Prenatal Exposure to Maternal Cigarette Smoke and Offspring Body Mass Index: A Prospective Study of Québec Children

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Abstract

Concern is mounting over the increase in prevalence and severity of overweight and obesity in children worldwide. Intrauterine life has been identified as a critical period for the development of overweight or obesity and other related chronic diseases. Prenatal exposure to maternal cigarette smoke (PEMCS) has consistently emerged as an important risk factor for excess weight in the offspring and is a targetable behaviour for prevention strategies.

This study examines first the relationship between PEMCS and overweight status of children at 10 years of age and second, whether PEMCS is associated with distinct longitudinal BMI trajectories. Analyses include multivariate and multinomial logistic regression and longitudinal group based modeling methods.

PEMCS was found to be a significant risk factor for overweight in children independent of birth weight and catch-up growth. However, PEMCS was not associated with BMI trajectory membership. Our results lend support to the paradigm of in-utero excess weight prevention.

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Chapter 1: Introduction

Concern is mounting over the increase in prevalence and severity of overweight and obesity in children worldwide. Over the past 25 years, increases in overweight and obesity rates have been observed among both sexes, and across all socio-economic groups in the developed and developing world (1,2). Although obesity was rarely seen in Canadian children only 30 years ago, it is now evident in children of all ages (3). This is of concern as excess weight during childhood tends to persist into adulthood (4). Obesity is associated with not only a wide range of adverse physical health outcomes (5) with life-long consequences, but also with negative psychological and social outcomes (6). It is well recognized that current unabated trends in both child and adult overweight and obesity pose threats to the Canadian health care system (7) and suggest a poor forecast for global health in the 21st century (8). 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.

At the population level, childhood obesity is rooted in a complex web of socioeconomic, psychosocial, behavioural and biological risks and deterrents. At the individual level, childhood overweight and obesity is ultimately a result of an energy imbalance between intake and expenditure (9), but the upstream biological mechanisms and the heightened susceptibility of certain individuals to this imbalance are not well understood (79). Many different conceptual models have framed the progression to obesity (10,11), but most tend to point to a complex multi-factorial causal pathway (Appendix 1).

A large volume of evidence suggests that intrauterine life may be a critical period for the development of childhood overweight and obesity. This paradigm stems from the seminal work of David Barker and colleagues who established that a less than ideal prenatal environment is associated with later chronic disease (83). This work has since been further developed through a wide range of population based studies (11) and animal work (12). Collectively, this body of work has led to a broad acceptance of the 'developmental origins of adult disease', or often coined the 'Barker hypothesis' (13).

The following chapter provides: background including a definition and overview of measurements of childhood overweight and obesity, Canadian and international prevalence of overweight and obesity, as well as short and long term consequences of overweight and obesity. Finally, the chapter summarizes the rationale for this study.

1.1 Background

In its simplest form, being overweight or obese is a condition where excess body fat has accumulated to an extent that may adversely affect an individual's health (14). Since it is quite challenging to measure directly, it is usually approximated by one's body weight being greater than what is considered healthy based on age, sex, height and race (15). Thus, an individual with a body weight above this conceptually hard to define 'healthy' weight may experience increased risk of morbidity or early mortality (5).

An ideal definition of overweight or obesity should not only be diagnostic of high body fat content, but also denote an increased risk of negative health outcomes. In most epidemiological research, indirect and relatively inexpensive estimating methods of overweight and obesity are used. These include skinfold thickness, waist circumference and Body Mass Index (BMI) (16). Each of these has limitations - as for example, little agreement exists on the optimal sites for skinfold thickness measurements in children (17).

The least intrusive and most widely used of the indirect methods for assessing excess weight or body fat content is BMI. BMI is calculated by dividing weight (kg) by height squared (m^2) (18). These anthropometric measures are ideally measured by a medical professional (19). However, in large epidemiological studies (20), they are often self-reported (21) or parent reported (22), as these are inexpensive and rapid alternatives to direct measurements. Many studies have reported high correlation between BMI and clinical measures of body fat (20) and BMI has been reported to be a moderately sensitive and specific indicator of excess adiposity among children (16). While the limitations of BMI are well documented (23), other more objective measures of percent body fat (Magnetic Resonance Imaging, Computerized Tomography, Dual-Energy X-ray Absorptiometry, Bioelectric Impedance and Dual X-ray Absorptiometry) are often too expensive and invasive for use in epidemiological research with large sample sizes. These alternatives are also often not well suited for measuring fat composition in young children (24). Furthermore, almost all international estimates of the prevalence of childhood overweight or obesity are based on BMI. Overall, BMI (even after adjustment for sex and age) can give an imperfect indication of the body composition of an

individual; however, it performs very well as a screening tool and in defining high risk groups in epidemiological research (25).

When using BMI as a measure of overall adiposity in children, three main classification systems exist. The first was developed by the International Obesity Task Force (IOTF) (26) and the second is based on the Center for Disease Control (CDC) growth curve cut-offs for overweight (27). Both the derivation and caveats of these classification systems are described further elsewhere (Chapter 4.3.1). The third classification system recently released by the World Health Organization (WHO) is based on growth curves generated from the Multicenter Growth Reference Study (MGRS) (28). This system differs from the IOTF and the CDC systems because the growth curves represent a desired standard (prescriptive-based) as opposed to a description of a reference population (descriptive-based) (29). The new system has yet to reach an acceptable level of prevalence in academic research, therefore limiting its current ability to allow cross study comparisons.

1.1.1 Canadian and International Prevalence of Overweight and Obesity

Worldwide prevalence of childhood overweight and obesity is increasing, with the strongest and most substantial increases in developed countries. Canada is among the countries with the highest prevalence of both adult and child overweight and obesity worldwide (30,31). The Canadian Health Measures Survey (CHMS), launched in 2007, is the most comprehensive direct health measures survey ever conducted on a nationally representative sample of

Canadians. According to the CHMS, approximately 17% and 6% of children and youth aged 6- to 18- years old are overweight and obese respectively (31).

The CHMS results are consistent with those of the Canadian Community Health Survey (CCHS), which found 26% of Canadian children and adolescents aged 2- to 17- years were overweight and 8% were obese in 2004 (3). In the past, obesity in very young children (≤ 5-years old) was very rarely observed (32), but this survey reports that 15.2% of Canadian children between the ages of 2- and 5- years were overweight and 6.3% were obese (3). There is considerable variability in the prevalence of childhood overweight and obesity across Canada, with the highest rates tending to be in the Atlantic provinces (3). In 2004, the prevalence of overweight in 2- to 17- year-olds was significantly above the national estimate in Newfoundland (36%), New Brunswick (34%), Nova Scotia (32%), and Manitoba (31%). The prevalence of overweight was significantly below the national estimate in Québec (23%) and Alberta (22%).

Increases in the prevalence of overweight and obesity among Canadian children over the last 25 years have been estimated by comparing the above CCHS prevalence estimates to those of the Canada Health Survey (CHS) administered in 1978-79. The prevalence of overweight has more than doubled in 12- to 17- year-olds while the prevalence of obesity has tripled (33).

Similar trends have been observed internationally. In the United States of America (USA), the prevalence of overweight and obesity have more than doubled for to 2- to 5- year-olds and more than tripled in 12- to 19- year-olds since the 1980's (34). In 2007, 9.5% of infants and toddlers in the USA were reported as being at or above the 95th percentile of the weight-for-

recumbent-length growth charts (35). Among children and adolescents aged 2- through 19- years of age, 16.9% were at or above the 95th percentile (35). In Australia, a recent study reported a prevalence of overweight of 23% in children from 2- to 18- years of age (36). Even higher prevalence estimates have been observed in some European countries. For example, in certain regions of Spain, the prevalence of obesity has been reported to be 32% in children of 4 years of age (37).

Based on data from self-reported heights and weights among adolescents in 34 different countries, it would appear that childhood overweight and obesity is highest in North America, southwestern Europe, the eastern Mediterranean, and the United Kingdom (38). It is estimated that more than 22 million children under 5 years of age are obese, and one in ten children are overweight across the globe (39). The increases in prevalence of overweight and obesity among children parallel trends in adults; between 1980 and 2008, mean BMI worldwide was estimated to have increased by 0.4kg/m^2 per decade in men and 0.5kg/m^2 in women (2).

1.1.2 Short and Long Term Consequences of Overweight and Obesity

Obesity is now the most common childhood disorder in the developed world and thus, its downstream consequences are of serious concern and interest. Evidence suggests that those who become obese during infancy tend to remain obese during the preschool years (40), and those who become obese before age 6 are at a heightened risk of being obese throughout childhood (41). Obesity during childhood is, in turn, a strong independent risk factor for being overweight

or obese in adulthood (42). Additionally, the correlation between childhood obesity and adult obesity has been reported to increase as the child ages (43).

The plethora of literature exploring the consequences of adult obesity tends to point to 8 definitively associated diseases: coronary artery disease, stroke, hypertension, colon cancer, postmenopausal breast cancer, type-2 diabetes, gall bladder disease and osteoarthritis (44). Although clinically diagnosable evidence of these disorders in children is rare, premature development of diseases formerly seen exclusively in adult populations has become more and more prevalent (1). Risk factors emerge early in the development of overweight and support the premature development of disease, including pulmonary, orthopaedic, gastroenterological, neurologic, cardiovascular and endocrine conditions (45). Overweight children are also more likely than non-overweight children to exhibit hyperlipidemia, low high density lipoprotein cholesterol, and hyperinsulinemia (46).

Beyond the impacts on the physical health of children, the first identifiable consequence of excess weight may be the detrimental impact on social and psychological health. For instance, overweight and obesity in children has been associated with both social exclusion and stigmatization (47). Obese children have also been shown to have a significantly lower health-related quality of life compared to children of normal weight. Health-related quality of life among obese children in one study was comparable to children diagnosed with cancer (48). Overweight and obese adolescents have also been reported to have a lower educational attainment and higher poverty rate (49).

The increase in prevalence of overweight and obesity and associated health outcomes in both adults and children will continue to place a serious, often difficult to estimate, burden on the Canadian health care system (50) and health care systems worldwide (51). The economic implications of a society trending towards a higher prevalence of many chronic diseases are substantial with increased costs estimated to be in the billions (7). Obesity is estimated to account for between 0.7% and 2.8% of a country's total healthcare expenditures and obese individuals report medical costs that are approximately 30% greater than their normal weight peers (51).

1.2 Study Rationale

Overweight and obesity are among the leading preventable causes of morbidity and mortality worldwide. There are many potential behavioural risk factors for overweight and obesity, but disentangling the individual effects of these factors is quite difficult as there may be different critical periods during which certain risk factors have a greater impact (52). Moreover, estimating cumulative risk is challenging as exposures change over time (53). However, evidence supporting early life determinants of overweight and obesity is strong (1,11) and knowledge building on potentially modifiable risk factors to properly target certain key periods or behaviours is of great interest.

Prenatal exposure to maternal cigarette smoking (PEMCS) is one of the most common insults to intrauterine life (54) and is associated with a wide range of adverse fetal, obstetrical and developmental outcomes (55). In Canada, the estimated prevalence of smoking at any time

during the third trimester of pregnancy remains above 10% (56) despite wide-spread public health campaigns. Of most interest, PEMCS has consistently emerged as an important risk factor for excess weight[1] in the offspring (57,58). However, no consensus exists on the mechanism of action, amount and timing of exposure needed to induce an increased risk, or duration of the impact.

This association is complex with numerous potential confounding and mediating factors. For example, women who smoke tend to have a lower income, be less educated, heavier and less likely to breastfeed (59). PEMCS is also a leading cause of fetal growth retardation (58) and consequently, it is associated with a reduction in birth weight (60). Children born from smoking mothers often demonstrate an increased catch-up growth in the first months of life (61). In turn, low birth weight and catch-up growth are both associated with excess weight in infancy (62). Thus, it is quite plausible that the combination of low birth weight and rapid catch-up growth may mediate the well documented epidemiological association between PEMCS and offspring excess weight.

Despite this, most studies on the association between PEMCS and excess weight have adjusted for birth weight and catch-up growth as a confounder or neglected these two variables altogether, even though they may be important intermediates on the causal pathway. Examination of birth weight and catch-up growth as mediating variables is of great interest as it may shed light on whether PEMCS is a risk factor for excess weight independent of growth

[1] From this point forward, **excess weight** will be used and is defined as a broad term that includes both overweight and obesity.

restriction and rapid postnatal growth. Past work on The Québec Longitudinal Study of Child Development (QLSCD) has reported that among low birth weight infants, those born from a smoking mother had double the odds of being overweight at 4.5 years old. Similarly, those experiencing the highest quintile of weight gain between birth and 5 months also had nearly double the odds of being overweight at 4.5 years of age (59).

The majority of research identifying risk factors for obesity such as PEMCS has been cross-sectional, prohibiting it from addressing the development of the condition. Although scarce, most longitudinal studies have previously used repeated measures analysis that assumes a homogenous population. Very few studies have examined BMI trajectories in children in distinct subgroups. Studying trajectories and the association with perinatal risk factors, such as PEMCS, may help to further our understanding of the variability in excess weight development and may identify sensitive periods when interventions may be most effective.

Chapter 2: Literature Review

The following chapter provides a summary of the background and past work on the relationship between PEMCS and excess weight. It first provides a brief overview of what is currently known about the association between PEMCS and neonatal outcomes. This is followed by a mini-review of the developmental origins of excess weight and other common correlates of excess weight. After this, the results of a thorough literature review on PEMCS and excess weight will be described including systematic reviews and meta-analyses, additional recent literature addressing the topic, mechanisms and causal pathways and the possibility of a dose-response relationship. Lastly, this chapter will include a summary of gaps in the literature.

2.1 PEMCS and Neonatal Outcomes

As tobacco smoke contains a wide range of known and suspected carcinogens, pulmonary irritants, cilia toxicants, cardiotoxins, teratogens and immunotoxicants (63), PEMCS has been reported as a risk factor for many adverse outcomes during pregnancy, the neonatal period, childhood and thereafter. Many of these substances have been shown to cross the placenta (64), thus potentially harming both pregnant women and their offsprings. Cigarette smoke also has strong anti-estrogenic effects that may lead to anovulation, a shorter luteal phase or early menopause (65). These factors may lead to decreased female fertility (66). The risk of having a miscarriage is also greater in women who smoked during pregnancy compared to those who did not (67). Placental complications, including placental abruption (66) and placenta previa, have also been reported in relation to PEMCS (68).

Probably the greatest risk associated with PEMCS is fetal growth restriction (reduced birth weight; <2500g) (60), which will be further described elsewhere (Chapter 2.4.3). PEMCS is also a risk factor for preterm delivery (<37 weeks gestation) (69) and in turn, preterm delivery of the offspring is associated with several adverse outcomes (70). Oral-facial cleft (71), sudden infant death syndrome (SIDS) (72), a number of childhood respiratory diseases including asthma and chronic obstructive pulmonary disease (COPD) (73), attention deficit disorders (74) and childhood cancers (75) have all been reported to be associated with PEMCS but with conflicting results (76,77). A recent study has further suggested that PEMCS may be associated with higher total cholesterol levels and an adverse lipoprotein profile in the offspring (78), and there is evidence of overall altered vascular and pulmonary function as well as altered neurological behaviour (77).

2.2 Developmental Origins of Excess Weight

The development of excess weight among children is complex. Although an energy imbalance is likely to be a final common pathway for overweight or obesity (9), the determinants of this imbalance are much debated (79). The obesogenic environment evident in industrialized countries and found in developing countries, where a process of westernization is occurring, will likely persist for many more generations. In fact, the combination of lower birth weight and higher attained BMI is characteristic of developing and developed world populations undergoing a transition to increasingly urbanized lifestyles (80). Thus, to properly create and manage intervention programs against this pathology, a deeper knowledge of the specific underlying preventable or modifiable factors is required.

The ‘developmental origins of adult disease’ hypothesis or the ‘Barker Hypothesis’ states that adverse influences acting early in development, and particularly during intrauterine life, can result in permanent changes in physiology and metabolism, which in turn leads to increased disease risk in adulthood (81,82). The hypothesis of profound influence of early life on lifelong health has its origins in the epidemiological associations of low birth weight and coronary artery disease in the early 20th century (83). Much support for this hypothesis has also come from research on the impact of the Dutch famine (84).

