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The effect of maternal prenatal tobacco smoking on offspring academic achievement: A systematic review and meta-analysis

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ABSTRACT

Background: Previous epidemiological studies examining the prospective association between maternal prenatal tobacco smoking and offspring academic achievement have reported conflicting results. Therefore, this systematic review and meta-analysis was conducted to examine the magnitude and consistency of association reported by those studies.

Methods: This systematic review and meta-analysis was guided by the PRISMA protocol. Relevant epidemiological studies on the topic were extracted from four main databases (PubMed/Medline, Embase, PsycINFO, and Scopus). The Newcastle-Ottawa Scale (NOS) was used to appraise the methodological quality of the included studies. We conducted a narrative assessment of the studies that did not report effect estimates. Inverse variance-weighted random effect meta-analysis was used to combine studies reporting effect sizes to estimate pooled adjusted odds ratio with 95% confidence intervals (95% CI). The review was prospectively registered in PROSPERO (CRD42022350901).

Results: Nineteen observational studies, published between 1973 and 2021 with a total of 1.25 million study participants were included in the final review. Of these, fifteen studies (79 %) reported reduced academic achievement in offspring exposed to maternal prenatal tobacco smoking. The eight primary studies (sample size = 723,877) included in the meta-analysis together suggested a 49 % higher risk of reduced academic achievement in offspring exposed to maternal prenatal tobacco smoking when compared to non-exposed offspring (Pooled odds ratio = 1.49, 95 % CI:1.17–1.91).

Conclusion: Our review found a positive association between maternal prenatal tobacco smoking and offspring reduced academic achievement. However, variation in the adjustment of potential confounders and significant heterogeneity across included studies limited more conclusive inference. Mechanistic studies to identify causal pathways and specific academic impacts are needed to inform targeted developmental programs to assist child learning and academic performance.

1. Background

Tobacco smoking remains a pervasive global public health concern, claiming the lives of approximately 8 million people annually and resulting in an estimated 229.77 million Disability Adjusted Life Years (DALYs) in 2019 (Murray et al., 2020). Recent data from the World

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Health Organization (WHO) underscore the alarming prevalence of smoking among women, with nearly 7 % reporting daily smoking in 2020 (Reitsma et al., 2021). This issue is particularly concerning during pregnancy, as approximately 2 % of pregnant women worldwide reported smoking tobacco in 2018 (Lange et al., 2018). These statistics highlight the urgent need for targeted interventions and policy initiatives to address tobacco use and its detrimental impact on public health.

Tobacco smoke comprises about 7000 hazardous compounds, many of which affect the development of the fetus (Benjamin, 2011; Wehby et al., 2011). Maternal prenatal tobacco smoking has been associated with increased risks of stillbirth (Marufu et al., 2015), preterm birth, low birthweight (Soneji & Beltrán-Sánchez, 2019), and poorer neurodevelopment (Wehby et al., 2011). It is also linked with adverse mental health outcomes and behavioral problems in offspring (Duko et al., 2020, 2021). There is compelling, although not conclusive, epidemiological evidence that suggests a prospective association between maternal prenatal tobacco smoking and a higher risk of delinquent behaviors in adolescents and young adults (Dürr et al., 2015; Cornelius et al., 2012). These behaviors, in turn, could lead to reduced academic achievement (Lau & Leung, 1992). Clear identification of the longer-term impacts for children prenatally exposed to tobacco is important to comprehensively elucidate the harms of smoking in pregnancy.

The extent to which early life adverse events, such as prenatal tobacco smoking, contribute to reduced academic achievement is not fully understood. Findings from available epidemiological studies suggest that offspring exposed to maternal prenatal tobacco smoking may experience lower academic achievement compared to non-exposed offspring (Ayano et al., 2021; O'Callaghan et al., 2010; Kristjansson et al., 2017). For instance, a study of 168,528 mother-offspring pairs from New South Wales, Australia reported higher risks of substandard academic performance in all domains investigated – spelling, writing, reading, and numeracy (Ayano et al., 2021). However, some studies did not observe such association (Collins et al., 2007; Fergusson and Lloyd, 1991). Notably, a population-based longitudinal study study conducted in the U.K. (n = 6,380) found insufficient statistical evidence to support associations between maternal prenatal tobacco exposure and offspring academic achievement (Collins et al., 2007).

A previous literature review of observational studies published until 2011 found only three studies suitable for inclusion and reported a positive association between prenatal maternal tobacco smoking and reduced academic achievement (Clifford et al., 2012). Over the past decade, there has been a considerable increase in the number of studies on similar topics and as a result, an update of the existing evidence by systematic review and meta-analysis is warranted. The aim of this study was to conduct a systematic review and meta-analysis to determine the magnitude and consistency of the association between maternal prenatal tobacco smoking and offspring academic achievement.

2. Methods

2.1. Study design

This systematic review and meta-analysis was guided by the methodological framework indicated in the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2015) (Supplementary file 1). The literature search strategy, identification of the relevant studies, data extraction and synthesis were conducted in accordance with a pre-defined review protocol. The protocol for this systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number of CRD42022350901.

