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Research Article

Prenatal Exposure to Maternal Cigarette Smoke and Offspring Risk of Excess Weight Is Independent of Both Birth Weight and Catch-Up Growth

Jonathan Gravel,[1,2] Beth Potter,[2] and Lise Dubois[1,2]

[1] *Institute of Population Health, University of Ottawa, Ottawa, ON, Canada K1N 6N5*
[2] *Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada K1H 8MS*

Correspondence should be addressed to Jonathan Gravel; jgravel@analysisgroup.com

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Prenatal exposure to maternal cigarette smoke (PEMCS) is one of the most common insults to the developing fetus and has consistently emerged as an important risk factor for excess weight in the offspring. However, no consensus exists on the mechanism of action or duration of impact. This study seeks to further examine the role of PEMCS on overweight status of children up to age 10. Mother and child pairs ($n = 1183$) were analysed from the *Québec Longitudinal Study of Child Development* (QLSCD) (1998–2010). Multivariable logistic regression models were used to control for confounders and assess mediation. PEMCS was associated with overweight status at age 10 (OR: 1.70; 95% CI: 1.20–2.43) after adjustment for early life exposures and childhood behaviours. This relationship remained robust after adjustment for birth weight and catch-up growth. Other significant predictors included APGAR score, mother's immigrant and weight status, family type and child energy intake. The elevated risk of excess weight among the offspring of smoking mothers was not accounted for by other known determinants, and PEMCS appears to play a role independent of birth weight and catch-up growth. Our research suggests that young mothers may be an important audience for targeting preventive strategies.

1. Introduction

Concern is mounting over the increase in prevalence and severity of overweight and obesity in children worldwide. Increases in overweight and obesity rates have been observed among both sexes, and across all socioeconomic groups with the strongest and most substantial increases in the developed world [1, 2]. Canada is among the countries with the highest prevalence of both adult and child overweight and obesity worldwide [3, 4]. The Canadian Health Measures Survey reported that approximately 17% and 6% of Canadian children aged 6- to 18-years are overweight and obese, respectively [4]. Obesity is associated with not only a wide range of adverse physical health outcomes with lifelong consequences [5], but also with negative psychological and social outcomes [6]. An important area of research aims to identify causal factors for excess weight that operate early in life to inform preventative strategies aimed at reducing future morbidity and mortality.

Childhood excess weight is ultimately a result of an energy imbalance between intake and expenditure [7], but the upstream biological mechanisms and the heightened susceptibility of certain individuals to this imbalance are not well understood [8]. Intrauterine life may be a critical period for the development of childhood excess weight. According to the developmental origins of adult disease hypothesis (the "Barker Hypothesis"), adverse influences early in development can result in permanent changes in physiology and metabolism that in turn lead to increased disease risk in later life [9, 10]. Specifically, the current model hypothesizes that these intrauterine events act through processes of developmental plasticity or epigenetic modifications to alter the development of the fetus to an extent that they affect its capacity to cope with the environment of postnatal life.

Prenatal exposure to maternal cigarette smoking (PEMCS) is one of the most common insults to intrauterine life [11]; in Canada, the estimated prevalence of smoking at any time during the third trimester of pregnancy remains above 10% [12]. Smoking during pregnancy is associated with a wide range of adverse fetal, obstetrical, and developmental outcomes [13]. While PEMCS has consistently emerged as an important risk factor for excess weight among offspring [14, 15], many studies have been unable to control for important social factors. Smoking during pregnancy has been associated with lower income and education, higher body weight of the mother, and a lower probability of breastfeeding [16], any of which may confound the association between PEMCS and overweight among offspring. Moreover, there is evidence that PEMCS may cause fetal growth restriction [15], and it has been associated with lower birth weight [17]. Children of smoking mothers may experience "catch-up growth" in the first months of life [18]. In turn, low birth weight and catch-up growth have both been associated with excess weight in infancy [19]. Thus, low birth weight and rapid catch-up growth may mediate the association between PEMCS and offspring excess weight (i.e., they may be intermediate variables on the causal pathway). Despite this, most studies of this association have adjusted for birth weight as a confounder and have neglected catch-up growth altogether. The primary objective of this study was to investigate the association between PEMCS and excess weight among offspring in a large population-based sample while controlling for a wide range of social and biological factors. The secondary objective was to examine the possible mediation of the association between PEMCS and excess weight by birth weight and catch-up growth.