While there is a common misperception that the focus of the ‘Barker Hypothesis’ is on birth size; in fact, the paradigm is not based on a causal role for birth size, but rather on the consequences of fetal response to its in-utero environment (85). The most current model states that early life events, acting through the processes of developmental plasticity or epigenetic modifications, alter development of the fetus to an extent that they affect its capacity to cope with the environment of postnatal life. Experimental evidence suggests that this ‘period’ can extend from conception to infancy depending on the organ system involved; thus, the nomenclature changed from ‘fetal’ to ‘developmental’ origins. There is much controversy of the importance of prenatal versus postnatal components and it remains unclear as to whether they are independent or interdependent influences (86).

Earlier models that were suggested as the basis of the relationship between birth size and later disease risk include the thrifty-genotype model (87) and the thrifty-phenotype model (88). Recognitions of limitations with both models led to the development of the predictive-adaptation model (predictive adaptive response hypothesis). This hypothesis has been

extensively reviewed elsewhere (89,90). Predictive adaptive response has been applied to link prenatal exposures to postnatal pathological risk of excess weight (80). This model illustrates the way a fetus may choose a homeostatic response, not made for immediate advantage, but rather in expectation of the future postnatal environment, based on information obtained in-utero. The difference between the nutritional composition of the prenatal environment and that of the postnatal environment may then cause pathology. In other words, a deficient prenatal environment may cause the fetus to choose an energy balance regulatory system suited for a nutritionally poor postnatal environment. When this fetus enters a postnatal environment characterized by overconsumption, he or she may be more susceptible to overweight and obesity compared to others (86). Thus, conceptually, it is hypothesized that the greater the degree of mismatch, the greater the risk of disease (89).

2.3 Common Correlates of Excess Weight

In the first year of life, an important determinant of future weight status may be the type and duration of infant feeding. Feeding habits, which include the duration and timing of exclusive breastfeeding or formula use, as well as the timing of solid food introduction, have been reported to be associated with excess weight. However, studies of this association have yielded fairly inconsistent results. In 2004, Arenz and colleagues performed a meta-analysis of nine studies (69 000 participants) and found a protective effect of breastfeeding with respect to childhood obesity (91). Some further studies have shown similar associations (92), while others have not (93). Overall, the bulk of the evidence indicates no adverse effects of breastfeeding on later adiposity and a probable beneficial effect.

As a general pattern, infant BMI increases rapidly in the first year of life, but then decreases to a nadir at 4-8 years of age before rising again until adulthood (94). The start of the rise has been coined the ‘adiposity rebound’. The period of the adiposity rebound has been a prominent topic in the childhood obesity literature since the concept was put forward by Rolland-Cachera and colleagues in 1984 when they first published results showing that those whose nadir came at younger ages had higher BMI during their teenage years (95). However, the ‘adiposity rebound’ remains poorly replicated.

The genetic component of obesity remains very controversial in the literature. Twin studies have confirmed the potential importance of genetics in conditioning fat tissue in children (96). The Human Obesity Gene Map consortium has reported more than 240 genes involved in modulating body weight and adiposity (97) through a number of different physiological mechanisms, including food intake and energy expenditure, as well as lipid and glucose metabolism. The size of the role that genetics may play in the development of excess weight is not well defined, but its overall effect appears to be small and cannot fully account for the tremendous increase in the prevalence of overweight and obesity in the last few decades (98). Some studies have found significant heritability components of BMI and percent body fat (99), and it is well accepted that children having one or more overweight parents are at a greatly heightened risk of becoming overweight or obese (100) with the strongest association being with mother’s pre-pregnancy weight (101). It is reasonable to consider this association to have a genetic component as well as be a consequence of the family shared environment or other in-utero effects, including the transfer of nutrients through the placenta causing permanent energy metabolism changes (102).

A number of systematic reviews have examined socio-economic factors and risk of excess weight (103-105). These factors range from monoparental family status to complex derived composite measures. Composite measures take into account a wide range of indicators that include family income, food sufficiency, educational attainment and area of residence. Results differ both between developing versus developed countries and in men versus women. This relationship is complex, but most studies report the existence of an inverse relationship between BMI and socioeconomic status. Similarly, race has also been reported to explain some differences in childhood weight status. For example, both black and Hispanic populations seem to have a higher risk of excess weight (106). Studies of this type tend to examine immigrants in western countries and thus, may be more a reflection of socio-economic status than race proper.

Childhood behaviours as risks for excess weight have been identified in a broad range of populations and study types. For example, poor diet quality and overall elevated energy intake are risk factors for childhood excess weight (107) but with surprisingly conflicting results (108). Likewise, lower levels of physical activity and higher levels of sedentary behaviour have been reported to be risk factors (109). More recently, short sleep duration at night has been demonstrated to be strongly associated with excess weight during childhood (110). In addition to these behavioural characteristics, community and societal-level factors (e.g. the built environment) may impact susceptibility to excess weight in the population (111).

2.4 PEMCS and Excess Weight

To better understand the past work and hypotheses linking PEMCS and offspring excess weight, a thorough review of the literature was undertaken. A systematic review was deemed unnecessary as two systematic reviews have been published in the last three years. This review included searches in MEDLINE (*Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE*), EMBASE, CINAHL, as well as the Cochrane Library. These databases were searched for studies that reported on an association between maternal smoking during pregnancy and overweight or obesity in the offspring. The search was limited to studies published in English or French and published between January 1st 2000 and April 30th 2011. Historical studies published before the year 2000 are also referenced if they made a significant contribution to the field. The association between PEMCS and overweight or obesity has been extensively studied in both the epidemiological and basic sciences. Animal and more mechanistic work was essential for an understanding of the current mechanistic paradigms since this thesis project, although epidemiological, sought to further develop the mechanistic understanding of the association.

Please see Appendix 2 for the search strategy used in MEDLINE. Similar strategies were used with the other databases as well as simple key word searches and snowballing from primary studies identified.

2.4.1 Systematic Reviews and Meta-Analyses

At the epidemiological level, two systematic reviews and metal analyses have considered the association of PEMCS and excess weight since 2008. The most recent looked at the publication period between January 2000 and April 2008 and excluded any article not written in the English language (58). Seventeen studies were included in the final analysis after excluding all review articles and any paper that did not provide a multivariate analysis. All seventeen papers showed a positive association between PEMCS and excess weight in offspring of ages ranging from 3- to 33- years old. The meta-analysis (using the DerSimonian-Laird method) found the relationship to be statistically significant with a pooled odds ratio, adjusted for publication bias, of 1.52 (95% CI: 1.36 - 1.70). The review included studies from varying populations controlling for a wide range of correlates of both PEMCS and excess weight. Birth weight, breast feeding duration, socio-economic status, maternal age and obesity status of the mother were the most common. Most did not have any measure of diet or exercise and almost none controlled for catch-up growth. This review was limited to results from affluent countries and an important limitation was that no attention was given to how excess weight was defined in each individual study.

Another recent systematic review and meta-analysis by Oken and colleagues (2008) concluded that in parts of the world undergoing the epidemiological transition, continuing increases in smoking rates among young women may contribute to increases in obesity-related health outcomes (57). They reported the overall association between PEMCS and excess weight with a pooled odds ratio of 1.40 (95% CI: 1.26 - 1.55) which remained robust after adjustment

for parental socio-demographic factors and body size, gestational weight gain, infant feeding and child behaviours.

Despite a wide range of study designs and heterogeneity of reported measurements and quantitative effect estimates, the studies included in these reviews consistently gave evidence of PEMCS as an independent risk factor for offspring excess weight.

2.4.2 Additional Recent Literature

A number of key studies published between January 1st 2010 and April 30th 2011 were not included in either of the aforementioned systematic reviews. One of the most recent, conducted in the Montréal (Canada) area, investigated the relationship between PEMCS and objectively measured weight status of the offspring children (112). Syme and colleagues (2010) tested the hypothesis that PEMCS amplifies accumulation of abdominal fat during the accelerated weight gain occurring late in childhood in 508 adolescents from 12- to 18- years of age (237 exposed to maternal cigarette smoke prenatally). They found that, in early puberty, both exposed and unexposed groups did not differ in MRI-based levels of adiposity. However, in late puberty, exposed individuals had significantly higher levels of subcutaneous fat and intra-abdominal fat. Results were unchanged after controlling for sex, birth weight, and a number of other confounders.

Beyerlin and colleagues (2011) used data on 12 383 children (3- to 17- years of age) from a German population based survey, to compare mean BMI standard deviation scores across

different birth weight categories (113). The rationale for their study was that although the epidemiological evidence for an association between PEMCS and offspring overweight is overwhelming, the underlying mechanisms are largely unknown. They found that children whose mothers smoked during pregnancy had lower birth weights compared to those of non-smoking mothers. They did not detect any evidence for low birth weight being on the causal pathway and thus, concluded that low birth weight is unlikely to be the main cause for the association between intrauterine nicotine exposure and higher BMI in later life. The authors reference a previous study done by their group that also concluded that low birth weight did not lie on the causal pathway (114). However, both were limited by the fact that it was based on data from 1986 to 1988 and neither of these studies include a measure of catch-up growth.

2.4.3 Mechanisms and causal pathways

A mediation model seeks to identify and explicate the mechanism that underlies an observed relationship between an independent variable and a dependent variable via the inclusion of other explanatory variables, known as mediator variables. Rather than hypothesizing a direct causal relationship between the independent variable and the dependent variable, a meditation model hypothesizes that the independent variable causes the mediator variable, which in turn causes the dependent variable. The mediator variable, then, serves to clarify the nature of the relationship between the independent and dependent variables. It is important here to highlight the differences between a confounder and a mediator. First, statistically they are identical and without any prior knowledge, it would be impossible to differentiate it. A confounder needs to be both associated with the exposure (uneven across exposure categories)

and a cause (or a proxy measure of a cause) of the outcome. Most importantly, a confounding variable cannot be caused by the exposure. On the other hand, a mediator must be associated with predictor and the outcome but, contrary to the confounder, to sit on the causal pathway, it would need to be an effect of the predictor. Thus, the differentiation of the two is quite difficult and requires both statistical examination but also prior knowledge. The question remains, do birth weight and / or catch-up growth reside on the causal pathway between PEMCS and an increased risk or susceptibility to becoming overweight or obese? Do these two characteristics, in fact, explain the association between PEMCS and an increased susceptibility to excess weight?

Low birth weight (<2500 g) is an important determinant of life course health and it is one of several indicators of population health monitored globally by the WHO (115). Babies born light are at a heightened risk of dying throughout the neonatal period (116). Stemming again from the work of Barker and colleagues, low birth weight has been associated with a host of diseases, including diabetes, stroke, coronary heart disease and of most interest here, a greater level of central adiposity (117). The relationship between birth weight and risk of obesity has been described as U- or J- shaped, with a much higher prevalence of the outcome at both extremes (118). However, findings are inconsistent across studies. For example, a review by Rogers (2003) states that because the reasons for the positive association between birth weight and BMI are unclear, studies that include alternative measurements of body composition are needed to assess how far this relation is accounted for by changes in fat or lean mass (119). More recent studies using objective measures of adiposity (as opposed to BMI) have found a positive association between birth weight and lean mass, whereas the association with fat mass has been

reported to be much weaker (120). In addition, low birth weight infants form a heterogeneous group as low birth weight can be caused by prematurity or poor fetal growth (small for gestational age, an indicator of intrauterine growth restriction) (121). Many studies have poorly examined birth weight as a risk factor because they have not controlled for prematurity.

A baby born of low birth weight often experiences a rapid catch-up growth phase during infancy or childhood (62). 'Catch-up growth' is not a clearly defined term in the literature. Under this umbrella term, both linear and ponderal growth have been examined with the emphasis sometimes on weight and at other times on height. How infants who were restrained in-utero catch-up postnatally is poorly understood and no real definition exists to describe this phenomenon. Similar to the extremes of birth weight (119), catch-up growth has also been reported as an independent risk factor for overweight or obesity in the offspring (61). Children who show catch-up growth have been reported to be heavier and taller later in childhood with a greater percentage of body fat, total fat mass and central fat distribution (122).

It is well established that maternal smoking during pregnancy is a risk factor for intrauterine growth restriction (IUGR) and consequently, low birth weight (60). The average reduction in birth weight associated with PEMCS has been reported to be between 150 and 300 g (58). Thus, PEMCS may result in a smaller offspring with more rapid postnatal growth; both independently or interpedently associated with weight in later life (80). Fetal growth in the womb is influenced by environmental exposures, through their effect on the mother's body. The supply of both nutrients and oxygen determines fetal growth. This supply depends on many maternal factors, including mother's body composition, lifelong nutritional status, food intake

during pregnancy, and permeability of the placenta (123). The mechanism underlying the risk for being overweight caused by PEMCS is poorly understood. While some have argued that the risk is likely caused by fetal growth retardation, others suggest that the effect of PEMCS is independent of growth restriction. It is most probable that a mixture of a number of different physiological pathways is involved in explaining the effect.

The mechanisms underlying the fetal growth retardation association with PEMCS have been studied for several decades with no consensus. According to the adaptive-response hypothesis, smoking may mimic fetal malnutrition through nicotine's vasoconstrictive properties by reducing uteroplacental and fetoplacental blood flow (124) and hypoxemia by carbon monoxide (57). Nicotine has also been shown to induce maternal starvation or reduced appetite (125) which may also lead to fetal malnutrition. To explain catch-up growth consistent with this hypothesis, some have suggested that the child may undergo a similar response to quitting smoking as adults do: adult smokers tend to be skinnier and gain weight after quitting as serum nicotine levels drop (126). Support for this hypothesis has also come from primate studies have also demonstrated a possible "programming" of regulation of appetite as nicotine acts as an appetite suppressant (127).

Mechanisms with no growth retardation may involve both appetite and energy expenditure regulation. Both of which have complex physiological control with much involvement from the sympathetic nervous system (128). The sympathetic nervous system develops during the fetal period with impairment during this period possibly lasting into adulthood (129). Neurotoxicity of either the central or peripheral nervous systems may affect

both appetite control and adipose metabolism. Fetal nicotine overload may cause blunting of the nervous system (128). This may allow potentiation of overweight caused by a hypercaloric diet by altering the normal appetite feedback mechanisms that are intended to curb appetite. This blunting may also cause a decrease in lipogenesis allowing lipids to continue incorporating in the adipose tissue. At the cellular level, the neurotoxicity causing disturbances in adipose tissue metabolism may create permanent abnormalities in fat cells (130).

Overall, mechanisms underlying an increased risk of development of excess weight are generally grouped at a systemic level affecting appetite (sympathetic control or hypothalamic function) or at a cellular level (abnormalities in fat cells). They can also be separated by those that include growth retardation on the causal pathway and those that do not. However, many other fetal mechanisms could induce a greater susceptibility to being overweight or obese. These include but are not limited to: altered pancreatic structure and function causing beta-cell dysfunction, altered in-utero regulation of leptin and ghrelin pathways, altered catecholamine production or stimulation of the fetal hypothalamic-pituitary axis which causes increased levels of Adrenocorticotropic hormone (ACTH) (131).

2.4.4 Dose-Response Relationship

Establishing a dose-response relationship for PEMCS and childhood excess weight would lend much support to a causal relationship. A recent study of 3 038 children from 15 primary schools in the United Kingdom examined the combined dose-response effects of PEMCS on childhood overweight, obesity and short stature (131). They classified mothers as light (≤10

cigarettes/day) and heavy (>10 cigarettes/day) smokers and compared prevalence estimates of overweight in 5- and 11- year old children. They reported a dose-response relationship using prevalence estimates. However, they were not able to control for physical activity, diet of the child or body weight of the parents.

A study by Sharma and colleagues (2008) examined both the dose-response associations between maternal smoking during pregnancy and subsequent childhood obesity and effect modification by race or ethnicity of the mother (132). This study included over 150 000 respondents and incorporated data on maternal smoking collected at both pre-natal and postpartum visits. The authors were the first to report a dose-response relationship with both duration of smoking and quantity combined. Three dose categories were analyzed: 1-9 cigarettes/day, 10-19 cigarettes/day and ≥20 cigarettes/day. A significant dose-response relationship was observed after controlling for birth weight, but a limitation was a lack of generalizability, as the entire study sample consisted of low-income families (132). A number of other studies have reported that a higher daily quantity of cigarettes smoked during pregnancy is associated with greater offspring susceptibility to excess weight (42,133-135).

2.5 Gaps in the Literature

A wide body of literature addresses early risk factors for childhood excess weight, including the role that PEMCS may play. It is well established that smoking during pregnancy has widespread detrimental impacts on the fetus and puts the offspring at risk for a number of adverse downstream outcomes. PEMCS has been found, in numerous studies, to be a risk factor

for childhood excess weight. A relationship between smoking during pregnancy, birth weight and catch-up growth has also been established. However, it is not clear whether birth weight or catch-up growth sit on the causal pathway between smoking during pregnancy and excess weight. It is also unclear whether the relationship between PEMCS and offspring excess weight is causal or due to by residual confounding as some have hypothesized, since many studies have been unable to control for possible behaviour confounders such as nutrition and physical activity.