2.2. Database search and extraction

We conducted comprehensive systematic database searches on PubMed/Medline, Embase, PsycINFO, and SCOPUS to identify relevant articles on the topic. Search terms #1("prenatal" OR "antenatal" OR "pregnancy" OR "pregnant" OR "expectant") AND #2("tobacco" OR "tobacco exposure" OR "cigarette" OR "cigarette smoking") AND #3 ("offspring" OR "adolescents" OR "youths" OR "young" OR "children" OR "childhood") AND #4("academic performance" OR "school performance" OR "academic difficulties" OR "academic achievement" OR "scholastic achievement" OR "intellectual performance" OR "Educational achievement" OR "Educational attainment"). We also explored reference lists of included original studies. We screened the retrieved articles based on their contents in the title, abstract and full text. AB commenced the primary study search and selection. BD further checked the eligibility of full-text articles for inclusion. Full-text articles were reviewed by two independent reviewers. A third author resolved any conflicting scoring through discussion. We used a pre-designed specific form to facilitate extraction of data from the eligible studies. The following data were extracted from each research article: study name, country in which study originated, year of publication, study population characteristics, study design, sample size, study setting, and criteria used to classify prenatal tobacco smoking and offspring academic performance and a list of the control variables employed in the study. The comprehensive search was conducted in November 2022.

2.3. Eligibility criteria

Studies that met the following population, intervention/exposure, comparison, outcome, and study design (PICOS) criteria were used. Studies included in the review if; (1) the participant/population was offspring born to women with a term pregnancy, (2) the intervention/exposure group was offspring exposed to maternal prenatal tobacco smoking, (3) the comparison group was offspring not exposed to maternal prenatal tobacco smoking, (4) the outcome of interest was offspring's poor academic achievement that can also be described as poor school performance, educational achievement, scholastic achievement, reduced course proficiency score or academic difficulties, and (5) studies conducted using cohort, case-control, nested case-control, or cross-sectional study designs.

Non-peer-reviewed articles (but not grey literature), editorials, case reports, commentaries, and abstracts of conference proceedings were excluded. The eligibility of studies was screened by two independent reviewers (AB and BD).

2.4. Quality appraisal

The quality appraisal of the included studies was conducted using the Newcastle-Ottawa scale (NOS) (Wells et al., 2000). The NOS is a validated quality appraisal tool for observational studies with grade scores ranging from 0 to 10 for cross-sectional and 0–9 for case-control and cohort studies (Luchini et al., 2017). The tool has three components: selection, comparability, and outcome/exposure. The selection component of NOS grade graded from zero to five stars for cross-sectional studies and zero to four stars for cohort and case-control studies. The detailed scoring techniques have been described elsewhere (Luchini et al., 2017; Moskalewicz and Oremus, 2020).

2.5. Study outcome

The outcome of interest was academic achievement. Academic achievement included academic performance/achievement, intellectual performance, scholastic achievement, and academic proficiency score in specific subjects.

2.6. Data analysis

First, we conducted a narrative data synthesis as many of the studies used different statistical methods, did not report quantitative result or effect sizes (e.g., odds ratio (OR), relative risk (RR), hazard ratio (HR) or

provided data to calculate these). A narrative synthesis was conducted using the 'Conduct of Narrative Synthesis in Systematic Reviews' method (Popay et al., 2006). Studies that reported effect estimates using OR, RR or presented data to calculate these were included in the meta-analysis. If studies reported individual outcomes and aggregated outcomes (e.g., academic achievement), aggregated outcome was considered for a meta-analysis. For those two studies that did not report risk estimates for whole pregnancy period, the risk estimates for the first trimester (Lundberg et al., 2010) and second trimester (Collins et al., 2007) were included in the meta-analysis. For the remaining six studies, risk estimates for whole pregnancy period were included in the meta-analysis. Heterogeneity across included studies was examined using Q- and I^2-statistics (Borenstein et al., 2010). We did not check the influence of publications bias as such methods are unreliable when combining fewer than ten primary studies in a meta-analysis (Egger et al., 1997). Further, to explore the possible sources of heterogeneity we employed a random-effect univariate meta-regression model considering the sample size, publication year, and NOS quality score as moderators. STATA version 16.1 was used to perform the meta-analysis.

3. Results

3.1. Identification of studies

The literature search on PubMed/Medline, EMBASE, PsycINFO and SCOPUS databases retrieved 6709 articles (Fig. 1). A total of 6624 research articles were excluded as they were found to be duplicates or unrelated to the topic of interest. Of the remaining 85 articles for full-text review, 66 were further excluded as they did not meet the pre-defined inclusion criteria and then 19 articles remained for the final review. However, eight articles were identified as suitable for a meta-analysis (Ayano et al., 2021; O'Callaghan et al., 2010; Collins et al.,