2. Methods

2.1. Study Sample. The *Québec Longitudinal Study of Child Development* (QLSCD) is a prospective cohort study conducted by Santé Québec, a division of the Québec Institute of Statistics (http://www.iamillbe.stat.gouv.qc.ca/default_an.htm). The study seeks to examine the influence of a wide range of familial, social and biological factors on child development, including health, cognitive ability, and behaviour. At the onset of the study, the province of Québec had a population of just over 7.5 million and about 70 000 births per year. A representative sample (n = 2 120; 49% female) of children born in Québec in 1998 were recruited through the Master Birth Registry of the Ministry of Health and Social Services of Québec. The study used a stratified random sampling design. The sample was selected within strata that were based on (1) public health geographic regions, (2) birth rates, and (3) the ratio of males to females. Children born throughout the year were recruited to minimize any effect of seasonality. Exclusions from participation included nonsingleton births, children born with major diseases, and those who died before reaching 5 months of age. Followup is ongoing.

The QLSCD collects information about both children and their parents using structured self-completed questionnaires and face-to-face interviews with mothers and fathers (http://www.iamillbe.stat.gouv.qc.ca/outils_collecte_an.htm). From five months to eight years of age, data collection occurred annually but is now collected biannually as to minimize respondent burden. During each data collection period, participating families and interviewers signed a consent form. The consent form and study methods have been approved by the Ethics Committee of Santé Québec.

2.2. Outcome Ascertainment. Childhood weight status at ten years of age was the outcome of interest. Height (in meters) and weight (in kilograms) were measured by trained staff at the child's place of residence, using a detailed protocol and standard instruments (standard scale and measuring tape). Measurements falling between two major units were rounded down. Children were classified as being: "underweight/normal weight" or "overweight/obese" using the sex- and age-specific BMI cut-offs defined by the International Obesity Task Force (IOTF) [20]. These cut-offs for 2- to 18-year-olds are based on six nationally representative surveys from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore, and the United States and are an extrapolation of the World Health Organization's definitions of overweight (BMI $\geq$ 25 kg/m^2) and obesity (BMI $\geq$ 30 kg/m^2) at 18 years of age. As standard cutoffs used in the field of childhood obesity research, they allow for both interprovincial and international comparisons [21].

2.3. Exposure Ascertainment

2.3.1. Prenatal Exposure to Maternal Cigarette Smoking (PEMCS). The main predictor for the analysis was whether a child respondent was exposed to tobacco smoke in-utero. This variable was self-reported by the mother when the child was 5 months old.

2.3.2. Birth Weight. The study team received legal access to all participating families' medical records for a period of 90 days after the mothers signed an authorization form created by the Ministry of Health and Social Services. Birth weight was extracted from each child's delivery record from the birth hospital and recorded as a continuous variable. This variable was then categorized based on standard and clinically meaningful cut-points for analyses: low birth weight (<2.5 kg), normal birth weight (≥2.5 and ≤4 kg), and high birth weight (>4 kg).

2.3.3. Catch-Up Growth. Catch-up growth was derived as the difference between the mother-reported weight of the child at 5 months of age and the birth weight obtained from medical records. The continuous catch-up growth variable was converted into tertiles for analysis.

2.4. Covariates. Potential predictors of childhood overweight that were identified from published literature and available in the QLSCD database were considered for inclusion in final models. These variables included those related to birth and early life factors (whether the birth was premature,

the birth rank, the sex, and APGAR score of the baby, whether the baby suffered from a chronic disease at 5 months, and the duration of breastfeeding), maternal characteristics (age at child's birth, highest level of education, immigrant status, postnatal smoking habits, and weight status), child behaviour lifestyle factors (energy intake, relative physical activity, and sedentary behaviour), and family demographic and socioeconomic factors (household income, single-parent or two-parent home, and geographic living area). Covariate data were obtained from different cycles of the longitudinal study, based on data collection time points and response rates at each cycle. Data from the cycle deemed most epidemiologically relevant for each covariate were used whenever possible.