Chapter 3: Objectives and Study Framework

3.1 Overall Goal

The aim of this study was to further examine the association between PEMCS and risk of childhood overweight status[2] by simultaneously taking into account a wide range of possible confounders at the social, behavioural and familial level.

3.2 Study Objectives and Hypotheses

Three objectives and associated hypotheses guided this research project:

Objective 1: To a) describe the association between PEMCS and overweight status at age 10 and b) assess whether this relationship is mediated by birth weight and / or catch-up growth.

Hypotheses:

a) Offspring of mothers who smoked during pregnancy will have greater odds of being overweight at age 10 compared to those born to non-smoking mothers independently of a number of potential confounding factors.

b) This association will be attenuated after adjusting for birth weight and / or catch-up growth, indicating that these factors may mediate the association.

[2] The outcome of this study was overweight as defined by BMI; this category also contains all obese individuals. From this point forward, in reference to this analysis, **overweight** is equivalent to overweight and/or obese.

Objective 2: To a) establish whether a dose-response relationship (mean number of cigarettes smoked per day) exists between PEMCS and overweight status at age 10 and b) identify during which trimester PEMCS has the greatest impact on overweight status at age 10.

Hypotheses:

a) Offspring of mothers in the highest smoking category will have a greater odds of being overweight compared to those born to mothers in the lowest smoking category.

b) Offspring of mothers who smoked throughout pregnancy will have a greater odds of being overweight compared to those born to mothers who quit after the first or second trimester.

Objective 3: To a) longitudinally characterize the number and type of BMI trajectories from 2- to 10- years of age and b) examine whether trajectory membership is associated with PEMCS.

Hypotheses:

a) Children will exhibit a number of distinct BMI trajectories from 2- to 10-years of age.

b) PEMCS will be statistically significantly associated with overweight/high risk BMI trajectory membership.

3.3 Conceptual Study Framework

Based on the literature review, objectives and hypotheses and variable availability in the database, a study framework was developed and is presented in Figure 1. The framework outlines the main association of interest, as well as possible confounding and mediating factors.

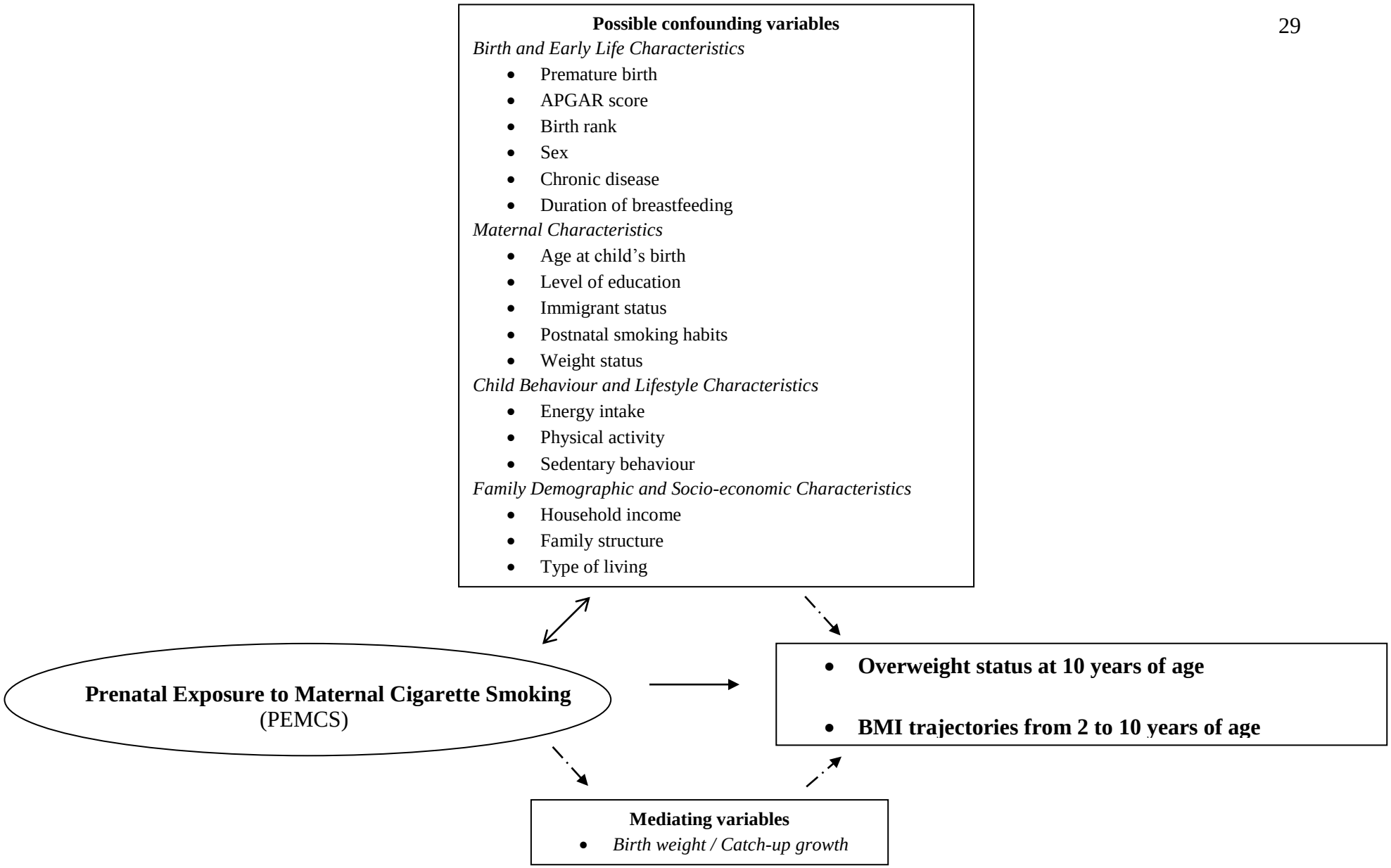

Figure 1: Study Framework

Chapter 4: Methods

The following chapter provides a summary of the methods used to elucidate the relationship between PEMCS and overweight status at 10 years of age. It provides first, a brief overview of the dataset used in the analysis, the Québec Longitudinal Study of Child Development (QLSCD), as well as the specific study samples used in these analyses. Second, the study measures including the outcomes, predictors and covariates are described. Lastly, this chapter presents a full break down of the statistical approach used.

4.1 The Québec Longitudinal Study of Child Development (QLSCD)

The Québec Longitudinal Study of Child Development (1998-2012) (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 is principally funded through the Québec Ministry of Health and Social Services, the Lucie and André Chagnon Foundation and the Ministry of Family and the Elderly. 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 beginning of the study (1998), the province of Québec had a population of just over 7.5 million and about 70 000 newborns 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 randomized stratified survey sample design to attain a representative sample. 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 in the study included non-singleton births, children born with major diseases or handicaps, and those who passed away before reaching 5 months of age. The original targeted sample size was 2 940 families (136). Of this sample, 452 families refused to consent to the study and 240 families were excluded for a wide range of reasons. Thus, Cycle 1 (5- months of age) included 2 223 children. However, only 2 120 were followed longitudinally as the additional 103 families were an over-sampling to examine the effects of the ice storm that occurred during January of 1998. See Table 1 for respondent counts from cycle 1 to cycle 10.

Table 1: QLSCD years, child ages and participation counts (137)

Cycle	Year	Approximate age of child	Number of respondents at each cycle
1	1998	5- months	2 223
2	1999	17 months	2 045
3	2000	29 months	1 997
4	2001	41 months	1 950
5	2002	45-56 months	1 944
6	2003	5 years	1 759
7	2004	6 years	1 529
8	2005	7 years	1 537
9	2006	8 years	1 526
10	2008	10 Years	1 280

The QLSCD gathers information on both children and their parents using standardized questionnaire-based face-to-face interviews with mothers and fathers, as well as standardized computer-based and self-administered questionnaires. The data from the QLSCD used for secondary analysis in this work were collected mainly using the *Interviewer Completed Paper Questionnaire (ICPQ)*, the *Interviewer Completed Computerized Questionnaire (ICCQ)*, and the *Self-Administered Questionnaire for the Mother (SAQM)* as well as family medical records and anthropometric measurements of the child. A full technical description including the construction and validation of these questionnaires and all other collection instruments can be found on the QLSCD website (http://www.iamillbe.stat.gouv.qc.ca/default_an.htm). Questions pertaining to the children were answered by the person deemed the most knowledgeable (PMK) about the child, generally the mother. Each year, participating families (either one or both parents) and interviewers sign a consent form approved by the Ethics Committee of Santé Québec. The form clearly describes the partnership between researchers involved with the QLSCD, the survey methods, the study's priority of maintaining confidentiality, and clearly states the right to refuse and/or withdraw at any time with absolutely no penalty.

Of the total longitudinal sample size (n=2 120), 1 522 children with a mean age of 49 months (between 44 and 56 months) participated in a full dietary assessment in 2002. These children were not randomly selected but were representative of the entire sample at this age. This nutrition sub-study consisted of an eating behaviour questionnaire, a 24-hour dietary recall interview, and objective measurements of children's heights and weights. The 24-hour recall was administered in the residence of the participant's families by a trained nutritionist. A second 24-hour recall was administered to 50% of the subsample a week later to examine usual food

consumption by adjusting recall data for random intra-child variability. Both recalls were administered throughout the week. Following this, height and weight continued to be measured by trained staff at the child's place of residence rather than reported by parents at every consecutive year for all QLSCD children. Staff were instructed and trained to follow a rigid protocol to take measures of body weight (in kilograms), height (in meters), skinfold thickness and waist circumference using standard instruments of measurement (e.g. standard scale and a measuring tape). Measurements falling between two major units were rounded down. A much more detailed description of the 24-hour recall survey and the procedures for measurements is available on QLSCD website (http://www.iamillbe.stat.gouv.qc.ca/default_an.htm).

4.2 Study Sample

This investigation is an analysis of QLSCD data from birth to age 10. A wide range of possible predictors of the outcome of interest collected at different time points were included in the analysis. Two different study samples were used in this study. The first sample was used for the analysis of a possible association between PEMCS and overweight status at age 10 and the examination of the possible mediation effects of birth weight and catch-up growth. A possible dose-response relationship was also examined on this dataset. This sample excluded any respondent missing data for one or more of the following variables: 1) PEMCS, 2) birth weight, 3) catch-up growth or 4) BMI at age 10. The sample was also further reduced depending on covariates included in each of the final logistic models.

The second study sample was a longitudinal sample used for the developmental trajectory building and multinomial analysis. The group based modeling technique used to create these trajectories is flexible enough to allow for missing data points (Chapter 4.4.3). BMI was modeled from age 2 up to age 10 incorporating data from each year with the exception of age 9 (data was not collected during this year). Respondents with missing data on BMI at more than three of the time points were excluded. The sample was also further reduced depending on covariates included in either the multinomial model or the two logistic models.

Thus, the relationship between PEMCS and BMI at age 10 and longitudinal BMI trajectories was analyzed on 1 183 and on 1 686 children from the Québec Longitudinal Study of Child Development respectively. See Appendix 3a and Appendix 3b for flow chart diagrams of respondents within both study samples.

4.3 Study Measures

4.3.1 Outcomes

Childhood overweight was the outcome of interest. BMI was used as a means of classifying children into weight categories. The BMI and presence of overweight in the respondent children was analyzed as an outcome at age 10 years and longitudinally from 2- to 10- years of age (seven different time points). At age 2 and 3, BMI was derived from mother-reported height and weight. At age 4 and every consecutive year thereafter, BMI was derived using objectively measured height and weight of the children. In the building of longitudinal

trajectories, raw continuous BMI was used (Objective 3). In all other analysis (Objective 1 & 2), children were classified as being: 'underweight or normal weight' or 'overweight or obese' using the sex- and age-specific BMI cut-offs defined by the International Obesity Task Force (IOTF) (26) (Appendix 4). These cut-offs (developed by Cole and colleagues) 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. These cut-offs are an extrapolation of the World Health Organization's adult definitions of overweight (BMI$\geq$25kg/m^2) and obesity (BMI$\geq$30kg/m^2) at 18 years of age traced back to equivalent BMI percentiles in children. These are standard cut-offs used in the field of childhood obesity research and allow for both interprovincial and international comparisons (138).

The use of different classification systems can result in substantial differences in the prevalence of overweight (139). Therefore, to determine whether the results were robust to a change in classification system, all final models were also tested using age-specific Center for Disease Control (CDC) growth curve cut-offs for overweight. The CDC classification is based on the 2000 CDC BMI for age- and-sex growth charts (27). Advantages of the CDC classification (140) are that it can be used for children under 2 years of age and can be converted into z-scores. Neither of these features is possible with the IOTF classification system. This method assigns a percentile rank to a child's BMI based on his or her age and sex group. Children above the 95th percentile are considered overweight and those above the 85th and below the 95th percentile are considered at risk of overweight which translate loosely to the IOTF cut-offs for overweight and obesity, respectively.

4.3.2 Main Predictor and Mediating Variables

Prenatal Exposure to Maternal Cigarette Smoking (PEMCS)

The main predictor for the analysis is 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 from the *Interview Completed Computerized Questionnaire (ICCQ):*

- Smoked during pregnancy; categorical: *yes/no*

The second predictor, also from the ICCQ, was used to assess a possible dose-response relationship between mean number of cigarettes smoked during pregnancy and overweight status at age 10:

- Mean number of cigarettes smoked; categorical: *1) did not smoke during pregnancy, 2) 1-19 cigarettes per day, 3) 20+ cigarettes per day*

The third predictor, also from the ICCQ, was used to assess possible trimester specific associations with overweight status at age 10:

- Smoked during which trimester; categorical: *1) first, 2) second, 3) third*

Birth Weight

Birth weight and nearly 50 other perinatal variables were included in the QLSCD database. The study team received legal access to all participating family medical records for a period of 90 days after the mothers signed an authorization form created by the Ministry of Health and Social Services of the province of Québec. Birth weight from each child's medical

record was recorded as a continuous variable, and a categorical variable was developed based on standard and clinically meaningful cut-points:

- Birth weight; categorical: *1) low birth weight (<2.5 kg), 2) normal birth weight (≥2.5 and ≤4kg), 3) high birth weight (>4kg)*

Catch-up growth

Catch-up growth is a derived variable in the QLSCD database and is 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 variable was converted into tertiles to quantify 'higher' versus 'lower' weight gainers after birth.

- Catch-up growth: categorical; *tertiles*

4.3.3 Covariates

Covariates identified during the literature review that were available in the QLSCD database were considered for inclusion in final models (Table 2). All covariates were analyzed as categorical variables. Covariates are listed below in 4 broad and mutually exclusive categories: 1) birth and early life, 2) maternal, 3) child behavioural and lifestyle, and 4) family demographic and socioeconomic. Covariates were obtained from different cycles of the study, based on data collection time point and response rates at each cycle. Furthermore, data from the cycle deemed most epidemiologically relevant for each covariate was used whenever possible.

Table 2: QLSCD variables considered for inclusion in final models

Covariate	*Possible values of variable*	*Cycle collected*
Birth and Early Life		
Premature birth (<37 weeks)	No / Yes	Medical records
APGAR score [α]	Other / High risk (0-6)	Medical records
Birth rank	First / Second / ≥ Third	Medical records
Sex	Female / Male	Medical records
Chronic disease [β]	No / Yes	5- months
Duration of breastfeeding (exclusive)	≥ 3 months / Never / Other	17 months
Maternal [δ]		
Age at child's birth	≤ 29 / 30-34 / 35-39 / ≥ 40	5- months
Level of education	≥ Secondary school diploma / < Secondary school diploma	10 years
Immigrant status	Non-immigrant / Immigrant	10 years
Postnatal smoking habits	Non-smoker / Smoker	10 years
Weight status	Normal / Overweight or obese	17 months
Child Behaviour and Lifestyle		
Energy intake (quintiles)	Other (1-4) / High (5)	4 years
Physical activity level (in comparison to other children)	Same / Higher or much higher	6 years
Sedentary behaviour level (≥ 3 hours of television / day)	No / Yes	6 years
Family Demographic and Socioeconomic		
Household income ($)	< 30,000 / 30,000 - 49,999 / 50,000 - 79,999 / ≥ 80,000	10 years
Family structure	Two parent / Monoparental	10 years
Geographical living area	Rural / Urban	10 years

[α] 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

[β] Excludes allergies but includes asthma

[δ] All parental variables considered for inclusion in final models related to the mother and not the father in order to eliminate collinearity between parents. Data from the mother was also chosen because response rates throughout the cycles of the QLSCD tended to be higher for the mother and because the mother was most frequently reported as being the PMK of her child

4.4 Statistical Approach

All statistical analyses were conducted using the SAS statistical software package version 9.2 (SAS Institute; Cary, NC). The statistical significance level for all analyses was set at an alpha value of 0.05 unless otherwise stated. Santé Québec created sampling weights for this survey according to a factor based on the inverse of selection probability, the probability of non-response and the post-stratification and attrition rates to ensure that the sample was longitudinally representative of infants born in Québec during 1998 (141). However, the sampling weight variables in the dataset were missing for a number of participants at age 10. Therefore, all models presented are unweighted.

