SYSTEMATIC REVIEW AND META-ANALYSIS OF THE ASSOCIATION BETWEEN MATERNAL SMOKING IN PREGNANCY AND CHILDHOOD OVERWEIGHT AND OBESITY

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ABSTRACT

Background: By 2020 it is predicted that 60 million children worldwide will be overweight. Maternal smoking in pregnancy has been suggested as a contributing factor. Our objective was to systematically review studies on this, thereby expanding the evidence base for this association.

Methods: Systematic Review with meta-analysis, Prospero Registration number CRD42012002859. We searched Pubmed, Embase, Global Health, Web of Science and the Grey literature. We included prevalence, cohort and cross-sectional studies involving full term, singleton pregnancies. Published and unpublished studies through to 1st January 2015 in all languages, demonstrating an objective overweight outcome up until 18 years of age and data presented as an odds ratio were included. Quality assessment was undertaken using an adaption of the Newcastle-Ottawa scale. Statistical analysis performed using Review Manager Version 5·3.

Findings: The meta-analysis included 39 studies of 236, 687 children from Europe, Australia, North & South America and Asia. Maternal smoking in pregnancy ranged from 5·5-38·7%, with the prevalence of overweight from 6·3-32·1% and obesity from 2·6-17%. Pooled adjusted odds ratios demonstrated an elevated odds of maternal smoking in pregnancy for both childhood overweight (OR 1·37, 95% CI 1·28-1·46, I_2 45%) and childhood obesity (OR 1·55, 95% CI 1·40-1·73, I_2 24%).

Interpretation: Our results demonstrate an association between maternal prenatal smoking and childhood overweight. This contributes to the growing evidence for the aetiology of childhood overweight, providing important information for policy makers and health professionals alike in planning cessation programmes or anti-smoking interventions for pregnant female smokers.

What is known on this subject?

Childhood obesity is a major public health problem with predictions that 60 million children worldwide will be overweight by 2020.

Maternal smoking in pregnancy is recognised to be associated with low birthweight but evidence increasing shows an association with overweight and obesity in childhood as well.

What this study adds?

This study provides robust evidence for an association between maternal smoking in pregnancy and an elevated risk of childhood overweight and obesity. The study identified papers from a wide range of databases and included both published and unpublished studies with comprehensive inclusion and exclusion criteria. It includes populations from an extensive geographical area demonstrating the association to exist across different regions.

INTRODUCTION

Childhood obesity is a major public health challenge of the 21st Century. The global prevalence of childhood overweight and obesity rose from 5% in 1990 to 7% in 2012 (1) with 42 million children worldwide under the age of 5 classified as overweight (2). By 2020, almost 60 million children worldwide are predicted to be overweight or obese (3). Obese children suffer mental, psychological and physical ill health and are at an increased risk of developing non-communicable diseases (NCDs) later in life. NCDs accounted for 68% of global deaths in 2012 (4) and are linked by risk factors including tobacco usage and overweight. Evidence suggests that once obesity in childhood is established it is difficult to reverse (5), and likely to continue to adulthood (6). Tackling this is a global health priority (7).

The Barker hypothesis describes adverse early life environmental factors disrupting normal growth and development resulting in a susceptible adult phenotype prone to cardiovascular disease. Identifying early development factors, such as maternal smoking in pregnancy, which may result in subsequent obesity, enables them to be addressed effectively. Children with a high birthweight have an increased risk of later obesity, but evidence also shows low birthweight can predispose to obesity. Maternal prenatal smoking is recognised to result in low birthweight and this could be the link between maternal prenatal smoking and childhood obesity. One longitudinal study (8) found different patterns of weight gain among children born to smokers versus non-smokers. Overweight children at 4.5 years old had a birthweight approximate to the population mean, but during the first five months of life those born to smoking mothers gained more weight than those born to non-smoking

mothers. Individuals with a lower birthweight who later develop obesity, are at the highest risk for cardiovascular morbidities in the long term (9). However, confounding factors are likely to be important in this association, in particular socioeconomic circumstances and lifestyle factors with one study (10) concluding that the link between maternal prenatal smoking and childhood obesity was independent of birthweight.

A systematic review of published data up until June 2006 (11) suggested maternal smoking was positively associated with childhood overweight. However, the meta-analysis comprised only 14 studies, 5 of which included children born prematurely (<37 completed weeks gestation). Preterm infants may have different growth patterns from term infants, at least up to 5 years of age (12, 13) and so it may not be appropriate to combine them when examining causes of childhood obesity. There has also been a marked increase in the number of studies published in this area since 2006. The 2010 UK Infant Feeding Survey found one in eight mothers (12%) continued to smoke throughout pregnancy (14). In many low and middle income countries, rates of smoking are rising, particularly among female adolescents (15).

Objective

The objective of this study was to assess the association between maternal smoking in pregnancy and the risk of developing overweight and obesity in childhood, through a systematic review of published and unpublished work through to 2015.

