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ORIGINAL PAPER

Prenatal Programming of Childhood Overweight and Obesity

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Abstract *Objective*: To review the scientific evidence for prenatal programming of childhood overweight and obesity, and discuss its implications for MCH research, practice, and policy.

Methods: A systematic review of observational studies examining the relationship between prenatal exposures and childhood overweight and obesity was conducted using MOOSE guidelines. The review included literature posted on PubMed and MDConsult and published between January 1975 and December 2005. Prenatal exposures to maternal diabetes, malnutrition, and cigarette smoking were examined, and primary study outcome was childhood overweight or obesity as measured by body mass index (BMI) for children ages 5 to 21.

Results: Four of six included studies of prenatal exposure to maternal diabetes found higher prevalence of childhood overweight or obesity among offspring of diabetic mothers, with the highest quality study reporting an odds ratio of adolescent overweight of 1.4 (95% CI 1.0–1.9). The Dutch famine study found that exposure to maternal malnutrition in early, but not late, gestation was associated with increased odds of childhood obesity (OR 1.9, 95% CI 1.5–2.4). All eight included studies of prenatal exposure to maternal smoking showed significantly increased odds of childhood overweight and obesity, with most odds ratios clustering around 1.5 to 2.0. The biological mechanisms mediating these relationships are unknown but may be partially related to programming of insulin, leptin, and glucocorticoid resistance *in utero*.

Conclusion: Our review supports prenatal programming of childhood overweight and obesity. MCH research, practice, and policy need to consider the prenatal period a window of opportunity for obesity prevention.

Keywords Prenatal programming · Childhood obesity · Overweight · Developmental programming · Fetal programming · Gestational diabetes · Maternal malnutrition · Cigarette smoking

Childhood overweight and obesity is a growing problem in the United States and worldwide. The prevalence of childhood overweight in the U.S. tripled between 1980 and 2000 [1]. Today approximately 1 in 6 (16%) U.S. children are overweight with significant racial-ethnic disparities. For example, nearly 1 in 4 (23%) non-Hispanic black girls ages 6 to 19 are overweight, a prevalence almost twice that of non-Hispanic white girls [1].

Overweight and obesity has significant lifelong consequences on the health and well-being of children [2, 3]. Childhood obesity is associated with early-onset Type II diabetes mellitus, hypertension, metabolic syndrome, and sleep apnea. It is also associated with cognitive or intellectual impairment and social exclusion and stigmatization as parts of a vicious cycle including school avoidance [3]. Childhood obesity tracks strongly into adulthood [4, 5]; obesity beyond

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12 years of age develops into adult obesity in greater than 80% of cases. Obese women have greater risks for polycystic ovary syndrome, subfertility, and a number of pregnancy complications including gestational diabetes, preeclampsia, and operative delivery, and their fetuses are at increased risk for spontaneous abortion, stillbirth, congenital malformations, and macrosomia. Long term follow-up studies have found greater risk of mortality and morbidity from coronary heart disease and atherosclerosis among men and women who were overweight in adolescence [6].

A growing body of evidence suggests that predisposition to a host of chronic diseases may be "programmed" *in utero* [7]. Most of these investigations were stimulated by the 'fetal origins' hypothesis proposed by Barker and colleagues, which showed a relationship between birthweight and adulthood hypertension [8], insulin resistance [9], vascular dysfunction [10], and dyslipidemia [11]. This hypothesis has evolved as a result of further investigation, and "developmental programming" is now more commonly ascribed to any situation where a stimulus or insult, at a sensitive or critical period of development, has lasting or lifelong impact on health or function [7, 12]. In this paper we explore whether predisposition to childhood overweight or obesity might be programmed *in utero* by prenatal insults. Specifically, we examined the relationship between three such prenatal insults – maternal diabetes, malnutrition, or cigarette smoking – and childhood overweight or obesity. The primary aim of this paper is to review the epidemiological evidence for prenatal programming of childhood overweight and obesity, with discussion of the implications of this literature for MCH research, practice, and policy.

Materials and methods

A systematic review of the literature was conducted using MOOSE guidelines for systematic reviews of observational studies [13]. The primary study outcome for our systematic review was childhood overweight or obesity, variably defined by body mass index (BMI) measured at ages 5 to 21 (Tables 1–3). We limited our search to 3 prenatal exposures: maternal diabetes, malnutrition, and cigarette smoking. Inclusion criteria were published studies examining or reporting a relationship between prenatal exposure to maternal diabetes, malnutrition, and smoking and childhood overweight or obesity as defined by BMI (or index of weight for height). Exclusion criteria were studies published solely in foreign languages, review articles, commentaries, studies observing outcomes in offspring less than 5 years of age (due to problems in defining overweight/obesity in children under 5) or greater than 21 years of age, studies which defined obesity by a target weight without reference to BMI, and studies which only reported mean relative weight, weight-to-height ratio, BMI, ponderal index, or skinfold thickness without reference to prevalence of overweight and obesity in their study groups. When studies that met inclusion and exclusion criteria followed offspring from childhood to greater than age 21 years, only outcomes observed in offspring between the ages of 5 and 21 years were included in our review.