2.5. Analyses. All statistical analyses were conducted using SAS version 9.2 (SAS Institute; Cary, NC). The statistical significance level for all analyses was set at an alpha value of 0.05. The Chi-squared test of independence and univariate logistic regression was used to examine crude associations between the outcome and main predictor variables (including possible mediating variables), between the outcome and covariates, and between the main predictor variables and covariates.

Automated stepwise logistic regression was used to create final models with the entry value set at 0.20 and retention value set at 0.05 for all models. The main predictor of interest (PEMCS) was forced into all models. Candidate covariates entered in automated regression models were chosen based on an association with the main predictor, an association with the outcome or based on an *a priori* decision stemming from a consistent association in the literature. The final model included the following covariates: sex, APGAR score, duration of exclusive breastfeeding, immigrant status of the mother, mother's BMI, energy intake, physical activity, sedentary behaviour, family income, and family type. Once the base model was created (model 1), the potential mediating effects of birth weight and/or catch-up growth on the relationship between the main predictor (PEMCS) and outcome (overweight status) were assessed qualitatively using model 1 with the addition of only birth weight (model 2); the addition of only catch-up growth (model 3); and the addition of birth weight and catch-up growth simultaneously (model 4). Qualitative mediation was assessed through examination of the beta estimates of PEMCS of models 2, 3, and 4 and comparing them to the baseline beta of model 1. Evidence of partial mediation was defined as a meaningful change in the odds ratio of the main predictor. Full mediation was defined as complete replacement of the effect of PEMCS by that of birth weight and/or catch-up growth. This definition is in line with the Baron and Kenny as well as the McArthur approach to assess mediation [22]. Model fit was assessed using the Hosmer and Lemeshow Goodness of Fit Test and outliers were assessed using index and DFBETA plots.

3. Results

3.1. Descriptive. Of 2120 family participants recruited into the QLSCD in 1998, 1280 children were still being followed at age 10, and 1183 (55.8% of the original sample) had no item-missing data for key variables (PEMCS, measured height and weight, birth weight, and catch-up growth). Children included in this analysis were similar to those excluded on available variables (data not shown).

Using the IOTF definitions for overweight, 25% of respondent children included in the analysis were overweight at age 10, with a mean BMI of 16.87 and 22.88 for the normal weight and overweight groups, respectively. Table 1 presents the descriptive characteristics of the children included in this study according to their overweight or obesity status. In comparison to others, overweight children were more likely to have been born premature ($P = 0.0287$) and to have had a high risk APGAR score ($P = 0.0086$). Mothers of overweight children were more likely to be overweight themselves ($P < 0.0001$). Being overweight at 10 years of age was significantly associated with being in the highest quintile of energy intake ($P < 0.0001$). Overall, families with an overweight child tended to have a lower household income ($P = 0.0015$) and were less likely to have a single-parent family structure ($P = 0.0019$).

At the bivariable level, PEMCS was significantly and positively associated with being overweight at age 10 ($P = 0.003$). As described above, PEMCS was positively associated with both low birth weight and catch-up growth; however, neither low birth weight nor catch-up growth was statistically significantly associated with being overweight at age 10, although the association did approach statistical significance ($P = 0.0851$).

From the multivariable logistic regression analysis, the adjusted association between PEMCS and overweight at age 10 was positive and statistically significant (OR: 1.70; 95% CI: 1.20–2.43) (Table 2). Additional significant predictors in the final multivariable model included APGAR score, maternal immigrant status, maternal weight status, family type, and energy intake. The strongest predictor of overweight status at age 10 was the weight status of the mother (OR: 2.90; 95% CI: 2.10–3.99) (Table 2).

In the multivariable examination of possible mediation of the relationship between PEMCS and overweight status at age 10 (Table 3), the addition of birth weight to the base model (model 1) had no meaningful impact the estimated odds ratio for PEMCS as a predictor of childhood overweight. A similar nonmeaningful change in magnitude occurred after the addition of catch-up growth to the model. When both birth weight and catch-up growth were added to the model, the point estimate changed again only very slightly.