METHOD

Selection criteria

The evidence was systematically reviewed with results reported in accordance with PRISMA guidelines (16). The review protocol is accessible through PROSPERO (registration number CRD42012002859). Eligibility criteria defined inclusion criteria as: children born at full term ($\geq$ 37 completed weeks gestation), outcome of overweight measured between 2 – 18 years, studies required a control group with maternal prenatal smoking status to be specified for all groups, objective and quantitative measurement of obesity with results presented as an odds ratio with 95% confidence intervals. Studies in all languages were included and data published through to 1st January 2015. Published and unpublished studies were included. Studies were excluded if they included premature infants (< 37 weeks completed gestation), multiple pregnancies, animal studies and studies with no comparison group or no exposure of maternal smoking in pregnancy. Studies were also excluded if all mothers had medical conditions potentially impacting offspring growth, for example gestational diabetes. Discussions, policy documents, reviews and case reports were excluded. If studies used data from the same cohort population, the study measuring outcomes at the older age was the one included.

Search Strategy

With the assistance of a professional librarian, the following online databases were systematically searched: Pubmed, EMBASE, Global Health, Cinahl and Web of Science. The search terms were: (pregnancy OR maternal OR mother OR pregnant) AND (smoking OR cigarette OR nicotine OR smoker* OR tobacco) AND (childhood OR offspring OR infant OR

children OR adolescent OR teen) AND (obesity OR overweight OR "body mass index" OR weight OR height OR percentile OR fatness OR adiposity). A total of 17, 247 studies were identified.

The Grey Literature search consisted of: databases "Dissertations & Theses" and "Index to Theses"; OPENGREY; Google search of organisational websites (org.uk, nhs,uk, gov.uk, .gov and .org) and ongoing clinical trials identified through clinicaltrials.gov and the WHO trials registry. A simplified version of the above search terms identified 408 studies and trials.

Following removal of duplicate references, titles & abstracts were reviewed for potential inclusion. Full text articles were obtained for included studies. For conference abstracts, the author was contacted to clarify if the data was subsequently published and if not, a copy of the study data was requested. If a grey literature article was suitable for inclusion, the author was contacted for a full copy of the study and data.

Data collection

Both authors (SR & EP) independently reviewed full text articles, resulting in 39 studies meeting the inclusion criteria and so suitable for the meta-analysis. Disagreements were resolved through discussion. The references for each included study were reviewed to identify possible further studies. The PRISMA flow diagram details reasons for study exclusion at each stage (Figure 1).

Definition of outcomes

The primary outcome was childhood overweight and obesity in relation to maternal prenatal smoking with data extracted as unadjusted and adjusted odds ratio with 95% confidence intervals. If the unadjusted odds ratio was not available, it was calculated from published data or authors contacted for raw data. Data was extracted on study location, decade of birth of participants, age outcomes were measured and specific definitions of overweight and obesity.

All studies, except one (17), used Body Mass Index (calculated as weight (kg)/height^2 (m^2)) as the objective outcome, however definitions of overweight and obesity varied. Nineteen studies (18-36) used the International Obesity Task Force definitions: "overweight" defined as age and sex specific cut offs corresponding to adult BMI of $\geq$25 and BMI $\geq$30 for "obesity" (37). Other studies defined overweight as BMI $\geq$ 85th or $\geq$ 90th percentile for age and sex; with obesity as BMI $\geq$95th or $\geq$ 97th percentile for age and sex. The study (17) not using BMI, defined overweight as "weight for height more than 2 standard deviations".

Where studies presented different levels of adjustment for confounding factors, the maximally adjusted model was included (confounding factors described in table one). If studies presented different levels of exposure, the lowest possible smoking dose and smoking early in pregnancy was used. When using raw data to calculate unadjusted odds ratio, categories were combined as "non-smoking in pregnancy" or "any smoking in pregnancy" to maximise the number of participants included. One study (25) had results on

two cohorts: the 1958 birth cohort, and data for offspring born to the original cohort. Only offspring data was included as another study (38) provided outcomes at an older age for the 1958 cohort. Two studies (38, 39) presented separate odds ratio for males and females, with no overall odds ratio, so the meta-analysis included subgroup data from each of these two studies as separate studies.

Statistical Analysis

Pooled odds ratios were calculated (with 95% confidence intervals) for included studies using a random effect model and generic inverse variance method in which the weight of each study is the inverse of the variance of the effect estimate. A random effect model was chosen due to likely variation in included studies and recognition that subjects in each study could differ from each other in a number of ways including geographical location and social circumstances. The I^2 calculation provided a percentage of the variation across study estimates due to heterogeneity rather than chance alone (40). Funnel plots were constructed to give a visual representation of possible publication bias. Statistical analysis was performed using Review Manager version 5·3.

Assessment of risk of bias in included studies

Each author (SR & EP) independently performed data extraction and quality assessment against purposefully designed forms. The quality assessment was adapted from the Newcastle Ottawa Quality Assessment Scale (41), grading each paper a number of stars for selection, comparability, exposure and outcome. The adaptations were minor, including

specifying the exact outcome (childhood overweight) and the criterion 'Demonstration That Outcome of Interest Was Not Present at Start of Study' was omitted as this was not relevant.

Role of the funding source

The funding sources had no direct role in study design, data collection, analysis, interpretation of data or writing of the report. Both authors had full access to the study data and had final responsibility for the decision to submit for publication.

