks at some specific gene regions were associated with ADHD and asthma, suggesting that epigenetic mechanisms may play an important role in their etiology [27–39]. In rat models, maternal nicotine exposure during pregnancy (F0) induced epigenetic changes not only in the first generation (F1), but also in the germ cells of F1 generation that form the second generation (F2) (termed as intergenerational epigenetic inheritance) and of F2 generation that form the third generation (F3) (as transgenerational epigenetic inheritance) [40–42]. Furthermore, recent human epigenome-wide association studies found that grandmaternal smoking during pregnancy was associated with differential DNAm in the grandchild [43, 44].

While the detrimental health effects of smoking during pregnancy on the exposed child are well established, it is unclear whether these effects are transmitted to the subsequent generation(s) through epigenetic inheritance. Whilst the plausibility of epigenetic inheritance is being elucidated [20, 45, 46], a number of epidemiologic intergenerational studies have investigated the impact of grandmaternal smoking during pregnancy on various health outcomes in the grandchild, but results are inconsistent for some outcomes (e.g., birth weight, asthma) [47–50]. To elucidate the underlying evidence, we undertook a systematic review of observational epidemiologic studies investigating the association between grandmaternal smoking during pregnancy and multiple health outcomes in the grandchild. We sought to comprehensively summarize the available evidence on the potential intergenerational transmission of the effects of maternal smoking during pregnancy.

Methods

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42017084039). This study was reported as per the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline [51] (Additional file 1). Ethical approval was not required for this study.

Literature search and eligibility criteria

We searched MEDLINE, EMBASE, Cochrane Library, ISI Web of Science, CINAHL, Google Scholar, Scopus, Global Health, PsycINFO, Zetoc, CAB International and WHO Global Health Library from inception to March 02, 2021. The database search was updated on October 18, 2021. No language restriction was applied. The search strategies are available in the PROSPERO protocol. Three investigators (GQZ, YL and HHZ) independently screened the titles and/or abstracts and

reviewed full-text articles for eligibility. Any discrepancies were resolved by discussion or by a third investigator (BIN). We also manually checked the references of included studies and relevant reviews to identify additional eligible studies.

Studies were selected for inclusion if they met the following Population, Exposure, Comparator, Outcome, Study design (PECOS) criteria: 1) Population: grandmother-mother/father-child triads of any ethnicity in any country or setting; 2) Exposure: maternal grandmaternal smoking during pregnancy (i.e., grandmother smoked any amount of cigarettes when pregnant with the mother) or paternal grandmaternal smoking during pregnancy (i.e., grandmother smoked any amount of cigarettes when pregnant with the father); 3) Comparator: no maternal or paternal grandmaternal smoking during pregnancy; 4) Outcome: any health outcome in the grandchild of any age; 5) Study design: analytic epidemiologic studies (prospective or retrospective cohort and case-control design). We also included studies investigating the effects of both grandmaternal and maternal smoking during pregnancy relative to neither of them smoked during pregnancy. We excluded reviews, commentaries, studies of grandmaternal smoking not during pregnancy, and studies of indirect outcome measures (e.g., DNAm, dietary inflammatory index, lung function parameters). For conference abstracts, corresponding authors were contacted to request additional data. If no information was provided, they were excluded from our review (eTable 1 in Additional file 2).

Data extraction and quality assessment

Three investigators (GQZ, YL and HHZ) independently extracted data by outcome using a customized data extraction form. For each article, we extracted first author, year of publication, country, study design, exposure group, reference group, sex and age of the grandchild, outcome examined, number of cases and controls in case-control studies or total population in cohort studies for binary outcomes, number of total population in cohort studies for continuous outcomes, type of effect measure (mean difference (MD), risk ratio (RR), odds ratio or hazard ratio), and maximally-adjusted effect estimate with 95% confidence interval (CI). When studies reported multiple effect estimates for different exposure levels relative to non-smoking [47, 49, 52, 53], or estimates relative to a reference group other than non-smoking [54], corresponding authors were contacted to obtain the estimates comparing smoking versus non-smoking. We received the requested data from three studies [47, 49, 54]. We categorized outcomes according to the International Classification of Diseases 11th Revision (ICD-11) [55].

Three investigators (GQZ, YL and HHZ) independently assessed the risk of bias of included studies by outcome using the Effective Public Health Practice Project (EPHPP) tool [56]. The EPHPP tool consists of six domains: study design, selection bias, confounders, exposure measurement, outcome measurement and statistical analysis. Each domain is rated as strong, moderate, or weak. Disagreements during data extraction and quality assessment were resolved by discussion or by a third investigator (BIN).

Data synthesis and analysis

We developed *a priori* an analysis protocol for this review (Additional file 3), which was adapted from our earlier work [57]. We used the random-effects robust variance estimation (RVE) method to calculate the summary average effect and its 95% CI [58]. The RVE method does not require any distributional assumptions on the population effects, can accommodate dependence among effect estimates (e.g., multiple estimates based on the same individuals at different time points, or computed using a common control group), and can provide correct inference even in meta-analyses with a small number of studies [58, 59]. We quantified the extent of heterogeneity by estimating the standard deviation of population effects [60, 61]. To evaluate the robustness of meta-analysis results to potential publication bias, we calculated the S-value [62], which represents the severity of publication bias that would hypothetically be required to shift the summary estimate to the null. For binary outcomes, we also calculated the E-value [63–65], which assesses how strong residual confounding would have to be to “explain away” an observed exposure-outcome association.

The primary analyses focused on the average effects of grandmaternal smoking during pregnancy. These analyses were conducted separately for maternal and paternal line. Subgroup analyses were conducted according to maternal smoking status during pregnancy (smoking versus non-smoking) and sex of the grandchild (boys versus girls). We also conducted analyses for the effects of grandmaternal and maternal smoking during pregnancy in combination compared to neither of them smoked during pregnancy. For binary outcomes, all estimates were converted to the RR scale [63, 66], and results were presented on that scale. All statistical analyses were performed using R software (version 4.0.4) [67]. The R scripts and datasets are respectively available in Additional file 4 and at the Open Science Framework.

