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# The Impact of Intrauterine Exposure to Gestational Diabetes Mellitus on Early Childhood Body Mass Index Trajectories

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THE IMPACT OF INTRAUTERINE EXPOSURE TO GESTATIONAL DIABETES
MELLITUS ON EARLY CHILDHOOD BODY MASS INDEX TRAJECTORIES

(Thesis format: Monograph)


by


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Graduate Program in Epidemiology and Biostatistics


A thesis submitted in partial fulfillment
of the requirements for the degree of
Master of Science in Epidemiology and Biostatistics


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# Abstract

Background: Although gestational diabetes mellitus (GDM) has been linked to pediatric obesity, there is limited research on the impact of intrauterine exposure to GDM on trajectories of childhood growth. Objective: To assess the effect of prenatal GDM exposure on childhood body mass index (BMI) trajectories. Design: Analyses were conducted using data from cycles 2 to 6 (1994-2004; N=3412 children) of the National Longitudinal Survey of Children and Youth. Latent growth curve modelling (LGCM) was used to model BMI trajectories from age 2 to 10 years with prenatal exposure to GDM as a predictor. Effect modification by breastfeeding was assessed. Results: Among males, prenatal exposure to GDM was associated with significantly lower initial BMI. There were no other statistically significant effects of prenatal exposure to GDM. Effect modification by breastfeeding was not statistically significant. Conclusions: Despite mainly non-significant findings, this study lays the groundwork for future pediatric obesity research using LGCM.

## Keywords

# Acknowledgments

I would like to thank Dr. Piotr Wilk for his guidance throughout the Master's program and through the process of producing this thesis. This project involved a learning curve that I could not have overcome without his instruction and support. I would also like to thank Dr. Karen Campbell for agreeing to serve as a committee member on short notice. Her expertise, advice, and constructive suggestions have helped shape this thesis at every stage. Assistance provided by Bradley Corbett throughout the past year at the Research Data Centre was greatly appreciated. I wish to also acknowledge the help provided by John Costella in guiding my literature search.

I would like to express my very great appreciation to Andrew Dundee for working with me to painstakingly reread and revise the final draft of this thesis.

Finally, I wish to thank my family and friends for the continuous support and encouragement they have given me from the beginning of my Master's studies through to the "home stretch".

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# List of Abbreviations

| | |
|---|---|
| AGA | Appropriate for gestational age |
| AIC | Akaike's information criterion |
| AR | Adiposity rebound |
| BIC | Bayesian information criterion |
| BMI | Body mass index |
| CCHS | Canadian Community Health Survey |
| CDC | Centers for Disease Control and Prevention |
| CFI | Comparative fit index |
| CHD | Coronary heart disease |
| DM | Diabetes mellitus |
| ER | Economic regions |
| EIER | Employment insurance economic regions |
| FIML | Full-information maximum likelihood |
| GDM | Gestational diabetes mellitus |
| HDL | High-density-lipoproteins |
| IGT | Impaired glucose tolerance |
| IOTF | International Obesity TaskForce |
| LDL | Low-density-lipoproteins |
| LFS | Labour Force Survey |
| LGA | Large for gestational age |
| LGCM | Latent growth curve modelling |
| MAR | Missing at random |
| NLSCY | National Longitudinal Survey of Children and Youth |
| OGTT | Oral glucose tolerance test |
| PMK | Person most knowledgeable |
| RMSEA | Root mean square error of approximation |
| SEM | Structural equation modelling |
| SGA | Small for gestational age |
| TLI | Tucker-Lewis index |

Chapter 1

# 1    Introduction and Literature Review

## 1.1    Introduction

Obesity is a morbid condition that is reducing the quality of life for increasing numbers of children and youth.[1]  Over the past few decades, the prevalence of childhood overweight and obesity has escalated in Canada and worldwide.[2,3] These trends are important because of the social stigma and reduced quality of life associated with being overweight[4] as well as the myriad of comorbidities linked to obesity.[4,5]  Indeed, as a result of the childhood obesity epidemic, children are experiencing earlier onset of chronic conditions once considered to be limited to adulthood.[6] Obese children are also at greater risk for adult obesity[7] and death in adulthood due to cardiovascular disease.[8,9] Strategies for prevention are becoming ever more important in light of these trends, not only to improve quality of life and reduce morbidity and mortality, but to conserve medical resources and lessen the overall burden of obesity on the Canadian health care system.

One area of research that is important for the development of targeted prevention strategies for childhood obesity is that which examines the developmental origins of overweight. There is a growing body of literature that suggests certain prenatal exposures are associated with increased risk of overweight and obesity in childhood and even adulthood.  One such risk factor that has been extensively studied is prenatal exposure to maternal impaired glucose tolerance (IGT) during pregnancy, and in particular, to gestational diabetes mellitus (GDM). GDM is a state of glucose intolerance that arises or is first recognized during pregnancy.[10] The principal theory for the biological mechanism linking GDM to childhood overweight, at its earliest stage of the mechanistic pathway, suggests that poor maternal glycemic control at critical stages in fetal development leads to fetal hyperglycemia, which triggers fetal hyperinsulinemia.[11] Fetal hyperinsulinemia is theorized to promote offspring overweight by stimulating fetal growth, resulting in macrosomia or very high birth weight, and programming hormones that regulate appetite

and food intake, resulting in postnatal risk of obesity in offspring.[12-15]

Despite recognition of this association, the evidence supporting GDM as a risk factor to target for childhood overweight and obesity prevention has been somewhat underwhelming. This may be due, in part, to inconsistency in study outcomes. The majority of studies that have examined the impact of maternal IGT during pregnancy on weight status at a single point in childhood have varied timing of outcome evaluation. Furthermore, studies use different standards for defining overweight and obesity in childhood. These are two common issues that make pooling of results across studies difficult and have likely lead to an overall weak body of evidence for the relationship between GDM and childhood overweight and obesity.

Studies that examine this association cross-sectionally may be missing important aspects of the potentially complex relationship between GDM and the change in child weight occurring in the unobserved period. Indeed, these studies may be erroneously concluding null associations between maternal IGT and childhood weight simply because of the limited timing of observation. A strategy to overcome these issues is to shift the focus of study outcomes from weight status at a single point in childhood to growth trajectories throughout childhood. This will allow for observation of the onset of overweight or obesity at any point throughout childhood. More importantly, childhood growth trajectories allow observation of growth patterns, which provide more insight into overall child health than weight status at a single point. Thus, an analysis of the impact of prenatal exposure to GDM on trajectories of childhood growth is a logical and important next step in determining the relationship between maternal IGT during pregnancy and childhood overweight and obesity. The current study takes this step by examining the association between prenatal exposure to GDM and early childhood BMI trajectories.

In the sections that follow there will be a review of the literature on the prevalence, measurement, and etiology of childhood overweight and obesity. Section 1.2 will discuss the epidemic nature of child obesity by outlining the Canadian trends in prevalence of childhood overweight and obesity (Section 1.2.1) and obesity-related illness and chronic disease (Section 1.2.2). Section 1.3 will examine the various strategies used to measure

trends in childhood overweight and obesity at the population level, discussing current definitions of childhood overweight and obesity (Section 1.3.1) and the importance of analysing developmental patterns and growth trajectories (Section 1.3.2). The remainder of this chapter will cover the literature on early life risk factors for childhood overweight and obesity. Section 1.4 will provide an overview of perinatal contributions to pediatric obesity, focusing on maternal characteristics associated with childhood overweight and obesity (Section 1.4.1) as well as risks associated with fetal growth and early nutrition (Section 1.4.2). Section 1.5 presents a review of the literature on the current trends in GDM prevalence (Section 1.5.1), risk factors for GDM (Section 1.5.2), and issues related to the study of GDM in population research (Section 1.5.3). Finally, Section 1.6 outlines the literature to date on the impact of exposure to GDM *in utero* on offspring weight, focusing on proposed biological mechanisms (Section 1.6.1) and the impact of GDM on birth weight (Section 1.6.2) and weight status throughout childhood (Section 1.6.3).

## 1.2   The Epidemic of Childhood Obesity

Worldwide, the prevalence of childhood overweight and obesity has been escalating. Indeed, due to the rate of increase in prevalence, childhood overweight and obesity is now widely recognized as an epidemic.[16] Further, overweight and obesity in childhood are associated with illness and chronic disease that threaten health not only in childhood, but also in adulthood. The morbidity and mortality related to childhood overweight and obesity is detrimental both on the individual level, in terms of reduced quality of life, and community level, in terms of the burden on health care systems and loss of productivity. To evaluate the extent of the burden of this epidemic, it is important to examine recent trends in prevalence of pediatric obesity as well as to review the literature on obesity-related illness and disease.

### 1.2.1    Canadian Trends in Childhood Overweight and Obesity

Trends in average weight among Canadian children over the past few decades indicate that, as in many other developed countries, childhood overweight and obesity is becoming increasingly more common. Indeed, it has been shown using three national databases  that between 1981 and 1996, the rate of increase in BMI was around 0.1 kg/m$^2$

per year for Canadian children aged 7 to 13 years.[17] That is, over this period average BMI for both male and female children in this age group increased by nearly 1.5 kg/m$^2$. During this time, overweight and obesity, defined respectively by the 85th and 95th percentiles for age- and sex-specific BMI, increased substantially.[17] Indeed, both overweight and obesity approximately doubled for males and females over the 15 years.[17]

More recently, using the 2004 Canadian Community Health Survey (CCHS), it was estimated that among all children and adolescents aged 2 to 17 years, 26% were either overweight or obese.[2] These estimates were obtained using age- and sex-specific BMI cut-offs for overweight and obesity as per International Obesity TaskForce (IOTF) guidelines.[2] Among 12 to 17 year-olds, the prevalence of overweight more than doubled from 1978 to 2004 while the prevalence of obesity tripled during the same time period.[2] These estimates were obtained using the 1978/1979 Canada Health Survey and the 2004 CCHS, both of which collected direct measures of weight and height used to calculate BMI.[2]

The most recent publication of The Chief Public Health Officer's Report on the State of Public Health in Canada indicated that adolescent overweight and obesity is still on the rise.[1] Among adolescents aged 12 to 19 years, it was estimated that 32% of males and 27% of females were either overweight or obese, as per IOTF weight classifications for children.[1]

These trends indicate that there is a pattern of increasing prevalence of overweight and obesity among Canadian children and adolescents that does not appear to have reached a plateau. This underscores the importance of identifying key determinants of childhood obesity as well as the urgent need for effective intervention and prevention strategies for childhood overweight and obesity in Canada.

## 1.2.2    Obesity-Related Illness and Chronic Disease

Perhaps the most insidious consequence of the increasing prevalence of childhood obesity is the myriad of diseases and other chronic health conditions associated with obesity that arise in childhood, adolescence, and adulthood.  Many of the comorbid health

conditions require lifelong care, thus creating a preventable burden on the health care system. Moreover, obesity-related physical health conditions that begin in childhood and persist throughout adulthood can cause premature death.[18] Indeed, as suggested by Daniels,[19] childhood obesity may be causing a decline in life expectancy in developed countries like Canada for the first time in recent history. Hence, childhood obesity is a public health crisis that not only warrants attention, but immediate action to intervene and prevent excessive weight gain in children.