4. Discussion

Despite the well-documented deleterious effects of PEMCS, it remains one of the most common insults to the developing fetus. The epidemiological evidence demonstrating an association between PEMCS and increased risk for excess weight is strong and consistent, but the underlying mechanisms remain largely speculative. Our study sought to evaluate the relationship between PEMCS and the risk of overweight or obesity of children and to examine the possible mediating

Table 1: Descriptive characteristics of children included in the analysis by overweight or obesity status at age 10 (n = 1183).

Cycle collected		Overweight or obese children (n = 305) n (%)	Normal weight children (n = 878) n (%)
	Birth and Early Life		
5 months	PEMCS		
	No	209 (68.5%)	692 (78.8%)*
	Yes	96 (31.5%)	186 (21.2%)
Medical records	Birth weight		
	>4 kg	45 (14.9%)	91 (10.3%)
	≤2.5 kg and ≤4 kg	249 (81.8%)	762 (86.8%)
	<2.5 kg	11 (3.3%)	25 (2.9%)
Medical records	Premature birth (<37 weeks)		
	No	285 (93.4%)	846 (96.4%)*
	Yes	20 (6.6%)	32 (3.6%)
Medical records	APGAR score[a]		
	Other	265 (87.0%)	809 (92.1%)*
	High risk (0–6)	40 (13.0%)	69 (7.9%)
Medical records	Birth rank		
	First	126 (41.4%)	407 (46.3%)
	Second	130 (42.7%)	333 (37.9%)
	≥Third	48 (15.9%)	139 (15.8%)
Medical records	Sex		
	Female	160 (52.3%)	467 (53.2%)
	Male	145 (47.7%)	411 (46.8%)
5 months	Catch-up growth		
	1st tertile	101 (33.1%)	316 (36.0%)
	2nd tertile	101 (33.1%)	310 (35.3%)
	3rd tertile	103 (33.8%)	252 (28.7%)
5 months	Chronic disease[b]		
	No	261 (85.4%)	751 (85.6%)
	Yes	44 (14.6%)	127 (14.4%)
17 months	Duration of breastfeeding (exclusive)		
	≥3 months	86 (28.2%)	234 (26.7%)
	Other	133 (43.7%)	421 (47.9%)
	Never	86 (28.1%)	223 (25.4%)
	Maternal		
5 months	Age at child's birth (years)		
	≤29	60 (19.5%)	185 (21.1%)
	30–34	92 (30.2%)	285 (32.5%)
	35–39	108 (35.4%)	288 (32.8%)
	≥40	45 (14.9%)	120 (13.6%)
10 years	Level of education		
	≥Secondary school diploma	270 (88.4%)	786 (89.5%)
	<Secondary school diploma	35 (11.6%)	92 (10.5%)
10 years	Immigrant Status		
	Nonimmigrant	279 (91.4%)	818 (93.2%)
	Immigrant	26 (8.6%)	60 (6.8%)
10 years	Postnatal smoking habits		
	Non-smoker	229 (75.1%)	751 (85.6%)*
	Smoker	76 (24.9%)	127 (14.4%)

Table 1: Continued.

Cycle collected		Overweight or obese children (n = 305) n (%)	Normal weight children (n = 878) n (%)
17 months	Weight status		
	Normal weight	163 (53.4%)	666 (75.8%)*
	Overweight/obese	142 (46.6%)	212 (24.2%)
	Child Behaviour and Lifestyle		
4 years	Energy intake (Quintiles)		
	Other (1–4)	218 (71.4%)	743 (84.6%)*
	High (5)	87 (28.6%)	135 (15.4%)
6 years	Physical activity (compared to other children)		
	Same	214 (70.1%)	576 (65.6%)
	Higher/much higher	91 (29.9%)	302 (34.4%)
6 years	Sedentary behaviour (≥3 hours of television/day)		
	No	285 (93.4%)	822 (93.7%)
	Yes	20 (6.6%)	56 (6.3%)
	Demographic and Socioeconomic		
10 years	Household income ($)		
	<30,000	34 (11.3%)	61 (7.0%)*
	30,000–49,999	98 (32.2%)	215 (24.5%)
	50,000–79,999	95 (31.2%)	318 (36.2%)
	≥80,000	77 (25.3%)	284 (32.3%)
10 years	Family type		
	Two parent	214 (70.2%)	694 (79.1%)*
	Single-parent	91 (29.8%)	184 (20.9%)
10 years	Geographical living area		
	Rural	103 (33.9%)	319 (36.3%)
	Urban	202 (6.1%)	559 (3.7%)