Results

Characteristics of included studies

Overall, we identified 1,152 records, scrutinized 49 full-text articles, and ultimately included 24 reports from 15 unique studies, including 18 reports from nine prospective cohort studies [48–50, 53, 54, 68–80], three reports from three retrospective cohort studies [47, 52, 81], one report from one nested case-control study [82], and two reports from two case-control studies [83, 84]. These reports were published between 2003 and 2021. Figure 1 shows the study selection process. Studies excluded at the full-text screening stage with reasons for their exclusion are available in eTable 1 in Additional file 2. Characteristics of the included studies are summarized in Table 1. Figure 2 presents a summary of quality assessment by outcome across all included studies. Each EPHPP domain judgment for each outcome is available in eTable 2 in Additional file 2.

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Diseases of the respiratory system							
Accordini 2018 [74]	Europe[a], Australia	Prospective cohort	Sampling method: all children Children born from parents who participated in the ECRHS I and III	Maternal line: 5,002/4,666 Paternal line: 4,563/4,192	Parent report at ECRHS I	Parent-reported ever asthma with or without nasal allergies in children aged 0–51 years	Grandmother's and grandfather's ever asthma and education level, maternal and paternal ever asthma, age, smoking and education level, and offspring's gender and age
Bråbäck 2018 [47]	Sweden	Retrospective cohort	Sampling method: general population Children born after June 31, 2005, from all mothers born between 1982-1986 in Sweden	Maternal line: 15,265/10,329 Paternal line: 15,265/10,329	Grandmother report at gestational week 8-12	Purchase of any asthma medication (inhaled steroid and/or leukotriene antagonist) by age 6 years	Maternal smoking habits, maternal and paternal grandmother's age, level of education, social welfare, BMI and asthma medication, maternal and paternal grandfather's asthma medication, maternal and paternal age, sex of the child, and county of residence at mother's and father's birth
Li 2005 [82]	USA	Nested case-control	Sampling method: controls were countermatched on *in utero* exposure to maternal smoking within grade, sex, and community of residence Cases: asthmatic children from public schools (grades 4, 7, 10) in 12 southern California communities in 1993; Controls: non-asthmatic children from the same cohort	Maternal line: Cases: 338/235 Controls: 570/335	Mother report	Parent-reported doctor-diagnosed asthma in the first 5 years of life	Grade, sex, community of residence, race/ethnicity, gestational age, and secondhand smoke exposure

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Lodge 2018 [52]	Sweden	Retrospective cohort	Sampling method: general population Children born between 1996-2010, from all mothers born between 1982-1986 in Sweden	Maternal line: 81,550/48,971	Grandmother report at gestational week 10-12	Purchase of any asthma medication (beta agonist, inhaled steroid, or leukotriene antagonist) by age 6 years	Child's gender and birth order, maternal nicotine exposure (smoking and snus), mother's years of education, family allowance, birth order, residence at childbirth, and age, grandmother's residence at childbirth, years of education, social allowance, asthma, age and BMI, and proxy for grandfather's smoking
Magnus 2015 [77]	Norway	Prospective cohort	Sampling method: general population Children born from all pregnant women in 1999-2008 in Norway	Maternal line: 110,291/46,564	Mother report at 18 gestational weeks	Current asthma at age 3 and 7 years based on mother-reported asthma diagnosis/symptoms and/or dispensed asthma medications	Maternal age, parity, education, salary, pre-pregnancy BMI, asthma and smoking during pregnancy
Mahon 2021 [78]	The Netherlands	Prospective cohort	Sampling method: all children Children whose parents participated in the LifeLines Cohort Study	Maternal line: 167,548/30,546 Paternal line: 167,548/20,923	Parent report	Grandchild- or parent-reported asthma from 4 to 50 years of age	Gender, maternal smoking, current or former smoking, passive environmental smoke exposure in childhood, maternal age, birth weight, gestational age, breast feeding and socioeconomic status
Miller 2014 [48]	UK	Prospective cohort	Sampling method: general population	Maternal line: NR/6,881 Paternal line:	Parent report during pregnancy	Mother-reported doctor-diagnosed asthma ever at age 7 to 8 years in	Family history of asthma, gestation, parity,

			Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	NR/5,625		association with a history of wheezing in the preceding 12 months	maternal education, breastfeeding, the amount the mother smoked during pregnancy, paternal smoking in pregnancy and exposure of the child to environmental tobacco smoke

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Disorders of newborn related to length of gestation or fetal growth							
Ding 2017 [49]	USA	Prospective cohort	Sampling method: all children Children born from women who participated in Nurses' Health Study II (the Growing Up Today Study 2)	Maternal line: 10,907/5,759	Grandmother report	Mother-reported birth weight	Grandmother's gestational age, age at birth, level of education, consumption of alcohol, vegetable, fruit and meat, physical activity and weight gain during pregnancy, and mothers' pre-pregnancy BMI, smoking during pregnancy, social-economic status, and diet score and physical activity during pregnancy
Gustavson 2017 [75]	Norway	Prospective cohort	Sampling method: general population Children born from all pregnant women in 1999-2008 in Norway	Maternal line: NR/82,550	Mother report at 18 gestational weeks	Birth weight records from the Medical Birth Registry of Norway	Maternal and paternal age, education, and ADHD symptoms, maternal (pre-pregnancy) and paternal BMI, maternal smoking and alcohol consumption during pregnancy and parity, child's birth year, and geographical region
Hyppönen 2003 [76]	UK	Prospective cohort	Sampling method: general population Children born from all mothers who were born from 3 to 9 March 1958 in England, Scotland, and Wales	Maternal line: NR/9,028	Grandmother report	Mother-reported birth weight	Child's gestational age, sex and birth order, and maternal smoking, height, BMI, and birth weight