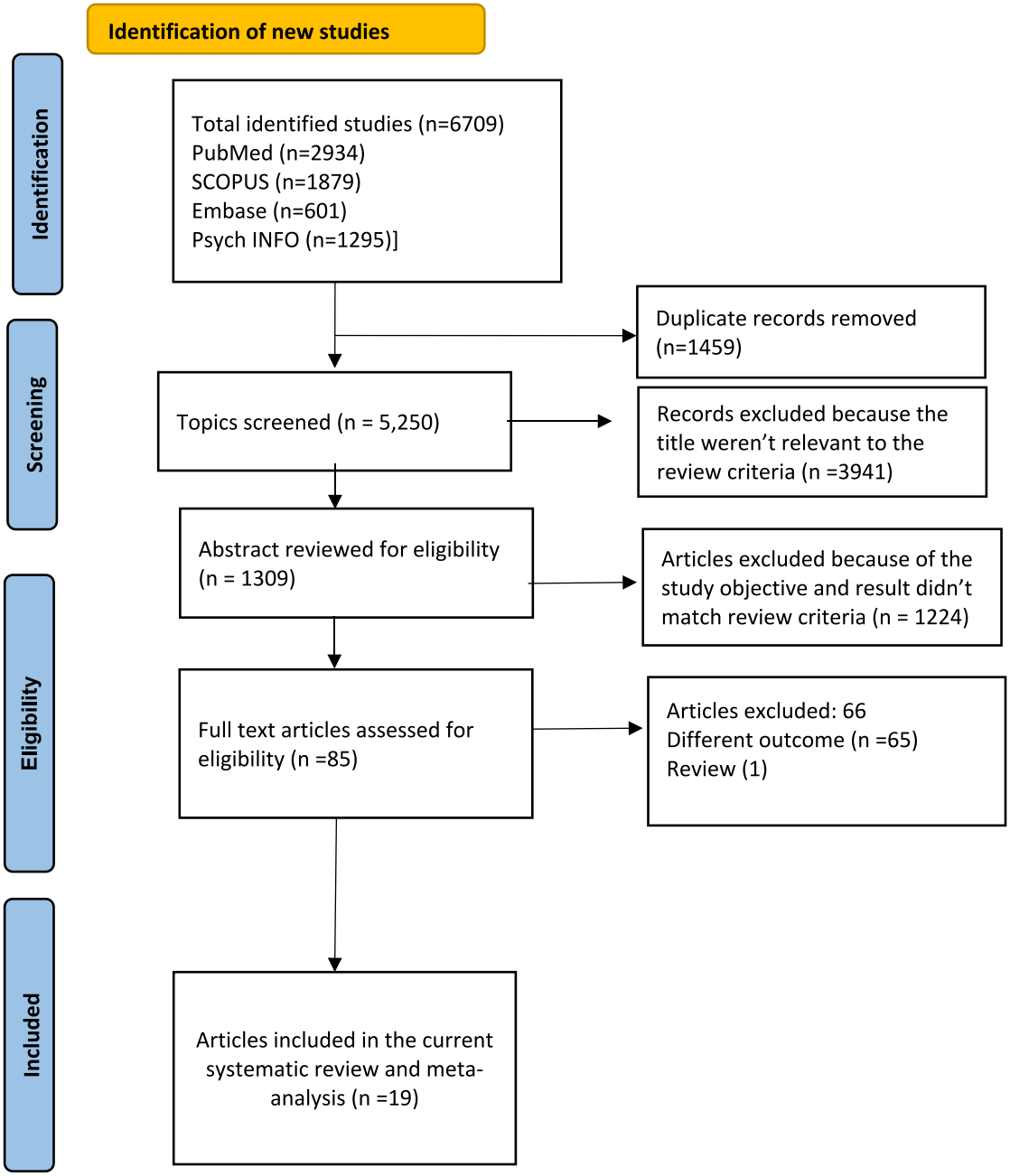

Fig. 1. PRISMA flow chart of the study identification process.

2007; Lundberg et al., 2010; Lambe et al., 2006; Anderko et al., 2010; Agrawal et al., 2010; Batstra et al., 2003).

3.2. Characteristics of included studies

All primary studies included in the systematic review were published between 1973 and 2021 and had a total of 1.25 million study participants (Table 1). Of the 19 studies, four studies each were conducted in the UK (Collins et al., 2007; Fogelman, 1980; Fogelman and Manor, 1988; Butler and Goldstein, 1973) and US (Anderko et al., 2010; Agrawal et al., 2010; Gilman et al., 2008; Batty et al., 2006), three in Sweden (Lundberg et al., 2010; Lambe et al., 2006; D'Onofrio et al., 2010); two studies each in Australia (Ayano et al., 2021; O'Callaghan et al., 2010) and Finland (Rantakallio, 1983; Martin et al., 2006), and one study each in Canada (Fried et al., 2003), Iceland (Kristjansson et al., 2018); New Zealand (Fergusson & Lloyd, 1991) and the Netherlands (Batstra et al., 2003). Sixteen studies included in our review were population-based studies and all the studies used maternal self-report to ascertain prenatal tobacco smoking status. Twelve studies (64 %) reported risk estimates for whole pregnancy tobacco exposure, four reported estimates for first trimester exposure and three reported for second trimester exposure. Statistical control for potential confounders and covariates varied throughout the included studies (Fig. 2).