Two investigators (JSH and TAL) conducted independent literature searches in PubMed and MDConsult for epidemiological studies published between January 1975 and December 2005, using search terms "prenatal," "intrauterine," "maternal smoking," "malnutrition," "undernutrition," "famine," "gestational diabetes," "maternal diabetes," "offspring obesity," and "childhood obesity". No search software was used, and no efforts were made to identify unpublished studies. Inclusion and exclusion criteria were independently applied by the two investigators to publications based on information in the title and abstracts of articles as provided on PubMed and MDConsult. Reference lists of obtained articles meeting inclusion and exclusion criteria were also hand searched by at least one investigator for inclusion in our review. No contacts were made with the authors. Data was extracted from articles by at least one investigator and was checked for both accuracy and precision. When unreported by primary researchers, odds ratios with confidence intervals were calculated from studies providing sufficient data using the CDC's Epi Info software program (Version 6).

Results

Maternal diabetes

Our search identified 11 studies examining the relationship between maternal diabetes and childhood overweight or obesity, of which 6 met inclusion and exclusion criteria [14–19]. Five studies were excluded because they only reported mean BMI or mean relative weight without reference to prevalence of overweight or obesity in their study groups, and one study was excluded because obesity was defined as greater than 140% of target weight without reference to BMI [20–24] (Table 4). Of the 6 included studies, 1 was prospective and 5 were retrospective cohort in design. Four studies [14–17] showed higher prevalence of obesity among offspring born to women with pre-gestational (PGDM) and gestational diabetes (GDM) compared to those born to non-diabetic mothers, although the difference between groups reached statistical significance in only one study and bordered on significance in two studies. One study [18] compared offspring of women with PGDM to those of women with GDM and found higher prevalence of obesity among offspring of PGDM women (Table 1).

Vohr et al. [16] conducted the first study on maternal diabetes and offspring obesity (defined as weight/height index

Table 1 Included studies examining the association between prenatal exposure to maternal diabetes and childhood overweight and obesity

Author	Year	Type of study	Exposure Variable	Outcome variable	Age at Outcome (yrs)	Result	Adjusted covariates
Gillman	2003	Retrospective cohort	GDM	Overweight: BMI >95th percentile	9–14	% overweight (GDM) = 45/465 (9.7%) % overweight (control) = 958/14416 (6.6%) Adjusted OR = 1.4 (1.0–1.9)	Age, gender, tanner stage, television watching, physical activity, energy intake, breast feeding duration, birth order, household income, mothers smoking, dietary restraint, weight cycling, weight cycling, weight concerns
Malee	2002	Retrospective cohort	GDM	Obesity: BMI >85th percentile	9	% obese (GDM) = 11/33 (33%), % obese (control) = 8/31 (26%) Unadjusted OR = 1.4 (0.4–4.9)	Obesity was not the dependent variable in the multivariate model
Plagemann	1997	Retrospective cohort	PGDM vs GDM	Overweight: BMI ≥ 95th percentile	5–9	% overweight (PGDM) = 8/31 (25.8%) % overweight (GDM) = 3/15 (20%) Unadjusted OR = 1.4 (0.3–8.2)	Race
Vohr	1980	Retrospective cohort	PGDM, GDM	Obesity: Weight/Height Index ≥ 1.2	7	% obese (study) = 8/34 (24%) % obese (control) = 2/34 (6%) Adjusted OR = 4.9 (0.9–37)	Age, race
Vohr	1999	Prospective cohort	GDM	Obesity: BMI >90th percentile	7	LGA % obese (GDM) = 14/37 (38%) % obese (control) = 6/42 (15%) Unadjusted OR = 3.7 (1.1–12.6) AGA % obese (GDM) = 3/50 (6%) % obese (control) = 8/40 (20%) Unadjusted OR = 0.3 (.05–1.2)	Pregnancy weight gain, race and socioeconomic status
Whitaker	1998	Retrospective cohort	GDM diet controlled	Obesity: BMI >85th percentile	5–10	% obese (GDM) = 11/58 (19%) % obese (controls) = 62/257 (24%) Unadjusted OR = 0.74 (0.3–1.6)	Age, sex, race, parental obesity, and socioeconomic status

Note. AGA: Appropriate for Gestational Age; BMI: Body Mass Index; GDM: Gestational Diabetes Mellitus; IDDM: Insulin Dependent Diabetes Mellitus; LGA: Large for Gestational Age; PGDM: Pregestational Diabetes Mellitus; OR: Odds Ratio.

*Confidence intervals are 95% unless otherwise noted.