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Miller 2014 [72]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women who did not smoke during pregnancy in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: NR/8,188 Paternal line: NR/6,773	Parent report during pregnancy	Birth weight, birth length, head circumference and BMI, measured by study staff	Child's gestational age, maternal age, parity, education, birth weight, alcohol use and housing tenure, and paternal smoking at the start of pregnancy
Pembrey 2014 [50]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women who smoked during pregnancy in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: NR/3,502 Paternal line: NR/2,354	Parent report during pregnancy	Birth weight, birth length, head circumference and BMI, measured by study staff	Child's gestational age, maternal age, parity, education, birth weight, alcohol use and housing tenure, and paternal smoking at the start of pregnancy
Rillamas-Sun 2014 [79]	USA	Prospective cohort	Sampling method: all children Children born from mothers who participated in MBHMS	Maternal line: NR/926	Mother report	Mother-reported birth weight	Child's first-born status and sex, maternal first-born status, singleton status, birth weight, birth year, marital status, education, and adult BMI and height, and grandmother's birth year, gestational age

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Rumrich 2021 [81]	Finland	Retrospective cohort	Sampling method: general population Children born between 2005 and 2016 from mothers who were born between 1991 and 2006 in Finland	Maternal line: NR/18,226	Grandmother report during pregnancy	Preterm birth, low birth weight, and small body size for gestational age from the Finnish Medical Birth Register	Maternal age, parity, socioeconomic status, low birth weight, preterm birth, and comorbidities during pregnancy, and grandmaternal age, parity, and socioeconomic status
Shen 2020 [80]	UK	Prospective cohort	Sampling method: all children Children born from mothers who participated in the Isle of Wight cohort study	Maternal line: 472/144	Grandmother report during pregnancy	Birth weight from hospital records	Grandmaternal pre-pregnancy BMI and socioeconomic status, maternal smoking, birth weight and BMI at age 18 years, and gender of the child
Neoplasms							
Azary 2016 [83]	Canada, USA	Case-control	Sampling method: controls were selected from among friends and relatives of cases and matched by age Cases: children newly diagnosed with sporadic retinoblastoma between January 1998 to June 2011 at 11 centers; Controls: children without sporadic retinoblastoma	Maternal line: Cases: unilateral 187/185; bilateral 301/286 Controls: 424/387	Mother report	Doctor-diagnosed sporadic retinoblastoma from 0 to 14 years of age	Child's age, and parents' race, education, household income, age at child's birth, drinking and smoking

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Ortega-García 2010 [84]	Spain	Case-control	Sampling method: controls were matched by child's age, mother's birth year and postal code Cases: children born between 2001 and 2005 newly diagnosed with cancer between 1 January, 2004 to 1 January, 2006 at one of six collaborating hospitals; Controls: children without cancer	Maternal line: Cases: 128/116 Controls: 128/125 Paternal line: Cases: 128/118 Controls: 128/126	Parent report	Doctor-diagnosed cancer at the mean age of 1.7 years	Age, socioeconomic status, mother's and father's educational level, history of the familial cancer syndrome and transplacental ionizing radiation
Neurodevelopmental disorders							
Golding 2017 [68]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: 14,062/10,025 Paternal line: 14,062/NR	Parent report during pregnancy	Autism diagnosis identified from sources such as mother report and educational system by age 16 years	Year of birth of the maternal grandmother, the ages of the grandparents when the study mother was born, the parity of the maternal grandmother, and mother's use of social housing, education, and locus of control

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Golding 2020 [70]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: NR/6,576 Paternal line: NR/5,393	Parent report during pregnancy	Intelligence quotient assessed by trained psychologists at age 8 and 15 years	Age of grandparent when parent was born, and ethnic background, education level and social class of grandparent
Gustavson 2017 [75]	Norway	Prospective cohort	Sampling method: general population Children born from all pregnant women in 1999-2008 in Norway	Maternal line: NR/82,944	Mother report at 18 gestational weeks	ADHD diagnosis records from the Norwegian Patient Registry at age 5–15 years	Maternal and paternal age, education, and ADHD symptoms, maternal (pre-pregnancy) and paternal BMI, maternal smoking and alcohol consumption during pregnancy and parity, child's birth year, and geographical region
Pembrey 2014 [50]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women who smoked during pregnancy in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: NR/1,163 Paternal line: NR/918	Parent report during pregnancy	Intelligence quotient assessed by trained psychologists at age 8 years	Child's gestational age, maternal age, parity, education, birth weight, alcohol use and housing tenure, and paternal smoking at the start of pregnancy

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Diseases of the visual system							
Williams 2019 [73]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: 14,062/6,995 Paternal line: 14,062/4,099	Parent report during pregnancy	Early-onset myopia assessed by study staff at age 7 years	Grandparents' birth year, ethnicity, education, age at birth of parent and social group, grandmother's parity, and maternal vision impairments
Disorders of hearing							
Hall 2020 [71]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: 14,062/6,657 Paternal line: 14,062/4,075	Parent report during pregnancy	Intolerance to loud sound determined through parental questionnaire at ages 6 and 13 years	Year of birth of each grandparent, age of grandfather at birth of the parent, and ethnic origins of both grandparents
Nutritional disorders							
Ding 2017 [49]	USA	Prospective cohort	Sampling method: all children Children born from women who participated in Nurses' Health Study II (the Growing Up Today Study 2)	Maternal line: 10,907/6,583	Grandmother report	Grandchild-reported weight and height (used for determining overweight/obesity and BMI) at age 17–22 years	Grandmother's gestational age, age at birth, level of education, consumption of alcohol, vegetable, fruit and meat, physical activity and weight gain during pregnancy, and mothers' pre-pregnancy BMI, smoking during pregnancy, social-economic status, and diet score and physical activity during pregnancy

Table 1. Characteristics of observational epidemiologic studies investigating grandmaternal smoking during pregnancy and health outcomes in the grandchild (continued)