3.3. Outcome measures

Out of 19 studies included in the systematic review: Wide Range Achievement Test (WRAT) was used in two studies; reading and mathematics test scores in three studies, National Assessment Program -Literacy and Numeracy (NAPLAN) test in one study, tool developed by Iceland Educational Testing Institute in one study, self-report of consistently receiving C's or lower grade in school in one study, grade-point summary score for 16 subjects in grade 9 in one study, composite learning scores in one study, Swedish conscript register in one study, nationally standardised achievement tests in one study, the sum of the numerical value of school grades in 16 subjects in one study, the numerical mean of all school grades received over the past year in selected subjects in one study, Peabody Individual Achievement Test (PIAT) in one study, short standardised Dutch Tests in one study, Progressive Achievement test in one study and self-reported school grade levels in three studies were used to ascertain academic achievement in offspring. Academic achievement was ascertained in offspring between ages 4 and 16 years in fourteen studies (Ayano et al., 2021; O'Callaghan et al., 2010; Fergusson and Lloyd, 1991; Lambe et al., 2006; Anderko et al., 2010; Batstra et al., 2003; Fogelman, 1980; Butler and Goldstein, 1973; Gilman et al., 2008; D'Onofrio et al., 2010; Rantakallio, 1983; Martin et al., 2006; Fried et al., 2003; Kristjansson et al., 2018) whereas the remaining five studies examined offspring for academic achievement at ages between 17 and 32 years (Collins et al., 2007; Lundberg et al., 2010; Agrawal et al., 2010; Fogelman and Manor, 1988; Batty et al., 2006) (Table 1).

3.4. Methodological quality of studies

Of studies included in the current review, six studies scored 9 on the NOS scale, seven studies scored eight and six studies scored seven (Supplementary file 2). Based on the methodologic quality appraisal, if an article gets a NOS score of six or more, it can be considered as high-quality research output with low risk of bias (Wells et al., 2000).

3.5. Systematic review findings

Fifteen studies reported a positive association between maternal prenatal tobacco smoking and reduced offspring academic achievement while the other four studies reported insufficient statistical evidence for an association (Table 1). For instance, findings from the two population-based prospective epidemiological studies from Iceland suggested that offspring exposed to maternal prenatal tobacco smoking was associated with 5–7 % lower scores on standardized academic achievement in the 4th, 7th, and 10th grades at ages between 10 and 16 years (Kristjansson et al., 2017) and lower academic achievement in mathematics courses (Kristjansson et al., 2018). These were corroborated by findings from the two population-based studies from Finland that reported lower mean ability on theoretical subjects at the age of 14 years (Rantakallio, 1983) and significantly lower grade performance at the age of 12 years (Martin et al., 2006) in offspring exposed to maternal prenatal tobacco smoking when compared to non-exposed. A similar observation was also reported in a prospective cohort study in the US that used existing data from the Collaborative Perinatal Project (CPP) (n = 4,827), suggesting that maternal prenatal tobacco smoking was associated with offspring reduced academic achievement on reading, spelling and arithmetic at the age of 7 years (Gilman et al., 2008). Further, findings from the National Child Development Study (NCDS) based in the UK indicated that maternal prenatal tobacco smoking was related to child's reduced reading and mathematics attainment at the age of 16 (Fogelman, 1980; Fogelman and Manor, 1988). Few epidemiological studies reported offspring outcome specific associations. For instance, a Dutch-based prospective cohort study that utilised data from the Groningen Perinatal Project (GPP) (n = 1181, aged 5.5–11 years) demonstrated that maternal prenatal tobacco smoking was linked to worse performance on the mathematics and spelling tests but not significantly linked to offspring reading performance after adjusting for potential confounders such as social and economic state, civil state of the parents, maternal sociodemographic factors, medication use during pregnancy, type of feeding, birth weight, and age of the child during follow-up (Batstra et al., 2003). Moreover, a Swedish population-based study reported similar observations (D'Onofrio et al., 2010). Nonetheless, a few studies reported no evidence of an association (Collins et al., 2007; Fergusson and Lloyd, 1991; Batty et al., 2006; Fried et al., 2003). For instance, results from a longitudinal analysis of birth cohort data of 6,380 mother-offspring pairs from the 1958 National Child Development Study (NCDS) did not detect an association between maternal prenatal tobacco exposure and offspring academic performance at age 23 years (Collins et al., 2007).

3.6. Meta-analysis

We conducted a random effect meta-analysis of eight epidemiological studies that examined the effect of maternal prenatal tobacco smoking on offspring academic achievement (Ayano et al., 2021; O'Callaghan et al., 2010; Collins et al., 2007; Lundberg et al., 2010; Lambe et al., 2006; Anderko et al., 2010; Agrawal et al., 2010; Batstra et al., 2003). Studies included in the meta-analysis had a total of 723,877 study participants. Findings from a meta-analysis suggested that offspring exposed to maternal prenatal tobacco smoking had 50 % higher risk of reduced academic achievement when compared to non-exposed offspring (Adjusted odds ratio = 1.49, 95 % CI:1.17–1.91) (Fig. 3). We observed a considerable heterogeneity between studies included in the meta-analysis (I^2 = 99 %; P < 0.000).