Childhood overweight and obesity have been linked to a number of poor health outcomes that can present in childhood, adolescence, and adulthood. These include type 2 diabetes,[20,21] hypertension,[4,22,23] hyperlipidemia,[4,23] fatty liver,[24] asymptomatic atherosclorosis,[18,25] and coronary heart disease (CHD).[18] Although these were once considered diseases of adulthood, increasingly more children are being diagnosed with many of these health conditions.[19,21,26,27]

Glucose tolerance disorders, such as type 2 diabetes, have long been associated with adult obesity. However, recent studies have shown an increase in type 2 diabetes diagnoses among overweight and obese children and youth.[4,19-21,26,27] It has also been shown that among youth with type 2 diabetes, the majority are often overweight or obese, that is, with mean BMI ranging from ~33 kg/m$^2$ to ~38 kg/m$^2$ in adolescence and young adulthood.[26,27] One study of a large group of 5 to 17 year-olds revealed that overweight individuals are 12.6 times more likely to exhibit insulin resistance than their normal weight counterparts.[23] High levels of total body fat and, more specifically, abdominal fat have also been associated with insulin resistance among pre-pubertal children.[28]

Abnormal levels of lipids and lipoproteins in the blood, or dyslipidemia, are associated with adult obesity and have been reported in pediatric populations among overweight and obese individuals.[4,23,29,30] Obese adolescents exhibit increased levels of serum low-density-lipoproteins (LDL) and triglycerides and diminished levels of serum high-density-lipoproteins (HDL).[29] This pattern of dyslipidemia is associated particularly with visceral, or abdominal, fat.[29] It has been shown that overweight schoolchildren 5 to 17 years of age are 2.4 times more likely to have high total cholesterol and 7.1 times more

likely to have high triglyceride levels than their normal weight counterparts.[23] This trend in pediatric hyperlipidemia among overweight and obese children is particularly worrisome as hyperlipidemia in adulthood is a known risk factor for cardiovascular disease. It follows that obesity in childhood increases the risk of death in adulthood due to cardiovascular disease.[8][9]

Although hypertension is relatively rare in pediatric populations, overweight and obesity in children has been linked to hypertension.[18][22][23][25][30] Indeed, among children with consistently high blood pressure, the majority have been shown to be overweight or obese.[18][23] It has been reported that overweight and obese individuals aged 5 to 18 years are 4.5 to 9 times more likely to have high blood pressure compared to normal weight individuals in the same age group.[4][23]

Clustering of cardiovascular risk factors, including hypertension, insulin resistance and high cholesterol levels, has also been examined in pediatric populations.[23][25][30] Studies have shown that the overwhelming majority of children and young adults that have more than two cardiovascular risk factors are overweight or obese.[23][30] Indeed, one study reported that among children aged 5 to 10 years 41%, 75%, and 100% with 2, 3, or 4 cardiovascular risk factors, respectively, were overweight.[23]

The combination of a number of the aforementioned health conditions have been described together under the term "metabolic syndrome".[31] In a report published by the American Heart Association, metabolic syndrome is described as a constellation of several cardiovascular risk factors including abdominal obesity, dyslipidemia, high blood pressure, and insulin resistance with or without glucose intolerance.[31] In adults, the combination of these metabolic risk factors increases the risk of CHD.[31] It has been estimated that the overall prevalence of metabolic syndrome in pediatric populations is 4%, but among obese children, the prevalence is 30%.[19]

Overweight and obesity in childhood and adolescence have a lasting impact on future health status. It was shown that, independent of adult weight status, overweight in adolescence was associated with various adverse health outcomes in adulthood, including all-cause mortality, disease-specific mortality, mortality due to CHD, morbidity due to

CHD and atherosclerosis, gout, arthritis, and colorectal cancer.[18]

## 1.3   Measuring Population Trends in Childhood Obesity

Examining trends in overweight and obesity in pediatric populations is more complex than in adult populations. The selection of measurement tools to determine weight status in children at the population level is complicated by several factors. Central to these factors is the issue that current definitions of pediatric overweight and obesity are not based on childhood morbidity. Rather, most studies examining obesity in pediatric populations use guidelines based on definitions for adult obesity and statistically extreme observations. As a result, it is unclear whether findings from studies using these techniques to define childhood overweight and obesity status are meaningful. It is therefore important to be aware of the shortcomings of current definitions of childhood overweight and obesity and to explore other measurement techniques that may yield more meaningful results.

### 1.3.1   Defining Childhood Overweight and Obesity

One of the most widely used measurement tools for defining overweight and obesity is the BMI, which serves to approximate body fatness by adjusting weight for height.[32] In adults, definitions of overweight and obesity have been established using BMI cut points associated with increased risk of morbidity and mortality.[33] Determining clinically relevant BMI cut points in pediatric populations is less straightforward since weight-related health issues, such as metabolic and cardiovascular disease, present later in development and are generally rare in young people.[32] Moreover, BMI throughout childhood is notably less consistent than in adulthood, which further complicates the task of defining specific cut points for overweight and obesity in children.

Current recommendations indicate children or adolescents at the 85th and 95th percentiles for age- and sex-adjusted BMI of a particular reference pediatric population should be considered at risk for overweight and obesity, respectively.[34 35] Studies examining the validity of these guidelines have reported generally high specificity but low sensitivity of these percentile cut-off values.[36-38] Among children aged 8 to 12 years, individuals identified using cut points at the 85th and 95th percentiles for BMI were overweight and

obese 95% and 99% of the time, respectively.[38] Thus, specificity of these cut points was high. However, these cut points failed to detect a large portion of truly overweight individuals, with sensitivity scores of 0.65 and 0.39 for the 85th and 95th percentiles for BMI, respectively.[38] Such low sensitivity scores are particularly problematic for weight classification systems used for population surveillance or epidemiological purposes, as many cases of overweight and obesity are not captured.

## 1.3.2    Assessing Developmental Patterns and Growth Trajectories

In public health and medical practice, BMI cut-off values defining overweight and obesity in childhood are often used as screening tools rather than diagnostic tools. These BMI cut points flag individuals who may be at risk for weight-related health issues, but do not indicate per se the true level of risk for health issues in overweight and obese children.

The shortcomings of current definitions of childhood overweight and obesity are highlighted in the findings of a study done by Bouhours-Nouet and colleagues.[39] These researchers studied children aged 8 to 12 years who were obese, defined as 2 standard deviations above age- and sex-adjusted BMI, and collected information about birth weight, postnatal weight gain, and existing cardiovascular and metabolic risk factors.[39] Interestingly, obese children who had high weight at birth and increased weight gain in the first two years of life also had the highest insulin sensitivity and were thus metabolically healthier than obese children with low to moderate fetal and postnatal growth.[39] Children with this particular growth pattern had higher insulin sensitivity even when compared to other high birth weight children who had less weight gain in the first two years of life.[39] Moreover, obese children who had high birth weight had significantly lower concentrations of fat in the abdominal area as well as lower systolic blood pressure than obese children with low or average weight at birth.[39]

The findings of the Bouhours-Nouet *et al.*[39] study highlight two guiding concepts for childhood obesity research. The first is that biological processes leading to childhood overweight and obesity are likely active early in development.  Thus, research examining causes of obesity should shift focus to events occurring during prenatal and postnatal

growth. The second is that patterns of growth from birth throughout childhood convey more information about health than weight status at a single point. Consistent with this concept Legler and Rose[40] discuss that from the perspective of physicians, weight status carries limited information about patient health. Indeed they suggest that although children may be at extreme ends of the BMI-for-age spectrum at various stages throughout development, growth that is gradual and consistent reflects good health while inconsistent or accelerated patterns of growth are often indicative of poor health.[40] Indeed, it is important to examine all aspects of early growth in order to obtain a more complete understanding of child health.

*Size at Birth*

A number of studies have suggested that size at birth plays an important role in later obesity.[41-53] The majority of these studies' findings indicate that high birth weight for gestational age, or macrosomia, is an important predictor of childhood obesity, although small size at birth has also been found to be associated with metabolic disease and obesity.[42]

 It has been reported that high birth weight can predict overweight and obesity by as early as preschool age.[46 49] Indeed, studies have shown that children born with high BMI are taller and heavier by the age of 3 years than their normal birth weight peers and that this discrepancy persists throughout early childhood.[43]  Some studies have indicated that children born large for gestational age (LGA) are at nearly twice the risk of being overweight compared to children born appropriate for gestational age (AGA).[44 48 51] Moreover it has been shown that among obese children, those born LGA have a much higher incidence of metabolic syndrome than children born AGA.[45] Despite the fact that high birth weight may reflect maternal weight, its association with childhood obesity has been shown to be independent of maternal BMI.[46 48] Thus, factors that affect birth weight independently likely play important roles in predicting childhood obesity.

*Rates of Postnatal and Childhood Growth*

Postnatal and early childhood growth rates also predict later childhood and adult obesity

as well as adult morbidity.[54-59] Specifically, studies have reported that abnormally slow growth in height, or stunting,[54] and abnormally rapid growth in weight resulting in adiposity,[55-57 59] can increase later obesity risk.

Children exposed to perinatal conditions that result in stunted height reportedly have increased risk of developing obesity in later childhood.[54] Popkin and colleagues[54] examined data from several countries experiencing a "nutrition transition," that is, a shift in economic conditions resulting in dietary changes that promote overweight and obesity in childhood. However, because of the transitional state of the countries studied, the data reflect pediatric populations that still experience stunted height as a result of poor perinatal care and infant feeding practices.[54] After adjustment for income, stunted children were up to 7.8 times more likely to be overweight than non-stunted children.[54] The study of these low-income countries revealed that early height trajectories may be an important indicator of future overweight.[54] This may be relevant and applicable to the childhood obesity problem in North America as these findings illustrate how the early nutritional conditions among low income families in general may contribute to the development of overweight and obesity.

During infancy, rapid increases in weight but normal growth in length or height has been shown to be associated with obesity risk in childhood.[55-57] The pertaining literature defines rapid infancy weight gain in various ways. A review of several papers examined the impact of rapid weight gain in the first two years of life on later obesity risk using standardized scores for change in weight over each year and defining rapid weight gain as any z-score change greater than 0.67.[55] This review concluded a positive association between rapid weight gain in the first two years of life and childhood obesity, independent of weight at birth.[55] Another study examined the impact of rapid weight gain in the first 4 months of life on overweight status at 7 years of age, measuring weight gain as a continuous rate of change in weight per 100 grams per month.[57] This study found that independent of weight achieved by the first year, the rate of weight gain in the first 4 months was positively associated with overweight at 7 years of age.[57] In fact, it has been shown that regardless of the criteria for rapid growth, the age range in which rapid growth is measured, or the age at outcome evaluation, rapid weight gain during infancy is

a significant predictor of later overweight and obesity.[56]

Rates of weight gain in early childhood have also been shown to predict later obesity.[59] The timing of accelerated weight gain that leads to adolescent obesity has been shown to differ between males and females.[59] When weight gain trajectories were compared within a large group of adolescent girls, it was found that overweight individuals exhibited steeper weight gain between the ages of 3 and 4 years than their normal weight counterparts.[59] A similar pattern was found among overweight adolescent boys, except accelerated weight gain occurred between the ages of 5 and 8 years.[59] For both females and males, growth in height remained similar between overweight and normal weight individuals.[59] This indicates that steep weight gain occurring during these early stages can serve as an early warning sign for later obesity.

Early growth patterns also have important implications for adult morbidity.[58][60] A large longitudinal study examined the impact of rates of weight gain in childhood on subsequent risk of coronary heart disease, type 2 diabetes, and hypertension in adulthood.[58] It was found that individuals who were small at birth or at 1 year of age and subsequently experienced rapid weight gain between the ages of 3 and 11 years were at highest risk for all three chronic conditions.[58] Another study found similar patterns of early growth that significantly increased risk of type 2 diabetes.[60] High birth weight, defined as greater than 3.5 kilograms, followed by steep growth in weight but not height between the ages of 2 and 12 years was associated with type 2 diabetes in later life.[60] Additionally it was found that the highest incidence of type 2 diabetes at age 40 years occurred among individuals who had high birth weight and subsequent stunted growth in length during the first 3 months of life.[60]

*Timing of Adiposity Rebound*

As previously discussed, particular patterns of weight gain within the first few years of life are associated with risk of obesity and later morbidity.[61-67] The timing of these early growth patterns also has important consequences for BMI in later childhood and early adulthood.[64-66] In typical development, after an initial decline in body fatness in the first years of life, the body regains fat at a consistent rate throughout childhood and into

adulthood.[65] The point at which the renewed incline in body fatness occurs has been termed the adiposity rebound (AR).[64] Studies have shown that the timing of this developmental event is an important predictor of later obesity.[61 64-66]

Earlier than average occurrence of AR is associated with increased risk of overweight and obesity in childhood,[66] adolescence,[64] and adulthood.[65] In fact, individuals who experience early AR are reportedly 6 times more likely to be obese as adults than individuals who experience normal or late AR.[65] This relationship has been shown to persist even after adjustment for BMI at the time of AR as well as adjustment for parental BMI.[65] Even among infants who are obese by 1 year of age, those who experience later AR have been shown to attain normal BMI by the age of 16 years while individuals who have early AR remain overweight into adolescence and early adulthood.[64]

Early AR has specifically been associated with increased fat mass.[66] Indeed, one study combined measures of triceps and subscapular skinfolds into a fat mass index and found that early AR was significantly associated with higher fat mass index scores.[66] The same study found that waist circumference at 26 years of age was also significantly associated with early AR.[66] Among overweight and obese individuals, the relative risks of waist girth exceeding international cut-offs were 2.12 and 3.32, respectively, comparing individuals who experienced early AR to those who experienced late AR.[66] These findings indicate the ability of the timing of AR to act as an even more sensitive indicator of unhealthy fat mass than BMI, which can only approximate overall body fat.