Study	Country	Study design	Participants		Exposure assessment	Outcome assessment	Confounding factors adjusted
			Sampling method, source	No. recruited/ analyzed			
Ding 2020 [54]	USA	Prospective cohort	Sampling method: all children Children born from women who participated in Nurses' Health Study II (the Growing Up Today Study 1 and 2)	Maternal line: 27,805/14,001	Grandmother report	Grandchild-reported weight and height (used for determining overweight/obesity and BMI) in adolescence and young adulthood	Grandmother's gestational age, age at birth, level of education, pre-pregnancy BMI, weight gain during pregnancy, diet quality score and physical activity
Dougan 2016 [53]	USA	Prospective cohort	Sampling method: all children Children born from women who participated in Nurses' Health Study II (the Growing Up Today Study 1)	Maternal line: NR/3,433	Grandmother report	Grandchild-reported weight and height (used for determining overweight/obesity) at ages 12 and 17 years	Grandmother's pre-pregnancy BMI, grandmother's age during pregnancy, grandmother's education at time of pregnancy, and child's age, television viewing, vigorous activity and Tanner stage of development
Golding 2014 [69]	UK	Prospective cohort	Sampling method: general population Children born from all pregnant women in southwest England with an expected delivery date between April 1, 1991 and December 31, 1992	Maternal line: 14,062/7,352 Paternal line: 14,062/5,994	Parent report during pregnancy	Weight, height, and BMI from 7 to 17 years of age, measured by study staff	Parity, maternal education, paternal smoking at the start of pregnancy, and housing tenure

Abbreviations: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; ECRHS, the European Community Respiratory Health Survey; MBHMS, the Michigan Bone Health and Metabolism Study; NR, not reported.

[a]Belgium, Denmark, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, and United Kingdom.

Figure 1. Flow diagram for study selection process

Figure 2. Quality appraisal by outcome presented as percentages across all included studies

Effects of grandmaternal smoking during pregnancy

In maternal line, 23 unique outcomes were reported from 24 study reports [47–50, 52–54, 68–84]. We conducted meta-analyses for birth weight, body mass index (BMI) after birth, overweight/obesity, and asthma. In paternal line, 12 unique outcomes were reported from 12 reports [47, 48, 50, 68–74, 78, 84], and meta-analysis was conducted for asthma.

Figure 3 summarizes the effects of maternal and paternal grandmaternal smoking on categorical outcomes in the grandchild. The effects on continuous outcomes are summarized in eFigure 2 in Additional file 2. Below we describe the main results for these outcomes. The effects of grandmaternal and maternal smoking in combination are described in eResults in Additional file 2. More detailed results are available in eTables 3 and 7 in Additional file 2.

Figure 3. Grandmaternal smoking during pregnancy and categorical outcomes in the grandchild

A. Maternal grandmaternal smoking. B. Paternal grandmaternal smoking. The effect estimates are for grandmaternal smoking compared to non-smoking regardless of maternal smoking status during pregnancy, unless otherwise indicated. The results for asthma and overweight/obesity are from robust random-effects meta-analysis. Abbreviations: Cc, case-control study; CI, confidence interval; Co, cohort study; NA, not available.

[a] Among grandchildren whose mothers did not smoke during pregnancy.

Diseases of the respiratory system

In maternal line, grandmaternal smoking was associated with a small increased risk of asthma (seven reports [47, 48, 52, 74, 77, 78, 82], 148,527 grandchildren, RR 1.10, 95% CI 1.02 to 1.18; Fig. 4A). In paternal line, no evidence of association was found for asthma (four reports [47, 48, 74, 78], 41,069 grandchildren, RR 1.01, 95% CI 0.85 to 1.19; Fig. 4B).

Figure 4. Grandmaternal smoking during pregnancy and asthma development in the grandchild

A. Maternal grandmaternal smoking. B. Paternal grandmaternal smoking. Abbreviations: CI, confidence interval; cigs, cigarettes; MGM+, maternal grandmaternal smoking during pregnancy; pres, prescriptions.

Disorders of newborn related to length of gestation or fetal growth

In maternal line, among grandchildren whose mothers did not smoke during pregnancy, grandmaternal smoking was associated with higher birth weight (four reports [49, 72, 76, 80], 19,478 grandchildren, MD (g) 40.04, 95% CI 22.60 to 57.49; eFigure 1 in Additional file 2); there was suggestive evidence that grandmaternal smoking was associated with a decreased risk of small birth weight for gestational age (one report [81], 14,558 grandchildren, RR 0.90, 95% CI 0.84 to 0.96; Fig. 3A), higher birth length (one report [72], 6,392 grandchildren, MD (cm) 0.19, 95% CI 0.02 to 0.35; eFigure 2A in Additional file 2) and higher BMI at birth (one report [72], 6,332 grandchildren, MD (g/m^2) 1.60, 95% CI 0.60 to 2.60; eFigure 2A in Additional file 2). No evidence of association was found for preterm birth, low birth weight, small birth length for gestational age, small head circumference for gestational age and head circumference at birth (Fig. 3A and eFigure 2A in Additional file 2). In paternal line, there was no evidence of association between grandmaternal smoking and birth weight, birth length, or BMI or head circumference at birth (eFigure 2B in Additional file 2).

Neoplasms

In maternal line, there was suggestive evidence that grandmaternal smoking was associated with increased risks of any cancer (one report [84], 241 grandchildren, RR 2.20, 95% CI 1.10 to 4.90; Fig. 3A) and acute lymphoblastic leukaemia (one report [84], 72 grandchildren, RR 3.00, 95% CI 1.10 to 8.80; Fig. 3A). No evidence of association was found for retinoblastoma (Fig. 3A). In paternal line, there was no evidence of association between grandmaternal smoking and cancer risk (Fig. 3B).

Neurodevelopmental disorders

In maternal line, there was suggestive evidence that grandmaternal smoking was associated with increased risks of ADHD (one report [75], 82,944 grandchildren, RR 1.22, 95% CI 1.09 to 1.36; Fig. 3A) and autism (one report [68], 10,025 grandchildren, RR 1.41, 95% CI 1.01 to 1.97; Fig. 3A). No evidence of association was found for IQ scores (eFigure 2A in Additional file 2). In paternal line, there was suggestive evidence that grandmaternal smoking was associated with lower IQ scores (one report [70], 5,406 grandchildren, MD -2.67, 95% CI -4.00 to -1.34; eFigure 2B in Additional file 2).