*Denotes a statistically significant difference of covariate proportion between overweight and nonoverweight participants ($P < 0.05$).
[a]A crude scale (0–10) of assessing a baby's health immediately after birth, by scoring points for heart rate, breathing, skin colour, tone, and the baby's reactions.
[b]Excludes allergies but includes asthma.
Source: Québec Longitudinal Study of Child Development (QLSCD) 1998–2010, Québec Institute of Statistics.

Table 2: Odds ratios (or) and 95% confidence intervals (CI) of PEMCS and relevant covariates included in the final model on overweight status (IOTF) at age 10.

Covariate	Category	Unadjusted OR	95% CI	Adjusted OR[a]	95% CI
PEMCS	No	1.00	—	1.00	—
	Yes	1.71	[1.23, 2.19]	1.70	[1.20, 2.43]
APGAR score	Other	1.00	—	1.00	—
	High risk	1.75	[1.15–2.66]	1.80	[1.09, 2.98]
Mother's immigrant status	Non immigrant	1.00	—	1.00	—
	Immigrant	1.29	[0.80, 2.08]	1.80	[1.00, 3.24]
Mother's weight status	Normal weight	1.00		1.00	
	Overweight	2.71	[2.06, 3.58]	2.89	[2.10, 3.99]
Family type	Two parent	1.00	—	1.00	—
	Single-parent	1.60	[1.15, 2.22]	1.62	[1.08, 2.45]
Energy intake	Other (1–4)	1.00	—	1.00	—
	High (5)	2.19	[1.57, 3.05]	2.17	[1.51, 3.13]

[a]Adjusted for all covariates in the final model: sex, APGAR score, duration of exclusive breastfeeding, immigrant status of the mother, mother's BMI, energy intake, physical activity, sedentary behaviour, family income, and family type.
Source: Québec Longitudinal Study of Child Development (QLSCD) 1998–2010, Québec Institute of Statistics.

Table 3: The Odds ratios (OR) and 95% confidence intervals (CI) for the association between overweight (IOTF) at age 10 and PEMCS with adjustment for possible mediators.

	Base model (model 1)[a]	Adjusted for birth weight (model 2)[b]	Adjusted for catch-up growth (model 3)[c]	Adjusted for both (model 4)[d]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
PEMCS				
No	1.00	1.00	1.00	1.00
Yes	1.70 (1.19–2.43)	1.76 (1.23–2.51)	1.64 (1.15–2.33)	1.73 (1.21, 2.48)

[a]Adjusted for: sex, APGAR score, duration of exclusive breastfeeding, immigrant status of the mother, mother's BMI, energy intake, level of physical activity, level of sedentary behaviour, family income, and family type.

[b]Adjusted for all variables listed for model 1 with the addition of birth weight.

[c]Adjusted for all variables listed for model 1 with the addition of catch-up growth.

[d]Adjusted for all variables listed for model 1 with the addition of birth weight and catch-up growth.

Source: Québec Longitudinal Study of Child Development (QLSCD) 1998–2010, Québec Institute of Statistics.

role of birth weight and catch-up growth. Since PEMCS has consistently emerged as an important risk factor for low birth weight, it has been proposed as a possible mediator of the PEMCS-overweight relationship. Babies of low birth weight often experience a rapid catch-up growth phase during infancy or childhood, and this has been proposed as a potential pathway to link PEMCS to excess weight. To our knowledge, our study is the first to empirically investigate the hypothesis of a combined mediation effect of low birth weight and catch-up growth.