It has been reported that early AR is associated with adult morbidity, specifically in terms of glucose tolerance.[67] One study showed that among adults aged 26 to 32 years, those who experienced early AR were most likely to suffer from diabetes or other forms of IGT.[67] This relationship was demonstrated despite the fact that BMI at the time of AR was within normal ranges and similar to individuals who had normal glucose tolerance in adulthood, suggesting that the timing of AR was the main predictor of later glucose tolerance disorders.[67]

It is evident that childhood obesity is a complex health issue that requires a more nuanced approach to its analysis as a health outcome in epidemiological study. The purpose of

preventing overweight and obesity in childhood is to prevent childhood and adult disease. Thus, it is important to examine other weight-related phenomena that may act as more sensitive warning signs for later obesity-related metabolic disease, such as the adiposity rebound. Indeed, the importance of examining growth trajectories in order to properly capture the entire phenomenon of childhood obesity is indisputable.

## 1.4 Early Influences on Childhood Weight Gain

The question that has not yet been addressed in this discussion is, of course, what causes childhood obesity? This is particularly complicated to answer since causality can only be examined if a causal factor precedes a particular outcome. In the case of childhood obesity, it is often difficult to determine the exact timing of onset. Indeed, as previously discussed, the developmental processes that lead to childhood overweight and obesity are already evident in infant growth patterns. An emergent avenue of research on the etiology of childhood overweight and obesity is one that focuses on risk factors present in the perinatal environment. In terms of causality, risk factors present prior to or shortly after birth can indeed be concluded to precede the outcome. Hence, examining perinatal risk factors can reveal more clues about the causes and development of childhood overweight and obesity.

### 1.4.1 Maternal Prenatal Characteristics, Behaviours, Diet, and Health

It has been suggested that maternal age, particularly very young or advanced maternal age, is associated with extremes of neonatal weight.[68 69] In terms of the low weight end of the spectrum, infants born to adolescent or advanced age mothers are at greater risk of low birth weight.[68 69] There is also evidence that primiparity is associated with low birth weight.[70] Interestingly, low weight babies born to primiparous mothers have been shown to demonstrate subsequent catch-up growth that results in children being heavier and taller than their peers.[70]

A similar pattern of low birth weight and subsequent catch-up growth and childhood overweight has been demonstrated in cases where mothers smoked during pregnancy.[70-72] Children born to mothers who smoked during pregnancy have been shown to be

significantly smaller for gestational age, that is they have lower birth weight and birth length, than children born to non-smokers.[70] However, smoking during pregnancy has also been associated with later childhood overweight and obesity despite causing initial low weight.[70-72] Indeed, a dose-response relationship has been shown between number of cigarettes smoked during pregnancy and risk of overweight and obesity in childhood.[71 72]

Several studies have reported that maternal diet during pregnancy, which directly impacts the prenatal nutritional environment, can impact later weight status of offspring.[5 73] Indeed, one retrospective cohort study showed that exposure to famine during pregnancy is linked to later obesity in children born to undernourished women.[73] Similarly, animal studies have demonstrated that permanent programming of accelerated fat tissue growth occurs as a result of maternal nutrient imbalance during gestation.[5]

Maternal health complications during pregnancy have been shown to impact later offspring weight and growth patterns. Gestational hypertension has been linked to an increased risk of high birth weight and large size for gestational age,[74] both of which have been shown to predict subsequent childhood overweight and obesity.[44 46 48 49 51] There is also strong evidence for the association between maternal glucose tolerance disorders during pregnancy and offspring weight at birth and childhood weight. Indeed, various forms of IGT during pregnancy have been shown to increase the risk of later adiposity in offspring.[15 75-93]

## 1.4.2    Fetal Growth and Early Nutrition

Fetal growth and postnatal nutrition have also been shown to impact later childhood weight status.  Birth weight for gestational age has been shown to be a more important indicator of later childhood growth patterns and health than absolute birth weight. In fact, it is when birth weight is abnormal for gestational age that effects on later childhood growth and weight are evident. Children who are born LGA often become heavier on average in childhood.[94] Being born small for gestational age (SGA) has also been shown to have lasting effects on growth in early childhood. Indeed, it has been shown that children born SGA are smaller on average by the age of 4 years than their AGA peers.[94] There is also evidence that both advanced maternal age and primiparity are associated

with increased risk of SGA infants.[95-98]

In terms of postnatal nutrition, many studies have demonstrated that whether infants are breastfed at all,[99-104] duration and consistency of breastfeeding,[46 99 101 105-110] and timing of the introduction of solid foods[111] all have a significant impact on later obesity risk. Indeed, most studies examining the effect of breastfeeding on infant, childhood, and adolescent weight that have had significant findings report a reduced risk of obesity associated with breastfeeding. It has been suggested that longer duration of breastfeeding may protect high risk children, for example those born LGA, from developing obesity.[104 108] In particular, a few studies have found that the association between prolonged breastfeeding and lowered obesity risk is particularly pronounced among children born to overweight and obese mothers.[107 112] One study further showed that prolonged breastfeeding coupled with delayed introduction of solid foods is associated with reduced odds of obesity and increased probability of healthy weight status at age 2 to 4 years.[111]

## 1.5   Gestational Diabetes Mellitus

The focus of the current study is the association between prenatal exposure to GDM and BMI trajectories in early childhood. This is particularly relevant since worldwide, the prevalence of GDM among women has reportedly been growing. Increasing trends in GDM prevalence raise many population health concerns. By definition, GDM may be a temporary state of glucose intolerance that resolves after delivery.  However, in some cases glucose intolerance may persist postpartum.  Indeed, many studies have reported a much higher risk of subsequent diabetes mellitus among women with GDM compared to women with a normal pregnancy.[113-118] Thus, increasing trends in prevalence of GDM may predict similarly increasing trends in diabetes mellitus among parous women.

Increasing GDM prevalence has important health implications for children, since offspring from pregnancies complicated by GDM often have poor health outcomes.  The association between forms of maternal IGT during pregnancy, including GDM, on offspring weight has been extensively studied. In particular, prenatal exposure to GDM is a known and common cause of fetal macrosomia,[119] which has been shown to be an important predictor of childhood obesity.[45-53 120]  Overweight and obesity in childhood

and adolescence have also been linked to prenatal exposure to GDM.[76][83][121] Although GDM is also associated with high maternal pre-pregnancy BMI, it has been found that the effects of GDM on offspring weight status may be independent of maternal pre-pregnancy BMI.[80] Thus, an increasing trend in GDM prevalence has important implications for the childhood obesity epidemic.

## 1.5.1    Trends in Prevalence of Gestational Diabetes Mellitus

An increasing prevalence of GDM among women in various populations worldwide has been documented by a number of studies.[122-129] In regions across North America, the prevalence of GDM has increased by approximately 60–120% over two decades.[122][124] More recently, over the last ten years GDM prevalence has increased by approximately 30–180% in different global populations.[125-127] In Canada, there have also been indications of increasing trends in GDM prevalence.[122][127] One study that investigated trends in GDM prevalence in Manitoba over a twenty-year period reported a 60% increase in GDM prevalence from 1985 to 2004.[122] Another study by Davenport and colleagues[127] observed GDM prevalence over a ten-year period in London, Ontario and reported a 45% increase in prevalence from 2000 to 2009.[127] These trends suggest the possibility of increasing GDM prevalence across Canada.

One important factor to consider when examining the trends in prevalence of GDM in Canada and around the world is changes in diagnostic criteria over time.  The Society of Obstetricians and Gynaecologists of Canada implemented the first national GDM screening guidelines in 1992.[122] These new guidelines required universal GDM screening for all pregnant women in the 24th to 28th week of pregnancy.[122] Following this, the only major changes to guidelines were made in 1998 by the Canadian Diabetes Association, which suggested different diagnostic criteria for glucose tolerance test results.[122]

Due to these changes in screening guidelines and diagnostic criteria for GDM, increasing trends in GDM prevalence in Canada after 1992 may be attributable to the implementation of universal screening.  Similarly, trends before and after 1998 would need to be examined against changes in diagnostic criteria.  However, since 1998 there

have been no substantial changes in screening guidelines and diagnostic criteria. Thus, trends in GDM prevalence in Canada during the past decade likely reflect true changes in GDM incidence over time. Indeed, the 45% increase in GDM prevalence in London, Ontario reported by Davenport et al.[127] occurred during a period when there were no changes in GDM screening guidelines or diagnostic criteria.

## 1.5.2    Factors Associated with Gestational Diabetes Mellitus Risk

*Maternal Body Mass Index*

One risk factor for GDM that has been well established is high pre-pregnancy BMI.[130] Torloni and colleagues[130] conducted a meta-analysis of 70 studies examining over 600,000 women and found that risk of GDM is strongly positively correlated with high pre-pregnancy BMI. Indeed, they found that the risk of GDM increased significantly with increasing pre-pregnancy weight, with overweight women being twice as likely and obese women being more than five times as likely to have GDM compared to women who had normal pre-pregnancy BMI.[130] Further, they showed that women who were underweight were less likely to have GDM compared to women who had normal pre-pregnancy BMI.[130]

*Maternal Ethnicity*

Previous studies have shown that trends in the increasing prevalence of GDM differ according to maternal ethnicity.[122 124 128 131-138] In the United States, the prevalence of GDM over the past 20 years has been increasing at a significantly higher rate among black women compared to white women.[124] Indeed, it was shown that the risk of developing GDM conferred by maternal BMI is higher in black women versus women of other ethnicities. Other studies in multiethnic populations have shown that there is an increased risk of GDM among other ethnic minorities, including Asian, Hispanic, and Middle Eastern women.[131 133 135] Among Asian women, the trends in GDM prevalence also vary, with higher prevalence of GDM in women of Indian descent compared to women of Japanese or Korean descent.[134 137 138] Other studies have compared prevalence of GDM in Aboriginal versus non-Aboriginal populations and found a higher risk of

GDM among Aboriginal women.[122 128 139 140]

These trends in GDM among different ethnic groups may reflect other differences between the groups, such as socioeconomic conditions, diet composition, health practices, and habits that may affect general health. Nevertheless, it is important to note how stable differences between ethnic groups may be affecting observed trends. Further, some studies have noted the independent effects of ethnicity on risk of GDM,[139 141] indicating that there may be genetic factors promoting differences in GDM prevalence between ethnic groups.

*Socioeconomic Factors*

Studies that have discussed the association of socioeconomic characteristics with risk and subsequent prevalence of GDM have considered education level, income and employment as potential predictors.[131 132 142-144] One study found a higher risk of GDM among unemployed women as well as a difference in risk between blue-collar and white-collar workers.[144] The same study observed that education level was inversely correlated with risk of GDM.[144] In most studies, socioeconomic level, defined for example by quartiles, has been identified as the strongest predictor of GDM.[132 143] Indeed, a large, multiethnic study in Australia found that socioeconomic status was inversely correlated with risk of GDM consistently across ethnic groups.[132]

*Maternal age*

A large number of studies have shown that the risk of GDM is associated with advanced maternal age.[95 122 125 131 132 139 141 145-148] Across studies, reported risks also appear to increase with increasing maternal age. One study that examined pregnant women with ages ranging from 19 to 27 years found that women aged 25 years or older were twice as likely to have GDM compared to all women under the age of 25 years.[145] Another study that looked at older women reported that maternal age greater than 40 years was associated with 6 times the risk of GDM compared to women aged 20 years or younger.[132]

*Parity*

Studies have shown that number of past pregnancies is also associated with increased risk of GDM.[149][150] Multiparity was found to be a significant risk factor for GDM among women in a large study examining the epidemiology of GDM among Native Canadians.[149] Another study showed that there is an increasing risk of GDM with the increasing number of past pregnancies complicated by GDM.[150] Indeed, women with one previous pregnancy complicated by GDM were 13 times more likely to have GDM than women who had a normal past pregnancy.[150]

## 1.5.3 Challenges in Examining Gestational Diabetes Mellitus in Population Studies

There are arguments that epidemiological studies examining GDM at the population level are faced with important methodological issues. The main issue is that determining the prevalence of GDM using population data is complicated by the clinical definition of GDM itself.[151] Since GDM is defined as either the onset or first recognition of glucose intolerance during pregnancy,[10] it is possible that a number of cases of GDM from population data may truly reflect populations of women with undiagnosed diabetes mellitus existing prior to pregnancy.[151] This is particularly true for younger women who are less likely to be screened for diabetes prior to pregnancy.[151] This issue is addressed by highlighting that the motivation for this study is the potential impact of a prenatal hyperglycemic environment caused by GDM on BMI throughout childhood. In this context, the current definition of GDM is acceptable given that the risk posed by GDM is through prenatal exposure to elevated maternal blood sugar levels due to the absence of previous diabetes diagnosis and thus the absence of treatment at initial stages of pregnancy.[80][81][88][93] Thus, whether or not a GDM diagnosis reflects maternal glucose intolerance that manifested during pregnancy or was present prior to pregnancy does not alter the exposure as defined in the current study.