Diseases of the visual system

There was suggestive evidence that grandmaternal smoking was associated with a decreased risk of early-onset myopia in both maternal (one report [73], 6,995 grandchildren, RR 0.60, 95% CI 0.40 to 0.91; Fig. 3A) and paternal line (one report [73], 4,099 grandchildren, RR 0.47 95% CI 0.28 to 0.79; Fig. 3B).

Disorders of hearing

In paternal line, there was suggestive evidence that grandmaternal smoking was associated with a decreased risk of intolerance to loud sound (one report [71], 4,075 grandchildren, RR 0.81, 95% CI 0.65 to 0.99; Fig. 3B). No evidence of association was found in maternal line (Fig. 3A).

Nutritional disorders

In maternal line, there was no evidence of association between grandmaternal smoking and overweight/obesity (three reports [49, 53, 54], 24,017 grandchildren, RR 1.06, 95% CI 0.83 to 1.35; Fig. 3A). In both maternal and paternal line, no evidence of association was found for weight, height, and BMI after birth (eFigure 2 in Additional file 2).

Subgroup analyses

The subgroup results by maternal smoking status during pregnancy are presented in eFigures 3 and 4 in Additional file 2. In maternal line, the point estimates among grandchildren whose mothers smoked tended to point in an opposite direction from those among grandchildren whose mothers did not smoke for autism, birth weight, birth length, and BMI and head circumference at birth. In paternal line, a similar tendency was found for birth weight, birth length, BMI at birth, and height after birth.

The subgroup results by sex of the grandchild are presented in eTables 6 and 10 in Additional file 2. In maternal line, there was suggestive evidence that the effects of grandmaternal smoking were more pronounced in boys than in girls for birth weight, birth length, BMI at birth, autism and intolerance to loud sound. In paternal line, there was suggestive evidence that the effect on early-onset myopia was more pronounced in boys than in girls.

Discussion

Summary of key findings

In maternal line, grandmaternal smoking during pregnancy was associated with an increased risk of asthma and higher birth weight in the grandchild. There was suggestive evidence that maternal grandmaternal smoking was associated with increased risks of acute lymphoblastic leukaemia, any cancer, autism, and ADHD, decreased risks of early-onset myopia and small birth weight for gestational age, and higher birth length and BMI at birth. In paternal line, no evidence of association was found between grandmaternal smoking and asthma. There was suggestive evidence that paternal grandmaternal smoking was associated with lower IQ scores and decreased risks of early-onset myopia and intolerance to loud sound. Subgroup analyses suggested that some of the effects were more pronounced in boys than in girls.

Limitations

In epidemiologic studies, it is vital that confounders are identified and adjusted for in the analysis as this is fundamental to deliberations on causal inference [85]. However, identification of a sufficient set of confounders to adjust for can be particularly challenging in multigenerational studies [38, 86]. Together with the data availability issues, the difficulty in confounder selection probably led to the inconsistency that a wide range of variables were controlled for across the included studies. In addition, the sensitivity analysis for residual confounding suggested that the results were generally not robust to potential residual confounding. Second, controversy exists that some maternal variables (e.g., smoking during pregnancy, birth weight, asthma) may in fact be potential mediators of (part of) the association between grandmaternal smoking and (some) grandchild outcomes [52, 80, 87]. That is, if the analytical goal is to estimate the overall causal effects of grandmaternal smoking, adjustment for these variables would be unwarranted; and if the analytical goal is to estimate the direct causal effects, adjustment for them would not reduce confounding, but rather introduce selection bias, when there are unmeasured common causes of the adjusted variables and the outcomes [88]. For example, maternal smoking during pregnancy can arguably be a mediator on a causal pathway between grandmaternal smoking and some grandchild outcomes (e.g., birth weight, asthma) (eFigure 5 in Additional file 2) [80, 87]. Studies often stratified on or adjusted for maternal smoking during pregnancy. The interesting observation is that the point estimates for grandchild birth anthropometric measures (e.g., birth weight, birth length, BMI at birth) tended to point in an opposite direction between non-smoking and smoking mothers, suggesting that maternal smoking might qualitatively modify the effects of grandmaternal smoking on these outcomes. A similar phenomenon was reported in the so-called “birth weight paradox” [89], where studies investigated the effects of maternal smoking during pregnancy on infant mortality stratified on a potential mediator (birth weight), and found that maternal smoking was associated with higher mortality among normal-birth-weight infants, but lower mortality among low-birth-weight infants. Third, the measurement of the exposure and the confounders can be another important challenge in multigenerational studies. With the difficulty in long-term tracking of participants across generations, studies often had to rely on parental report of grandmaternal exposure and maternal proxies for grandmaternal characteristics, which is likely subject to measurement bias [90]. Fourth, for most of the outcomes, only one study existed in which multiple subgroup results were often reported. Given the potential limitations in the studies and/or multiple comparisons [91], these results are most appropriately viewed as hypothesis generation.

Epigenetic inheritance

It has been hypothesized that germline epigenetic inheritance may underlie the intergenerational transmission of the effects of maternal smoking during pregnancy [92]. Rat models found that perinatal nicotine exposure in F0 generation led to DNAm changes and histone modifications in the germ cells of F1 generation that will form F2 generation [40, 41]. Human epigenome-wide association studies reported that grandmaternal smoking during pregnancy was related to differential DNAm in the grandchild [43, 44]. In mammals, efficient epigenetic reprogramming occurs in the germline and in the early embryo to remove most of the epigenetic marks acquired during development or imposed by the environment [20]. Nevertheless, these studies provided evidence that some of the perinatal smoking/nicotine-induced epigenetic marks in F1 germ cells may escape the reprogramming and be transmitted to F2 generation. Importantly, epigenetic regulation is increasingly recognized to mediate at least in part the effects of maternal smoking during pregnancy [17, 18]. On the other hand, experimental animal evidence exists on the intergenerational transmission of perinatal nicotine-induced asthma and neurodevelopmental disorders (e.g., ADHD, autism). Perinatal nicotine exposure in F0 rats induced an asthma-like phenotype in F2 offspring [40, 42]. Nicotine exposure prior to and throughout breeding in F0 mice resulted in neurodevelopmental disorder-like phenotypes in F2 offspring, along with DNA hypomethylation in striatum and frontal cortex [93–95]. Taken together, the co-transmission of perinatal nicotine-induced epigenetic marks and some disease risks observed in rodent models as well as the potential role of epigenetic regulation in disease pathogenesis indicates that germline epigenetic inheritance may underlie the intergenerational effects.