Table 2 Included study examining the association between prenatal exposure to maternal malnutrition and childhood obesity

Author	Year	Type of study	Exposure variable	Outcome variable	Age at Outcome (yrs)	Result	Adjusted covariates
Ravelli	1976	Retrospective cohort	Maternal famine during the first 2 trimesters of pregnancy	Obesity: weight for height ≥120% of standard	19	% obese (famine) = 119/4300 (2.77%) % obese (control) = 230/15900 (1.45%) Unadjusted OR = 1.94 (1.54–2.44)[a]	Social class, time place
			Maternal famine during last trimester of pregnancy and the first 3–5 months of life	Obesity: weight for height ≥120% of standard	19	% obese (famine) = 51/6200 (0.82%) % obese (control) = 148/11200 (1.32%) Unadjusted OR = 0.62 (0.44–0.86)a	Social class, time place

Note. OR: Odds Ratio.

Confidence intervals are 95% unless otherwise noted.

greater than or equal to 1.2). The study included 34 children born to women with pregestational (PGDM) and gestational (GDM) diabetes and 34 age- and race-matched controls. At age 7, 24% of offspring of diabetic mothers and 6% of controls were obese, but the difference was not statistically significant due to the small sample size. Vohr and colleagues [17] conducted another prospective study on a different sample involving 4 groups: large-for-gestational-age (LGA) and appropriate-for-gestational-age (AGA) infants born to women with and without laboratory evidence of gestational diabetes. Among LGA children, 38% of offspring of GDM mothers and 15% of controls were obese (BMI >90th percentile) at age 7 (OR = 3.7; 95% CI = 1.1–12.6). No significant difference was observed in offspring born AGA.

More recently, Malee et al. [15] conducted a retrospective cohort study of 9-year-old children born to women with and without GDM. One in 3 (33%) of the offspring of women with GDM and 26% of control offspring had a BMI above the 85th percentile, but the difference did not reach statistical significance. Gillman et al. [14] conducted the largest study of maternal diabetes and offspring obesity. Among the 465 subjects whose mothers had GDM, 17.1% were at risk for overweight (BMI 85th to 95th percentile) and 9.7% were overweight (BMI >95th percentile) in early adolescence. Among 14416 adolescents whose mothers did not have diabetes, these estimates were 14.2% and 6.6%, respectively. The adjusted odds ratio for adolescent overweight was 1.4 (95% CI = 1.0 to 1.9), controlling for multiple demographic, dietary and other behavioral factors.

Plagemann et al. [18] conducted a retrospective cohort study comparing children born to women with PGDM and GDM. At ages 5–9, 25.8% of children of PGDM mothers and 20% of children of GDM mothers were obese (BMI >95th percentile). Whitaker et al. [19] conducted a retrospective chart review and found a prevalence of obesity (>85th percentile) of 19% among the offspring of mothers with diet-treated GDM, compared to 24% among the offspring of mothers with negative glucose screen values.

Maternal malnutrition

Our search identified 3 studies of maternal malnutrition, of which only one met inclusion and exclusion criteria [25]. Two other studies were excluded because the subjects were adults (age>21) at the time of assessment [26, 27] (Table 4). The included study [25] was a historical cohort study of 300000 19-year-old men exposed to the Dutch famine of 1944–1945. Obesity was defined as weight for height greater than 120% of the standard. Compared to unaffected controls, intrauterine exposure to famine during the first two trimesters of pregnancy was associated with a significant 94% increase in risk of obesity (2.77% of exposed group vs.

Table 3 Included studies examining the association between prenatal exposure to maternal smoking and childhood overweight and obesity

Author	Year	Type of study	Exposure variable	Outcome variable	Age at outcome (yrs)	Result	Adjusted covariates
Bergmann	2003	Prospective cohort	Maternal smoking during pregnancy	Obesity: BMI >97th percentile Overweight: BMI >90th percentile	6	% obese (smoke) = 25/177 (14.1%) % obese (control) = 54/659 (8.2%) Adjusted OR for obesity = 2.30 (1.15–4.60) Adjusted OR for overweight = 2.08 (1.19–3.63)	Breastfeeding, overweight mother, social status
						Males	
Power	2002	Retrospective cohort	Maternal smoking after the 4th month of pregnancy	Obesity: BMI >90th percentile	7, 11, 16	Unadjusted OR (age 7) = 1.12 (0.94–1.33) Unadjusted OR (age 11) = 1.16 (0.97–1.39) Unadjusted OR (age 16) = 1.29 (1.06–1.55)	Gender of offspring
						Females	
						Unadjusted OR (age 7) = 1.07 (0.90–1.28) Unadjusted OR (age 11) = 1.22 (1.02–1.46) Unadjusted OR (age 16) = 1.32 (1.12–1.65)	
Salsberry	2005	Retrospective cohort	Maternal smoking during pregnancy	Overweight: BMI >95th percentile	6–7.9	Adjusted OR 1.74 (1.32–2.29)	Race, gender of offspring, child age, parity,% weight for gestational age, breastfeeding, prepregnancy weight, maternal age at birth, maternal education, marital status, height measured, weight measured, birth cohort
Toschke	2002	Cross-sectional	Maternal smoking throughout pregnancy	Obesity: BMI >97th percentile Overweight: BMI >90th percentile	5–6.99	% obese (smoke) = 6.2%% obese (control) = 2.8% Adjusted OR for obesity = 1.92 (1.29–2.86) Adjusted OR for overweight = 1.58 (1.23–2.04)	Breasfeeding, parental education, birthweight, and prematurity
						Obesity	
Toschke	2003	Cross-sectional	Maternal smoking during the 1st trimester of pregnancy only or throughout pregnancy	Obesity: BMI ≥ 30 Overweight: BMI ≥ 25	5–6	%obese (smoke 1st trimester) = 4.5% %obese (smoke all pregnancy) = 5.9% %obese (contol) = 1.9% Adjusted OR (smoke 1st trimester) = 2.22 (1.33–3.69) Adjusted OR (smoke all pregnancy) = 1.70 (1.02–2.87)	Breastfeeding, parental educational level, parental obesity, watching TV, playing electronic games, physical activity, and high infant weight gain
						Overweight	
						% overweight (smoke 1st trimester) = 14.4% %overweight (smoke all pregnancy) = 15.8% %overweight (control) = 9.2% Adjusted OR (smoke 1st trimester) = 1.52 (1.14–2.01) Adjusted OR (smoke all pregnancy) = 1.23 (0.89–1.70)	