## 1.6 Gestational Diabetes Mellitus and Child Weight

The current study was motivated by a growing body of evidence for the association between maternal IGT during pregnancy, specifically GDM, and offspring overweight or

obesity in infancy,[75-77 89] childhood,[15 75 78-87 92 93] adolescence,[78 81 88 90] and even adulthood.[85 86] Past studies providing evidence for these associations are summarized in table format in Appendix A. The possibility that a prenatal environment altered by GDM can cause permanent metabolic changes that promote development of obesity suggests the potential for implementation of childhood obesity prevention strategies during the perinatal period.

The biological mechanisms underlying the association between prenatal exposure to GDM and child weight are difficult to elucidate for a number of reasons. Arguably the most important barrier to understanding how maternal IGT may influence child obesity is the difficulty in producing evidence that this association exists independent of important confounding factors such as maternal pre-pregnancy BMI and genetic predisposition. However, a few studies offer compelling evidence that this association does exist. Indeed, studies of siblings with discordant intrauterine exposure to maternal IGT,[79] studies examining maternal versus paternal IGT,[79] and studies of prenatal exposure to maternal IGT that control for other important risk factors for child obesity such as maternal BMI[80] support the notion that the association between maternal IGT and child weight is likely due to environmental rather than genetic factors.

One study strongly supports the role of intrauterine exposure to maternal IGT rather than genetic predisposition in subsequent risk of overweight and diabetes in offspring. This was a study done by Dabelea and colleagues[79] that examined siblings of the same parents who were discordant for prenatal exposure to maternal IGT, with at least one sibling born before and at least one sibling born after maternal diabetes diagnosis. Among families in which none of the children had diabetes, it was found that siblings born after their mother was diagnosed with diabetes had significantly higher BMI than their siblings born prior to the diagnosis at a similar age.[79] Analyses controlling for sibship revealed that although siblings who were exposed to maternal diabetes *in utero* initially had lower BMI at the ages of 6 to 9 years, after 9 years of age these siblings had BMI that was on average 2.6 kg/m$^2$ higher than their siblings who were not exposed to maternal diabetes prenatally at a similar age.[79] Further supporting the importance of intrauterine exposure to diabetes over genetic predisposition, this study showed that among families in which at least one

sibling had diabetes, the risk of diabetes was almost 4 times greater for siblings born after maternal diagnosis of diabetes. Even more compelling was the finding that the timing of paternal diabetes diagnosis had no significant effect on either BMI or the risk of diabetes among siblings.[79] Taken together, these findings support the notion that, independent of genetic factors, maternal IGT exerts an important effect on the prenatal environment that has a lasting impact on later offspring growth and metabolism.

The environmental or epigenetic mode of impact of maternal hyperglycemia during pregnancy has also been demonstrated in animal studies done by Dörner, Plagemann, and colleagues.[11 152 153] These studies demonstrated that artificially induced gestational diabetic rat mothers gave birth to offspring who exhibited overweight, overeating, IGT, and hyperinsulinemia. Not only did offspring acquire these abnormal metabolic patterns through artificially induced changes to the prenatal environment, these changes were passed on epigenetically to the next generation through the female offspring, despite mating with healthy males.[11] Indeed, unlike their mothers, the first generation of female offspring exhibited spontaneous (i.e., not artificially induced) gestational diabetes during their pregnancies that resulted in the same abnormal metabolic patterns as the original offspring.[11] These studies provide a strong case for the environmental or epigenetic action of maternal IGT during pregnancy.

## 1.6.1    Proposed Biological Mechanisms

This assertion that maternal IGT during pregnancy can result in changes to the prenatal environment that alter offspring growth and metabolism is supported by biological theories. One popular theory explains that changes in offspring growth in response to a hyperglycemic prenatal environment occur through over-nutrition, which results in fetal overgrowth, macrosomia at birth, and subsequent overweight and obesity.[15] This theory further goes on to suggest that intrauterine exposure to maternal hyperglycemia results in permanent changes in offspring metabolic response that increase postnatal risk of overweight and obesity.[12 13] Thus, according to this theory, not only does intrauterine exposure to maternal hyperglycemia during pregnancy result in fetal overgrowth and overweight in neonatal life, it results in changes that maintain overweight throughout life.

The causal mechanisms linking maternal hyperglycemia to both fetal overgrowth and permanent changes in offspring metabolic response occur through fetal hyperinsulinemia. Exposure to maternal hyperglycemia *in utero* results in a fetal regulatory response to increase insulin production, thereby creating a state of fetal hyperinsulinemia. Insulin in the prenatal environment is known to have growth-promoting properties, and in high concentrations can cause teratogenic effects that result in macrosomia or enlargement of internal organs.[11][14] The association between fetal hyperinsulinemia and permanent changes in offspring metabolic response has been demonstrated by Plagemann and colleagues[13] through an animal model. In their study, rat mothers were either artificially induced to have GDM or given a placebo treatment. Plagemann and colleagues found that offspring of GDM rat mothers exhibited hyperinsulinemia, which was associated with elevated levels of two neurotransmitters that stimulate food intake, neuropeptide Y and galanin.[13] Since insulin is able to cross the blood-brain barrier and alter the activity of these neurotransmitters,[154][155] it is theorized that hyperinsulinemia occurring at critical stages in fetal development may permanently alter this neural regulatory system.[11][13] A permanently altered neural system that normally regulates appetite and food intake has obvious consequences for postnatal weight gain. Indeed, Plagemann and colleagues have shown that hyperphagia, or overeating, and overweight were consequences of this observed causal mechanism among rat offspring.[11]

The most compelling finding from the studies done by Plagemann and colleagues[11] was that permanent malprogramming of the neural regulatory system for food intake caused by fetal hyperinsulinemia was entirely preventable through adequate control of maternal hyperglycemia during pregnancy in rat mothers. Thus, there is biological evidence that maternal IGT during pregnancy exerts effects on offspring that are directly associated with later weight and weight gain.  Further, these findings indicate that the mechanisms by which maternal IGT affect offspring growth and metabolism indeed act through maternal blood glucose concentration.

## 1.6.2    GDM and Birth Weight

In Section 1.3.2 the association between high birth weight or macrosomia and subsequent overweight and obesity in childhood was discussed. As the theories of the biological

mechanisms linking maternal IGT to offspring growth and metabolism suggest, prenatal exposure to maternal hyperglycemia can result in fetal overgrowth and high birth weight. Indeed, a number of studies have shown that high birth weight for gestational age is associated with prenatal exposure to various forms of maternal IGT during pregnancy.[76] [77 82 85 89] Although high birth weight has been linked to maternal overweight, several of these studies clearly support the independent relationship between intrauterine exposure to maternal hyperglycemia and subsequent high birth weight.

Buzinaro and colleagues[76] found that women diagnosed with GDM gave birth to infants with significantly higher birth weight than women without a GDM diagnosis who either exhibited some gestational hyperglycemia or normal glucose tolerance. Notably, women in their study with GDM had significantly higher fasting and daily blood glucose concentrations than women with some hyperglycemia or normal glucose tolerance despite that the three groups of women did not differ in age, pre-pregnancy BMI, or weight gain during pregnancy.[76] Another study that examined the risk of macrosomia according to maternal plasma glucose concentration during the third trimester of pregnancy found a significant linear trend between increasing plasma glucose concentration and increasing frequency of macrosomia, even after exclusion of women who had relative body weight in excess of 119% to normal body weight.[89] Among women with mild GDM in an Australian study done by Gillman and colleagues,[82] random assignment to an intervention that involved monitoring and management of blood glucose through dietary counselling and insulin therapy when needed was associated with a decrease in prevalence of macrosomia by almost 75% compared to a routine care group.[82]

## 1.6.3    GDM and Childhood Weight

The body of evidence for the association between maternal IGT during pregnancy and childhood weight is vast and continues to grow as the current obesity epidemic generates more interest in the prenatal origins of childhood overweight and obesity.[15 75 76 78-88 90 92 93] Studies examining the impact of intrauterine exposure to maternal IGT on childhood adiposity between the ages of 1 and 3 years have shown evidence of increased adiposity associated with maternal IGT during pregnancy.[75 80 91 92] However, some studies

examining very young children only found significant differences between those who were exposed to maternal IGT *in utero* and those who were unexposed when adiposity was measured by direct measures of body fat (i.e., skinfold thickness) rather than indirect measures (i.e., BMI),[92] while others were able to show differences using both types of measures.[91]

Evidence for the association between maternal IGT during pregnancy and childhood adiposity appears to become more complicated when studies examine weight outcomes in later childhood. In the previously mentioned Australian study done by Gillman and colleagues,[82] in which mothers with mild GDM were randomly assigned to routine care or an intervention to manage blood glucose during pregnancy, recorded data on children's height and weight at ages 4 to 5 years were also analysed. Although children born to mothers who were given routine care had higher incidence of macrosomia, by the ages of 4 to 5 years this study found no significant differences in BMI between the groups.[82] A different study done by Lee and colleagues[84] examined two groups of women with different levels of hyperglycemia during pregnancy, one group with diagnosed GDM and one group defined as having a milder form of IGT during pregnancy. Women in the study with diagnosed GDM exhibited higher blood glucose levels than women with IGT. Interestingly, the study found no significant differences in child BMI measured at the ages of 3 to 4 years. However after the age of 5 years, children of mothers with GDM had significantly higher BMI than children of mothers with mild IGT.[84] These findings seem to suggest that the two studies were capturing different stages of the same phenomenon and that the impact of intrauterine exposure to maternal hyperglycemia may continue to have important effects on adiposity throughout childhood.

Despite this large body of evidence, interpreting the literature as a whole is complicated as offspring weight outcomes are evaluated at many different stages in childhood, adolescence, and adulthood depending on the availability of data in any given study. As a result, different studies have reported associations between maternal IGT during pregnancy and offspring adiposity at 1 year of age[91] up to 19 years of age[85] as well as many increments in between. One can speculate about the phenomenon linking maternal IGT during pregnancy to adiposity throughout childhood by considering studies that

examine adiposity at adjacent time points in childhood together such as the Gillman *et al.*[82] and Lee *et al.*[84] studies. However differences in study design would inevitably result in erroneous conclusions. Further complicating the matter of summarizing the overall evidence for the association between maternal IGT during pregnancy and adiposity throughout childhood, different studies measure adiposity in various ways. These include different measures, such as direct and indirect measurements, as well as different cut points for defining overweight and obesity.

## 1.7 Summary

Determining the prenatal origins of childhood overweight and obesity is becoming ever more important in light of the increasing prevalence of childhood obesity in Canada and around the world. Although a number of studies have suggested that prenatal exposure to GDM is a predictor of obesity status in childhood, there is a lack of research dedicated to how GDM exposure may be impacting childhood growth trajectories. [76 83 121] Furthermore, the few studies that have considered the impact of GDM exposure on BMI at different time points throughout childhood do not model growth data continuously from infancy throughout childhood.[75 156] Later morbidity associated with overweight and obesity is not necessarily predicted by weight status at a single point in time,[39] but rather by patterns of growth. Thus when establishing whether risk factors such as GDM are causally related to overweight and obesity in childhood, it is important to examine the effects of these factors on trajectories of growth.

This thesis takes the important next step for the research on the prenatal origins of childhood obesity by examining the effect of an important risk factor for childhood overweight and obesity on childhood BMI trajectories. The role of intrauterine exposure to GDM in shaping early childhood BMI trajectories may reveal the mechanisms by which this risk factor can lead to later childhood overweight and obesity and also guide early obesity prevention strategies.

# Chapter 2

## 2    Objectives and Hypothesis

## 2.1   Objectives

The main purpose of this thesis is to examine the association between prenatal exposure to GDM and early childhood BMI trajectories modelled continuously from infancy through early childhood. The study population was derived from the National Longitudinal Survey of Children and Youth (NLSCY), described in the next chapter. The three specific objectives are summarized below. The sub-sections that follow provide detailed rationale for each objective.

*Objective 1*

Examine the direct effect and indirect effect (through birth weight for gestational age) of prenatal exposure to GDM on BMI trajectories of Canadian children aged 2 to 10 years who participated in the NLSCY.

*Objective 2*

Assess whether the direct effect and indirect effect (through birth weight for gestational age) of prenatal exposure to GDM are partially explained by maternal demographic, lifestyle, and socioeconomic characteristics including age, parity, highest level of education achieved, smoking during pregnancy, and income adequacy for the household.