Furthermore, perinatal nicotine exposure in F0 rats could even induce gonadal DNAm changes in F2 generation as well as an asthma-like phenotype in F3 generation [42, 96]. The potential transgenerational effects of maternal smoking during pregnancy have not been explored in epidemiologic studies. In mammals, it is generally thought that environmentally induced epigenetic changes are rarely transgenerationally inherited [20, 45]. Future animal studies are warranted to replicate these findings and elucidate the plausibility of transgenerational inheritance of perinatal nicotine-induced epigenetic marks.

Maternal smoking during pregnancy is associated with lower birth weight in the child, partly mediated through epigenetic regulation [2, 21–26]. However, we found that maternal grandmaternal smoking during pregnancy was associated with higher birth weight in the grandchild. To our knowledge, no animal models exist in this regard and the potential mechanisms are yet unknown. One possible conjecture is that under *in utero* smoking exposure (F0), the fetal environment could modify the development of the fetus (F1) and/or its germ cells to prepare the subsequent generation (F2) for a future smoking environment [20, 76]. Mechanistic studies are warranted to understand the potential mechanisms underlying the increased birth weight in the grandchild exposed to maternal grandmaternal smoking.

Implications

The degree to which the observed associations between grandmaternal smoking and grandchild outcomes reflect causal effects or are due to biases remains unclear. As discussed above, one possible explanation for the associations could be residual confounding or other biases in the design of existing studies. However, given the significant concern over the potential intergenerational transmission of the effects of maternal smoking during pregnancy, there is a need to raise public awareness that the adverse effects of smoking during pregnancy may not be limited to the exposed child, but be transmitted to the grandchild. In many countries, smoking during pregnancy remains an ongoing public health challenge [1]. There is a need to stimulate further public health efforts to enhance smoking cessation programs for pregnant women.

Further longitudinal multigenerational studies across different settings are warranted to strengthen the evidence. To handle confounding, investigators should explicitly specify the causal network linking the variables under investigation using their *a priori* subject-matter knowledge, which can intuitively be presented in a causal diagram (e.g., directed acyclic graph (DAG)) [86, 88]. The causal question that motivates the analytical approach should also be stated. It is worth noting that while identifying the direct causal effects of grandmaternal smoking may contribute to our understanding of the causal mechanisms for grandchild outcomes, from a public health perspective, the overall causal effects may be of greater interest [89]. Clarifying these aspects will help to provide a clearer framework for the interpretation and discussion of the results as well as for the evaluation of the proposed causal structures and analytical approaches. Further epigenetic research is needed to understand the potential role of germline epigenetic inheritance in the transmission of disease risks across generations.

Conclusions

Grandmaternal smoking during pregnancy, particularly from the maternal than paternal line, is a risk factor for multiple health outcomes in the grandchild, indicating a transmission of effects across generations. Germline epigenetic inheritance might explain these intergenerational effects. There is a need for further public awareness on the intergenerational adverse effects of maternal smoking during pregnancy, which should inform smoking cessation programs for pregnant women.

Abbreviations

ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CI, confidence interval; DNAm, DNA methylation; EPHPP, the Effective Public Health Practice Project; IQ, intelligence quotient; MD, mean difference; PECOS, Population, Exposure, Comparator, Outcome, Study design; PROSPERO, the International Prospective Register of Systematic Reviews; RR, risk ratio; RVE, robust variance estimation.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the Open Science Framework repository, https://osf.io/hav3t/?view_only=0c4f6c44aa994b0291cb7923bd5b633e.

Competing interests

HK reports personal fees and non-financial support from AstraZeneca, personal fees from Chiesi Pharma AB, personal fees and non-financial support from Boehringer-Ingelheim, personal fees from Novartis, personal fees from Mundipharma, personal fees and non-financial support from Orion Pharma, personal fees from SanofiGenzyme, personal fees from GlaxoSmithKline, outside the submitted work. All other authors have declared that no competing interests exist.

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Authors' contributions

AS and BIN conceived the study. BIN performed the database searches. GQZ, YL, and BIN performed literature screening. GQZ, YL, and HHZ extracted data from the included studies and assessed study quality. GQZ performed the statistical analyses. GQZ and YL drafted the manuscript. All authors interpreted the results and critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