RESULTS

Thirty-nine studies were included in the meta-analysis (figure one): Twenty-six cohort studies (8, 18, 19, 21-23, 25, 26, 29, 30, 32-35, 38, 39, 42-51), twelve cross-sectional studies (17, 20, 24, 27, 28, 36, 52-57) and one case control study (31). Table one details characteristics for each included study. The combined number of participants was 236, 687, with children born between 1958 and 2010. Study populations were from Europe, Australia, North & South America and Asia. The prevalence of maternal smoking in pregnancy ranged from 5.5% (21) to 51.4% (39) (mean 19.1%). The age of outcome ranged from two (34, 51) to eighteen (30) years of age. The prevalence of childhood overweight ranged from 6.3%(17) to 42% (28) (mean 17.2%), and obesity prevalence from 2.0% (30) to 17% (44) (mean 6.9%). Not all studies contained prevalence data for both overweight and obesity. Table two outlines the quality assessment of included studies.

Table 1: Characteristics of included studies

Study: 1st Author (year), location	Cohort population used (if applicable)	No. in analysis	Smoking exposure (prevalence)	Covariates	Decade of birth	Age outcome measured (mean)	Outcome (prevalence)	Overweight		Obesity	
								Unadjusted OR (95% C.I)	Adjusted OR (95% C.I)	Unadjusted OR (95% C.I)	Adjusted OR (95% C.I)
Von Kries (1999), Germany	-	9206	Maternal smoking in pregnancy (8.01%)	Breastfeeding, high level parental education, birthweight <2500g, own bedroom, consumes butter >x3/week	1997	5 – 6years	BMI – overweight >90th percentile for age and sex (10.7%) and obesity >97th percentile for age and sex (3.5%)	1.51 (1.20-1.89)	1.52 (1.18-1.95)	1.82 (1.28-1.58)	1.85 (1.26-2.71
Power (2002), UK Male	1958 British Cohort	5113 (9948 total)	Maternal smoking in pregnancy (33.5%)	Maternal BMI, social class, birthweight, infant feeding, social class at age 7 years, physical inactivity, diet, social class	1958	16 years	BMI – "obesity" was classified as >90th percentile for age and sex. However, this data was included as "overweight" for the meta-analysis. No prevalence available.	1.29 (1.06-1.55)	-	-	-
Power (2002), UK Female	1958 British Cohort	4835 (9948 total)	Maternal smoking in pregnancy (33.5%)	Maternal BMI, social class, birthweight, infant feeding, social class at age 7 years, physical inactivity, diet, social class	1958	16 years	BMI – "obesity" was classified as >90th percentile for age and sex. However, this data was Included as " Overweight" for the meta-analysis. No prevalence available.	1.32 (1.12-1.65)	-	-	-
Von Kries (2002), Germany	-	6483	Maternal smoking in pregnancy (8.6%)	High parental education, BMI parent >30, birthweight >90th percentile,	1999-2000	5-6 years	BMI: overweight >90th percentile for age and sex (no prevalence	1.97 (1.52-2.56)	1.43 (1.07-1.90)	2.96 (1.97-4.46)	2.06 (1.31-3.26)

				watching TV >1 hr/day, any breastfeeding, eating snacks while watching TV			available); obesity >97th percentile for age and sex (no prevalence available)				
Wideroe (2003), Norway & Sweden	-	336	Maternal smoking of 1-10 cigarettes/day in pregnancy (31.03%)	Maternal age, maternal skin fold thickness, maternal education, paternal education, duration of breastfeeding, total energy intake in week 17, % fat intake week 33, % carbohydrate intake in week 33, birthweight	1986-1992	5 years	BMI: overweight >85th percentile (14.9%)	2.68 (1.36-5.27)	3.8 (2.0-7.2)	-	-
Salsberry (2005), USA	National Longitudinal Study of Youths, child-mother file	3022	Maternal smoking in pregnancy (26%)	(only unadjusted OR available)	1982-1996	7 years	BMI "overweight" classified as $\geq$95th percentile for age and sex (12%). However, this data was included as obesity for the meta-analysis	-	-	1.74 (1.32-2.29)	-
Al Mamum (2006), Australia	Birth Cohort	3253	Maternal smoking in pregnancy (36.6%)	Age, sex, socioeconomic position at birth, breastfeeding, consumption of fast food, salad, soft drinks, red meat, TV watching and participation in	1981-1984	14 years	BMI: overweight $\geq$95th percentile for age and sex (CDC reference) (19%); obesity $\geq$95th percentile for age and sex (6/2%)	1.28 (1.06-1.55)	1.30 (1.05-1.61)	1.36 (1.01-1.83)	1.40 (1.01-1.94)