Table 3 Continued

Author	Year	Type of study	Exposure variable	Outcome variable	Age at outcome (yrs)	Result	Adjusted covariates
von Kries	1999	Cross-sectional	Maternal smoking during pregnancy	Obesity: BMI>97th percentile Overweight: BMI>90th percentile	5–6	Adjusted OR for obesity = 1.85 (90% CI 1.26–2.71) Adjusted OR for overweight = 1.52 (90% CI 1.81–1.95)	Breastfeeding, parental education, birthweight, own bedroom, consumes butter $\geq$ 3x/wk
von Kries	2002	Cross-sectional	Maternal smoking during pregnancy	Obesity: BMI>97th percentile Overweight: BMI>90th percentile	5–6.99	Adjusted OR for obesity = 2.06 (1.31–3.23) Adjusted OR for overweight = 1.43 (1.07–1.90)	Parental education, parental obesity, birthweight, breastfeeding, watching TV/playing video games for >1 hr daily, and snacking in front of the TV
Wideroe	2003	Prospective cohort	Maternal smoking during week 17 of pregnancy	Overweight: BMI $\geq$ 85th percentile	5	Adjusted OR = 2.9 (1.3–6.6)	Maternal age/skinfold thickeness/education, paternal education, duration of breastfeeding, total maternal energy intake in week 17, maternal% fat intake at week 33, maternal% carbohydrate intake at week 33

Note. OR: Odds Ratio.

*Confidence intervals are 95% unless otherwise noted.

1.45% of control group were obese, OR 1.94, 95% CI = 1.54–2.44), whereas intrauterine exposure to famine during the last trimesters of pregnancy and the first 3–5 months of life was associated with a significant 38% reduction in the risk of obesity (0.82% of exposed group vs. 1.32% of control group were obese, OR = 0.62, 95% CI = 0.44–0.86) (Table 2).

Maternal smoking

Our search identified 13 studies examining the relationship between prenatal exposure to maternal smoking and childhood overweight or obesity, of which 8 met inclusion and exclusion criteria [28–35]. One study was excluded because the outcome (obesity) was assessed at age 33 [36]. Four studies were excluded because they only reported mean BMI, ponderal index, or skinfold thicknesses without reference to prevalence of overweight and obesity in their study groups [37–40] (Table 4). Of the 8 included studies, 4 were cross-sectional and 4 cohort in design (Table 3). Prenatal exposure was variably defined as smoking $\geq$ 1 cigarette per day after the 4th month of pregnancy [29], smoking one or more cigarettes per day in week 17 of pregnancy [35], or an indication of 'yes' when maternal smoking status during pregnancy was dichotomized into a 'yes' or 'no' variable on study questionnaires [28, 30–34]. All 8 included studies showed significantly higher odds of childhood overweight or obesity associated with prenatal exposure to maternal smoking. Odds ratios for childhood obesity ranged from 1.1 to 2.9, with most of the OR's clustering around 1.5 to 2.0 (Table 3).