4.4.1 Preliminary and Bivariate Analysis

Simple descriptive statistics were calculated to assess the distribution of the data across categories and to examine cell counts for predictor variables. Categories were collapsed or re-categorized when counts were deemed too low. The Chi-squared test of independence and univariate logistic regression were used to examine the crude associations between the outcome and main predictor variables (including possible mediating variables), between the outcome and covariates, and finally between the main predictor variables (including possibly mediating variables) and covariates.

4.4.2 Logistic Model Building and Dose-Response

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 unless otherwise stated. The main predictor of interest (PEMCS) was forced into all models with an inclusion statement. Covariates entered in automated regression models were chosen based on an association with the main predictor, an association with the outcome or based on *a priori* decision stemming from a consistent association in the literature. Final models were rerun with CDC outcome classification, but only IOTF (Chapter 4.3.1) results are reported. A list and description of all final models is found below (Figure 2). Possible two-way interactions between PEMCS and all other covariates considered for inclusion in the final models were assessed through inclusion of an interaction term. Retention value for interactions was set conservatively at 0.01.

Model 1: PEMCS + confounding variables (Objective 1a)

Model 2: PEMCS + confounding variables + birth weight (Objective 1b)

Model 3: PEMCS + confounding variables + catch-up growth (Objective 1b)

Model 4: PEMCS + confounding variables + birth weight + catch-up growth (Objective 1b)

Model 5: PEMCS + confounding variables (dose-response) (Objective 2a)

Model 6: PEMCS + confounding variables (trajectories; multinomial) (Objective 3b)

Model 7: PEMCS + confounding variables (trajectories; combined low risk vs. increasing risk) (Objective 3b)

Model 8: PEMCS + confounding variables (trajectories; combined low risk vs. high risk) (Objective 3b)

Figure 2: List and description of all final models

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. Three separate models were run: 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 a meaningful change in the odds ratio of the main predictor. Full mediation was reported if the effect of PEMCS was completely replaced by that of birth weight and/or catch-up growth.

A possible dose-response relationship between PEMCS and overweight status was assessed using the Cochran-Armitage Trend Test (Merck Research Labs; Rahway, NJ) in SAS 9.2 (SAS Institute; Cary, NC). This test can be used when the dose levels of a predictor are ordinal and the effect variable is binary, which is the case in this study. Fairly common variations of this test include the Monte Carlo resampling adjusted test and the Bootstrap resampling adjusted test. The dose-response variable replaced PEMCS in the base model (model 1) and the asymptomatic test was performed within the logistic procedure. The null hypothesis of the test was that there is no linear trend in binomial proportions of responses across increasing dosages (in this case, number of cigarettes smoked per day). Results of this logistic model with the dose-response variable as the main predictor are also reported (model 5).

4.4.3 Developmental Trajectory Building and Analysis

New statistical advances (non-normative models) now allow for the examination of heterogeneity in longitudinal analysis. Examples of these include growth mixture modeling, latent transition analysis and group based techniques (142). To identify distinct subgroups of children with different developmental BMI trajectories from 2- to 10- years of age, a SAS (SAS Institute; Cary, NC) Macro, PROC TRAJ (142) was used. This macro is useful in this investigation as it allows individuals to have missing data points. The procedure fits discrete semi-parametric mixtures of censored normal distributions to longitudinal data and uses a posterior probability rule to assign each individual's set of repeated measures over time to a distinct trajectory group. This approach complements both hierarchical and latent growth curve modeling for analyzing developmental trajectories. In contrast with a traditional regression or growth curve modeling strategy that models only one mean within a study population, TRAJ estimates a regression model for each discrete group within the population. However, it does not provide any individual level information because subjects are grouped and assumed to follow the same trajectory (142). The number of trajectories and shape of each relation was determined using the Bayesian information criterion (BIC).

Once the number and shape of the trajectories were determined, trajectory membership of the children was converted into a categorical variable and used as an outcome. Multinomial logistic regression with the same predictive model created before (model 1) was run to determine whether the same covariates predict group membership as those that predict overweight status at age 10 (model 6). Multinomial logistic regression is a more complex model than binary logistic

regression, but its flexibility allows categorical outcomes to have more than two levels. In contrast with ordinal logistic regression, the outcome levels in multinomial need not have a natural order. To further narrow the analysis, both lower BMI groups were combined to create a 'low risk' group, and two separate logistic models (model 7 and model 8) were run for each of the overweight groups ('increasing risk' and 'high risk') to determine whether PEMCS predicted their membership compared to the combined 'low risk' group.

4.4.4 Model fit, Influence and Diagnostics

Model fit was assessed by using the Likelihood Ratio Test (LRT), the Hosmer and Lemeshow Goodness of Fit Test and examination of the c statistic. The Likelihood Ratio Test is useful to compare two models with the same outcome but with different predictors. It is essentially the difference in the deviance between two models. It was used to compare models where multiple potential covariates represent the same construct (e.g. family structure versus family income). Results of this test are not reported but aided in the finalizing of covariates considered eligible to be included in final models. The Hosmer and Lemeshow Test assesses the adequacy of the data as well as the calibration of the model. Essentially, it measures how well the model describes the response variable by investigating how close the predicted values are to the observed values. A Chi-squared p-value greater than 0.05 (a failure to reject the null hypothesis of adequate fit) indicates a good fit. As for the c statistic, or the area under the ROC curve, it provides a measure of the overall discrimination ability of the logistic model or how well the model distinguishes between who has the outcome and who does not. A c statistic under

0.5 indicates no discrimination at all and from 0.7 up to 1 indicates acceptable (>0.7) to outstanding (>0.9) discrimination.

The existence of outliers was assessed using index plots. An index plot displays standardized Pearson residuals for a specific model against the ordered observation numbers. Since logistic regression outcomes are binary, the residuals cluster in two groups and thus, the graphical display is not as useful as in the case of linear regression. Standardized Pearson residuals consider this clustering effect and are a fairly good method of identifying outliers. Absolute cut-offs were determined after examination of specific plots, but in general, standardized Pearson residuals greater than 2 were considered large. DFBETA plots were also used for outliers and high leverage point identification. A DFBETA plot refers to DFBETA values plotted against the estimated outcome probabilities. DFBETA measures how much the estimated coefficient for a fitted model would change if the observation was deleted. See Appendix 5 for Diagnostics and Goodness-of-fit of the base model (model 1).

As in much perinatal and chronic disease research, many of the independent variables had a potential of being highly correlated to one another. The existence of multicollinearity inflates the variances of the parameter estimates. This may cause a lack of significance in individual variables with an overall model being very strong or may result in wrong signs or magnitudes of regression coefficient estimates. Thus, this can cause the drawing of incorrect conclusions about relationships between predictor and outcome variables. To address this, a test of the Variance Inflation Factors (VIFs) was used. VIFs of greater than 10 were considered to signify the

presence of multicollinearity between covariates. See Appendix 6 for VIF estimates of covariates in the base model (model 1).

Chapter 5: Results

5.1 Descriptive Statistics

The total number of respondents available for analysis at age 10 was 1 280 which is 60.4% of the initial sample in 1998 (n=2 120). This number was further reduced to respondents with no missing data on the predictor of interest, possible mediating variables or the outcome. In other words, to be included in this analysis, a child needed a non-missing value for PEMCS, birth weight, catch-up growth and overweight status at age 10. This brings the total number of respondents included in the analysis to **1 183**.

In the included sample, children tended to be non-premature babies with a low risk APGAR score and with no chronic diseases (Table 3). They also tended to have a daily energy intake value in the lower quintiles (1-4), have an average level of physical activity (comparable to other children) and tended to watch less than 3 hours of television per day (weekdays and weekends). Their mothers were generally non-immigrants, had their children between 30-39 years of age and had received at least a secondary school diploma. The majority of these mothers did not smoke and were neither overweight nor obese. Overall, families tended to be in the higher categories of household income, have a two parent family structure and live in an urban setting.

Table 3 highlights any statistical differences ($p < 0.05$) between the children included in the study compared to those excluded. Differences included the immigrant status of the mother

(p<0.001) and postnatal smoking habits of the mother (p=0.046). Thus, children excluded were more likely to be from an immigrant and/or smoking mother.

Table 3: Descriptive characteristics of children included and excluded from the analysis at age 10

	Characteristics of children included in the analysis	**Characteristics of children excluded from the analysis** *(Missing data on: PEMCS or BMI at age 10 or birth weight or catch-up growth)*
Covariate	%	%
Birth and Early Life Characteristics	(n=1183)	(n=97)
Premature birth (<37 weeks)		
No	95.60	96.91
Yes	4.40	3.09
APGAR score		
Other	90.82	90.11
High risk (0-6)	9.18	9.89
Birth rank		
First	45.05	34.02
Second	39.14	47.42
≥ Third	15.81	18.56
Sex		
Female	53.00	45.36
Male	47.00	54.64
Chronic disease		
No	85.55	84.54
Yes	14.45	15.46
Duration of breastfeeding (exclusive)		
≥ 3 months	27.05	29.90
Other	46.83	42.27
Never	26.12	27.84
Maternal Characteristics		
Age at child's birth (years)		
≤ 29	20.71	18.56
30-34	31.87	27.84
35-39	33.47	41.24
≥ 40	13.95	12.37
Level of education		
≥ Secondary school diploma	89.25	86.60
< Secondary school diploma	10.75	13.40
Immigrant status		
Non-immigrant	92.72	76.29 †
Immigrant	7.28	23.71

Postnatal smoking habits		
Non-smoker	82.99	72.88*
Smoker	17.01	27.12
Weight status		
Normal weight	70.15	73.12
Overweight/obese	29.85	26.88
Child Behaviour and Lifestyle Characteristics		
Energy intake (Quintiles)		
Other (1-4)	81.39	76.19
High (5)	18.61	23.81
Physical activity (in comparison to other children)		
Same	66.73	66.67
Higher / much higher	33.27	33.33
Sedentary behaviour (≥ *3* hours of television / day)		
No	93.61	92.22
Yes	6.39	7.78
Family Demographic and Socio-economic Characteristics		
Household income ($)		
< 30,000	8.07	11.46
30,000 – 49,999	26.51	25.0
50,000 – 79,999	34.92	34.38
≥ 80,000	30.50	29.17
Family Structure		
Two parent	84.65	83.16
Monoparental	15.35	16.84
Geographical living area		
Rural	35.67	32.29
Urban	64.33	67.71

** Denotes a statistically significant difference in the proportion between those included and excluded from the analysis (Chi-squared test, two sided, p ≤0.05)*

† Denotes a statistically significant difference in the proportion between those included and excluded from the analysis (Chi-squared test, two sided, p ≤0.01)

***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.1.1 Overweight and Obesity

Using both the CDC and the IOTF definitions for overweight, 25% and 25.73% of respondent children included in this analysis were overweight at age 10, respectively, as seen in Figure 3. Mean BMI within the normal and overweight categories are also comparable between the two definitions (Table 4).

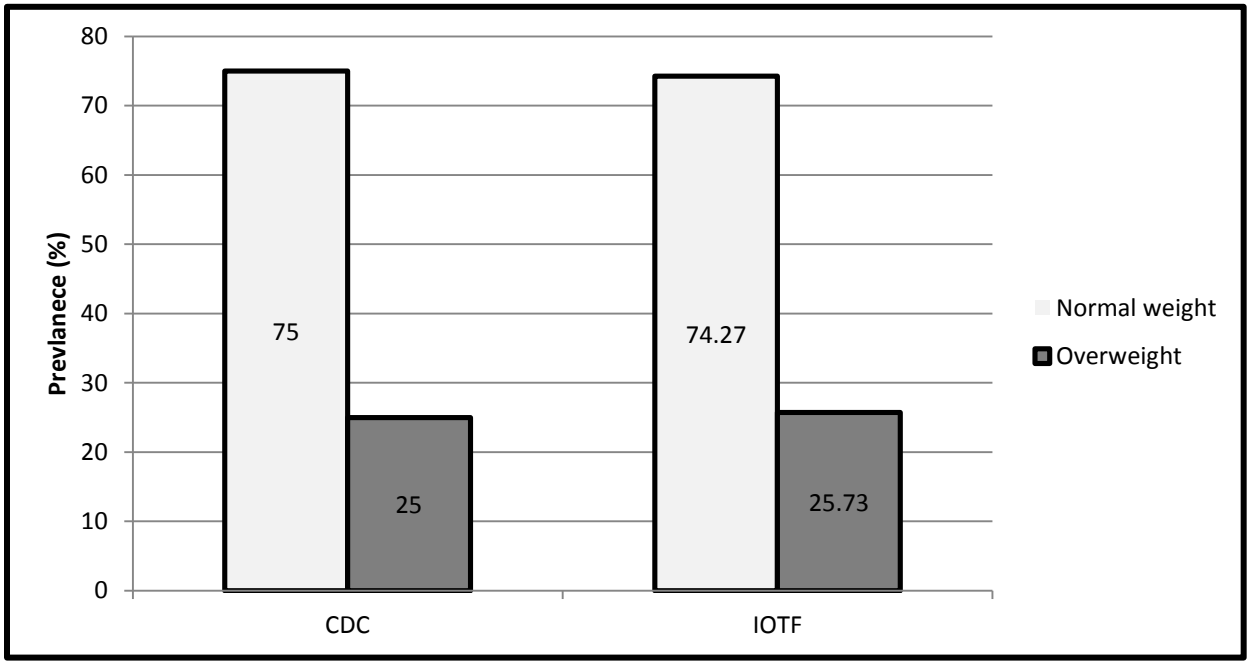

Figure 3: Weight category prevalence using CDC and IOTF definitions at age 10

Table 4: Mean BMI of children using the CDC and the IOTF cut-offs at age 10

Weight status	Mean BMI (Standard deviation, Range[σ])	
	CDC definition	*IOTF definition*
Normal weight	16.90 (1.53, 7.48)	16.87 (1.50, 6.99)
Overweight/obese	22.97 (2.96, 21.86)	22.88 (2.96, 21.78)

[σ] *Range is defined as the interval between the absolute lowest and absolute highest value*

5.2 PEMCS and Covariates

The descriptive characteristics of respondents by prevalence of PEMCS are presented in Table 5. In comparison to others, children exposed to maternal cigarette smoke in the womb were more likely to be born of low birth weight (<2.5 kg) (p=0.0038) and more likely to be in the highest tertile of catch-up growth (p=0.0004). They were also less likely to have been

exclusively breastfed for at least 3 months (p<0.0001). In comparison to others, mothers who smoked during pregnancy tended to be younger (p<0.0001), less educated (p<0.0001) and more likely to be immigrants (0.0478). Overall, families where the mother smoked during pregnancy tended to have a lower household income (p<0.0001) and were more likely to be monoparental (p>0.0001) compared to others.