				sport and exercise							
Chen (2006), USA Male	CPP: Collaborative Perinatal project	6181 (12 416 total)	Maternal smoking in pregnancy (51.4%)	Centre, race, Socioeconomic Status, maternal age at recruitment, prepregnancy BMI, child live birth order, breastfeeding, age of measurement	1959-1965	8 years	BMI: "at risk of overweight" $\geq 85^{th}$ percentile for age and sex (data included as overweight for meta-analysis); "overweight $\geq 95^{th}$ percentile for age and sex (data included as obesity for the meta-analysis.	-	1.21 (1.05-1.39)	-	1.21 (0.96-1.51)
Chen (2006), USA Female	CPP: Collaborative Perinatal project	6235 (12 416 total)	Maternal smoking in pregnancy (51.4%)	Centre, race, Socioeconomic Status, maternal age at recruitment, prepregnancy BMI, child live birth order, breastfeeding, age of measurement	1959-1965	8 years	BMI: "at risk of overweight" $\geq 85^{th}$ percentile for age and sex (data included as overweight for the meta-analysis); "overweight $\geq 95^{th}$ percentile for age and sex (data included as obesity for the meta-analysis.	-	1.37 (1.19-1.58)	-	1.31 (1.06-1.51)
Dubois (2007), Canada	Quebec Longitudinal study of child development 1998-2002	1450	Maternal smoking in pregnancy (25.2%)	Gestational age, birthweight	1998-2002	4.5 years	BMI: "overweight" $>95^{th}$ percentile for age and sex (8.5%)(data included as obesity for the meta-analysis)	-	-	1.6 (1.1-2.4)	1.8 (1.2-2.8)
Salsberry (2007), USA	-	3368	Maternal smoking in pregnancy (27%)	Age of child, gender, age of mother at birth, time trend, height + weight collection	1980-1990	12 – 13 years	"Overweight" as BMI $\geq 95^{th}$ percentile for age and sex (17%). Data Included as	-	-	-	1.36 (1.04-1.77)

				method, first born. Socioeconomic factors			obesity in the meta-analysis				
Toschke (2007), Germany	-	5472	Maternal smoking in pregnancy (22.8%)	Low educational level of parents, parental obesity, reduced physical activity, watching TV >1 hr/day, no breastfeeding, Less than 5 meals/day	1995-1996	5-6 years	BMI – overweight (11.3%) and obesity (3.2%) as per IOTF definitions	1.59 (1.32-1.91)	1.32 (1.10-1.61)	2.31 (1.70-3.14)	1.75 (1.25-2.43)
Mendez (2008), Spain	-	369	Maternal smoking in early pregnancy (15.7%)	Child age, gender, breastfeeding duration, maternal age, height, overweight/obesity prior to pregnancy, education, parity, TV watching, child diet	1997-1998	5 – 7 years	BMI – Overweight as per by IOTF definitions (23.6%)	2.16 (1.18-3.97)	2.65 (1.26-5.54)	-	-
Moschonis (2008), Greece	GENESIS: Growth, Exercise & Nutrition Epidemiological Study in preschoolers	1667	Maternal smoking in pregnancy (10.5%)	Gender, birthweight, postnatal feeding patterns, birth rank, size at birth, alcohol consumption, parental weight, education of mothers, mothers age	1998-2002	3-5 years	"At risk of overweight and overweight" defined as BMI >85th percentile for age + gender (17%)	1.07 (0.77 – 1.50)	1.14 (0.76-1.90)	-	-
Fasting (2009), Norway	PACT: Prevention of Allergy among Children in Trondheim study	711	Maternal smoking in early pregnancy (13.6%)	Child gender, maternal education, maternal age, Physical exercise, birth weight	2000-2003	4 years	BMI – overweight as per IOTF definitions (10.1%)	1.25 (0.61-2.5)	1.29 (0.62- 2.68)	-	-
Hawkins (2009), UK	Millenium Cohort Study	13 188	Mothers smoking 1-9 cigarettes in pregnancy (11.8%)	Child gender + ethnicity, birthweight, Breastfeeding,	200-2002	3 years	BMI – overweight as per IOTF definitions	1.17 (1.00-1.36)	1.34 (1.17-1.54)	-	-

				solids, TV, Socioeconomic factors, maternal education, Lone mother, household income, community + area factors			(23.5%)				
Kleiser (2009), Germany	KiGGs Study	10 021	Maternal smoking in pregnancy (16.9%)	Socioeconomic status, migration background, parental overweight, paternal smoking, weight gain in pregnancy, high birthweight, breastfeeding, sleep, Media consumption, physical activity, intake of energy food	1989-2006	3-17 years	BMI – overweight (19.7%) and obesity (5%) as per IOTF definitions	1.65 (1.49-1.83)	1.68 (1.5-1.9)	1.9 (1.6-2.26)	1.37 (1.0-1.8)
Olson (2009) USA	Basset Mother's Health Project	321	Maternal smoking in pregnancy (16.5%)	Maternal BMI, gestational weight gain, birthweight, maternal BMI x birthweight, gestational age, parity, income, gender	2004-2005	4 years	BMI: overweight defined as $\geq 85^{th}$ percentile for age + sex (32.1%); obesity defined as $\geq 95^{th}$ percentile for age + sex (14.6%)	1.92 (1.03 – 3.58)	1.99 (0.98– 4.04)	2.01 (0.87-4.60)	1.86 (0.70-4.93)
Suzuki (2009), Japan	Project Koshu (formerly Enzan)	1282	Maternal smoking in pregnancy (5.5%)	Maternal Age, maternal BMI, , sleep deprivation, breakfast	1991-1999	9-10 years	BMI – overweight (16.7%) and obesity (4.5%) as per IOTF definitions	2.22 (1.30-3.77)	1.91 (1.03-3.53	4.06 (1.96-8.42)	2.56 (1.02-6.38)
Ajslev (2010), Denmark	Danish National Birth Cohort	21 121	Maternal smoking in pregnancy 1-10 cigarettes/day (22.7%)	(only unadjusted OR available)	1997-2002	7 years	BMI – overweight as per IOFT definitions (9.6%)	1.46 (1.36-1.57)	-	-	-