Von Kries et al. [31] made the first suggestion of a link between prenatal exposure to maternal smoking and childhood obesity in 1999 by studying the relationship between breastfeeding and offspring obesity and finding maternal smoking to be an independent risk factor for childhood obesity in the course of their analyses. In the study, von Kries et al. used cross-sectional data on 5- to 6-year old children who completed 1997 obligatory school health entrance examinations and parent questionnaires in Bavaria, Germany. In the final logistic regression model, maternal smoking during pregnancy was associated with an odds ratio for obesity of 1.85 (90% CI = 1.26–2.71). From 2002 to 2003, von Kries and Toschke worked together and with other investigators to publish three studies that directly examined the relationship between prenatal exposure to maternal smoking and risk of childhood obesity [32–34]. They again utilized cross-sectional data obtained from obligatory school health examinations in Bavaria, Germany and limited their studies to children aged 5 to 7 years. Their analysis of cross-sectional data from 1997, 1999, and 2001 demonstrated that exposure to maternal smoking was associated with an adjusted odds ratio for childhood obesity of 1.92 (95% CI = 1.29–2.86) [32], 2.06 (95% CI = 1.31–3.23) [34], and 1.70 (95% CI =

Table 4 Characteristics of excluded studies and rationale for exclusion

Author	Year	Type of study	Exposure variable	Outcome variable	Age at outcome (yrs)	Result	Reason for exclusion
Dabelea	2000	Retrospective cohort	GDM	Mean difference in BMI between related offspring of diabetic and nondiabetic pregnancies	Mean 13	Mean BMI 2.6 higher in offspring of diabetic pregnancies (CI = 0.9–4.3) p = 0.003	Reported mean BMI without reference to prevalence of obesity in study groups
Pettitt	1987	Retrospective cohort	PGDM, GDM	MRW	5–19	Age 5–9 MRW (nondiabetic) = 115.7 MRW (prediabetic) = 113.7 MRW (diabetic) = 135.8 p = 0.004 Age 10–14 MRW (nondiabetic) = 127.1 MRW (prediabetic) = 126.9 MRW (diabetic) = 152.4 p = 0.01 Age 15–19 MRW (nondiabetic) = 127.0 MRW (prediabetic) = 130.6 MRW (diabetic) = 147.1 p = 0.203	Reported MRW without reference to BMI or to prevalence of obesity in study groups
Pettitt	1983	Retrospective cohort	PGDM, GDM	Obesity: ≥ 140% of target weight	15–19	% obese (study) = 14/24 (58%) % obese controls = 87/512 (17%) p < 0.001 Unadjusted OR = 6.84 (2.75–17.22)[a]	Defined obesity by target weight without reference to BMI
Silverman	1995	Prospective cohort	PGDM, GDM	Mean BMI	11–14	Mean BMI (study) = 22.8 ± 5.4, Mean BMI (controls) = 20.3 ± 4.0 p = 0.001	Reported mean BMI without reference to prevalence of obesity in study groups
Silverman	1998	Prospective cohort	PGDM, GDM	Mean BMI	14–17	Mean BMI (study) = 24.6 ± 5.8, Mean BMI (controls) = 20.9 ± 3.4	Reported mean BMI without reference to prevalence of obesity in study groups
Ravelli	1999	Retrospective cohort	Maternal famine during early, mid, or late gestation	Mean BMI	50	Mean BMI of 50-year-old women exposed to famine in early gestation was significantly higher by 7.4% (0.7%–14.5%) than that of controls	Outcome at age >21 years
Stanner	1997	Retrospective cohort	Maternal famine during gestation	BMI	50	BMI (famine) = 24.6 (23.6–25.6) BMI (control) = 25.2 (24.1–26.3)	Outcome at age >21 years
Blake	2000	Retrospective cohort	Maternal smoking during pregnancy as reported at 18 weeks of GA	Mean BMI	6	Mean BMI (smoke) = 16.1 Mean BMI (control) = 15.7 p < 0.01	Reported mean BMI without reference to prevalence of obesity in study groups

Table 4 Continued

Author	Year	Type of study	Exposure variable	Outcome variable	Age at outcome (yrs)	Result	Reason for exclusion
						Age 6	
Fried	1999	Prospective cohort	Light (0–16 cigarettes/day) or heavy ($\geq$ 16 cigarettes/day) maternal smoking during pregnancy	PI, weight-to-height ratio	6–12	Children exposed to heavy maternal smoking had higher PI than children exposed to light or no maternal smoking [F(2128) = 2.7, p = 0.07] Age 9–12 Children exposed to heavy maternal smoking had greater weight-to-height ratio than controls [F(2, 129) = 2.8, p = 0.07]	Reported PI and weight-to-height ratio without reference to prevalence of obesity in study groups
Montgomery	2002	Retrospective cohort	Medium, variable and heavy maternal smoking	BMI >30	33	Adjusted OR (medium) = 1.34 (1.07 to 1.69) Adjusted OR (variable) = 1.35 (0.95 to 1.92) Adjusted OR (heavy) = 1.38 (1.06 to 1.79)	Outcome at age >21 years
						Age 8–11	
Hill	2005	Retrospective cohort	Maternal smoking during pregnancy	BMI	8–18	BMI (smoke) = 20.14 BMI (control) = 18.73 X^2 = 9.94 (0.002) Age 12–15 BMI (smoke) = 24.4 BMI (control) = 21.58 X^2 = 8.16 (p = 0.004) Age 16–18 BMI (smoke) = 26.9 BMI (control) = 24.22 X^2 = 4 (p = 0.05)	Reported BMI without reference to prevalence of obesity in study groups
Vik	1996	Prospective cohort	Maternal smoking of 1–25 cigarettes/day during pregnancy as reported at the time of conception	PI, SST, TST	5	PI (smoke) = 1.43 (SD 0.13) PI (control) = 1.39 (SD 0.13) p < 0.01 SST (smoke) = 6.3 (SD 2.8) SST (control) = 5.5 (SD 1.5) p < 0.01 TST (smoke) = 10.7 (SD 2.7) TST (control) = 10.0 (SD 2.3) p < 0.05	Reported PI, SST, and TST without reference to prevalence of obesity in study groups