*Objective 3*

Assess whether the direct effect and part of the indirect effect (i.e., the pathway leading from birth weight for gestational age to childhood BMI trajectories) of prenatal exposure to GDM on childhood BMI trajectories differ between children who were not breast fed and children who were breast fed.

### 2.1.1    Objective 1

Based on the proposed theories of the biological mechanisms linking prenatal exposure to GDM with overweight and obesity in childhood,[12][13][15] the first objective was to assess

both direct effects of GDM on early childhood BMI trajectories as well as the indirect effect through birth weight for gestational age. The indirect effect reflects the fetal over-nutrition theory that maternal hyperglycemia during pregnancy, and subsequent fetal hyperinsulinemia, causes fetal overgrowth that leads to high birth weight and overweight and obesity in childhood.[15] The direct effect reflects all other potential causal mechanisms linking prenatal exposure to GDM with childhood BMI trajectories. One theory that can account for this effect posits that exposure to maternal hyperglycemia *in utero* results in permanently reduced sensitivity to hormones that regulate appetite and fat cell growth, which increases the risk of later development of obesity.[12][13] These hypothesized causal mechanisms are summarized in Figure 2.1.
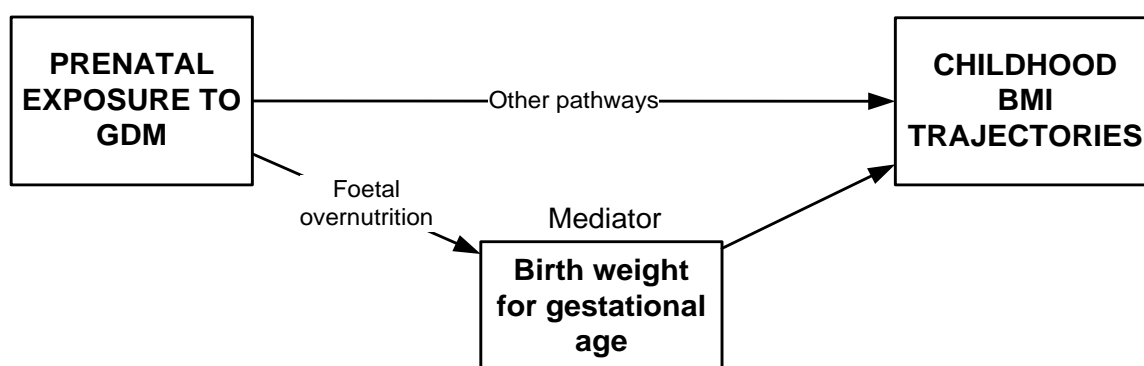


**Figure 2.1.** Causal model for Objective 1. Hypothesized association between prenatal exposure to GDM and childhood BMI trajectories

## 2.1.2    Objective 2

A number of factors that are associated with GDM diagnosis are also causally related to birth weight for gestational age as well as childhood BMI trajectories. Thus, confounding by these other factors needs to be addressed. The most notable confounder for the association between prenatal exposure to GDM and childhood BMI trajectories is maternal pre-pregnancy BMI. However, questions regarding maternal weight prior to and during pregnancy were not asked in the NLSCY and thus the current study was unable to control for this important confounder. To approximate the conditions in which maternal

and childhood overweight and obesity may arise and to account for other factors associated with GDM risk, various lifestyle, demographic, and socioeconomic factors that were available in the NLSCY were included in this analysis. Thus the second objective was to assess whether maternal and lifestyle characteristics such as age, parity, highest level of education achieved, smoking during pregnancy, and household income adequacy partially explain the observed association between prenatal exposure to GDM and childhood BMI trajectories. The adjusted causal model for Objective 2 is shown in Figure 2.2 below.
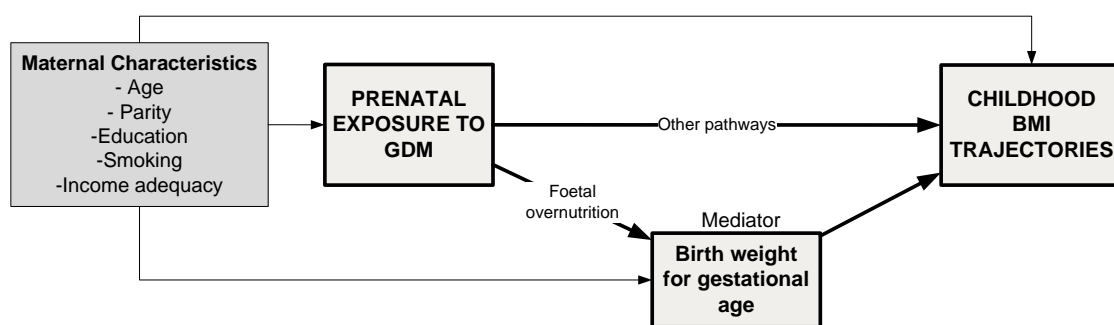


**Figure 2.2.** Causal model for Objective 2. The direct and indirect effects of prenatal exposure to GDM on childhood BMI trajectories adjusted for maternal demographic (age, parity), lifestyle (smoking), and socioeconomic characteristics (highest level of education achieved, income adequacy for the household).

## 2.1.3    Objective 3

The final objective is to assess whether the nature of the direct effect and indirect effect (through birth weight for gestational age) of prenatal exposure to GDM on childhood BMI trajectories differ by breastfeeding initiation/non-initiation (Figure 2.3). Modification of the association between prenatal exposure to GDM and early childhood BMI trajectories by breastfeeding initiation/non-initation is of particular interest since studies have suggested that breastfeeding may be a protective factor against development of childhood obesity. Specifically, breastfeeding has been shown to reduce the risk of childhood obesity despite the presence of early life risk factors, for example macrosomia

at birth. Examining whether the effects of prenatal exposure to GDM on childhood BMI trajectories differ according to breastfeeding initiation/non-initiation is further justified as breastfeeding may be a potential avenue for the prevention of child overweight associated with prenatal exposure to GDM.
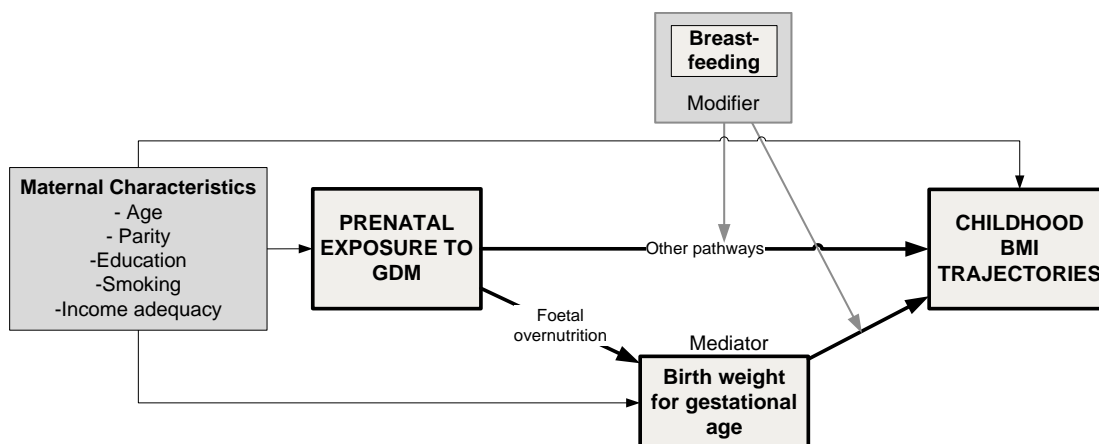


**Figure 2.3.** Causal model for Objective 3. The adjusted direct and indirect effects of prenatal exposure to GDM on childhood BMI trajectories are modified by breastfeeding.

## 2.1.4    Stratifying Analyses by Sex

Due to the *a priori* expectation that female and male children are essentially two distinct populations that have different patterns of growth throughout childhood, all analyses are stratified by sex. Since the indirect effect of prenatal exposure to GDM is mediated by birth weight, and on average males have higher birth weight than females,[157] it is necessary to separate analyses by sex. The results of stratified analyses may reveal effect modification by sex of the direct effect and/or indirect effect of prenatal exposure to GDM on childhood BMI trajectories. However, there are no explicit hypotheses about the differences between females and males in terms of either the direct effect or indirect effect through birth weight for gestational age of prenatal exposure to GDM on childhood BMI trajectories.

## 2.2  Hypotheses

*Objective 1*

It is hypothesized that children who were exposed to GDM prenatally will have higher BMI at 2 years of age compared to their unexposed peers. It is also hypothesized that the rate of increase in BMI between the ages of 2 and 10 years will also be higher among children who were exposed to GDM prenatally than their unexposed peers. These two explicit hypotheses about the effects of prenatal exposure to GDM on initial BMI (at age 2 years) and the rate of increase in BMI throughout childhood are contingent on the hypothesis that prenatal exposure to GDM acts through the direct and/or indirect pathways. Therefore, it is also expected that the results for either the direct pathway between prenatal exposure to GDM and childhood BMI trajectories or the indirect pathway through birth weight for gestational age, or both, will be significant.

*Objective 2*

Statistical control for maternal demographic, lifestyle, and socioeconomic factors is expected to attenuate the associations between prenatal exposure to GDM and childhood BMI trajectories. Taken together, maternal age, parity, highest level of education achieved, smoking during pregnancy, and household income adequacy are hypothesized to act in the mediated causal pathway by predicting GDM diagnosis and thus prenatal exposure to GDM, as well as birth weight for gestational age and childhood BMI trajectories. As previously discussed, maternal age and parity are associated with both the risk of GDM as well as child weight outcomes. Smoking is also correlated with GDM[148] and is a predictor of childhood overweight and obesity.[71][72] Maternal education and household income adequacy are socioeconomic factors that are also associated with both risk of GDM and childhood weight status. Socioeconomic status is also a well established predictor of adult obesity, and thus maternal education and household income adequacy also act as proxy variables for maternal obesity.

*Objective 3*

Breastfeeding is expected to modify the association between prenatal exposure to GDM and early childhood BMI trajectories. Specifically, it is hypothesized that the magnitude of the direct effect and the partial indirect effect (i.e., the pathway from birth weight for gestational age to childhood BMI trajectories) of prenatal exposure to GDM on childhood BMI trajectories from Objective 2 will be reduced for children who were breastfed compared to children who were never breastfed. Thus, it is expected that breastfeeding will attenuate the association between prenatal exposure to GDM and childhood BMI trajectories.

# Chapter 3

# 3 Methods

This chapter outlines the secondary data analysis that was conducted in the current study, beginning with a description of the data source (Section 3.1) followed by a description and discussion of the treatment of measurement instruments used in analyses (Section 3.2). The next section gives an overview of the analytic technique used in the current study, latent growth curve modelling (Section 3.3). Section 3.4 discusses some model considerations, covering the issues of time scores (Section 3.4.1), model fit (Section 3.4.2), and missing data (Section 3.4.3). The final section details the analyses that were done to address each of the research objectives (Section 3.5).

## 3.1 Data Source

This study analysed the longitudinal component of the National Longitudinal Survey of Children and Youth (NLSCY). This dataset was accessed through the Statistics Canada Research Data Centre at Western University following approval of a peer-reviewed application for data access. The survey was designed by Human Resources Development Canada and conducted by Statistics Canada to measure child development and well-being with the intention of creating a national database of characteristics and experiences of Canadian children and youth from infancy to adulthood. The NLSCY sampling design involved both cross-sectional and longitudinal components. Beginning in 1994, data from a nationally representative longitudinal cohort of children, initially aged 0 to 11 years, were collected biennially. In addition to the longitudinal sample, cohorts of children aged 0 to 1 year were added at each cycle. Data were collected biennially from these children until the age of 5 years for the purpose of monitoring development in early childhood. This study used data exclusively from the longitudinal cohort, specifically from cycles 2 through 6 for children who were 2 to 3 years of age in cycle 2. The description of the study population is elaborated in Section 3.1.3. Cycle-specific data files were linked using unique child identification numbers and combined to form a single longitudinal dataset for analyses.

### 3.1.1    Content of the NLSCY

The main objectives of the NLSCY were to collect data on the prevalence of biological, social, economic, and environmental factors that are predictive of child health outcomes and how these factors are involved in child development. To obtain information pertaining to all of these objectives, data collection was administered in households and in schools. The household component of data collection consisted of survey instruments completed by the person most knowledgeable (PMK) about the child (usually the child's biological mother) and when applicable, questionnaires completed by the child. Instruments completed by the PMK included the following: (1) a questionnaire on household contact information and demographic data, (2) the Parent Questionnaire, (3) the Child Questionnaire, and (4) the Informed Consent Questionnaire.