Braun (2010), USA	Health outcomes & measures of the environment study	352	Maternal smoking in pregnancy (13.6%)	Maternal age, BMI, race & education, marital status, depression, breastfeeding duration, parity, income	2003-2006	2-3 years	Overweight defined as BMI $\geq 85^{th}$ percentile for age and gender (16.2%)	2.5 (1.0-6.1)	1.9 (0.6-6.1)	-	-
Ferreira (2010), Brazil	Nutrition & health of mother-child population of Alagoas Semi-Aridi region	716	Maternal smoking in pregnancy (20.4%)	(only unadjusted OR available)	2002-2006	1-5 years	Overweight defined as children with weight for height > 2 SD (6.3%)	1.8 (0.9-3.5)	-	-	-
Kuhle (2010), Canada	CLASS: Children's lifestyle & school performance study	3351	Maternal smoking in pregnancy, 0-0.5 packs of cigarettes/day (26%)	Pre-pregnancy weight, parity, physical activity, sedentary activity, weight for gestational age	1991-1992	11-12 years	BMI – overweight as per IOFT definitions (33%)	-	1.39 (1.14-1.70)	-	-
Mangio (2010), Sweden	-	8621	Maternal smoking in pregnancy (10.2%)	Year, gender, maternal education, parents country of birth, crowded living, first born, parental education programme & economic stress), parental overweight, child intake of sweetened beverages	1999-2004	4 years	BMI – overweight (15%) and obesity (3%) as per IOTF definitions	1.48 (1.24-1.77)	1.48 (1.17-1.87)	2.29 (1.68-3.13)	2.1 (1.37-3.23)
Pinot de Moira (2010), UK	1958 British Birth Cohort: **Offspring data**	1889	Maternal smoking in pregnancy (24.1%)	Gender, age, parental BMI, birthweight, gestational age, , breastfeeding, social class	1982-1987	4-9 years (6.9 years)	BMI – overweight (29.9%) & obesity (6.8%) as per IOFT definitions	-	1.02 (0.71-1.47)	-	-
Seach (2010), Australia	MACS: Melbourne Atopy Cohort Study	307	Maternal smoking in pregnancy (5.6%)	Breastfeeding, paternal smoking, socio-economic status, childcare	1990-1994	10 years	BMI – overweight (25.1%) & obesity (2.6%)	-	1.65 (0.53-5.11)	-	-

				attendance, Birthweight			as per IOFT definitions				
Gorog (2011), Central Europe	CESAR: Central European Study on Air pollution % Respiratory health	8926	Maternal smoking in pregnancy (12.5%)	Breastfeeding, <1 person/room winter fruit, exercise, mothers education, fathers education, high birthweight, summer fruit, mothers occupation, study area	-	9-12 years	BMI – overweight (14.3%) & obesity (2.7%) as per IOFT definitions	1.2 (0.94-1.52)	1.26 (1.03-1.55)	1.69 (0.87-3.27)	1.82 (0.95-3.5)
Raum (2011), Germany	-	1954	Maternal smoking in pregnancy (16.5%)	Parity, birthweight, breastfeeding, TV, sports, visits to fast food restaurants, parental education, maternal BMI, age of mother, smoking at other times	1995-1996	6 years (5.8 years)	BMI – Overweight (8.9%) as $\geq 90^{th}$ percentile & obesity (4.2%) as $\geq 97^{th}$ percentile for age & gender	1.83 (1.27-2.63)	0.89 (0.51-1.55)	-	-
Laitinen (2012), Finland	Northern Finland 1986 Birth Cohort	6637	Maternal smoking in pregnancy, 1-10 cigarettes/day in pregnancy (8.3%)	Gender, Parity, Maternal pre-pregnancy BMI, level of Haemoglobin in early pregnancy, smoking in early pregnancy, level of education	1986	16 years	BMI – overweight as per IOFT definitions (14.8%)	1.39 (1.11-1.75)	1.36 (1.04-1.77)	-	-
Messiah (2012), USA	NHANES: National Health & Nutrition Examination survey	3644	Maternal smoking in pregnancy (17%)	Age, gender, family poverty/income ratio, year of survey, mothers age at birth, race.	1999-2008	3-6 years	Overweight (26.5%) defined as $\geq 85^{th}$ percentile & obesity (13.8%) defined as $\geq 95^{th}$ percentile for age & gender	1.27 (0.98-1.64)	1.64 (1.16-2.30)	1.54 (1.15-2.06)	1.97 (1.34-2.89)
Risvas (2012), Greece	GRECO: Greek Childhood Obesity study	2093	Maternal smoking in pregnancy, 1-9 cigarettes/day at	Child age, gender, Physical activity status, quality of	1996-1997	10-12 years (10.8 years)	BMI – overweight (42%) & obesity	1.28 (0.99-1.65)	1.32 (0.99-1.77)	-	-