Table 5: Descriptive characteristics of children included in the final analysis by prevalence of prenatal exposure to maternal cigarette smoke at age 10

	Prenatal exposure to maternal cigarette smoke	**No prenatal exposure to maternal cigarette smoke**
Covariate	%	%
Birth and Early Life Characteristics		
Birth weight		
> 4 kg	6.74	12.99 †
≤ 2.5kg and ≤ 4 kg	88.65	84.57
< 2.5 kg	4.61	2.44
Premature birth (<37 weeks)		
No	93.97	96.12
Yes	6.03	3.88
APGAR score		
Other	91.79	90.51
High risk (0-6)	8.21	9.42
Birth rank		
First	43.26	45.62
Second	41.13	38.51
≥ Third	15.60	15.87
Sex		
Female	56.74	51.83
Male	43.26	48.17
Catch-up growth		
1st tertile	26.60	37.96 †
2nd tertile	35.46	34.52
3rd tertile	37.94	27.52
Chronic disease		
No	85.11	85.68
Yes	14.89	14.32
Duration of breastfeeding (exclusive)		
≥ 3 months	13.48	31.30 †
Other	47.52	46.61
Never	39.01	22.09

Maternal Characteristics		
Age at child's birth (years)		
≤ 29	33.69	16.55 †
30-34	28.72	32.85
35-39	27.30	35.41
≥ 40	10.28	15.09
Level of education		
≥ Secondary school diploma	79.43	92.32 †
< Secondary school diploma	20.57	7.68
Immigrant Status		
Non-immigrant	95.39	91.88 *
Immigrant	4.61	8.12
Postnatal smoking habits		
Non-smoker	44.10	94.91 †
Smoker	55.90	5.09
Weight status		
Normal weight	69.78	70.27
Overweight/obese	30.22	29.73
Child Behaviour and Lifestyle Characteristics		
Energy intake (Quintiles)		
Other (1-4)	78.21	82.32
High (5)	21.79	19.68
Physical activity (in comparison to other children)		
Same	70.70	65.49
Higher / much higher	29.30	34.51
Sedentary behaviour (≥ *3* hours of television / day)		
No	94.94	93.19
Yes	5.06	6.81
Family Demographic and Socio-economic Characteristics		
Household income ($)		
< 30,000	17.20	5.23 †
30,000 – 49,999	31.90	24.83
50,000 – 79,999	34.77	34.97
≥ 80,000	16.13	34.97
Family Structure		
Two parent	76.43	87.21 †
Monoparental	23.57	12.79
Geographical living area		
Rural	32.97	36.52
Urban	67.03	63.48

* *Denotes a statistically significant difference in the proportion between those born from smoking mothers and those that were not (Chi-squared test, two sided, p ≤0.05)*

† *Denotes a statistically significant difference in the proportion between those born from smoking mothers and those that were not (Chi-squared test, two sided, p ≤0.01)*

***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.3 Overweight and Covariates

The descriptive characteristics of respondents by prevalence of overweight are presented in Table 6. In comparison to others, overweight children were more likely to be born premature (p=0.0287) and have a high risk APGAR score (p=0.0086). In comparison to others, 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 more likely to be have a monoparental family structure (p=0.0019) compared to others.

Table 6: Descriptive characteristics of children included in the final analysis by prevalence of overweight (IOTF) at age 10

	Overweight or obese children *(Boys: BMI >19.84, Girls: BMI >19.86)*	**Normal weight children**
Covariate	%	%
Birth and Early Life Characteristics		
Premature birth (<37 weeks)		
No	93.38	96.37 *
Yes	6.62	3.63
APGAR score		
Other	87.04	92.11 †
High risk (0-6)	12.96	7.89
Birth rank		
First	41.39	46.31
Second	42.72	37.91
≥ Third	15.89	15.78
Sex		
Female	52.32	53.23
Male	47.68	46.77
Chronic disease		
No	14.57	14.42
Yes	85.43	85.58

Duration of breastfeeding (exclusive)		
≥ 3 months	28.15	26.67
Other	43.71	47.90
Never	28.15	25.43
Maternal Characteristics		
Age at child's birth (years)		
≤ 29	19.54	21.11
30-34	30.13	32.46
35-39	35.43	32.80
≥ 40	14.90	13.62
Level of education		
≥ Secondary school diploma	88.41	89.53
< Secondary school diploma	11.59	10.47
Immigrant status		
Non-immigrant	91.39	93.17
Immigrant	8.61	6.83
Postnatal smoking habits		
Non-smoker	75.10	85.58 †
Smoker	24.90	14.42
Weight status		
Normal weight	53.44	75.83 †
Overweight/obese	46.46	24.17
Child Behaviour and Lifestyle Characteristics		
Energy intake (Quintiles)		
Other (1-4)	71.43	84.59 †
High (5)	28.57	15.41
Physical activity (in comparison to other children)		
Same	70.07	65.59
Higher / much higher	29.93	34.41
Sedentary behaviour (≥ 3 hours of television / day)		
No	93.41	93.67
Yes	6.59	6.33
Family Demographic and Socio-economic Characteristics		
Household income ($)		
< 30,000	11.30	6.96 †
30,000 – 49,999	32.23	24.54
50,000 – 79,999	31.23	36.19
≥ 80,000	25.25	32.31
Family Structure		
Two parent	86.56	79.07 †
Monoparental	13.44	20.93
Geographical living area		
Rural	33.89	36.29
Urban	66.11	63.71

* *Denotes a statistically significant difference in the proportion between overweight and non-overweight children (Chi-squared test, two sided, p ≤0.05)*

† *Denotes a statistically significant difference in the proportion between overweight and non-overweight children (Chi-squared test, two sided, p ≤0.01)*

***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.4 Overweight and Main Exposures

An analysis of the associations between the outcome of interest and the main predictors including possible mediating variables is presented in Table 7. At the bivariate level, chi-square tests of independence showed that PEMCS was significantly associated with being overweight at age 10 (p=0.003). Catch-up growth was not statistically associated with being overweight at age 10 but birth weight hovers on significance (p=0.0851).

Table 7: Bivariate analysis of main exposure and mediating variables by weight status category (IOTF) at age 10

	Overweight or obese children *(Boys: BMI >19.84, Girls: BMI >19.86)*	**Normal weight children**
Covariate	%	%
PEMCS		
No	68.54	78.77 †
Yes	31.46	21.23
Birth weight		
> 4 kg	14.90	10.33
≤ 2.5kg and ≥ 4 kg	81.79	86.83
< 2.5 kg	3.31	2.84
Catch-up growth		
1st tertile	33.11	35.98
2nd tertile	33.11	35.30
3rd tertile	33.77	28.72

** Denotes a statistically significant difference in the proportion between overweight and non-overweight children (Chi-squared test, two sided, p ≤0.05)*
† Denotes a statistically significant difference in the proportion between overweight and non-overweight children (Chi-squared test, two sided, p ≤0.01)
***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.5 Final Logistic Model

The association between PEMCS and overweight at age 10 while controlling for a number of other possible confounding or independently predicting variables was assessed using multivariate logistic regression. PEMCS remained an independent predictor of being overweight

at age 10 (OR: 1.704; 95% CI: 1.197 - 2.427) (Table 8). APGAR score, which was associated with overweight but not with PEMCS at the bivariate level, remained in the model after selection. Conversely, immigrant status of the mother which also remained in the model after selection was not associated with being overweight at the bivariate level but was associated with PEMCS. The strongest independent predictor of being overweight at age 10 was the weight status of the mother (OR: 2.898; 95% CI: 2.102 - 3.994). Having a monoparental family structure, which was associated with both PEMCS and overweight status at age 10 at the bivariate level, remained a strong predictor in the final model. Energy intake remains in the model as the second strongest predictor.

Table 8: 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* [α]	*95% CI*
PEMCS					
	No	1.000	-	1.000	-
	Yes	1.642	1.229 - 2.192	1.704	1.197 - 2.427
APGAR score					
	Other	1.000	-	1.000	-
	High risk	1.752	1.155 - 2.657	1.804	1.091 - 2.983
Mother's immigrant Status	*Non immigrant*	1.000	-	1.000	-
	Immigrant	1.286	0.796 - 2.078	1.802	1.001 - 3.244
Mother's weight status					
	Normal weight	1.000		1.000	
	Overweight	2.715	2.061 - 3.578	2.898	2.102 - 3.994
Family Structure					
	Two parent	1.000	-	1.000	-
	Monoparental	1.597	1.146 - 2.224	1.622	1.075 - 2.446
Energy intake					
	Other (1-4)	1.000	-	1.000	-
	High (5)	2.186	1.565 - 3.053	2.171	1.508 - 3.125

[α] *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, level of physical activity, level of sedentary behaviour, family income, and family structure*

5.5.1 Assessing Mediation

Examination of mediation of the relationship between PEMCS and overweight status at age 10 is presented in Table 9a to 9d. The addition of birth weight to the base model (model 1) has no impact on significant covariates. Of interest, birth weight causes a slight increase in the point estimate of PEMCS with an accompanying shift upwards of the confidence interval. A similar change in magnitude occurs after the addition of catch-up growth to the model but in the opposite direction. When adding both, the point estimate changes again only very slightly.

Table 9a: Odds Ratios (OR) and 95% confidence intervals (CI) for overweight (IOTF) according to PEMCS with adjustment for relevant covariates at age 10 (model 1)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [β]	*95% CI*
PEMCS					
	No	1.000	-	1.000	-
	Yes	1.642	1.229 - 2.192	1.704	1.197 - 2.427

Table 9b: Odds Ratios (OR) and 95% Confidence Intervals (CI) for overweight (IOTF) according to PEMCS with the addition of adjustment for birth weight at age 10 (model 2)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [β]	*95% CI*
PEMCS					
	No	1.000	-	1.00	-
	Yes	1.642	1.229 - 2.192	**1.758**	1.230 - 2.512

Table 9c: Odds Ratios (OR) and 95% Confidence Intervals (CI) for overweight (IOTF) according to PEMCS with the addition of adjustment for catch-up growth at age 10 (model 3)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [β]	*95% CI*
PEMCS					
	No	1.000	-	1.00	-
	Yes	1.642	1.229 - 2.192	**1.637**	1.149 - 2.332

Table 9d: Odds Ratios (OR) and 95% Confidence Intervals (CI) for overweight (IOTF) according to PEMCS with adjustment for birth weight and catch-up growth at age 10 (model 4)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [β]	*95% CI*
PEMCS					
	No	1.000	-	1.00	-
	Yes	1.642	1.229 - 2.192	**1.730**	1.209 - 2.475

[β] *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, level of physical activity, level of sedentary behaviour, family income, and family structure*

5.5.2 Dose-Response Relationship

A possible dose-response relationship was assessed with the same predictive model and selection strategy as above with the replacement of the dichotomous PEMCS with the dos-response predictor variable (Table 10). Again, no changes to the covariates that remained in the model after selection but slight changes to point estimates and accompanying confidence intervals did exist. The variable of the number of cigarettes smoked showed significant odds ratios at both smoking 1-19 cigarettes per day (OR: 1.758; 95% CI: 1.160 - 2.665) and smoking 20+ cigarettes per day (OR: 1.809; 95% CI: 1.001 - 3.269). Inputting this model into the trend test yields a rejection of the null hypothesis of no linear trend (p=0.001).

Table 10: Odds Ratios (OR) and 95% Confidence Intervals (CI) of # of cigarettes smoked/day and relevant covariates included in the final model on overweight status (IOTF) at age 10 (model 5)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [α]	*95% CI*
# of Cigarettes					
	Zero	1.000	-	1.000	-
	1-19	1.656	1.183 - 2.319	1.758	1.160 - 2.665
	20+	1.701	1.044 - 2.771	1.809	1.001 - 3.269
APGAR score					
	Other	1.000	-	1.000	-
	High risk	1.752	1.155 - 2.657	1.829	1.105 - 3.028
Mother's immigrant Status	*Non immigrant*	1.000	-	1.000	-
	Immigrant	1.286	0.796 - 2.078	1.810	1.004 - 3.265
Mother's weight status					
	Normal weight	1.000		1.000	
	Overweight	2.715	2.061 - 3.578	2.963	2.145 - 4.092
Family Structure					
	Two parent	1.000	-	1.000	-
	Monoparental	1.597	1.146 - 2.224	1.612	1.068 - 2.432
Energy intake					
	Other (1-4)	1.000	-	1.000	-
	High (5)	2.186	1.565 - 3.053	2.206	1.533 - 3.175

[β] *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, level of physical activity, level of sedentary behaviour, family income, and family structure.*

5.6 Group Trajectories

5.6.1 Descriptive Statistics

The total number of respondents available for this analysis between age 2 and age 10 was **1 686** which is 79.5% of the initial sample in 1998 (n=2 120). Respondents were eligible for inclusion to the group based development trajectory building if they had responded to at least four of seven possible time points used from 2- to 10- years of age.

Children included tended to be non-premature babies with a low risk APGAR score and with no chronic diseases. They also tended to have a daily energy intake level in the lower quintiles (1-4), have an average level of physical activity (comparable to other children) and tended to watch television for less than 3 hours per day (weekdays and weekends). In comparison to those excluded, mothers tended to be non-immigrant, have their child between 30-39 years of age and have received at least a secondary school diploma. The majority of these mothers also did not smoke and were neither overweight nor obese. Overall, families tended to be in the higher categories of household income, have a two parent family structure and live in an urban setting.

Table 11 highlights any statistical differences ($p < 0.05$) between the children included in the study compared to those excluded. Differences included the sex of the child ($p<0.0001$) and duration of exclusive breastfeeding ($p=0.0417$). For the mothers, differences between those included and excluded were only observed for postnatal smoking habits ($p=0.0193$).

Table 11: Descriptive characteristics of the children included and excluded from the longitudinal analyses from age 2 to age 10

	Characteristics of children included in the analysis	**Characteristics of children excluded from the analysis** *(Missing data on: BMI at > 3 time points)*
Covariate	%	%
Birth and Early Life Characteristics	(n=1686)	(n=414)
PEMCS		
No	75.05	73.75
Yes	24.95	26.25
Birth weight		
> 4 kg	10.97	9.36
≥ 2.5kg and ≤ 4 kg	85.79	87.32
< 2.5 kg	3.24	3.33
Premature birth (<37 weeks)		
No	95.12	96.01
Yes	4.88	3.99
APGAR score		
Other	91.06	92.04
High risk (0-6)	8.94	7.96
Birth rank		
First	43.61	44.31
Second	39.72	40.52
≥ Third	16.68	15.17
Sex		
Female	51.45	41.32 †
Male	48.55	58.68
Catch-up growth		
1st tertile	33.72	32.78
2nd tertile	33.84	33.20
3rd tertile	32.44	34.02
Chronic disease		
No	85.54	85.27
Yes	14.46	14.73
Duration of breastfeeding (exclusive)		
≥ 3 months	26.13	21.76 *
Other	46.76	46.11
Never	27.12	32.14
Maternal Characteristics		
Age at child's birth (years)		
≤ 29	21.94	21.96
30-34	32.20	29.34
35-39	31.89	36.13
≥ 40	13.97	12.57

Level of education		
≥ *Secondary school diploma*	88.65	91.02
< *Secondary school diploma*	11.35	8.98
Immigrant status		
Non-immigrant	91.59	91.43
Immigrant	8.41	8.57
Postnatal smoking habits		
Non-smoker	81.30	88.42 *
Smoker	18.70	11.58
Weight status		
Normal weight	70.38	73.27
Overweight/obese	29.62	26.73
Child Behaviour and Lifestyle Characteristics		
Energy intake (Quintiles)		
Other (1-4)	61.21	59.38
High (5)	38.79	40.62
Physical activity (in comparison to other children)		
Same	65.77	68.07
Higher / much higher	34.23	31.93
Sedentary behaviour (≥ *3* hours of television / day)		
No	92.88	93.09
Yes	7.12	6.91
Family Demographic / Socio-economic Characteristics		
Household income ($)		
< 30,000	8.49	13.24
30,000 – 49,999	26.03	29.41
50,000 – 79,999	34.84	29.41
≥ 80,000	30.63	27.94
Family Structure		
Two parent	83.73	76.47
Monoparental	16.27	23.53
Geographical living area		
Rural	35.59	36.79
Urban	64.41	63.21

[*] *Denotes a statistically significant difference in the proportion between those included and excluded from the analysis (Chi-squared test, two sided, p ≤0.05)*

[†] *Denotes a statistically significant difference in the proportion between those included and excluded from the analysis (Chi-squared test, two sided, p ≤0.01)*

***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.6.2 Trajectory Characteristics

The four distinct BMI trajectories from age 2 to age 10 identified for this population are represented in Figure 3. Trajectory 1 (lowest risk of overweight) comprises the largest proportion of the population with 46.4% of the children falling in this group. This trajectory remains stable with a slight increase towards age 10. Trajectory 2 (low risk of overweight), comprising the second largest proportion of the population with 37.8%, is virtually parallel with trajectory 1 with a consistently slightly higher mean BMI. Trajectory 3 (increasing risk of overweight), comprises a significantly smaller percentage of the respondents with 12.1%, starting below trajectory 2 and increasing steeply throughout. Trajectory 4 (high risk of overweight) comprises the smallest percentage of the population with only 3.6% of respondents. This trajectory starts much higher than all others and increases steeply throughout at a similar slope to trajectory 3.

A chi-squared test of independence was used to examine any possible differences between characteristics of the children within each trajectory group (Table 12). A significant difference existed only for the sex of children within each trajectory group ($p=0.0178$).