The analysis of a random-effect univariate meta-regression model, employed to identify the possible source of heterogeneity, found that none of the variables (i.e., sample size (Coefficient = 1.80, P = 0.175), publication year (Coefficient = 0.112, P = 0.071), and NOS quality score (Coefficient = 0.128, P = 0.633)) have detectable significant linkage with heterogeneity.

4. Discussion

The objective of this study was to thoroughly examine the magnitude and consistency of association reported by 19 epidemiological studies examining the effect of maternal prenatal tobacco smoking on reduced academic achievement among offspring. With the exception of four

Table 1
Characteristics of studies included in the current systematic review and meta-analysis.

Study name	Country	Sample size	Study design/cohort name	Prenatal tobacco smoking ascertained	Offspring outcome	Offspring outcome ascertained by	Effect size (Adjusted odds ratio) (AOR, 95 %CI)
Ayano et al. (2021)	Australia	168,528	Register-based cohort study/used linked data from New South Wales educational and health registries in Australia	Self-report (whole pregnancy)	Academic performance at age 14 years (categorical outcome)	National Assessment Program – Literacy and Numeracy test (NAPLAN) was used to assess the educational performance	2.87 (2.74–2.99)
Kristjansson et al. (2017)	Iceland	1,150	Prospective cohort study/Life course study)	Self-report (first trimester)	Academic achievement at age between 10 and 16 years (continuous outcome)	Academic achievement tool developed by the Iceland Educational Testing Institute (ETI) under the Ministry of Education, Science, and Culture	Effect estimates were not reported. At 4th grade (B = −5.79, $p < 0.05$), 7th grade (B = −5.98, $p < 0.01$) and 10th grade (B = −6.22, $p < 0.05$).
Agrawal et al. (2010)	USA	1342	Prospective cohort/ part of offspring-of-twins (OOT) studies project	Self-report (Whole pregnancy)	Academic achievement at age 12–32 years (categorical outcome)	Academic achievement was ascertained by self-report of consistently receiving C's or lower grades in school.	1.41 (1.01–1.97)
Anderko et al. (2010)	USA	5420	Cross-sectional survey/	Self-report (whole pregnancy)	Academic difficulty at ages between 4 and 15 years (categorical outcome)	Self-report	1.6 (1.1–2.6)
D'Onofrio et al. (2010)	Sweden	654,707	Quasi-experimental design/a Swedish population-based study	Self-report (Whole pregnancy)	Academic achievement at age 15 years (Mathematics Proficiency score) (continuous outcome)	Mathematics proficiency score was assessed by a grade-point summary score for 16 subjects in grade 9 (pass = 10; pass with distinction = 15 and pass with honours = 20).	Effect estimates were not reported.
O'Callaghan et al. (2010)	Australia	4294	Prospective cohort/ Mater University of Queensland Study of Pregnancy	Self-report (Whole pregnancy)	School performance at age 14 years (categorical outcome)	Composite learning scores (Mothers and adolescents completed learning questionnaires)	1.35 (1.07–1.70)
Lundberg et al. (2010)	Sweden	161, 048	Prospective cohort /Data from population-based registers	Self-report (first trimester).	Academic performance at age 18 years (categorical outcome)	The Swedish Conscript Register (this tool has four dimensions: logical/ inductive, verbal, spatial, theoretical, or technical; each contains 40 questions for every four dimensions contains 40 questions)	1.25 (1.18–1.33)
Gilman et al. (2008)	USA	4827	Prospective cohort study/Collaborative Perinatal Project (CPP).	Self-report (Whole pregnancy).	Academic performance at age 7 years (continuous outcome)	Wide Range Achievement Test (WRAT) was used to measure academic performance	Academic achievement at age of seven years (reading: $\beta = -1.41$, Spelling: $\beta = -0.99$, arithmetic: $\beta = -0.25$. Heavy maternal prenatal tobacco exposure was associated with reduced academic achievement.
Collins et al. (2007)	UK	6,380	Prospective cohort study/The 1958 NCDs	Self-report (second trimester)	Academic achievement at age 23 years (categorical outcome)	Nationally standardised achievement tests result was used.	0.82 (0.62–1.08)
Lambe et al. (2006)	Sweden	375,679	Prospective cohort/ Extracted data from population-based registers.	Self-report (Whole pregnancy)	Academic achievement at age 15 years (categorical outcome)	Poor school performance was calculated as the sum of the numerical value of school grades in 16 subjects.	1.58 (1.53–1.62)
Martin et al. (2006)	Finland	676	Prospective cohort/ Helsinki Longitudinal Project	Self-report (whole pregnancy)	Academic achievement at age 12 years (continuous outcome)	The numerical mean of all school grades received over the past year on science, language arts, and mathematics scored out of 10.	Effect estimates were not reported. Offspring exposed to prenatal tobacco smoke had significantly lower grade performance compared to those who were not exposed.
Batty et al. (2006)	USA	5578	Prospective longitudinal study /National Longitudinal Survey of Youth 1979	Self-report (Whole pregnancy)	Academic achievement at ages between 14 and 21 years (continuous outcome)	Peabody Individual Achievement Test was used to measure mathematics skills, reading comprehension, and reading recognition.	Effect estimates were not reported. Maternal prenatal tobacco exposure was not associated with reduction in academic achievement.
Fried et al. (2003)	Canada	145	Prospective cohort/ Ottawa Prenatal Prospective Study	Self-report (whole pregnancy)	Academic achievement at ages 13 and 16 years (continuous outcome)	Wide Range Achievement Test (WRAT) was used to measure reading, spelling, and arithmetic skills	Effect estimates were not reported. Prenatal tobacco exposure was not associated with WRAT