The Parent Questionnaire collected information about the parent and spouse (if applicable) on health, maternal history, education, income, neighbourhood safety, family functioning, labour force, social support, and socio-demographic characteristics. The Child Questionnaire collected information about the child on a wide variety of subjects, notably health, medical and biological information, child development, temperament, activities, relationships, and behaviour. The household component of data collection also included vocabulary tests for children who were 4 to 6 years old, reading and mathematical aptitude tests for children in grade 2 or higher, and self-completed questionnaires for children aged 10 to 13 years. The school component of the NLSCY included self-completed questionnaires for teachers and principals for children aged 4 to 13 years and reading comprehension and mathematical skills tests for children in grade 2 or higher. The current study used data collected through the Parent and Child Questionnaires, focusing specifically on survey questions related to maternal history, pregnancy characteristics, maternal health during pregnancy, and reported child weight and height at birth and throughout childhood.

### 3.1.2    NLSCY Sampling Design

The sampling frame for the NLSCY was the sample collected for the Labour Force Survey (LFS), and thus the sampling design was the stratified, multi-stage design used by

the LFS. The LFS aimed to collect information on a nationally representative target population of civilian, non-institutionalized Canadians aged 15 years or older living in the ten provinces. The NLSCY sample was subject to the exclusions of the LFS sampling design, which excluded populations living in the Yukon, Nunavut, or Northwest Territories as well as individuals living on First Nation reserves, full-time members of the Canadian Armed Forces, and inmates in institutions. In total, individuals outside the LFS survey coverage represent 2% of the Canadian population aged 15 years or older. Furthermore, unrepresented individuals from institutions or First Nation reserves represent only 0.5% of children living in provinces aged 0 to 11 years. Thus the exclusions in the NLSCY sampling design are not a major limitation and the study results maintain generalizability to the Canadian population.

The stratification design was the same for each province. The first stage of stratification was done by dividing each province by economic regions (ER) and employment insurance economic regions (EIER). The primary strata in the LFS were defined by the ER/EIER intersections. Within the primary strata, three types of areas were defined as urban, rural, and remote. Urban areas, which have the highest population densities and the largest census metropolitan areas were further stratified. This secondary stratification was done by dividing urban areas into apartment frames and area frames to account for representation of apartment dwellers and to minimize the impact of clusters. Urban areas were further divided into regular, high-income, and low density population strata and rural areas were stratified by population density. These formed the final strata, which were divided into clusters that were sampled within each stratum. Households or dwellings were then selected from the sampled clusters. Probability sampling was used at each stage of the study design. Depending on the size and type of stratum, different numbers of dwellings were selected.

## 3.1.3   Study Population

To model childhood BMI trajectories from age 2 to age 10 years, children included in the study population were required to have contributed longitudinal data and be approximately 2 years of age in the first cycle of data used. Longitudinal children were selected using assigned longitudinal flags used in the NLSCY. The study population also

had to consist of individuals who were asked questions about maternal health and pregnancy characteristics, as these questions were not mandatory for all respondents. Indeed, only PMK's who were the biological mothers of children under the age of 2 years at the time of the interview were asked questions about the pregnancy with the child included in the survey. Thus the cohort of interest consisted of children who were 0 to 1 year of age in cycle 1 (1994-1995) who entered the current study at cycle 2 (1996-1997) when they reached 2 to 3 years of age. Five cycles of data were used for individuals aged 2 to 3 in 1996: cycle 2 (collected between 1996 and 1997), cycle 3 (collected between 1998 and 1999), cycle 4 (collected between 2000 and 2001), cycle 5 (collected between 2002 and 2003), and cycle 6 (collected between 2004 and 2005). By cycle 6 in 2004, most of the children in the study population had reached 10 to 11 years of age.

The vast majority (91.6%) of PMK's for the study population were the biological mothers of the children included in the survey. The Child Questionnaire component of the NLSCY, from which data for the current analyses were derived, was completed by the PMK for the child included in the survey until children reached the age of 12 years. Thus, data on individuals 12 years and above were not included to ensure height and weight data were provided by the same respondent throughout cycles. Overall response rates for the NLSCY declined substantially from 1994 to 2004. The response rates for children in the longitudinal cohort were 86.5% in cycle 1 in 1994 and only 57.6% by cycle 6 in 2004.

## 3.2   Measurement Instruments

The aim of the this study was to estimate the direct effect of prenatal exposure to GDM on early childhood BMI trajectories as well as the indirect effect through birth weight for gestational age. A secondary focus was to determine the role of maternal age, parity, smoking during pregnancy, maternal education, household income adequacy, and breastfeeding initiation in attenuating or modifying the effects of prenatal exposure to GDM on childhood BMI trajectories. The following section outlines how these constructs were measured in the NLSCY or derived using existing variables in the NLSCY (if applicable) as well as how variables were used in the statistical analyses.

### 3.2.1    Prenatal Exposure to GDM

The NLSCY captured prenatal exposure to GDM through the following question in the Child Component of the survey answered by the biological mother of the child included in the survey: "During the pregnancy with [this child] did you suffer from any of the following: ...Pregnancy diabetes?" If the respondent answered "yes" to this question, the index child was considered to have been "exposed to GDM *in utero*". Similarly, if the respondent answered "no" to the above question, the index child was considered to have been "not exposed to GDM *in utero*". The variable for prenatal exposure to GDM was thus treated as a binary categorical variable in analyses.

### 3.2.2    Body Mass Index

Body mass index (BMI) at each cycle of follow-up was used to model BMI trajectories for children aged 2 to 10 years. The NLSCY collected information on height and weight for children up to the age of 10 years at each cycle through maternal report. These measures were used to compute BMI scores by dividing weight in kilograms by height in metres squared. Prior to computing BMI, child height data were scanned for implausible changes in height (e.g. negative changes) and erroneous height values were corrected by imputing a complex average height value using surrounding data points and taking time of data collection into account. The imputed values were calculated as follows:

$$h_b = h_a + \left[ |h_c - h_a| \times \left( \frac{age_b - age_a}{age_c - age_a} \right) \right]$$

where $h_b$ was the height value to be corrected, $h_a$ and $h_c$ were the surrounding height values from which the imputed value was to be derived, $age_b$ was the age in months at the time of the interview in which the erroneous height value ($h_b$) was recorded, and $age_a$ and $age_c$ were the ages in months at the interviews in which the two surrounding correct height values ($h_a$ and $h_c$) were recorded.

Following computation of BMI using corrected child height data, BMI data were scanned for biologically implausible BMI-for-age-and-sex values using the Centers for Disease Control and Prevention (CDC) guidelines based on the 2000 CDC growth charts.[158]

Biologically implausible values for BMI were treated as missing values in analyses.

### 3.2.3 Birth Weight for Gestational Age Z-Score

A continuous variable for birth weight for gestational age z-score was derived using questions in the NLSCY about child birth weight and gestational age. PMK's for the children included in the survey were asked to state the child's birth weight in kilograms and grams and gestational age in days. Birth weight in kilograms and grams was converted to birth weight in grams. Gestational age in days was converted to gestational age in weeks. The z-scores were then calculated based on guidelines for birth weight for gestational age established by Kramer and colleagues.[159] Briefly, Kramer *et al.* [159] used population-based Canadian data to derive means and standard deviations for birth weight in grams at each week of gestational age from 22 to 43 weeks for females and males, separately. These reference means and standard deviations were then used to calculate z-scores for birth weight for gestational age through the following equation:

$$z = \frac{reported\ birth\ weight - mean\ birth\ weight}{standard\ deviation}$$

The z-scores were calculated for each child using the reference mean and standard deviation for birth weight associated with their gestational age in weeks.[159] The birth weight for gestational age z-score was treated as a continuous variable in statistical analyses.

### 3.2.4 Maternal Age

A variable for maternal age at time of delivery was derived using questions asked in the NLSCY about the age of the biological mother at the time of interview as well as the child's age at the time of interview. Child's age in years at the time of the interview was subtracted from the age of the biological mother in years at the time of interview to obtain maternal age at delivery. Maternal age was treated as a continuous variable in all statistical analyses.

### 3.2.5 Parity

The NLSCY includes the following question to determine parity: "How many babies

have you had?" Since there were no specific hypotheses regarding the number of past pregnancies, parity was dichotomized as primiparous (one past pregnancy) and multiparous (more than one past pregnancy). Thus parity was treated as a binary variable in all statistical analyses.

## 3.2.6    Maternal Education

The NLSCY allocated a section in the Parent Questionnaire to collect information on education for the PMK. As mentioned previously, the vast majority (91.6%) of PMK's were the biological mothers of the children included in the survey. A variable for the highest level of education obtained by the PMK was derived in the NLSCY from the following questions: "Excluding kindergarten, how many years of elementary and high school [have you] successfully completed," "[Have you] graduated from high school," "[Have you] ever attended any other kind of school such as university, community college, business school, trade or vocational school, CEGEP or other post-secondary institution," and "What is the highest level of education that [you have] attained?"

The derived "recoded highest level of education obtained" variable contained information about years and type of schooling as well as obtained diplomas, certifications, and degrees. This variable had 11 categories that were ranked in the following order:

1. Elementary school (8 years of schooling or less)
2. Some secondary school (9 years of schooling or more with no secondary school graduation)
3. Secondary school graduation
4. Other beyond high school
5. Some trade school etc.
6. Some community college etc.
7. Some university
8. Diploma/certificate trade school etc.
9. Diploma/certificate community college etc.
10. Bachelor degree (includes LLB)
11. Masters, degree in medicine, doctorate

Since the categories were ranked in order of schooling level, this variable is considered to be ordinal. However, as the most important information for the purposes of the current study was contained in the ranking number, this variable was treated as a continuous variable in statistical analyses.

### 3.2.7    Smoking During Pregnancy

In the NLSCY smoking during pregnancy is captured in the following question: "Did you smoke during your pregnancy with…?" The response was binary and thus smoking during pregnancy was treated as a binary variable in analyses.

### 3.2.8    Income Adequacy for the Household

The variable for household income adequacy in the NLSCY was derived using information about total household income and number of individuals in the household. Level of household income adequacy was defined using five categories: lowest, lower middle, middle, upper middle, and highest. The lowest income adequacy category was for households of 1 to 4 individuals with a total income of less than $10,000 or households of 5 or more individuals with a total income of less than $15,000. Lower middle income adequacy was defined as households of 1 to 2 individuals with a total income of $10,000 to $14,999, households of 3 to 4 individuals with a total income of $10,000 to $19,999, or households of 5 or more individuals with a total income of $15,000 to $29,999. Middle income adequacy was defined as households of 1 to 2 individuals with a total income of $15,000 to $29,999, households of 3 to 4 individuals with a total income of $20,000 to $39,999, or households of 5 or more individuals with a total income of $30,000 to $59,999. Upper middle income adequacy was defined as households of 1 to 2 individuals with a total income of $30,000 to $59,999, households of 3 to 4 individuals with a total income of $40,000 to $79,999, or households of 5 or more individuals with a total income of $60,000 to $79,999. The highest income adequacy category was for households of 1 to 2 individuals with a total income greater than or equal to $60,000 or households of 3 or more individuals with a total income greater than or equal to $80,000. These categories were used by both the General Social Survey and the National Population Health Survey.

Since these categories were ranked in order of level of income adequacy, this variable is

considered to be ordinal. However, as the most important information for the purposes of the current study was contained in the ranking number, this variable was treated as a continuous variable in statistical analyses.

## 3.2.9    Breastfeeding

The NLSCY includes the following survey question for determining whether children were breastfed: "Did this child's mother ever breast-feed this child, even if only for a short time?" This question had a dichotomous response and thus breastfeeding was treated as a binary categorical variable in all analyses.

## 3.3    Overview of Latent Growth Curve Modelling

Latent growth curve modelling (LGCM) is an analytic technique for longitudinal data that allows the assessment of trajectories of change, growth, or development of a particular outcome over time.[160] This type of analysis is particularly well suited for panel data, where repeated observations are collected at approximately the same intervals.[160] Specifically, LGCM is able to accomplish three tasks important for the analysis of longitudinal data.  First, it can be used to model and describe change or development of a particular outcome at the group level by producing estimated means of parameters of an overall trajectory. In the case of a linear trajectory involving three or more observations, LGCM can produce model-estimated means of the intercept and slope of the overall trajectory. Second, LGCM can describe differences between individuals by producing estimates of the variance of intercept and slope parameters. Thus, a single analysis using LGCM can describe change or development of a particular outcome at the group level as well as the level of individual variance in developmental trajectories. Finally, LGCM can be used to assess the effects of predictors on the variance in trajectories in order to determine their impact on initial levels and rates of change of an outcome.