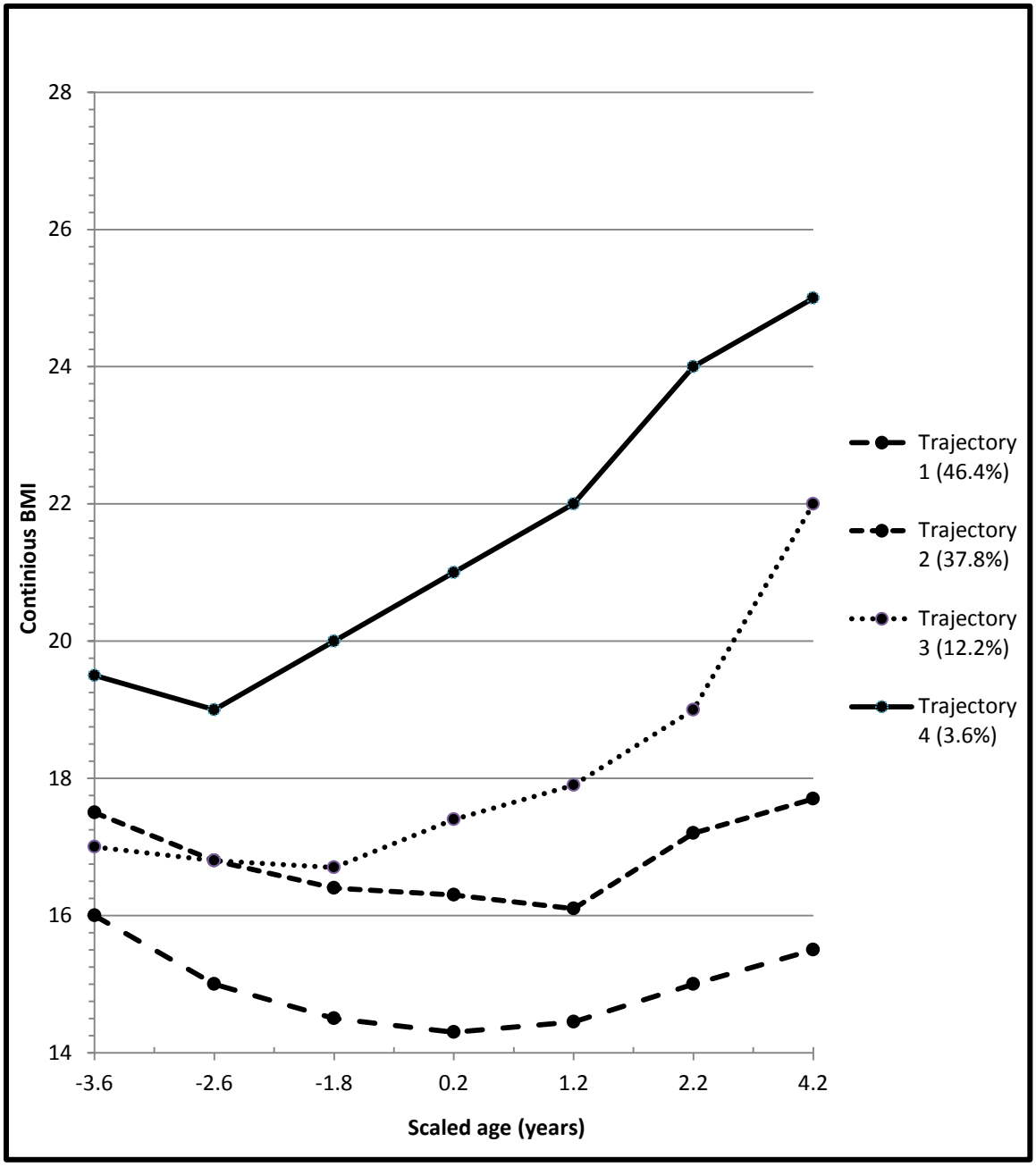

Figure 4: Group based development BMI trajectories of children from 2- to 10- years of age
***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

Table 12: Descriptive characteristics of children included by group-based developmental trajectories from age 2 to age 10

Covariate	*Trajectory 1* %	*Trajectory 2* %	*Trajectory 3* %	*Trajectory 4* %
Birth and Early Life Characteristics				
PEMCS				
No	74.53	74.34	77.84	76.27
Yes	25.47	25.66	22.16	23.73
Birth weight				
> 4 kg	10.39	12.32	7.51	8.93
≥ 2.5kg and ≤ 4 kg	86.19	84.40	90.17	87.50
< 2.5 kg	3.42	3.28	2.31	3.57
Premature birth (<37 weeks)				
No	96.0	95.69	97.18	89.83
Yes	4.0	4.31	2.82	10.17
APGAR score				
Other	90.69	92.62	88.0	86.44
High risk (0-6)	9.31	7.38	12.0	13.56
Birth rank				
First	40.75	44.77	48.59	45.76
Second	43.38	37.08	36.16	40.68
≥ Third	15.88	18.15	15.25	13.56
Sex				
Female	45.13	50.62	55.37	57.63*
Male	54.88	49.38	44.63	42.37
Catch-up growth				
1st tertile	33.08	35.61	32.95	29.31
2nd tertile	33.72	31.80	38.73	32.76
3rd tertile	33.20	38.71	28.31	37.93
Chronic disease (excludes allergies but includes asthma)				
No	15.63	12.71	18.18	6.45
Yes	84.38	87.29	81.82	93.55
Duration of breastfeeding (exclusive)				
≥ 3 months	25.25	23.54	30.51	23.73
Other	44.63	46.77	46.89	50.85
Never	30.13	29.69	22.60	25.42
Maternal Characteristics				
Age at child's birth (years)				
≤ 29	20.65	21.69	24.86	22.03
30-34	31.66	29.85	30.51	28.81
35-39	33.17	34.77	30.51	35.59
≥ 40	14.52	13.69	14.12	13.56
Level of education				
≥ Secondary school diploma	88.98	87.59	91.60	87.88
< Secondary school diploma	11.02	12.41	8.40	12.12
Immigrant status				
Non-immigrant	91.58	90.57	94.12	87.88
Immigrant	8.42	9.43	5.88	12.12

Postnatal smoking habits				
Non-smoker	83.98	82.33	77.0	77.78
Smoker	16.02	17.67	23.0	22.22
Weight status				
Normal weight	72.69	69.40	71.86	67.27
Overweight/obese	27.31	30.60	28.14	32.73
Child Behaviour and Lifestyle Characteristics				
Energy intake (Quintiles)				
Other (1-4)	60.25	60.88	62.02	60.0
High (5)	39.75	39.12	37.98	40.0
Physical activity (in comparison to other children)				
Same	65.03	65.24	69.12	61.11
Higher / much higher	34.97	34.76	30.88	38.89
Sedentary behaviour (≥ *3* hours of television / day)				
No	92.47	93.21	92.65	97.22
Yes	7.53	6.79	7.35	2.78
Family Demographic and Socio-economic Characteristics				
Household income ($)				
< 30,000	9.54	7.62	9.73	0.00
30,000 – 49,999	25.84	27.52	23.01	35.14
50,000 – 79,999	35.19	35.38	36.28	43.24
≥ 80,000	29.42	29.48	30.97	21.62
Family Structure				
Two parent	86.08	80.34	78.76	86.49
Monoparental	13.92	19.66	21.24	13.51
Geographical living area				
Rural	36.79	36.05	38.60	39.29
Urban	63.21	63.95	61.40	60.71

[*] *Denotes a statistically significant difference in the proportions across the trajectory groups (Chi-squared test, two sided, p ≤0.05)*
[†] *Denotes a statistically significant difference in the proportions across the trajectory groups (Chi-squared test, two sided, p ≤0.01)*
***Source**: Québec Longitudinal Study of Child Development (QLSCD) 1998-2010*

5.6.3 Multinomial Analysis

To determine whether the model derived in section 5.5 predicts trajectory membership as it did overweight status at age 10, multinomial logistic regression with a similar selection strategy was used (Table 13). PEMCS seemed to show a small protective effect for trajectory 2 and trajectory 3 compared to trajectory 1. On the other hand, the point estimate for trajectory 4 showed a greater risk for PEMCS compared to trajectory 1. However, all 3 respective confidence

intervals cross 1 and thus, show no significant results. PEMCS was forced into the model as it is the predictor of interest, but no other included covariate made the initial cut-off for model entry.

Table 13: Odds Ratios (OR) and 95% confidence intervals (CI) for group-based developmental trajectories according to PEMCS with adjustment for relevant covariates (model 6)

Covariate	*Trajectory*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [β]	*95% CI*
PEMCS					
	1	1.000	-	1.000	-
	2	0.910	0.554 - 1.496	0.910	0.554 - 1.496
	3	0.748	0.357 - 1.567	0.748	0.357 - 1.567
	4	1.587	0.507 - 4.966	1.587	0.507 - 4.966

[β] 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, level of physical activity, level of sedentary behaviour, family income, and family structure

5.6.4 Logistic Analysis

Since both trajectory 1 (lowest risk) and trajectory 2 (low risk) comprise just over 85% of the population, it was of interest to identify the factors predicting group membership in trajectory 3 or 4. Again using the predictive model developed in section 5.5, multivariate logistic regression was used to assess model covariates as possible risk factors for membership in trajectory 3 compared to combined trajectories 1 and 2, as well as trajectory 4 compared to combined trajectories 1 and 2 (Table 14). Similar to the multinomial analysis, PEMCS shows no significant association in both unadjusted and adjusted models. Another early risk factor, APGAR score, shows a significant association with trajectory 3 compared to combined trajectories 1 and 2 in both unadjusted and adjusted models (OR: 2.685; 95% CI: 1.122 - 6.429).

Table 14a: Odds Ratios (OR) and 95% Confidence Intervals (CI) of PEMCS and relevant covariates included in final logistic model on group based developmental trajectory 3 (increasing risk) versus combined trajectories 1 and 2 (low risk) combined (model 7)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [α]	*95% CI*
PEMCS					
	No	1.000	-	1.000	-
	Yes	0.780	0.384 - 1.582	0.779	0.382 - 1.588
APGAR score					
	Other	1.000		1.000	-
	High risk (0-6)	2.684	1.122 - 6.419	2.685	1.122 - 6.429

Table 14b: Odds Ratios (OR) and 95% Confidence Intervals (CI) of PEMCS and relevant covariates included in final logistic model on group based developmental trajectory 4 (high risk) versus combined trajectories 1 and 2 (low risk) combined (model 8)

Covariate	*Category*	*Unadjusted OR*	*95% CI*	*Adjusted OR* [α]	*95% CI*
PEMCS					
	No	1.000	-	1.000	-
	Yes	1.654	0.539 - 5.071	1.654	0.539 - 5.071

[α] *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, level of physical activity, level of sedentary behaviour, family income, and family structure*

Chapter 6: Discussion

In recent years, much research has supported the role of the fetal environment and early life in the development of overweight or obesity both during childhood or adulthood. More specifically, a number of cross-sectional and prospective studies have suggested a priming effect of PEMCS on offspring risk of excess weight. Despite the well documented effects of PEMCS, it remains one of the most common insults to the developing fetus in industrialized countries. Even though, the epidemiological evidence is strong and consistent, the underlying mechanisms remain largely unknown. It is generally implied to result from permanent physiological changes during fetal development. Although many different mechanisms have been hypothesized and the effect is most likely to be a combination of them, it is accepted that PEMCS is an important risk factor for low birth weight (small for gestational age). Babies of low birth weight often experience a rapid catch-up growth phase during infancy or childhood, often becoming overweight or obese. This, as a pathway to link PEMCS to excess weight, lends strong support to the thrifty-phenotype hypothesis. However, some have reported inconsistencies in this hypothesis and no true consensus exists on whether birth weight and/or catch-up growth do sit on the causal pathway or even whether the association itself is in fact due to residual confounding.

To our knowledge, this study is the first to explore the potential mediating effect of both birth weight and a measure of catch-up growth in a longitudinal population based study of the association between PEMCS and overweight in young children while controlling for a wide range of confounders.

The following chapter provides: a summary of findings, an interpretation of these findings, followed by a few study limitations, study strengths and finally possible conclusions that may be drawn from this body of work.

6.1 Summary of Findings

The prevalence of overweight in this study was found to be approximately 25% using the IOTF age- and sex- specific BMI cut-offs and approximately 25.73% using the CDC cut-offs. These prevalence measures are similar to the national overweight prevalence in children (26%) as reported by the CCHS in 2004 (3), and higher than the prevalence (17%) reported by the CHMS in 2010 (31). However, the approximate prevalence reported here is for 10 year old children from Québec only compared to national averages that combine children aged from 2- to 17- years of age.

The prevalence of PEMCS, the exposure of interest, was found to be approximately 25% amongst the mothers included in this study. This is comparable to other studies that have used this QLSCD database with different outcomes at different time points (59,143). National estimates of smoking prevalence during pregnancy differ greatly but tend to range from 10% (56) to 20% (144). Québec is consistently reported as having one of the highest smoking rates, at any time, among all Canadian provinces (145).

6.1.1 Objective 1

Children who were exposed to smoke in-utero were different than those who were not at a number of different levels as seen in Table 5. Similarly, overweight children were different from those of normal weight at a number of different levels as seen in Table 6. In line with its respective hypothesis (hypothesis 1a), PEMCS was found to be a significant and independent predictor of childhood overweight at 10 years of age in this group of children (Table 8). This association remained significant even after controlling for sex, APGAR score, duration of exclusive breastfeeding, mother's immigrant status, BMI of the mother, energy intake, level of physical activity, level of sedentary behaviour, family income, and family structure. Covariates that remained in the model, and thus constitute independent predictors of overweight status at 10 years of age in this group of children, included: APGAR score, mother's immigrant status, mother's weight status, family structure and energy intake.

In contrast with hypothesis 1b, no attenuation of the PEMCS-overweight status association occurred when birth weight or catch-up growth or both were controlled for (Table 9). In other words, the association between PEMCS and excess weight did not seem to be mediated by low birth weight and/or subsequent catch-up growth. Indeed in the bivariate and multivariate models, neither birth weight nor catch-up growth was significantly associated with overweight status at age 10.

6.1.2 Objective 2

In terms of both the examination of a possible dose-response relationship and the examination of trimester specific exposure, results were found to be null. The examination of a categorical variable of the average number of cigarettes smoked per day during pregnancy as an outcome (Table 10) yielded the same model components as did PEMCS alone with independent predictors of overweight status at 10 years of age including: APGAR score, mother's immigrant status, mother's weight status, family structure and energy intake. However, the two categories of cigarettes smoked (0-19, 20+) had both very similar point estimates as well as overlapping confidence intervals. This would seem inconsistent with the result of the Cochran-Armitage Trend Test which indicated that a significant dose-response trend existed. However, this test does not indicate the direction or the strength of a suspected trend and thus, only lends mildly stronger support than the Chi-squared test than the two variables are independent of one another. The examination of the odds ratios from the regression, although qualitative, allow for better conclusions. Thus, both quantities of cigarettes smoked per day were significant risk factors for overweight status at 10 years of age, but the higher category of smoking was not found to induce a significantly greater risk compared to the low category of smoking which would be indicative of a dose-response relationship.

Trimester specific exposures was of interest at the time when the research proposal was finalized as there is much conflicting literature speculating on the importance of first trimester nicotine exposure compared to throughout pregnancy exposure. However, there was such

extensive overlap in the women who smoked during each trimester that the results would be identical when examined via regression analysis.

6.1.3 Objective 3

The BMI developmental trajectory analysis yielded four distinct trajectories (Figure 4) supporting hypothesis 3a. The only significant predictor of trajectory membership was sex. The percentage of girls progressively increased from trajectory 1 to trajectory 4.

Multinomial analysis yielded unexpected results which contradict those of the results produced from objective 1. PEMCS was not significantly associated with trajectory membership. This is contrary to hypothesis 3b that predicted PEMCS would be a risk factor for overweight trajectories. Logistic regression analysis that combined the low risk groups yielded null results as well. PEMCS, although forced into the model, was not an independent risk factor for being in either the increasing risk or high risk trajectory group. When examining the high risk group as the outcome compared to the combined low risk groups, no covariates reached a significance value deemed high enough to be included in the model (Table 14b). However, APGAR score did remain a significant independent predictor of the increasing risk trajectory compared to the combined low risk groups (table 14a).

In conclusion, PEMCS was positively associated with excess weight at age 10 independent of a wide range of potential confounders including birth weight and subsequent catch-up growth. PEMCS was not associated with longitudinal BMI trajectories.