(*continued on next page*)

Table 1 (*continued*)

Study name	Country	Sample size	Study design/cohort name	Prenatal tobacco smoking ascertained	Offspring outcome	Offspring outcome ascertained by	Effect size (Adjusted odds ratio) (AOR, 95 %CI)
							reading and arithmetic skills.
Batstra et al. (2003)	Netherlands	1186	Prospective cohort study/Groningen Perinatal Project	Self-report (Whole pregnancy)	Academic achievement at ages > 6 and <11 years (Mathematics, spelling and reading performance) (categorical outcome)	Academic achievement was ascertained by short standardised Dutch tests	Maternal smoking was significantly linked to worse performance in mathematics. Reading skill was not associated (AOR = 1.06 (0.30, 1.82).
Fergusson and Lloyd (1991)	New Zealand	1265	Prospective cohort study/Christ church Child Development Study.	Self-report (Whole pregnancy)	Academic achievement at ages between 8 and 12 years (continuous outcome)	Progressive Achievement Tests (PAT) and the New Zealand revision of the Burt word reading test were used to measure reading comprehension and mathematical ability and word recognition, respectively.	Effect estimates were not reported. No detectable significant association between prenatal tobacco smoking and word recognition at 8, 10, and 12 years (all p > 0.05).
Fogelman and Manor (1988)	UK	8,305	Prospective follow-up study/National Child Development Study	Self-report (2nd & 3rd trimesters)	Academic achievement at age of 23 years (Reading and mathematics test score (23 years) (continuous outcome)	Academic achievement was ascertained using 1–4 ordinary level grade (from grade A–C) score on reading and mathematics test.	Effect estimates was not reported. Offspring exposed to prenatal tobacco smoking showed a slight reduction in educational achievement (mathematics score) among those whose mothers had smoked 10 or more cigarettes/day during pregnancy.
Rantakallio (1983)	Finland	2823	Prospective cohort/ population-based cohort	Self-report (first trimester)	Academic achievement at age 14 years (continuous outcome)	Based on a report from children's school performance.	Effect estimates were not reported. Children exposed to prenatal tobacco smoking had poor mean ability in theoretical subjects at school than children of non-smokers.
Fogelman (1980)	UK	5910	Prospective follow-up study/National Child Development Study	Self-report (after 2nd trimester)	Academic achievement at age of 16 yearswas ascertained by reading and mathematics test score (16 years) (categorical outcome)	Reading and mathematics test scores were examined using a 35 and 31-item test constructed by the NFER.	The effect of prenatal tobacco smoking effect on reading (X^2 = 34.8, P < 0 001) and mathematics attainment in offspring (X^2 = 34.8, P < 0 001).
Butler and Goldstein (1973)	UK	1489	Prospective follow-up study/National Child Development Study	Self-report (After 2nd trimester)	Academic achievement at age 11 years (Reading comprehension & mathematics ability) (categorical outcome)	Reading and mathematics test scores were used to ascertain academic achievement.	Children of mothers who smoked ten or more cigarettes a day are retarded on reading, mathematics ability compared with the Offspring of non-smokers (X^2 = 230: P < 0 001), mathematics (X^2 = 59.6, P < 0.001).

studies (Collins et al., 2007; Fergusson and Lloyd, 1991; Batty et al., 2006; Fried et al., 2003), the remaining epidemiological studies included in the systematic review demonstrated a detrimental effect of maternal prenatal tobacco smoking on offspring academic achievement. Furthermore, a meta-synthesis of the results of eight epidemiological studies that reported effect estimates, in the form of odds ratio, showed a higher risk of reduced academic achievement in offspring exposed to maternal prenatal tobacco smoking compared to non-exposed offspring.

The association between maternal prenatal tobacco smoking and offspring reduced academic achievement is not yet confirmed. However, several plausible biological mechanisms have been proposed. One of the proposed mechanisms is that maternal tobacco smoking during pregnancy could limit the supply of fetal and placental nutrients and oxygen, which could, in turn, adversely affect the fetus's brain development (Dempsey and Benowitz, 2001; Mezzacappa et al., 2011). Further, evidence from some epidemiological studies has also suggested that maternal prenatal tobacco smoking may cause fetal hypoxic stress (D'Onofrio et al., 2010), and a disruption in protein synthesis, amino acid transportation, and enzyme activity, which have a long-term effect on brain development (Dempsey and Benowitz, 2001; Jauniaux et al., 2001). Furthermore, tobacco smoke ingredients contain several hazardous compounds that can easily pass through the placenta (Dempsey & Benowitz, 2001) and disrupt the neurotransmitters and the levels of receptors in the fetal brain (Roy et al., 2002; Slotkin et al., 2006; Slotkin, 2004). These neurotransmitters play a crucial role in the development of offspring's memory, learning and cognitive ability (Hasselmo, 2006; Levey, 1996).