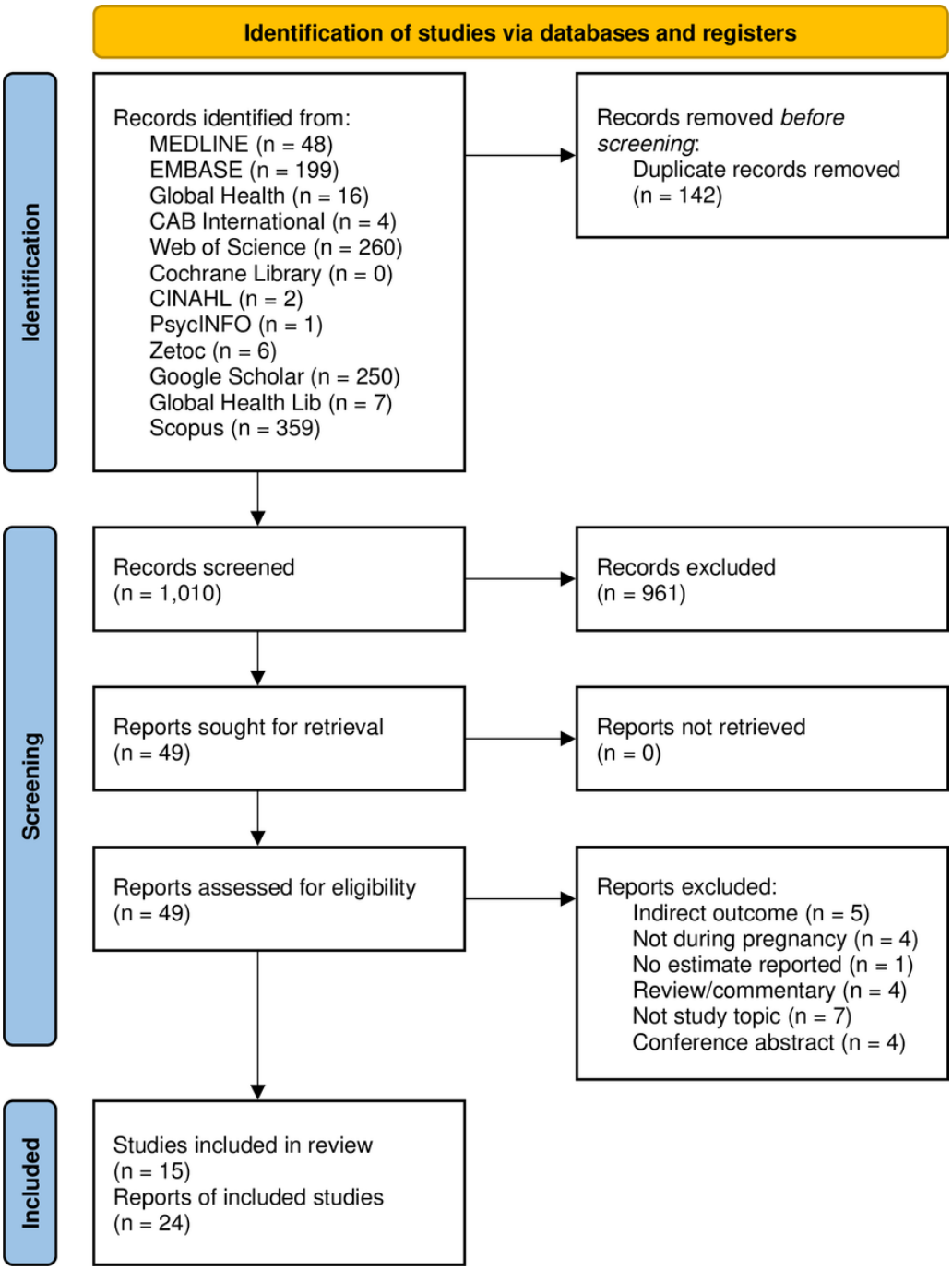


Figure 1

Flow diagram for study selection process

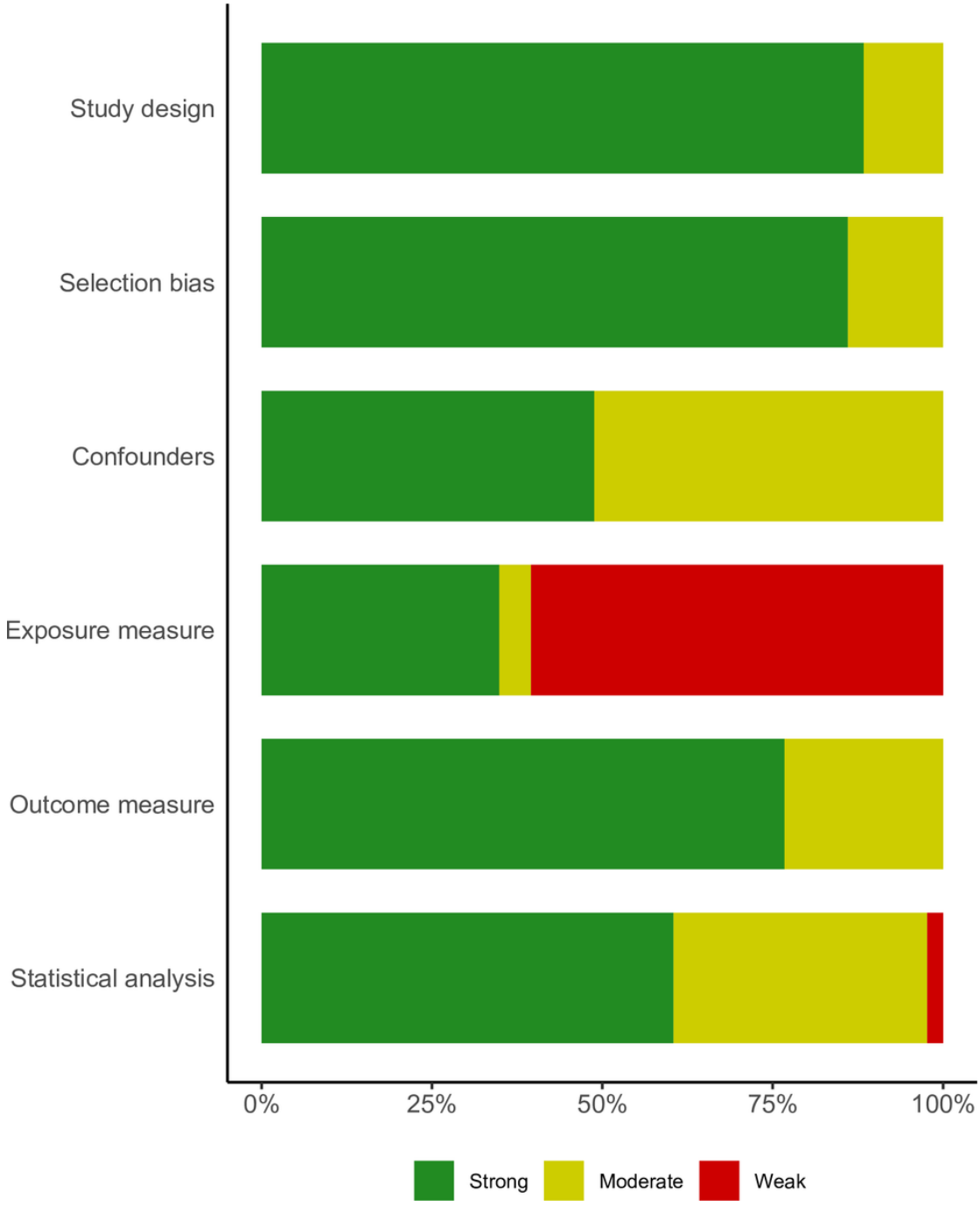
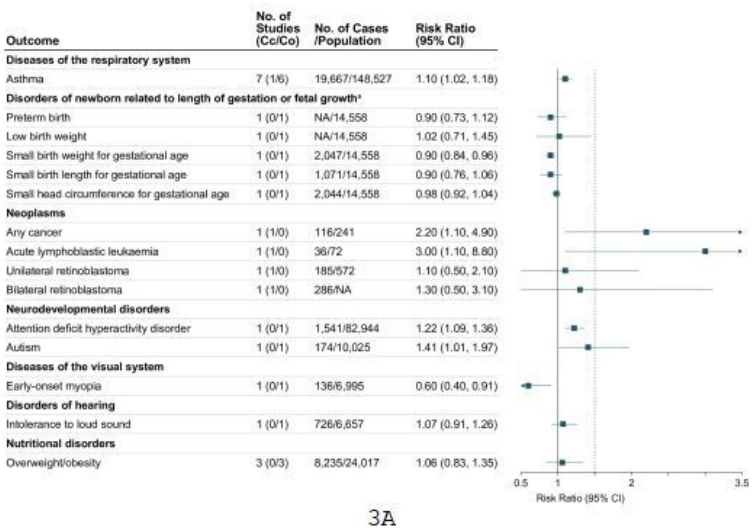