Note. OR: Odds Ratio; MRW: Mean Relative Weight; PI: Ponderal Index; SST: Subscapular Skinfold Thickness; TST: Triceps Skinfold Thickness.

*Confidence intervals are 95% unless otherwise noted.

1.02–2.87) [33], respectively. Various confounding factors in these studies were controlled for including but not limited to parental BMI, childhood nutrition (e.g. breastfeeding, eating snacks while watching TV, butter consumption), childhood activity (e.g. watching TV, playing electronic games), and socioeconomic status. Notably, Toschke et al. [33] compared risk of childhood obesity in offspring born to mothers who smoked only during the first trimester of pregnancy compared to those born to mothers who smoked throughout pregnancy and found no significant difference.

In 2002, Power et al. [29] also published studies on the association between *in utero* exposure to maternal smoking and risk of childhood obesity using retrospective data from the British National Child Development Study that contained information on 17414 children born in Wales, England, and Scotland from March 3–9, 1958. Analyzing data on cohort members with follow-up information available at age 7, 11, and 16 years, Power et al. [29] demonstrated that children of smokers had an elevated risk of being in the most obese decile of BMI, which was significant by 11 and 16 years, respectively, for females and males, with odds ratios of 1.29 (95% CI 1.06–1.55) for males and 1.32 (95% CI = 1.12–1.65) for females at age 16 years.

In 2003, Bergmann et al. [28] and Wideroe et al. [35] continued to support a positive association between prenatal exposure to maternal smoking and childhood obesity and overweight. Bergmann et al. [28] analyzed longitudinal data from the German Multicenter Atopy study of a subset of singleton term infants born in rural and urban Germany in 1990. In the study, it was found that 14% of children exposed to maternal smoking were obese compared to 8% of children not exposed to maternal smoking at 6 years of age (OR = 1.84; 95% CI 1.08–3.14). Wideroe et al. [35], who conducted the only prospective study found in our review, followed 482 women in Norway and Sweden throughout their pregnancy and followed their children from birth until 5 years of age. Based on BMI recorded for 336 children at age 5 years, Wideroe et al. reported that exposure to maternal smoking during pregnancy was associated with an increased risk of childhood overweight (RR 2.5; 95% CI = 1.5–4.2). After adjusting for potential confounders including maternal age, maternal skinfold thickness, maternal education, parental education, duration of breastfeeding, and maternal dietary intake during pregnancy, the increased risk of childhood overweight associated with maternal smoking persisted (OR of 2.9; 95% CI = 1.3–6.6).

More recently, Salsberry et al. [30] conducted a retrospective cohort study based on data from the National Longitudinal Survey of Youth's Child-Mother file to study prenatal characteristics that drive development of childhood overweight. The study sample comprised 3022 children and found that prenatal exposure to maternal smoking was associated with increased risk of childhood overweight (OR 1.74; 95% CI = 1.32–3.29) in children aged 6 to 7.9 years.

Discussion

In discussing our findings, we first evaluate the evidence for a causal relationship between prenatal exposure to maternal diabetes, malnutrition, and cigarette smoking and childhood overweight and obesity. This is then followed by a discussion of implications for MCH research, practice, and policy.

Evaluating the evidence for causality

We applied previously published guidelines [41] to evaluate evidence of a causal relationship between the prenatal factors studied in our review and childhood overweight and obesity. The guidelines include four major criteria (temporal relationship, biologic plausibility, consistency, and alternative explanations) and three additional considerations (dose-response relationship, strength of association, and coherence).

The first criterion, the presence of a temporal relationship, implies that exposure always precedes the outcome. Hill [41] introduced this reflection with the proverb "Which is the cart and which is the horse?" In none of the studies we reviewed was there any confusion that the exposure (maternal diabetes, malnutrition, or smoking during pregnancy) might have occurred after the outcome (overweight or obesity in the offspring); all studies satisfied the temporal relationship criterion for causality.

The second criterion, biologic plausibility, refers to the presence of a biological explanation for the observed association. In animal studies, intrauterine exposure to maternal smoking, maternal malnutrition, and maternal diabetes has been linked to postnatal obesity [42–47] and changes in organs involved in the fetal metabolic pathways. While many proposed mechanisms of prenatal programming of obesity remain speculative, there is evidence to support prenatal programming of resistance to endocrine hormones such as leptin, insulin, and glucocorticoids that may predispose to obesity in postnatal life [48].