6.2 Interpretation of Findings

6.2.1 Objectives 1 and 2

The literature linking PEMCS and excess weight is consistent but perpetually limited by potential confounding given the necessary observational nature of all studies. The finding here that PEMCS remains a significant risk factor for excess childhood adiposity independent of a wide range of possible confounding variables and common correlates of both the exposure and the outcome supports the conclusions of recent systematic reviews (57,58) (Chapter 2.4). The fact that this association held strong after adjustment for birth weight coincides with more recent findings by the group of Beyerlein and colleagues (113,114) and is also in accordance with a number of older studies that did not assess this association directly but were able to control for low birth weight (115,134). However, several studies have reported low birth weight as a mediator of the relationship between PEMCS and overweight status (132,146). The fact that the association of PEMCS and excess weight was unchanged after adjustment for a measure of catch-up growth has not been evaluated before and is unique to this analysis.

Our results conflict with a recent publication which found that familial factors confound the association between maternal smoking during pregnancy and young adult offspring overweight (147). This study reported that the association between PEMCS and risk of overweight in male offspring can be explained partly by parental socio-economic status and education but also by unmeasured family factors. The method used for elucidating the importance of immeasurable confounders common to both exposure and outcome was by

investigating the effects of changing smoking patterns in subsequent pregnancies and within families. A within-sibling analysis was performed which showed that the association between PEMCS and overweight diminished in both full and half sibling, indicating that regardless of how many genes siblings have in common, it is the shared environment that accounts for the association and that the direct effects of maternal smoking may be quite small. However, the study had a small sample size so further research on potential confounders that may help to explain the PEMCS and excess weight association are needed.

It could be debated that these findings (and those of any epidemiological study of this topic) may be biased by mothers who did not smoke during pregnancy but lived with a smoking partner and thus, in this case, were classified as an unexposed pregnancy. But this would be expected to diminish the observed association and other work has reported that excess weight in the offspring can only be partially explained by paternal smoking (148). Strong support of this notion has also come from work stemming from the Generation R Study, a population based prospective cohort of pregnant women and their children from fetal life onwards in the Netherlands (78). They reported that in non-smoking mothers, paternal smoking was not associated with postnatal growth characteristics (149). The role of maternal as opposed to paternal smoking is also supported by an Australian study which demonstrated that prevalence of overweight children whose mothers smoked before and/or after pregnancy but not during pregnancy were similar to those who had never smoked at all (150).

A common critique of PEMCS and BMI related studies is that it has been shown by some that size at birth is associated with the distribution of body fat rather than BMI (22). However,

many smaller clinical studies that used more objective adiposity measures have yielded findings which support a positive association between PEMCS and excess weight in the offspring (112,151). It has been proposed by some that studies of this association should be run separately for each sex. A few recent studies have also found no association in female offspring (147,152,153). Gender differences have also been reported elsewhere in regards to the association between birth weight and excess weight (154), where high birth weight was a risk factor for excess weight in both girls and boys but low birth weight was reported as protective in girls and harmful in boys. No such interaction with sex was seen in this work other than the difference in sex ratio between trajectories. More work is needed to determine whether the association between PEMCS and excess weight is different for boys and girls and, if so, to elucidate the mechanisms involved in a differential association.

Given that we found no strong evidence of mediation involving birth weight or catch-up growth of the association between PEMCS and overweight status of offspring, the mechanism through which PEMCS does affect offspring excess weight remains unclear. Our results support rodent work showing that nicotine exposure can cause increased body weight with no difference in mean birth weight between the exposed and the unexposed (155,156). Possible alternative mechanisms to explain the PEMCS and offspring excess weight association exist at the hypothalamic or fat cell level (Chapter 2.4.3). These include altered appetite behaviour due to alterations of cholinergic neurotransmitter systems (157) or even changes in food digestion efficiency (156). Much support has also come for the notion of inappropriate setting of systemic hypothalamic control of both appetite and energy expenditure (158). 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 (159). Some have shown that, even at birth, infants born to smoking mothers have a preserved ponderal index (weight for length) (160) with relatively more body fat mass (161). It is also important to consider the fact that most mechanistic information from the basic sciences and animal models has concentrated on nicotine, which is only one of the thousands of chemicals or toxins in a commercial cigarette.

In conclusion, smoking during pregnancy may be a serious risk factor for the development of childhood overweight. In our study, the increased risk could not be attributed to a wide range of possible confounding variables. Our study may, at first, support the 'developmental origins of excess weight', but the risk in the offspring was independent of birth weight and catch-up growth and thus, may be attributed to other specific effects of nicotine or other components of cigarette smoke, as seen above. It may, in fact, be the adaptation of the fetus to maintain its growth rather than a direct effect of maternal smoking on fetal growth itself that underlie changes in body composition.

There is also much to be learned from the other covariates that remained significant in final models of this large sample of Québec children. The independent contribution of immigrant status coincides with most literature which has demonstrated both an independent and joint association of racial/ethnic background and socio-economic status (162). Interestingly, race/ethnicity has been reported to modify the association between PEMCS and excess weight (132), although there was no significant interaction in our analysis. The contributions of maternal BMI and childhood energy intake were no surprise and support the role of overall maternal health pre-pregnancy and the role of nutrition in future obesity prevention programs.

Monoparental family, a surrogate measure of socio-economic status, was significantly associated with overweight status and supports existing evidence documenting disparities across social classes. APGAR score was unexpectedly significantly and independently associated with overweight status at age 10 and was associated with increased risk BMI trajectory membership. We were unable to identify any other studies supporting or refuting this finding. As APGAR score is a crude indictor of newborn health and both the prenatal and perinatal environment, it may lend support in this study, again, to the importance of early life in long term health.

The null finding of a dose-response relationship is in disagreement with the vast majority of recent literature; however, publication bias is a serious concern in this case as those who have not observed a dose-response relation were less likely to attempt publication of such work. We can also assume that women who tend to continue smoking during pregnancy may also be those who are on the higher end of the spectrum of the number of cigarettes smoked. The lack of useful data to assess trimester specific associations may be due to the fact that this information was self-reported by the mother after pregnancy. Women who quit smoking during pregnancy may not precisely remember at which point they quit and thus, rendering trimester specific information of lesser quality compared to, for example, repeated questionnaires administered during pregnancy to assess timing of exposure.

6.2.2 Objective 3

The weight status of children tends to persist throughout childhood and into adulthood (42). In other words, overweight children tend to remain overweight as adults and normal weight

children tend to remain normal weight as adults. However, some children go from being normal weight to overweight (or low risk to high risk) or vice versa. These changes can only be examined using longitudinal methods that allow for intra-individual growth over time and thus, the possibility for identification of aggregated patterns of weight development.

The results obtained from the analysis of objective 3 are null, which is consistent with a few other longitudinal cohort studies that failed to demonstrate a clear relationship between PEMCS and childhood weight (163,164). However, the number of longitudinal studies is scarce. Six other studies were identified in the literature that used group-based methods for examining weight development in children. Four of these used continuous BMI, like this work, as an outcome. The first, by Nonnemaker and colleagues (2009) identified four trajectory groups in adolescents from 12- to 17- years of age: low risk (44%), low-to-moderate risk (36%), moderate-to-high risk (16%) and high risk (4%) (165). O'Brien (2007) identified five subgroups in a group of Canadian children from 2- to 12- years of age: never overweight (60%), preschool overweight (19%), elementary overweight (10%), return to normal weight (7%) and variable trajectories (4%) (166). Ventura and colleagues (2009) identified four groups in 5- to 15- year-olds: 50^{th} percentile tracking (37%), 60^{th} percentile tracking (29%), upward percentile crossing (14%) and delayed downward percentile (20%) (167). Lastly, Hejazi and colleagues (2009) reported four trajectories in girls: stable normal BMI (64%), accelerating risk to obesity (14%), early-declining BMI (8%), and late-declining BMI (14%) (168). After stratification, they reported three trajectories in boys: stable normal BMI (70%), j-curve rise to obesity (11%) and transient high BMI (19%).

It is quite challenging to compare the findings of these studies and only two of the four studies demonstrated a rise from normal weight to overweight status (or low risk to increasing risk); although, this change has been seen in other studies using dichotomous BMI (169,170). BMI trajectories have the potential to reveal critical ages at which weight status may change and where intervention may be most beneficial. Likewise, specific characteristics that predict trajectory membership may also shed light on possible interventions. However, lack of similar trajectories across different study populations may be due to differences in study design and methods of analysis. Similarly, the predictors examined in these studies, to date, have been quite variable and identified with a number of different methods (i.e. multinomial regression, multivariate analysis of variance, discriminant function analysis). Overall, these methods are still novel and need much work and a consensus on how best to use weight cut-offs before they can really be evaluated and combined by meta-analysis. Although this analysis identified minimal correlates of the trajectories, it is important to consider these findings cautiously.

6.2.3 Future Research and Interventions

Future research, especially of the longitudinal type, is needed to substantiate the findings of this study in other populations and further examine the underlying mechanisms of the association between PEMCS and offspring excess weight independent of both birth weight and catch-up growth. This is of importance as the strong findings of objective 1 and 2, contrary to the study hypothesis, were not replicated using group-based longitudinal methods used in objective 3. A 1994 commentary in the American Journal of Public Health in which the author saw serious flaws in the status quo of fetal origins research (171) still remains relevant today and should be

seriously considered when embarking on perinatal research of this kind. It stated that a higher bar for admissible scientific evidence on fetal exposure should be strived for in three ways: (i) disentangling the suspected single exposure from correlated exposures; (ii) bracketing the timing of the suspected exposure to fetal life alone; and (iii) pinpointing its timing to a specific epoch in fetal life.

As seen in Appendix 1, it is nearly impossible to separate the complex web of associations and of reciprocal or counter effect influencing childhood excess weight. Mechanisms that lead to excess adiposity are often biologically unclear as they are difficult to create in an animal model and there are many different pathways from which a specific determinant may affect the outcome.

The large number of potential determinants and correlates found in the literature and briefly described throughout this work means that for each of them, the actual association may not be very strong (11). However, even interventions targeted at very small attributable risks may have very large effects on the outcome (156) if the risk factor is highly prevalent in the population of interest, as seen with PEMCS (141). It is also important to consider the ability to intervene; a single behaviour risk factor such as PEMCS may be much simpler to target than, for example, sedentary behaviour in children.

6.3 Study Limitations

The findings and the interpretations summarized in the previous two sections need to be considered while acknowledging certain study flaws and limitations. Firstly, the QLSCD

excluded Cree regions, Inuit regions and most Indian reserves due to logistic and financial restrictions. This is unfortunate as these groups suffer from heightened levels of overweight and fairly high smoking rates. However, the QLSCD is still representative of 98% of the children born in the province of Québec in 1998.

The primary outcome of this study was weight status of children as quantified by BMI (Chapter 1.2). The limitations of BMI are very well known (23). For instance, it has been found to underestimate the prevalence of overweight (172) and it is often criticized for having poorly defined cut-offs, for not being able to differentiate between types of fat, skeletal and muscle mass, and for perpetuating a focus on weight instead of health. However, BMI remains the most practical and most commonly used measure to screen overweight and obese children and is considered the most appropriate measure of body fatness when controlling for age and sex by the WHO for population level research. It is also the most feasible measure for a study; other objective methods are neither financially sound nor well suited for large cohorts of young children. Two of the seven BMI variables used for the developmental trajectory building were reported by mothers and thus, likely resulted in a higher degree of misclassification compared to the measured values used at the remaining time points. Some have concluded that parent estimation of height and weight is inaccurate for classifying children by BMI (173). Work on this dataset has reported that mothers tend to overestimate their children's weight more than their height, resulting in an overestimation of overweight children (174). However, others have reported that parent-reported height and weight does accurately classify children into BMI categories when the sample size is large enough, as it is in this case (175).

The exposure of interest, PEMCS, relied on maternal self-report of smoking behaviours 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 serious challenge. Different patterns of timing, duration, type and quantity of maternal smoking may alter the effect on weight outcomes. For more accuracy in measuring the degree of tobacco exposure, some have recommended the use of costly biological specimens or repeated self-report measures of smoking collected throughout pregnancy. With such designs, there are multiple substantially correlated indices that can be integrated via statistical methods to identify patterns of prenatal exposure (176). Although validity may be higher with more advanced collection and methods of analysis, self-report of smoking during pregnancy has reasonable validity (177). Further, misclassification of smoking would likely bias towards the null in the estimated association between PEMCS and excess weight.

Due to the observational nature of the study, it was also impossible to differentiate the effect of in-utero smoking exposure from postnatal second hand smoke. Postnatal smoking habits of mother and father were available but the level of missing data was very high and thus, was not included in this analysis. These two exposures may be quite difficult to separate as women who smoke during pregnancy are likely to continue. A recent study tackled the question of in-utero active or passive exposure by quantifying prenatal exposure to tobacco smoke via serum cotinine biomarkers (178). The study followed 292 mother-child dyads from birth to 3 years of age and their findings suggest that both active and secondhand prenatal tobacco smoke may be risk factors for greater adiposity in childhood. The publication emphasizes that accurate quantification of prenatal secondhand tobacco smoke exposure is essential to obtaining valid

estimates from epidemiological studies. Additionally, paternal smoking has been reported to affect postnatal offspring weight by altering childhood appetite as opposed to altering in-utero growth (179). Thus, future studies may seek, when feasible, to tease out in-utero active or passive exposure.

The survey and database used in this analysis had considerable information on child and family characteristics, yielding an ability to control for a wide range of confounders. However, the inability to control for gestational weight gain, which has been shown to be associated with an increased BMI in childhood and adulthood (180), is recognized as a limitation. Although data are available for children's energy intake and diet quality, due to the design of the study, maternal diet during pregnancy was not collected; this also has been shown to be associated with metabolism in the offspring (181). Similarly, in a meta-analysis by Dallongeville and colleagues, smokers tended to have a nutrient intake substantially different from that of non-smokers, with higher intakes of energy, total fat, saturated fat, cholesterol, and alcohol (182).

It was decided that all final models in this body of work were to be run without the weight provided by Santé Quebec (Chapter 4.4). This decision was not made without much thought and analysis. Current unweighted prevalence of the exposure, the outcome and all candidate covariates were compared to weighted prevalence with an estimated binomial confidence interval. No significant statistical differences existed and thus, it was deemed more legitimate to run analysis without weights and thus, not delete a number of respondents for lack of a cross-sectional weight. This also has another advantage as weights cannot be used for the building of trajectories; thus, prevalence estimates remain consistent across this thesis.

A final possible methodological limitation of this study was the qualitative method used to examine mediation. The methods employed in this study are not suited to quantitatively assess mediation. Mediation is of significant interest for many early risk factors for excess weight in both adults and children, regardless of the nature of the exposure, due to the large number of both genetic and lifestyle factors that may confound, mediate or moderate associations between exposures and long term outcomes. Mediation is very difficult to define statistically and is approached in many different ways. The *Sobel Test* has been proposed to quantitatively assess mediation (183) but is not well suited to accommodate multinomial outcomes. A recent publication on the topic of this thesis used spline regression models to assess mediation (113). Others have used Structural Equation Modeling (SEM) (184), but this was beyond the scope of this work. The method employed in this study is well documented in the literature and since no mediation was detected at all qualitatively, it would not be expected that more quantitative methods would report different results.

6.4 Study Strengths

Despite the aforementioned limitations, the strength of this study is evident for a number of reasons. The outcome of objective 1 and 2 as well as the majority of data points in the building of developmental BMI trajectories (objective 3), were BMI variables derived by objectively measured heights and weights by trained staff. Objectively measured BMI has been shown to be a significantly better indicator of overall adiposity as opposed to self- or parent report (185).

This study included a large longitudinal sample of children from a Canadian province with an extensive range of recorded child and family characteristics repeatedly collected and thus, potentially the greatest strength was the breadth of this dataset. All models were controlled for well established independent determinants of childhood excess weight and potential differential characteristics of smokers and non-smokers. Thus, we were able to control for observed confounders related to both PEMCS and overweight status. As evaluated by way of meta-analysis (57), the most common controlling variables in other studies of this association were maternal obesity, social status, birth weight and breastfeeding. Although each is very important, many confounders were missing especially at the social level, which is a serious caveat with detrimental effects on generalizability. This study was able to take into consideration a wide range of important child, parent and family socio-demographic characteristics to account for potentially confounding variable including a measure of both energy intake and physical activity which lends much support to causality as these two behaviours represent the paradigm of energy in and energy out. Energy intake, used as a controlling variable in this study, is based on a 24-hour recall administered to the children by a trained nutritionist. Dietary assessment in this form may be one of the best forms viable for large sample size epidemiological research (186).