There is also compelling evidence that suggests there is a prospective association between maternal prenatal tobacco smoking and epigenetic modifications such as DNA methylation in the offspring (Stroud et al., 2014; Gao et al., 2015). This is corroborated by findings of a recent meta-analysis that synthesized the results of sixteen prospective cohort studies examining genome-wide DNA methylation in offspring exposed to maternal prenatal tobacco smoking (Joehanes et al., 2016). That

Study Name	Maternal sociodemographic						Health behavior during pregnancy/pre-pregnancy			Postnatal period			Pre/pregnancy medical/psychiatric illness					Offspring		
	Age	Marital status	Education	Race	Income	Language spoken	Alcohol	Pre-pregnancy tobacco	Other drugs	Tobacco	Alcohol	Other drugs	Hypertension		Diabetes		Psychiatric d/o	BWT	Gestational age	Sex
													HDM	Pre-preg HTN	Pre-existing/ pregnancy	Gestational				
Ayano 2021	+	+	+	x	x	+	x	x	x	X	X	X	x	+	x	+	+	+	x	+
Kristiansen 2018	+	x	+	x	+	x	x	+	x	X	X	X	x	x	x	x	x	+	x	X
Batty, 2014	+	x	+	+	+	x	x	x	+	X	X	X	x	x	x	x	x	+	+	X
Agrawal 2010	x	x	+	+	x	x	x	X	x	+	X	X	x	x	x	x	x	x	x	x
D'Onofrio 2010	+	+	+	x	x	x	x	x	x	X	X	X	x	x	x	x	x	x	+	+
O'Callaghan 2009	+	+	+	x	+	x	+	x	x	X	X	X	x	x	x	x	+	+	x	+
Lundberg 2009	+	+	x	x	+	x	x	x	+	x	x	x	x	x	x	x	x	+	+	x
Gilman 2008	+	+	x	+	+	x	x	x	+	x	x	x	x	x	x	x	+	x	x	+
Collins 2007	+	x	x	x	+	x	x	+	x	x	x	x	x	x	x	x	x	x	x	+
Lambe 2006	+	x	+	x	+	x	x	x	x	x	x	x	x	x	x	x	x	+	+	x
Martin 2006	+	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x	+	x	x	x
Fried 2005	+	x	+	x	x	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x
Batstra 2003	+	x	x	x	+	x	x	x	+	x	x	x	x	x	x	x	x	+	+	x
Fergusson,1991	x	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Fogelman 1980	+	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x	x	+	+	+
Rantakallio 1983	+	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	+
Fogelman 1988	x	x	x	x	+	x	x	x	x	x	x	x	x	x	x	x	x	+	x	x
Butler 1973	+	+	+		+	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X
Anderko 2010	+	x	x	+	+	x	x	x	x	x	x	x	x	x	x	x	x	+	x	+

+ = adequate control for, x = not controlled for, HDP -any of hypertensive disorders of pregnancy (Pre-eclampsia, gestational hypertension, etc), HTN: Hypertension, BWT: Birth Weight

Fig. 2. Confounder matrix by variable adjustment for 19 observational studies included in the meta-analysis examining the association between prenatal tobacco exposure and offspring academic outcome. + = adequate control for, x = not controlled for, HDP -any of hypertensive disorders of pregnancy (Pre-eclampsia, gestational hypertension, etc.), HTN: Hypertension, BWT: Birth Weight.