The main purpose of the current study was to assess whether prenatal exposure to GDM can explain individual differences in early childhood BMI trajectories in order to ascertain the impact of prenatal exposure to GDM on the starting point and rate of increase in BMI throughout early childhood. Achieving this aim first required estimation of the means of BMI trajectory parameters for all children. The next step required

variances in BMI trajectory parameters to be estimated in order to determine whether significant differences exist between individual BMI trajectories. The final step was to assess whether prenatal exposure to GDM could partially explain the existing differences between individual trajectories in order to ascertain its potential role as a risk factor for high childhood BMI. The main characteristics of LGCM, as previously described, dovetail the aims of the current study, and thus it was the most appropriate analytic technique. For a detailed explanation of latent growth curve modelling please see Appendix B. All preliminary analyses were completed using IBM SPSS Statistics Software Version 21.[161] Latent growth curve analyses were conducted using MPlus Version 7 Software.[162]

## 3.4   Model Considerations

### 3.4.1   Time Scores

Although the NLSCY cycles occurred at two-year intervals, in reality, data were collected over a span of two years for each cycle. This raised the issue of unequal intervals at the individual level, thus intervals needed to be adjusted for time of data collection. In Mplus, this is done using time scores, which account for individually varying times of observation in panel data by using variables containing information about individual times of observation to model trajectories over time. The use of time scores in the current study ensures that estimates for the parameters of individual BMI trajectories are based on data that reflect the correct timing of change in BMI rather than assuming changes in BMI consistently occurred over two years between data collection points.

### 3.4.2   Model Fit

Establishing model fit, that is, assessing how well a given model reflects the data is an important preliminary step in latent growth curve analyses. Several goodness of fit indices are available in Mplus[162] that take into account differences between observed and implied variance-covariance matrices as well as degrees of freedom and model complexity to produce a measure of model fit.[160] Some of these indices include the chi-square test statistic, the comparative fit index (CFI), the Tucker-Lewis index (TLI), and

the root mean square error of approximation (RMSEA).[160] These model fit indices produce absolute measures of goodness of fit, for example, the closer the RMSEA value is to zero the better the model fit.[160] Other model fit indices produce values that must be compared between models to assess improvements in model fit, such as the Bayesian information criterion (BIC), Akaike's information criterion (AIC), and the loglikelihood.[160]

In the current study, the chi-square test statistic and other chi-square related model fit statistics (CFI, TLI, RMSEA) were unavailable due to the use of time scores. This is because the use of time scores requires LGCMs to be modelled with random slopes, which results in insufficient statistics (means, variances, and covariances) for model estimation using these model fit assessment tools. Model fit was therefore assessed using BIC value comparisons and loglikelihood differences for all LGCMs. Model suggestions produced by program outputs were only taken into consideration if they were theoretically sound and reduced BIC values by a large degree.

### 3.4.3    Missing Data

In Mplus, the issue of missing data is addressed in different ways depending on the type of data that are missing.[162] First, Mplus does not allow missing data for any exogenous variables, that is, for variables that are not predicted by other variables in the model and are thus considered external to the model.[162] Cases that have missing values for any exogenous variables are automatically excluded from all analyses.[162] This is because models are conditional on the exogenous variables and cannot be estimated overall if there are any missing values in these predictor variables.[162] In the current study missing data of this nature are a concern as there are a number of predictor variables included in analyses, which could result in many excluded cases due to missing values in any of the predictors. Since Mplus allows for missing data in endogenous variables,[162] that is, variables that are predicted by others in the model, this problem is attenuated by specifying causal relationships between predictors and thus converting exogenous predictors into endogenous predictors. A description and justification of the added causal relationships between predictors is provided in Section 3.5.3 below in the description of analyses for Objective 2.

In the current study, missing data on child BMI was inevitable due to attrition throughout cycles of the NLSCY. Missing data of this nature are considered to be "missing at random" (MAR) since the reason for missingness is not related to the missing values themselves.[163][164] In this case, missing data on child BMI are likely not explained by specific BMI values. Instead, probabilities of missingness in the MAR scenario may be a product of other observed variables included in the models,[163][164] for example household income, maternal education, or other predictor variables included in analyses. However, this type of missingness is considered "ignorable" and does not require further consideration or adjustment.[163][164] In Mplus, full-information maximum likelihood (FIML) is used to adjust for MAR data.[162] FIML does not impute missing values, rather it calculates the maximized likelihood of MAR data given a set of observed values in order to produce parameter estimates.[165] For cases with incomplete data, FIML uses all data available for each case to produce casewise likelihood functions that are summed across the study sample and maximized.[165]

### 3.4.4    Power and Precision

The use of Monte Carlo simulations has been recommended for calculating power and minimal sample size for growth analyses and analyses using structural equation modelling (SEM).[166]  However, this technique requires specification of a conceptual model with population values for all parameters using "best estimates" from previous studies.[166] This is not feasible for the current study since no previous studies have used a structural equation-based model for the effect of GDM exposure on childhood growth trajectories.  Thus, the current study followed general sample size guidelines suggested in the literature for sufficient statistical power to conduct SEM-based analyses such as LGCM.[166][167] These guidelines suggest a minimum of 200 subjects per group,[168][167] which in the case of the current study would suggest a minimum of 200 females and 200 males for analyses. Indeed, Hoyle[167] suggests that a sample of 300 subjects used for SEM analyses typically results in stable model estimates.

## 3.5   Statistical Analyses

### 3.5.1     Preliminary Analyses

Preliminary analyses were done to determine the characteristics of the study population. For the main outcome of interest, BMI, means and standard deviations of BMI scores at each time point were calculated.  Descriptive statistics for all other key variables in the analyses were also produced. For the categorical variables, parity, smoking during pregnancy, highest level of maternal education, income adequacy, prenatal exposure to GDM, and breastfeeding, frequencies and percentages were calculated. For the continuous variables, maternal age, and birth weight for gestational age z-score, means and standard deviations were calculated. All descriptive statistics were produced separately by child gender and weighted using cross-sectional weights from the first cycle of data collection to reflect initial sampling design.

The following is the trajectory equation that summarizes all latent growth curve analyses.

$$BMI_{it} = \alpha_i + \lambda_t \beta_{1i} + \lambda_t{}^2 \beta_{2i} + \epsilon_{it} \tag{1}$$

where $BMI_{it}$ represents the BMI score for the $i$th individual at time $t$; $\lambda_t$ is a constant fixed to the values 0, 1, 2, 3, and 4 for the linear component of the slope of the trajectory; and $\lambda_t{}^2$ are simply these values squared for the quadratic component of slope. The symbol $\epsilon_{it}$ indicates the random error for each individual observed measure ($i$) at each time point ($t$).

After establishing model fit, the first step was to ensure that variances in overall BMI trajectories were statistically significant to justify subsequent conditional analyses with explanatory variables. This was done using the unconditional LGCM.  This model included specified latent variables for the intercept, the linear component of slope, and the quadratic component of slope as well as the observed variables for BMI at ages 2, 4, 6, 8, and 10 years (Figure 3.1).  The unconditional latent growth curve analyses were done separately for females and males.

To account for differences in child age at the first cycle used in the study, a new age correction variable was calculated by centring age in years at Cycle 2 on 2, since this was the expected age of children at this initial cycle. The intercept, the linear component of

slope, and the quadratic component of slope were then regressed on this age correction variable. This was done in all subsequent latent growth curve analyses. For simplicity, the age correction variable will not be shown in regression equations for the intercept or the linear and quadratic components of slope in the sections that follow.
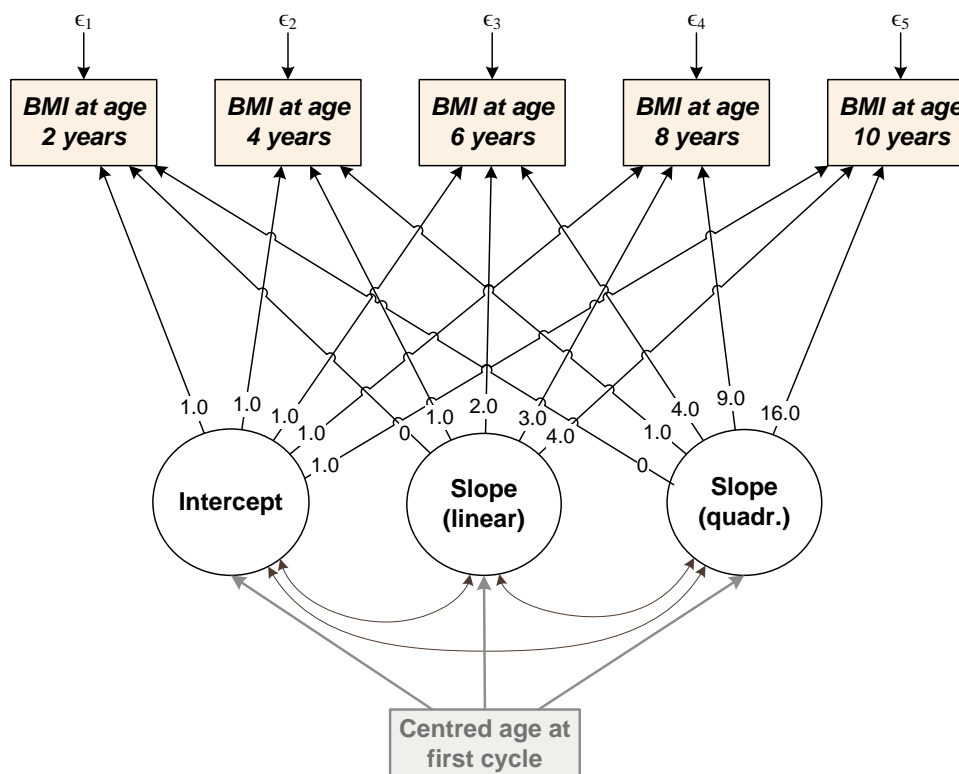


**Figure 3.1.** Unconditional latent growth curve model for preliminary analyses, showing each of the fixed factor loadings for intercept and linear and quadratic slope for the theorized quadratic model.

## 3.5.2    Analyses for Objective 1

The first objective was to assess the direct effect and indirect effect, through birth weight for gestational age, of prenatal exposure to GDM on childhood BMI trajectories from 2 to 10 years of age. This was done by converting the unconditional LGCM to a conditional LGCM by adding the variables for prenatal exposure to GDM and birth weight for gestational age to the model (Figure 3.2). The conditional LGCM in Figure 3.2 is summarized by the regression equations 1.1 – 1.4 below. The direct effect of prenatal exposure to GDM was modelled by regressing the intercept, the linear component of

slope, and the quadratic component of slope on the variable for prenatal exposure to GDM ($x_{GDM_i}$). The indirect effect was modelled first by regressing the variable for birth weight for gestational age ($x_{bwt_i}$) on the variable for prenatal exposure to GDM (1.4) and subsequently regressing the intercept, the linear component of slope, and the quadratic component of slope on the variable for birth weight for gestational age (1.1-1.3). The conditional latent growth curve analyses for Objective 1 were done separately for females and males.
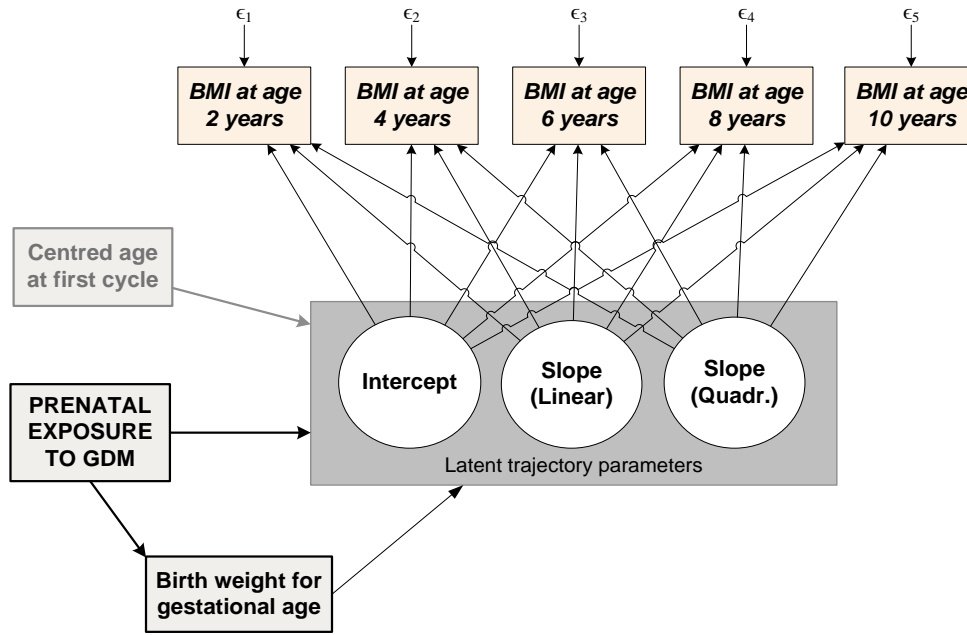


**Figure 3.2.** Conditional latent growth curve model for Objective 1. Direct and indirect effects of prenatal exposure to GDM on BMI trajectories. Note: Covariances are not shown. Latent variables are grouped in the diagram for simplicity.