			conception (38.7%)	diet, mothers age at pregnancy, mothers BMI pre-conception, mothers % BMI change, smoking habits at conception & gestation			(13.8%) as per IOFT definitions				
Harris (2013), USA	Nurses Health Study II	35 370	Any maternal smoking in pregnancy (26.1%)	age, maternal/paternal /prenatal factors, parental smoking, birthweight, body size in childhood	1989	18 years	BMI: Overweight BMI >25 (no prevalence available); Obesity BMI >30 (no prevalence available)	0.94 (0.75-1.17)	1.27 (1.12-1.43)	1.36 (1.16-1.58)	1.35 (1.08-1.68)
Shi (2013), Canada	-	968	Maternal smoking in pregnancy (17%)	age, sex, ethnicity, , bf experience, physical activity, Birthweight	2007-2009	6-11 years (8.6 years)	BMI Z scores: overweight Z score 1-2 standard deviations above mean (21%); obesity Z score >2 standard deviations above mean (13%)	1.82 (0.82-4.06)	2.25 (0.98-5.15)	2.26 (1.18-4.31)	2.41 (1.33-4.36)
Yang (2013), Belarus	PROBIT trial	12 192	Maternal smoking in pregnancy (18%)	cluster, child sex and age at outcome measure	1996-1997	6.5 years	BMI: overweight BMI >95th percentile (prevalence not available) (CDC cut offs)	-	1.05 (0.63-1.75)	-	-
Anderson (2014), Hawaii	Special supplemental nutritional programme for Women, Infants and Children (WIC) data	15 106	Maternal smoking in pregnancy (7.9%)	n/a	2005-2009	2 years	BMI: overweight BMI 85th-95th percentile (CDC cut off) (12.5%); obesity BMI >95th percentile (8.5%)	1.06 (0.88-1.27)	-	1.49 (1.23-1.80)	-
Bammann	IDEFICS	1024	Maternal smoking	sex, age, country,	2007-2008	4-8 years	BMI –obesity as	-	-	1.52	1.43

(2014), Europe			in pregnancy (16.9%)	gestational weight gain, Caesarean section, breastfeeding at 4-11 months, early introduction solids, maternal and paternal BMI, parental educational level			per IOFT definitions (no prevalence as case control trial)			(1.16-1.98)	(0.94-2.16)
Grazulevicie ne (2014), Lithuania	KANC cohort PHENOTYPE project	1489	Maternal smoking in pregnancy (12.7%)	n/a	2007-2009	4-6 years	BMI – overweight as per IOFT definitions (7.5%)	2.42 (1.38-4.21)	-	-	-
Moller (2014), Denmark	Danish National birth cohort	32 747	Maternal smoking in pregnancy (23.4%)	sex, parity, BWT, maternal gestational weight gain, maternal age, pre-pregnancy BMI, paternal smoking, Socioeconomic status	1996-2002	7 years	BMI – overweight as per IOFT definitions (9.4%)	-	1.31 (1.15-1.48)	-	-
Suzuki (2014), Japan	Project Koshu (formerly Enzan)	2230	Maternal smoking in pregnancy (24.9 %)	n/a	1991-2006	3 years	BMI – overweight as per IOFT definitions (no prevalence)	1.20 (0.81-1.77)	-	-	-
Timmermans (2014), Netherlands	KOALA birth cohort study	398	Maternal smoking in pregnancy (7.9%)	gender, recruitment group, maternal age at pregnancy, maternal BMI, pre-pregnancy age and smoking interaction	2000	6-7 years	BMI: overweight BMI >85th percentile for age and sex (9.5%)	3.65 (1.44-9.25	3.72 (1.33-10.4)	-	-
Wen (2014), Australia	Health Beginnings trial	242	Maternal smoking in pregnancy (12%)	n/a	2007-2010	2 years	BMI – overweight as per IOFT definitions (14%)	1.1 (0.35-3.43)	-	-	-