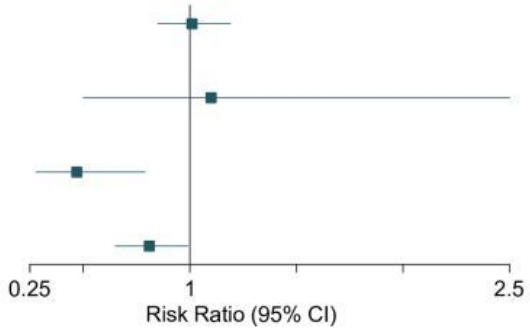
Figure 2

Quality appraisal by outcome presented as percentages across all included studies



3A

Outcome	No. of Studies (Cc/Co)	No. of Cases /Population	Risk Ratio (95% CI)
Diseases of the respiratory system			
Asthma	4 (0/4)	5,295/41,069	1.01 (0.85, 1.19)
Neoplasms			
Any cancer	1 (1/0)	118/244	1.10 (0.50, 2.50)
Diseases of the visual system			
Early-onset myopia	1 (0/1)	113/4,099	0.47 (0.28, 0.79)
Disorders of hearing			
Intolerance to loud sound	1 (0/1)	444/4,075	0.81 (0.65, 0.99)



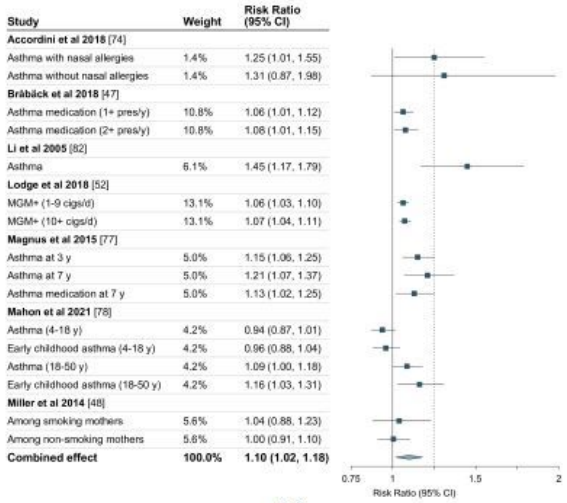
3B

Figure 3

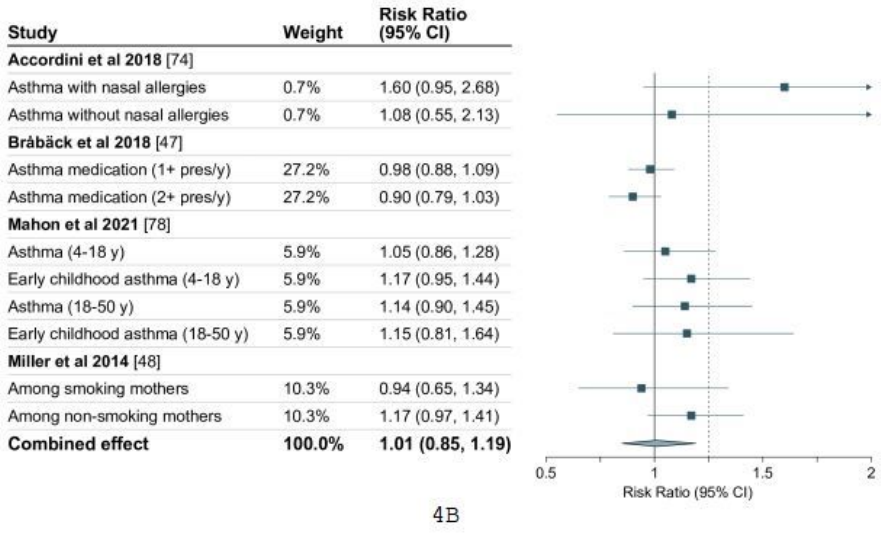
Grandmaternal smoking during pregnancy and categorical outcomes in the grandchild

A. Maternal grandmaternal smoking. B. Paternal grandmaternal smoking. The effect estimates are for grandmaternal smoking compared to non-smoking regardless of maternal smoking status during pregnancy, unless otherwise indicated. The results for asthma and overweight/obesity are from robust random-effects meta-analysis. Abbreviations: Cc, case-control study; CI, confidence interval; Co, cohort study; NA, not available.

[a] Among grandchildren whose mothers did not smoke during pregnancy.



4A



4B

Figure 4

Grandmaternal smoking during pregnancy and asthma development in the grandchild

A. Maternal grandmaternal smoking. B. Paternal grandmaternal smoking. Abbreviations: CI, confidence interval; cigs, cigarettes; MGM+, maternal grandmaternal smoking during pregnancy; pres, prescriptions.

Supplementary Files

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