PEMCS was found to be a significant and independent predictor of childhood overweight at 10 years of age among Québec children even after adjusting for several important social and biological factors. Although our study demonstrated a positive association between PEMCS and both low birth weight and catch-up growth, neither potential mediator was related to overweight at age 10 in our sample. Furthermore, no attenuation of the PEMCS-overweight status association occurred when birth weight, catch-up growth, or both were included in the multivariable model. Thus, our findings do not support the hypothesis that low birth weight and/or catch-up growth are mediators of the PEMCS-childhood overweight relationship.

That PEMCS remained a significant risk factor for excess childhood adiposity independent of a wide range of common correlates of both the exposure, and the outcome supports the conclusions of recent systematic reviews [14, 15]. The fact that this association held strong after adjustment for birth weight supports findings from Beyerlein and colleagues [23, 24] and previous studies that did not assess this association directly but controlled for low birth weight in multivariable analyses [25, 26]. Our results are also supported by rodent work showing that fetal nicotine exposure can cause an increase in body weight with no difference in mean birth weight between the exposed and the unexposed [27, 28]. However, several studies have reported low birth weight as a mediator of the relationship between PEMCS and overweight status [29, 30]. The finding that the association of PEMCS and excess weight were unchanged after adjustment for a measure of catch-up growth has not, to our knowledge, been described in previous research.

Given that we found no strong evidence of mediation involving birth weight or catch-up growth, the mechanism through which PEMCS may lead to excess weight among offspring remains unclear. Possible alternative mechanisms exist at the hypothalamic or fat cell level. These include altered appetite behaviour due to alterations of cholinergic neurotransmitter systems [31] or even changes in food digestion efficiency [32]. There is some empirical support for the role of inappropriate setting of systemic hypothalamic control of both appetite and energy expenditure [33]. Fetal exposure to nicotine has also been shown to cause abnormal fat cell proliferation, differentiation, and synaptic activity in both the brain and peripheral autonomic pathways [34]. Some have shown that, even at birth, infants born to smoking mothers have a preserved ponderal index (weight for length) [35] with relatively more body fat mass [36]. Most of this mechanistic evidence is from ex vivo research and from animal models. Among the challenges in drawing conclusions from this evidence, these studies have concentrated on nicotine, which is only one of the thousands of chemicals found in a commercial cigarette.

It may be argued that the relationship between PEMCS and excess weight in offspring is not causal at all, but due to an unaccounted confounding factor, such as postnatal exposure to smoking. However, previous studies have suggested that paternal smoking can explain little [37] or none [38] of the association between PEMCS and offspring overweight, which refutes this idea. Furthermore, in a recent Australian study, the prevalence of overweight among children whose mothers smoked before and/or after pregnancy but not during pregnancy was similar to those who had never smoked at all [39].

Our findings need to be considered while acknowledging certain limitations. The primary outcome of this study was weight status of children based on established international cut-offs for BMI. The limitations of BMI are very well known [40]; however, BMI remains the most practical and most commonly used measure to screen overweight and obese children. In our study, BMI was derived from objectively measured heights and weights by trained staff, which has been shown to improve BMI as an indicator of overall

adiposity [41]. The exposure of interest, PEMCS, relied on maternal self-report of smoking behaviors with no biochemical validation. Because smoking during pregnancy is a complex behaviour with both daily fluctuations and changes over the course of pregnancy, quantifying tobacco exposure is a challenge. Different patterns of timing, duration, type, and quantity of maternal smoking may alter the effect on weight outcomes. However, misclassification of smoking would likely bias the estimated association between PEMCS and excess weight towards the null. Despite the aforementioned limitations, this study included a large longitudinal sample of children. We were able to take into consideration a wide range of important child, mother, and family sociodemographic characteristics to account for potentially confounding variables, including measures of both energy intake and physical activity.

The developmental origins of excess weight and the notion of priming chronic disease early in life are complex. Prospective longitudinal studies with repeated measures of heights and weights are needed to further quantify and compare the effects of early life risks. Regardless of the mechanism of action, if the evidence continues to support a causal role for PEMCS in contributing to childhood overweight and obesity, this represents an important opportunity for prevention. PEMCS is a key modifiable risk factor for a number of adverse pregnancy outcomes, highlighting its importance as a target for preventive action. Given the tracking of relative weight status from childhood through to adult life, targeting overweight and obesity early in life in turn may have lifelong impacts on physical health and quality of life.

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