Table 2: Summary of Quality Assessment

Study: First author (year), location	Quality Assessment Stars Allocation				Total Score (max 12)	Quality
	Selection (max 3)	Comparability (max 2)	Exposure (max 3)	Outcome (max 4)		
Von Kries (1999), Germany	3	2	1	4	10	High
Power (2002), UK	2	1	1	3	7	Medium
Von Kries (2002), Germany	3	2	1	4	10	High
Wideroe (2003), Norway & Sweden	2	2	1	4	9	Medium
Salsberry (2005), USA	1	2	2	2	7	Medium
Al Mamum (2006), Australia	2	2	2	3	9	Medium
Chen (2006), USA	2	2	2	4	10	High
Dubois (2007), Canada	3	0	2	4	9	Medium
Salsberry (2007), USA	1	2	1	2	6	Medium
Toschke (2007), Germany	3	1	1	3	8	Medium
Mendez (2008), Spain	3	2	2	4	11	High
Moschonis (2008), Greece	2	1	1	3	7	Medium
Fasting (2009), Norway	2	1	1	3	7	Medium
Hawkins (2009), UK	3	2	2	3	10	High
Kleiser (2009), Germany	2	2	1	3	8	Medium
Suzuki (2009), Japan	3	1	1	4	9	Medium
Ajslev (2010), Denmark	2	0	2	2	6	Medium
Braun (2010), USA	2	2	2	3	9	Medium
Ferreira (2010), Brazil	2	0	1	2	5	Low
Kuhle (2010), Novo Scotia	1	1	1	2	5	Low
Mangio (2010), Sweden	2	2	1	3	8	Medium
Olson (2010), USA	2	2	1	3	8	Medium
Pinot de Moira (2010), UK	2	2	1	3	8	Medium
Seach (2010), Australia	2	2	2	3	9	Medium
Gorog (2011), Central Europe	2	2	1	3	8	Medium
Raum (2011), Germany	3	1	1	3	8	Medium
Laitinen (2012), Finland	3	1	2	4	10	High
Messiah (2012), USA	3	2	1	3	9	Medium
Risvas (2012), Greece	1	1	1	3	6	Medium
Harris (2013), USA	3	1	1	2	7	Medium
Shi (2013), Canada	3	1	1	3	8	Medium
Yang (2013), Belarus	2	2	2	4	10	High
Anderson (2014), Hawaii	2	1	2	4	9	Medium
Bammann (2014), Europe	2	2	1	3	8	Medium
Grazuleviciene (2014), Lithuania	1	2	1	2	6	Medium
Moller (2014), Denmark	3	2	2	3	10	High
Suzuki (2014), Japan	3	1	1	4	9	Medium
Timmermans (2014), Netherlands	2	2	1	4	9	Medium
Wen (2014), Australia	2	0	2	4	8	Medium

The primary outcome was childhood overweight compared to maternal smoking in pregnancy (twenty-eight studies provided unadjusted odds ratio). The pooled unadjusted odds ratio of 1·43 (95% CI 1·32-1·56) (figure two) demonstrated an elevated risk of overweight among children whose mothers smoked prenatally compared to those who did not. There was moderate heterogeneity with an I^2 of 64%. The pooled adjusted odds ratio for childhood overweight in relation to maternal smoking in pregnancy was 1·37 (95% CI 1·28-1·46) (figure three), I^2 of 45% (thirty-one studies). This demonstrates an increased risk of childhood overweight in relation to maternal prenatal smoking even when adjusted for potential confounders. Funnel plots for unadjusted odds ratio and adjusted odds ratio for overweight are presented in supplementary Figures one and two respectively.

Given the different definitions of childhood overweight, sensitivity analysis was performed restricting to studies using the international obesity task force definitions. This marginally reduced the pooled adjusted odds ratio for overweight, but confidence intervals were similar at OR 1·33 (1·23-1·46 95% confidence interval). The heterogeneity was reduced with an I^2 of 52%.

For childhood obesity in relation to maternal smoking in pregnancy, the pooled unadjusted odds ratio was 1.77 (95% CI 1·56-2·03), I^2 58% (Supplementary figure three), and pooled adjusted odds ratio was 1·55 (95% CI 1·40-1·73), I^2 24% (Supplementary figure four). The pooled adjusted odds ratio demonstrates a clear increased risk of childhood obesity following maternal prenatal smoking despite adjustment for confounders. Confounding

factors varied between studies (Table one), often including a measure of parental education, breastfeeding and socioeconomic status.

The pooled results used the lowest exposure smoking dose and at the earliest available point in pregnancy, demonstrating the minimal effect of prenatal smoking. Most included studies (27 in total) classified maternal prenatal smoking as “yes” or “no”, but the remaining studies categorised the level of cigarette exposure. Eight studies (18, 23, 29, 38, 39, 42, 52, 53) demonstrated a dose response association of increasing odds of overweight with increasing numbers of cigarettes smoked per day, or persistent smoking throughout pregnancy. However, two studies (19, 30) found higher odds ratios for moderate rather than heavy smokers, whereas another study (28) had the lowest odds ratio for childhood overweight in moderate smokers. The final study (46) demonstrated a higher odds ratio for overweight in mothers who only smoked in the first trimester compared to mothers who continued to smoke throughout their pregnancy.

DISCUSSION

This review provides robust data demonstrating maternal smoking during pregnancy is associated with an elevated odds of childhood overweight and obesity; if a child’s mother smoked during pregnancy, the odds of the child becoming overweight are 37% greater and 55% greater for obesity than if the mother did not smoke. A number of plausible mechanisms have been put forward for this relationship. Smoking in pregnancy leads to low birthweight, likely through a vasoconstrictive action of nicotine and fetal hypoxia (58). This

may affect postnatal growth patterns, leading to a higher likelihood of childhood obesity. There is also increasing evidence that tobacco smoke exposure at other periods in childhood increases the risk of childhood overweight (54, 59, 60).