The proposed mechanisms linking maternal diabetes to childhood obesity posits that maternal diabetes, especially with poor glycemic control, results in fetal hyperglycemia which, in turn, induces fetal hyperinsulinemia [49, 50]. It is hypothesized that fetal hyperinsulinemia, during critical periods of fetal development, can induce insulin and leptin resistance in part by down-regulation of insulin and leptin receptors. Programmed central insulin and leptin resistance can lead to hyperphagia, while pancreatic insulin and leptin resistance can lead to hyperinsulinemia and overgrowth of fat cells, both of which may increase risk of obesity in postnatal life [46, 50, 51].

The proposed mechanisms linking maternal malnutrition to childhood obesity also involves programmed structural and functional abnormalities of various endocrine systems [7]. In animal studies, maternal protein-calorie restriction has been linked to phenotypic postnatal insulin resistance [52] and alterations in the structure and function of the fetal pancreas [48, 53]. Some authors have observed that abnormal insulin/glucose homeostasis is consistently programmed by dietary insult *in utero* and that associated changes to pancreatic structure and function in fetal life persist into adulthood [7, 54]. Offspring leptin resistance may also be programmed by prenatal exposure to nutrient restriction as maternal malnutrition has been shown to impact the development of leptin-sensitive neural pathways in utero [55, 56]. Prenatal exposure to maternal malnutrition has also been linked with programmed central glucocorticoid resistance [57, 58] and possible increased peripheral glucocorticoid sensitivity in offspring [59].

The mechanisms linking maternal smoking to offspring obesity are not as well elucidated. While there is some evidence linking postnatal exposure to nicotine to alterations in plasma leptin and expression of leptin receptors [60, 61], we identified no studies that have established leptin resistance in offspring who were exposed to maternal smoking *in utero*. Similarly, we found no evidence directly relating prenatal exposure to maternal smoking to postnatal insulin or glucococorticoid dysregulation, although one study showed decreased insulin levels and increased β-cell apoptosis in offspring of dams exposed to nicotine in pregnancy [43]. It is plausible that some of the programming effects of maternal smoking may be mediated through maternal malnutrition, as nicotine has been shown to suppress maternal appetite and induce uteroplacental vasoconstriction. In addition, carbon monoxide may reduce oxygen unloading to the fetus, and cyanide compounds may affect fetal oxidative metabolism [30].

The third criterion, consistency, refers to the replication of findings by different studies with "different persons, places, circumstances, and time" [41]. The strongest evidence of consistency is provided by the studies on maternal smoking; All 8 included studies demonstrated increased odds of childhood obesity associated with maternal smoking, with most odds ratios clustering around 1.5 to 2.0. Four of 6 included studies on maternal diabetes also found higher prevalence of obesity among offspring born to diabetic mothers, though only one study reached statistical significance largely because of small sample sizes in most other studies. The evidence of consistency is more limited for maternal malnutrition, as only 1 study was included and demonstrated a significant relationship between *in utero* exposure to famine and offspring obesity based on the timing of exposure.

The last major criterion, alternative explanations, refers to the adequacy of control for confounding. Confounding refers to a spurious relationship between an exposure and outcome created by an extrinsic factor that is associated with both exposure and outcome. Tables 1, 2, and 3 list confounders that were accounted for in individual studies, but many potential confounders remained unaccounted. The criterion is met most satisfactorily by the studies on maternal smoking, which controlled for a large number of potential confounders and continued to find a consistent, positive relationship between prenatal exposure to maternal smoking and childhood obesity. Other than the study by Gillman et al. [14], most studies of maternal diabetes controlled for very few confounders. The study on maternal malnutrition controlled for only maternal socioeconomic class, time, and place.

The three additional considerations for causality include dose-response, strength of association, and coherence. Dose-response implies that the outcome increases monotonically with increasing dose of exposure. Dose-response is suggested in the study by Plagemann et al. [18], which showed higher prevalence of childhood obesity among offspring born to women with PGDM, who presumably had greater degree of glucose intolerance and insulin resistance than women with GDM. Three of the nine studies on maternal smoking that met inclusion and exclusion criteria were able to demonstrate some evidence of a dose-response relationship between number of cigarettes smoked and risk of obesity in postnatal life [29, 34, 35]. Power et al. [29] reported a significant linear trend between prevalence of obesity in offspring at age 16 years and quantity of cigarettes consumed by mothers during pregnancy; in addition, offspring of persistent smokers had a higher prevalence of obesity than offspring of mothers who quit smoking during pregnancy. Von Kries et al. [34] and Wideroe et al. [35] reported greater prevalence of overweight and obesity in offspring of mothers who smoked 10 or more cigarettes daily versus those who smoked less than 10 cigarettes daily or no cigarettes at all.