6.5 Conclusions

As worldwide obesity prevalence continues to rise, research capacity building in both the population and biological sciences to fully comprehend the root causes and underlying factors is of the utmost importance. Effectively addressing such a complex issue with an interacting system of factors, calls for a sustained multi-sectorial response.

Our findings further support that PEMCS is a risk factor for excess weight during childhood independent of many known important contributors to weight status. They also suggest that low birth weight and catch-up growth are unlikely to mediate the association. This finding underscores the importance of addressing the prevention of PEMCS and not just the downstream neonatal outcomes. However, low birth weight and catch-up growth have been found to negatively affect long-term health in a wide range of study types and populations and thus, this finding does not imply that these should be abandoned as targets for preventative measures. Our findings would also suggest that PEMCS is not associated with heterogeneous development of height and weight over time. However, as it has been found to be associated in other studies, more work is needed to fill in the gaps and to gain a greater understanding of the methodological implications of these group-based techniques.

The developmental origins of excess weight and the notion of priming chronic disease early in life are undoubtedly very complex. To address this, well-designed prospective longitudinal studies with repeated measures of heights and weights to further the work of trajectory analysis and to properly quantify the effects of early life risks are needed. Additionally, studies are needed with longer follow up in both children and adults to identify the association between PEMCS and more refined measures of the metabolic syndrome and detailed measures of body composition.

There is ample evidence to conclude that promotion of positive lifestyle habits during the reproductive ages of women is important for both neonatal outcomes and downstream risk of overweight or obesity and associated chronic diseases. PEMCS is a key modifiable risk factor for

adverse pregnancy outcomes. Success in prevention is most likely to be achieved when preventative measures are initiated as early as possible and sustained through childhood. Early intervention is warranted as excess weight tracks from childhood to adulthood and lifestyles become more difficult to modify as one ages. The overall implication for current public health practice, then, is that the prevention of excess weight early in life is critical as it may have lifelong, perhaps even multigenerational impacts.

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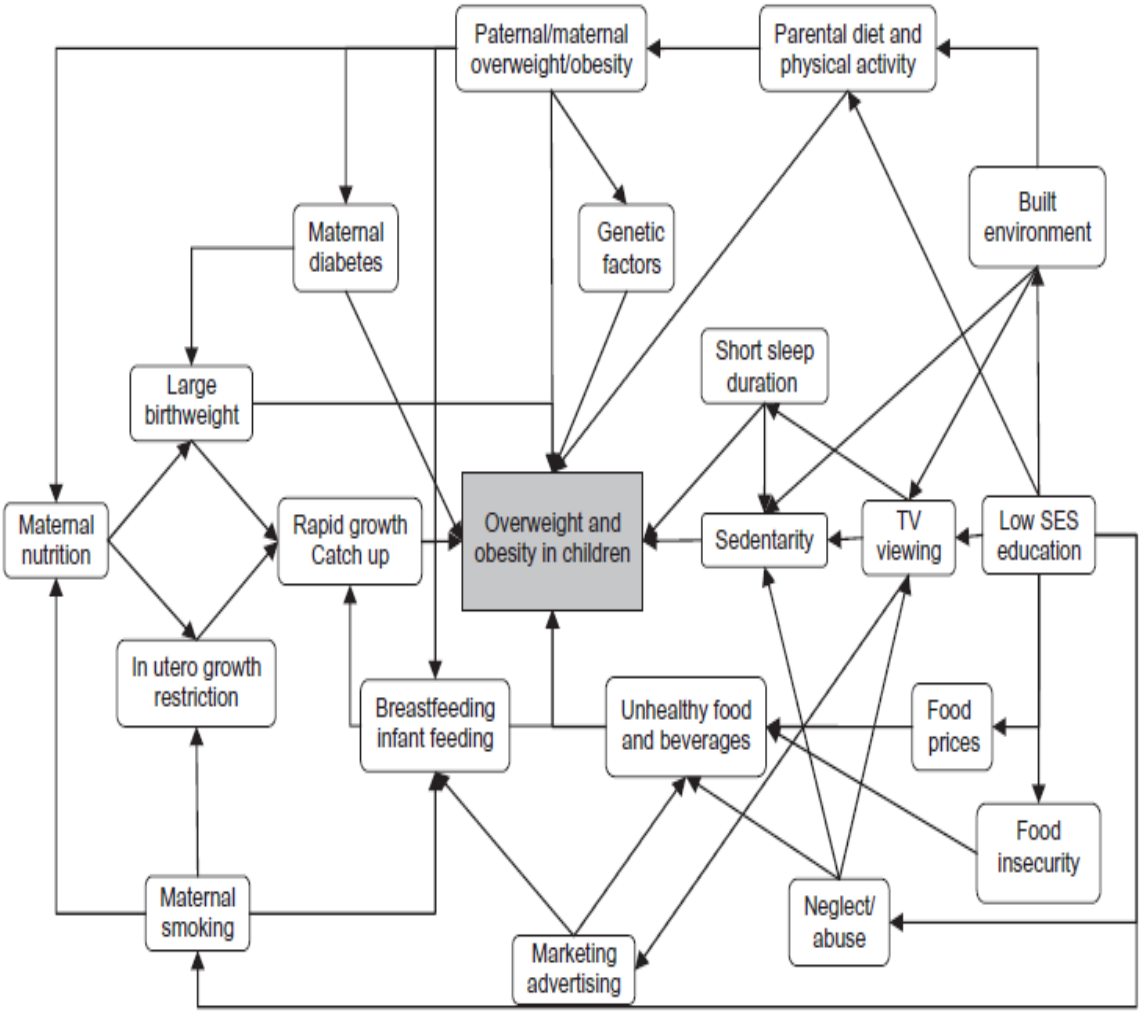
Appendices

Appendix 1: Complex web of potential determinants of overweight and obesity in children (11)



Appendix 2: MEDLINE search strategy

1 Smoking/ (98325)

2 smok$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (180012)

3 Obesity/ (93705)

4 obes$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (151151)

5 overweight.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (24842)

6 Pregnancy/ (609317)

7 pregnancy.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (655677)

8 Child/ (1173246)

9 child$.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (1598738)

10 1 or 2 (180012)

11 3 or 4 or 5 (157157)

12 6 or 7 (655677)

13 8 or 9 (1598738)

14 10 and 11 and 12 and 13 (256)

15 Birth Weight/ (28359)

16 exp Infant, Low Birth Weight/ (21639)

17 (birth adj2 weight).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (57833)

18 birthweight.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (9781)

19 catch-up growth.mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier] (1666)

20 15 or 16 or 17 or 18 or 19 (64323)

21 11 and 12 and 13 and 20 (369)

22 limit 21 to ((english or french) and last 10 years) (267)

23 from 21 keep 1-279 (279)

24 10 and 12 and 13 and 20 (989)

25 limit 24 to ((english or french) and last 10 years) (488)

26 Epidemiologic Studies/ (4801)

27 exp case-control studies/ (478316)

28 exp Cohort Studies/ (1046486)

29 case control.ab,ti. (54168)

30 (cohort adj (study or studies)).ab,ti. (51422)

31 cohort analy$.ab,ti. (2417)

32 (follow up adj (study or studies)).ab,ti. (31080)

33 (observational adj (study or studies)).ab,ti. (26162)

34 longitudinal.ab,ti. (101233)

35 retrospective.ab,ti. (191637)

36 cross-sectional.ab,ti. (108415)

37 Cross-Sectional Studies/ (116369)

38 association$.ab,ti. (577443)

39 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (1840081)

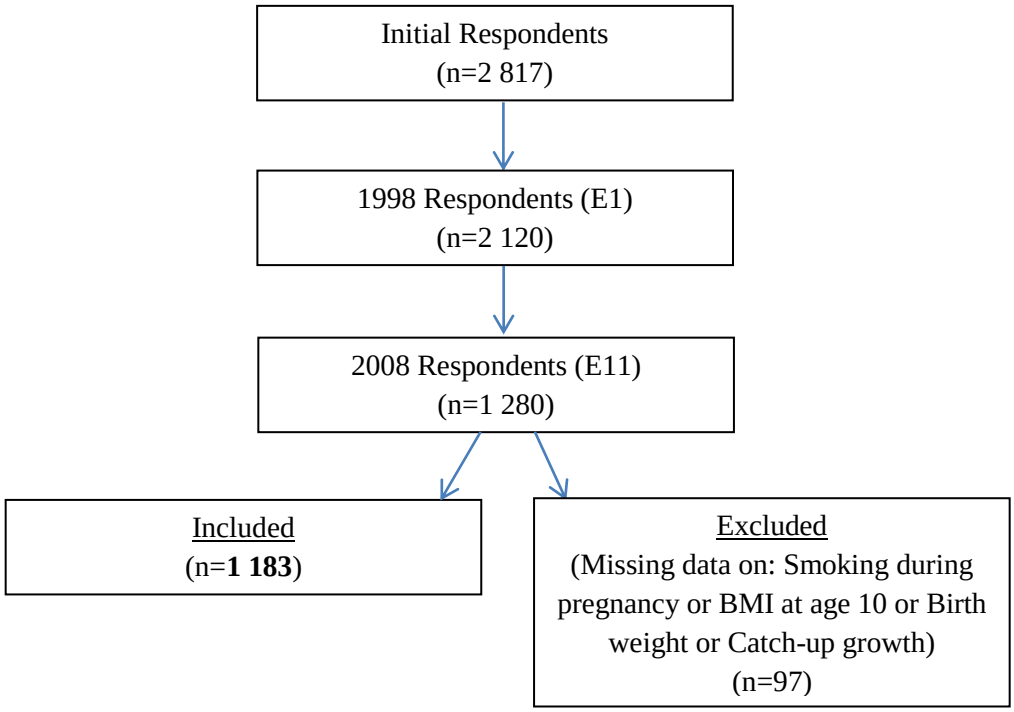
40 14 and 39 (170)

41 limit 40 to ((english or french) and last 10 years) (139)

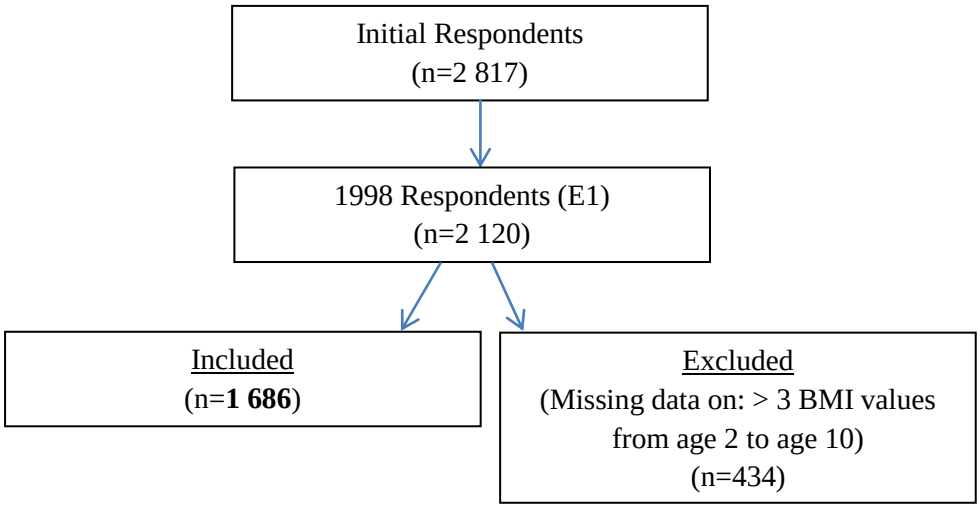
42 20 and 40 (72)

43 limit 42 to ((english or french) and last 10 years) (64)

Appendix 3a: QLSCD flow chart of respondents (logistic model)



Appendix 3b: QLSCD flow chart of respondents (group model)



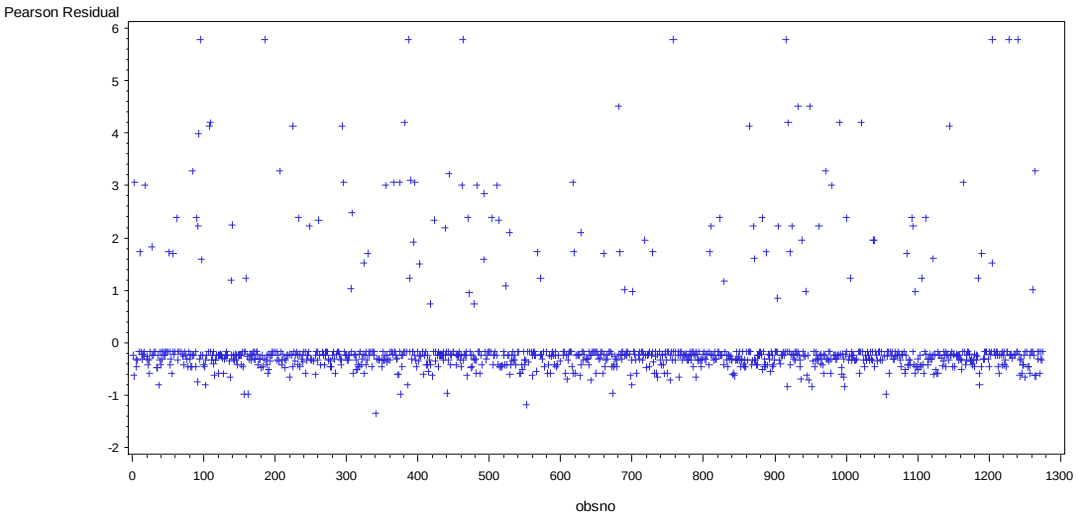
Appendix 4: IOTF childhood overweight and obesity BMI cut-offs (26)

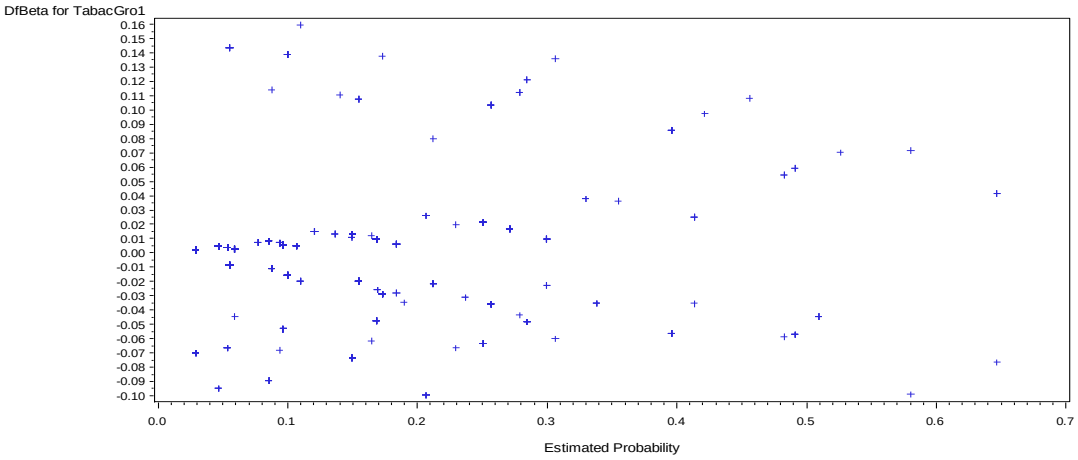
International cut-off points for body mass index for overweight and obesity by sex between 2 and 18 years of age, defined to pass through body mass index of 25 and 30 kg/m^2 at age 18, obtained by averaging data from Brazil, Great Britain, Hong Kong, Netherlands, Singapore, and United States

	Body mass index 25 kg/m^2		**Body mass index 30 kg/m^2**	
Age (years)	Males	Females	Males	Females
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11

Appendix 5: Diagnostics and Goodness-of-fit

Base Model (model 1)





Model	Hosmer and Lemeshow test (p-value)	c statistic
Base model (model 1)	0.6102	0.694
Dose-response (model 5)	0.6436	0.692

Appendix 6: Examination of collinearity using Variance Inflation Factors (VIF's)

Model	**VIF**
Intercept	0
PEMCS	1.11009
Birth weight	1.17848
APGAR score	1.0217
Catch-up growth	1.21417
Sex	1.06974
Duration of breastfeeding (exclusive)	1.08710
Mother's immigrant status	1.03427
Mother's weight status	1.05175
Energy intake	1.02604
Physical activity	1.03171
Sedentary behaviour	1.02009
Household income	1.35501
Family structure	1.22443