Confounding factors, such as socio-economic status and parental education, are clearly important in the relationship between maternal smoking and childhood obesity. However, a clear relationship remained despite adjustment; implying measured confounders cannot fully explain this association. Nevertheless, residual confounding is likely to be relevant. Howe et al (61) found measured confounders did not impact the relationship between maternal prenatal smoking and adiposity changes, however comparisons with partner smoking in pregnancy implied unmeasured familial factors are important. Iliadou et al (10) concluded that parental socioeconomic status and education partly explained the association between maternal prenatal smoking and childhood obesity, but unmeasured familial factors, including lifestyle factors and dietary habits, were also relevant. Whilst included studies in this review did adjust for known confounders, there was no adjustment for potential (but unmeasured) confounders and so residual confounding is likely to affect the results.

Compared to a previous systematic review (11), these results demonstrate a lower pooled adjusted odds ratio for overweight (1·37 vs 1·5) but similar pooled adjusted odds ratio for obesity (1·55 vs 1·52). The strengths of this more recent meta-analysis are that it includes almost three times as many children as the previous study (11), using a wider range of

databases, including both published and unpublished studies. More confidence can be placed in these findings as premature infants were excluded and outcomes were assessed only during childhood. This meta-analysis included populations from an extensive geographical area (Europe, Australia, North & South America and Asia), demonstrating the association exists across different regions. However, populations included were predominantly high income western countries despite smokers in low and middle income countries (LMICs) accounting for nearly 80% of global tobacco consumption (62). The increasing prevalence of overweight and obesity affects all counties, with close to 31 million overweight children living in LMICs, so this highlights an important gap in global health research. Publication bias may be a factor and also affecting the results as a whole. Although we constructed and presented funnel plots, they have limitations for assessing publication bias. Visual interpretation of funnel plots may be too subjective to be useful (63) and some effect estimates can produce spurious asymmetry in a funnel plot (64).

The quality of each included paper was assessed with most scoring well. However, some study populations were not entirely representative of the wider population, with some cohort studies losing large numbers to follow up, potentially introducing bias. It is possible that more overweight or obese children were lost to follow up leading to an underestimate of the effect size. All included studies were observational, so may all be subject to similar biases including selection and recall bias. All studies used maternal self-reporting for the exposure of smoking during pregnancy. However, studies show self-reporting has high validity in both early and late pregnancy (65). There is more propensity for people to misrepresent themselves as non-smokers while continuing to smoke, leading to an under

estimation of the true association between maternal smoking and childhood overweight. This meta-analysis included data on the lowest smoking dose and smoking early in pregnancy, implying the results are the minimum effect that any smoking in pregnancy can have. Whilst the design of included studies means it is not possible to infer causality, this review contributes to the mounting body of evidence of a clear association between maternal smoking and childhood overweight.

Given the diversity of included studies, the moderate heterogeneity between studies is not surprising. This can be attributed to the variability in study design, participants and definitions of exposures. Outcome definitions differed between studies and children were assessed at different ages in different studies. There may have been differences in the measurement of exposure variables such as socioeconomic status, and with participants coming from a number of different countries, this would have further introduced variability.

This systematic review highlights maternal smoking in pregnancy as an important factor contributing towards the childhood obesity pandemic. This reinforces the need for ongoing public health interventions regarding smoking cessation in all countries, particularly focusing on women of child bearing age. The pathway to childhood overweight is multifactorial, but also largely preventable. Estimates show 40% of childhood obesity could be prevented through a combination of healthy eating promotion, active living and the cessation of smoking during pregnancy (23). Prevention of childhood obesity should start at the earliest

possible stage of development and a smoke free environment for all will be an important part of this

In conclusion, this systematic review has confirmed evidence for an association between maternal smoking in pregnancy and childhood overweight and obesity. This knowledge is relevant to all from policy makers to those health care professionals in regular contact with women of child bearing age. Smoking cessation is of benefit to the long term health of the mother, it benefits the growing fetus during pregnancy, and now this study confirms evidence of benefit to her offspring's future health and wellbeing through removing this increased risk of overweight.

AUTHORS CONTRIBUTIONS

SR devised the study, established inclusion criteria, did all searches of published and unpublished work, evaluated each article for possible inclusion, completed data extraction and quality assessment of each included study, contacted authors of relevant studies, was responsible for statistical analysis and interpretation of the data and drafted the manuscript.

EP established inclusion criteria, provided supervision, evaluated each article for possible inclusion, completed data extraction and quality assessment of each included study, assisted with interpretation of the data and critical revision of the manuscript.

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SR is a Public Health trainee salaried by Oxford University Hospitals NHS Trust

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

Competing interests: None Declared

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Figure titles

Table 1: Characteristics of included studies

Table 2: Summary of quality assessment

Figure 1: PRISMA flow diagram – the association between maternal smoking during pregnancy and childhood overweight

Figure 2: Pooled unadjusted odds ratio for maternal prenatal smoking and childhood overweight

Figure 3: Pooled adjusted odds ratio for maternal prenatal smoking and childhood overweight

Supplementary information

Figure 1: Funnel plot for unadjusted odds ratio – maternal prenatal smoking and childhood overweight

Figure 2: Funnel plot for adjusted odds ratio for maternal prenatal smoking and childhood overweight

Figure 3: Pooled unadjusted odds ratio for maternal prenatal smoking and childhood obesity

Figure 4: Pooled adjusted odds ratio for maternal prenatal smoking and childhood obesity