Strength of association between exposure and outcome is usually measured by an odds ratio or relative risk. The studies on maternal smoking suggest a modest association (OR 1.5 to 2.0) with childhood obesity. For maternal diabetes, the study by Gillman et al. [14] suggests a modest (OR 1.4) association with childhood overweight; all other studies of maternal diabetes have odds ratios with confidence intervals too wide to be reliable. The study by Ravelli et al. [25] also demonstrated a modest association (OR 1.9) between prenatal exposure to famine in the first two trimesters of pregnancy and offspring obesity.

The final criterion, coherence, implies that the association should be consistent with existing theory and knowledge. For example, studies on both maternal smoking [33] and maternal famine [25] were able to show evidence that the effect of prenatal factors on postnatal obesity may be more important

in the first two trimesters of pregnancy. This is consistent with the notion of a "critical period" for developmental programming and demonstrates the principle of coherence with existing theory and knowledge.

In summary, our review found fair to good evidence in support of a causal relationship between prenatal exposures to maternal diabetes, malnutrition, and cigarette smoking and childhood overweight and obesity.

Implications for MCH research, practice, and policy

Research

Our review identified several new priority areas for MCH research on the prevention of childhood obesity. First, research efforts need to be expanded to identify what other prenatal factors may contribute to developmental programming of obesity. For example, does maternal stress, by activating placental CRH gene expression and fetal HPA axis [62], play a role in prenatal programming of insulin, leptin, and glucocorticoid resistance? Second, biological mechanisms mediating prenatal programming of obesity need to be further elucidated by more basic and clinical research studies. Such studies might include investigation of a possible role for genetics and epigenetics in prenatal programming of obesity. Third, new research methodologies need to be developed, such as longitudinal tracking of study participants in birth cohort studies, identification of novel biomarkers that are more predictive of future obesity risk, and development of more sophisticated analytic techniques for longitudinal modeling. Lastly, more intervention studies with appropriate experimental designs need to be conducted to identify effective preconceptional and prenatal strategies for primary prevention of obesity in the offspring. For example, does tighter glycemic control in mothers with gestational diabetes result in risk reduction for offspring obesity?

Practice

Our review suggests new approaches for clinical and public health practice for childhood obesity prevention. Obstetricians, family practitioners, midwives, childbirth educators, W.I.C. dieticians, and other prenatal care providers must now take on new roles in the prevention of childhood obesity. Health educators now have one more reason to encourage tight glycemic control, good nutritional intake, and smoking cessation during pregnancy. Pediatricians and neonatologists need to reexamine current feeding practices and recommendations for low birthweight infants. Overfeeding and rapid catch-up growth in low birthweight infants that have been prenatally programmed for postnatal obesity may be detrimental to long-term health. Public health practitioners also need to reexamine current approach to prevention of childhood obesity. How does the emerging evidence on prenatal programming of obesity reshape the core public health functions of assessment, assurance, and policy development with respect to childhood obesity prevention?

Policy

Our review has several important implications for public policy. First, current guidelines on screening for gestational diabetes need to be reconsidered in light of the growing evidence linking gestational diabetes to childhood obesity and early-onset diabetes in the offspring. In issuing their recommendations for screening for gestational diabetes, the USPSTF and ACOG considered only evidence for prevention of infant outcomes such as macrosomia, operative delivery, neonatal hypoglycemia, and neonatal hyperbilirubinemia [63–64]. The cost-benefit ratio of population-based screening is likely to improve substantially if childhood obesity and early-onset diabetes are included as outcomes. Second, in light of the evidence linking poor maternal nutrition to childhood and adult obesity in the offspring, public policy response to food insecurity in the U.S. needs to be expanded, particularly among pregnant women. One recent population-based survey in California found that nearly one in three pregnant women who were income-eligible for the Women, Infants, and Children (WIC) program reported being food-insecure [65]. Access to and the contents of WIC services need to be enhanced. Third, the strong evidence linking maternal smoking to childhood obesity calls for expanded and intensified public health efforts to prevent maternal smoking before and during pregnancy. Lastly, public health response to the epidemic of childhood obesity must be reframed in light of the growing body of evidence on prenatal programming of obesity. Presently *Healthy People 2010*, *the Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity* and other action plans for obesity prevention do not address prenatal factors [66, 67]. By the time the baby is born, the battle may be lost. The public health response needs to be expanded to include action steps to be taken not only in families and communities, healthcare, media, and schools, but also *in utero*.

Conclusion

Our review found fair to good evidence in support of prenatal programming of obesity. Although the exact mechanisms are still largely being worked out, the positive associations between prenatal exposure to maternal diabetes, malnutrition, and smoking and childhood overweight and obesity suggest that the prenatal period may be a critical period for public health intervention in curbing the epidemic of childhood obesity. Clinicians, researchers, and public health professionals

should focus on the prenatal period as an early and effective window of opportunity for childhood obesity prevention.

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