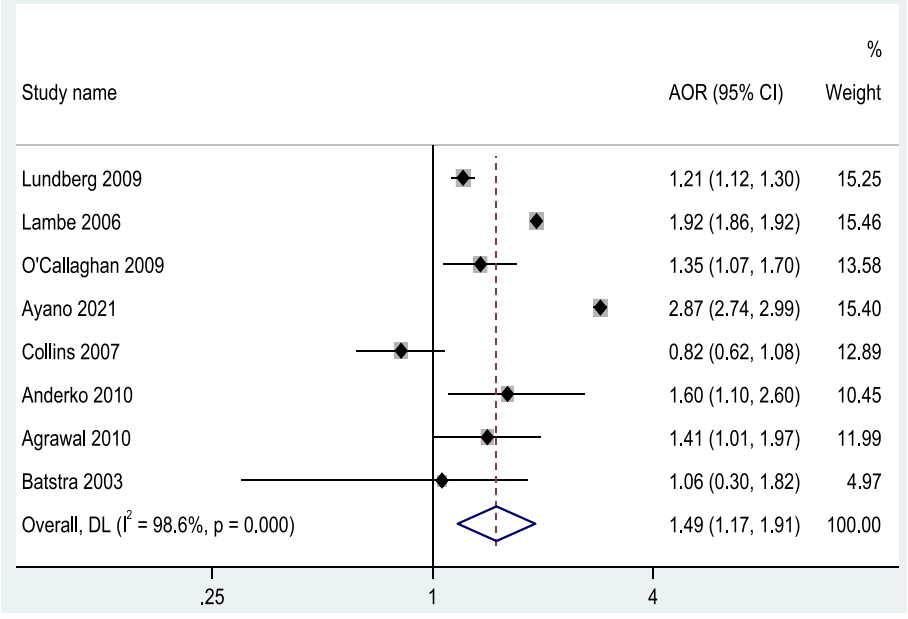

Fig. 3. Meta-analysis of the effect of maternal prenatal tobacco smoking on offspring academic achievement based on random-effect estimator.

meta-analysis found more than 6000 differentially methylated cytosine nucleotide–phosphate–guanine nucleotide (CpGs) sites in the babies' cord blood (Joehanes et al., 2016). The corresponding modification in DNA methylation is believed to result in irreversible changes in the hypothalamus–pituitary–adrenal axis (HPA-axis) (Bick et al., 2012), which mainly regulates the body's reaction to stress and could

potentially impact the development of the brain (Sandström et al., 2011).

There are likely to be additional factors that could play significant roles in the association between maternal prenatal tobacco smoking and offspring reduced academic achievement that remain inadequately controlled. For instance, no association was observed between maternal prenatal tobacco smoking and low scholastic achievement in the study from the US after adjusting for maternal alcohol dependence, maternal conduct problems, and maternal drug use (Agrawal et al., 2010), suggesting that other familial risk factors that correlate with both maternal prenatal tobacco smoking and offspring academic achievement may partly explain the observed associations. Further, epidemiological studies have also suggested higher risks of getting lower grades in schools among offspring born to mothers suffering from psychiatric disorders during pregnancy (Lin et al., 2017). This indicates that studies not accounting for risk factors such as this might have produced less valid estimates. Furthermore, postnatal tobacco exposure has been associated with reduced offspring academic achievement (De Genna et al., 2016; Cho et al., 2010); suggesting that studies not including this risk factor in the model might have overestimated the association. Moreover, smoking phenotypes are genetically correlated with genes for reduced educational attainment, and mothers who smoke likely pass on these genes along with exposing children to smoke prenatally. Therefore, adjusting for the confounding role of genetics is necessary, given the gene-environment correlation between these two traits (Nakamura et al., 2021).

This review has some limitations to be acknowledged. Most of the studies included in the dataset defined maternal prenatal tobacco smoking using maternal self-report, which was not verified biologically, suggesting prenatal tobacco smoking is likely to be under-reported. This would in turn serve to attenuate any association with offspring reduced academic achievement. We have also observed heterogeneity among included studies due to varying levels of confounder and covariate adjustment across the included studies, and this may limit the generalizability of our review findings. Of 19 studies, only 8 reported effect estimates in the form of OR. This limited our study not to conduct a meta-synthesis of all available epidemiological studies on the topic. Further, some of studies included in the review defined academic achievement in various ways. This should be kept in mind when interpreting the results of our study.

5. Clinical, policy and research implications

Our review findings have some clinical and policy implications. Strategies to encourage and to assist pregnant women to quit tobacco smoking are vital, not only to support maternal and child health (Chamberlain et al., 2017) but to decrease the risk of reduced academic achievement. Reducing tobacco smoking during pregnancy requires a coordinated and comprehensive approach (Canuto et al., 2021). Health promotion initiatives delivered via psychological counselling, education campaigns, and incentives for reduction in tobacco use during pregnancy will have important intergenerational effects (Canuto et al., 2021). Further, children exposed to prenatal tobacco smoking may benefit from additional educational support. Future mechanistic studies to identify causal pathways and specific academic impacts are needed to inform targeted developmental programs to assist child learning and academic performance. Finally, future studies examining the effect of prenatal tobacco exposure on offspring academic achievement should consider adjusting for other social and economic determinants of health (e.g., occupational status, family income, parent education, and housing condition) to confirm the current finding.

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7. Availability of data and material

All data generated or analysed during this systematic review and meta-analysis were included in this article and attached as supplementary files.

8. Ethics statement

This study was conducted in compliance with principles outlined in the Declaration of Helsinki. Ethical committee approval for this study was not required.

CRediT authorship contribution statement

Bereket Duko: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Asres Bedaso:** Writing – original draft, Methodology, Investigation, Data curation. **Berihun Assefa Dachew:** Writing – original draft, Visualization, Software, Methodology, Investigation, Conceptualization. **Elizabeth Newnham:** Writing – review & editing, Resources, Methodology, Investigation, Conceptualization. **Amanuel Tesfay Gebremedhin:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gizachew Tessema:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Kristjana Einarsdottir:** Writing – review & editing, Methodology, Investigation. **Rosa Alati:** Writing – review & editing, Methodology, Investigation, Conceptualization. **Gavin Pereira:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary material to this article can be found online at https://doi.org/10.1016/j.addbeh.2024.107985.

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