Intercept equation:

$$\alpha_i = \mu_\alpha + \gamma_{\alpha_A} x_{GDM_i} + \gamma_{\alpha_B} x_{bwt_i} * + \zeta_{\alpha i} \tag{1.1}$$

Slope equation (linear component):

$$\beta_{1i} = \mu_{\beta_1} + \gamma_{\beta_{1A}} x_{GDM_i} + \gamma_{\beta_{1B}} x_{bwt_i} * + \zeta_{\beta_1 i} \tag{1.2}$$

Slope equation (quadratic component):

$$\beta_{2i} = \mu_{\beta_2} + \gamma_{\beta_{2A}} x_{GDM_i} + \gamma_{\beta_{2B}} x_{bwt_i} * + \zeta_{\beta_2 i} \qquad (1.3)$$

*Birth weight for gestational age equation:

$$x_{bwt_i} = \beta_0 + \beta_{GDM} x_{GDM_i} + \epsilon \qquad (1.4)$$

The use of time scores, explained in Section 3.4.1, to model BMI trajectories did not permit Mplus software to test indirect effects using the MODEL INDIRECT command. Therefore, the indirect effect of prenatal exposure to GDM on BMI trajectories through birth weight for gestational age was calculated manually using the Sobel test for indirect effects.[169-171] Figure 3.3 is presented to conceptualize the Sobel test, in which the model with the mediator to be tested is pictured. The letters $a$ and $b$ represent the estimates of each pathway of the indirect effect, while the letter $c$ represents the estimate of the pathway for the direct effect (Figure 3.3). The calculation of the test statistic for the Sobel test of indirect effects is presented in the equation below:

$$t = (ab)/\surd(a^2\sigma^2{}_b + b^2\sigma^2{}_a) \qquad (2)$$

where the denominator is the pooled standard error, in which $\sigma^2{}_b$ is the variance of the estimate $b$ and $\sigma^2{}_a$ is the variance of the estimate $a$. This test statistic was calculated separately for each trajectory parameter to test the indirect effect on BMI trajectories.
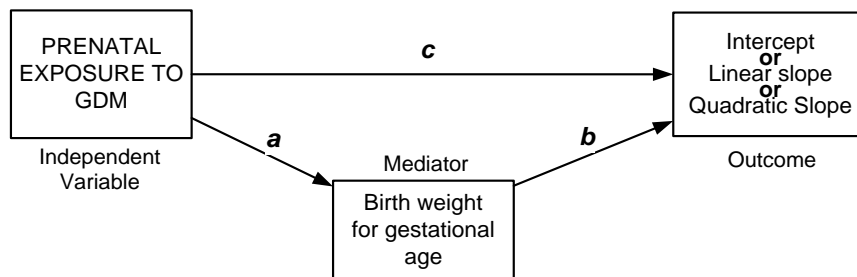


**Figure 3.3.** Parameters of the Sobel test for indirect effects.

### 3.5.3    Analyses for Objective 2

The second objective was to assess whether the effect of prenatal exposure to GDM could be partially explained by maternal demographic, lifestyle, and socioeconomic factors that are associated with GDM and that also predict birth weight for gestational age and childhood BMI trajectories. These potential confounders were maternal age, parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household, which were included in a new conditional LGCM (Figure 3.4).

The conditional LGCM in Figure 3.4 is summarized by the regression equations 1.5 – 1.14 below. This conditional LGCM differs from the conditional LGCM for Objective 1 in several ways. First, the intercept, the linear component of slope, and the quadratic component of slope are now also regressed on the variables for maternal age ($x_{mat\_age_i}$), parity ($x_{parity_i}$), smoking during pregnancy ($x_{smoke_i}$), maternal highest level of education ($x_{education_i}$), and income adequacy for the household ($x_{income_i}$) (1.5 – 1.7). Birth weight for gestational age is also regressed on these variables in the new conditional LGCM (1.8). The variable for prenatal exposure to GDM becomes an endogenous variable in this conditional LGCM as it is regressed on maternal age, parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household (1.9).

The variables for parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household were regressed on maternal age (1.10 – 1.14). These variables were modelled in this way to reduce the number of missing cases due to missing values on exogenous variables, as maternal age was the variable containing the fewest missing values. Maternal age is also a theoretically sound predictor of parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household. Other relationships between the predictor variables were not of substantive interest to the hypotheses under examination. However, the variables for parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household were correlated in the model. The conditional latent growth curve analyses for Objective 2 were done separately for females and males.
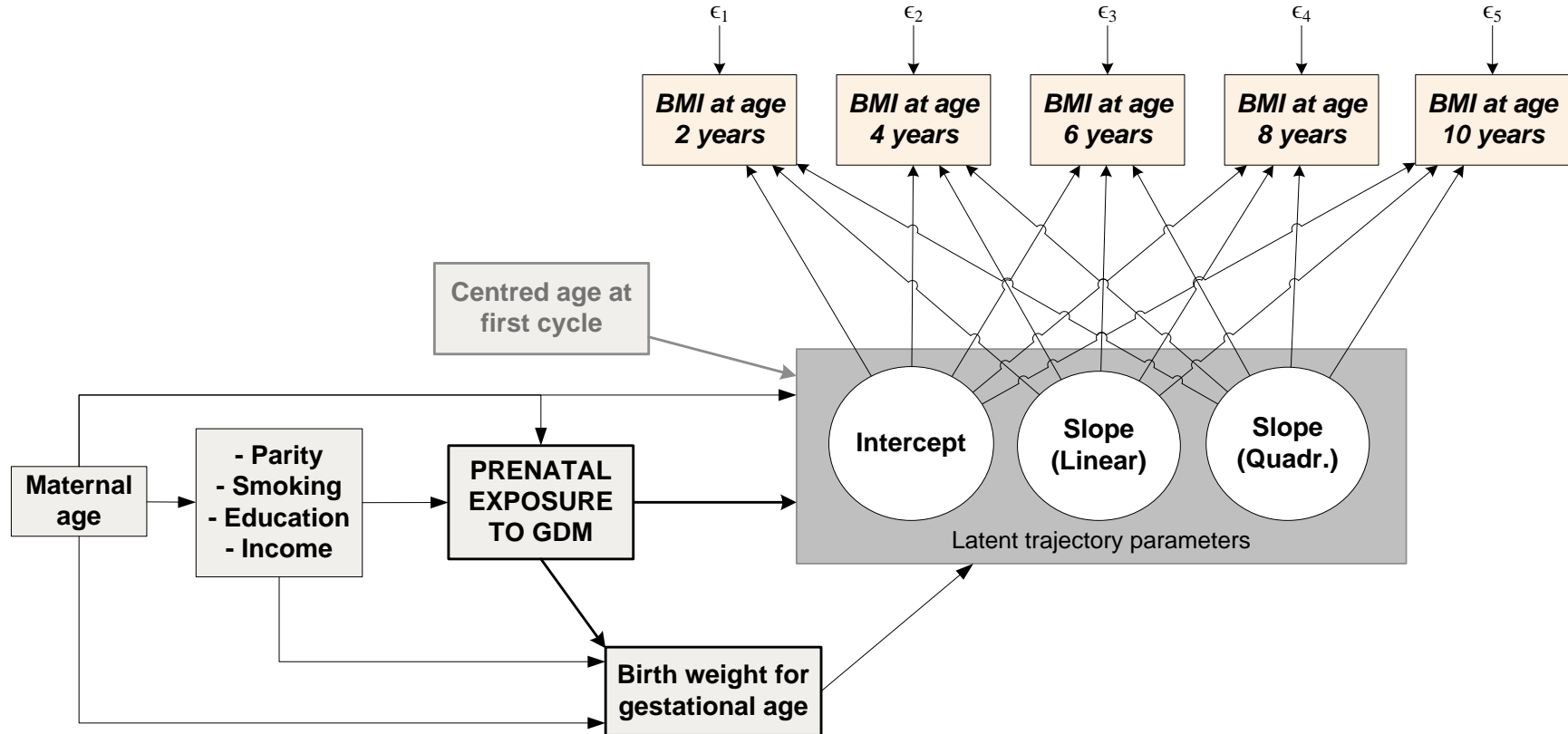
**Figure 3.4.** Conditional latent growth curve model for Objective 2. Direct and indirect effects of prenatal exposure to GDM on BMI trajectories adjusted for maternal age, parity, smoking during pregnancy, maternal highest level of education, and income adequacy for the household. Note: Covariances are not shown. Latent variables are grouped in the diagram for simplicity.

Intercept equation:

$$\alpha_i = \mu_\alpha + \gamma_{\alpha_A} x_{GDM_i} + \gamma_{\alpha_B} x_{bwt_i} * + \gamma_{\alpha_C} x_{mat\_age_i} + \gamma_{\alpha_D} x_{parity_i} + \gamma_{\alpha_E} x_{smoke_i} +$$

$$\gamma_{\alpha_F} x_{education_i} + \gamma_{\alpha_G} x_{income_i} + \zeta_{\alpha i} \tag{1.5}$$

Slope equation (linear component):

$$\beta_{1i} = \mu_{\beta_1} + \gamma_{\beta_{1A}} x_{GDM_i} + \gamma_{\beta_{1B}} x_{bwt_i} * + \gamma_{\beta_{1C}} x_{mat_{age_i}} + \gamma_{\beta_{1D}} x_{parity_i} +$$

$$\gamma_{\beta_{1E}} x_{smoke_i} + \gamma_{\beta_{1F}} x_{education_i} + \gamma_{\beta_{1G}} x_{income_i} + \zeta_{\alpha i} \tag{1.6}$$

Slope equation (quadratic component):

$$\beta_{2i} = \mu_{\beta_2} + \gamma_{\beta_{2A}} x_{GDM_i} + \gamma_{\beta_{2B}} x_{bwt_i} * + \gamma_{\beta_{2C}} x_{mat_{age_i}} + \gamma_{\beta_{2D}} x_{parity_i} +$$

$$\gamma_{\beta_{2E}} x_{smoke_i} + \gamma_{\beta_{2F}} x_{education_i} + \gamma_{\beta_{2G}} x_{income_i} + \zeta_{\alpha i} \tag{1.7}$$

*Birth weight for gestational age equation:

$$x_{bwt_i} = \beta_0 + \beta_{GDM} x_{GDM_i} + \boldsymbol{\beta}_{mat\_age} \boldsymbol{x}_{mat\_age_i} + \boldsymbol{\beta}_{parity} \boldsymbol{x}_{parity_i} + \boldsymbol{\beta}_{smoke} \boldsymbol{x}_{smoke_i} +$$

$$\boldsymbol{\beta}_{education} \boldsymbol{x}_{education_i} + \boldsymbol{\beta}_{income} \boldsymbol{x}_{income_i} + \epsilon \tag{1.8}$$

Additional equations:

$$x_{GDM_i} = \beta_0 + \boldsymbol{\beta}_{mat_{age}} \boldsymbol{x}_{mat_{age_i}} + \boldsymbol{\beta}_{parity} \boldsymbol{x}_{parity_i} + \boldsymbol{\beta}_{smoke} \boldsymbol{x}_{smoke_i} +$$

$$\boldsymbol{\beta}_{education} \boldsymbol{x}_{education_i} + \boldsymbol{\beta}_{income} \boldsymbol{x}_{income_i} + \epsilon \tag{1.9}$$

$$x_{bwt_i} = \beta_0 + \boldsymbol{\beta}_{mat_{age}} \boldsymbol{x}_{mat_{age_i}} + \boldsymbol{\beta}_{parity} \boldsymbol{x}_{parity_i} + \boldsymbol{\beta}_{smoke} \boldsymbol{x}_{smoke_i} +$$

$$\boldsymbol{\beta}_{education} \boldsymbol{x}_{education_i} + \boldsymbol{\beta}_{income} \boldsymbol{x}_{income_i} + \epsilon \tag{1.10}$$

$$x_{parity_i} = \beta_0 + \boldsymbol{\beta}_{mat\_age} \boldsymbol{x}_{mat\_age_i} \tag{1.11}$$

$$x_{smoke_i} = \beta_0 + \boldsymbol{\beta}_{mat\_age} \boldsymbol{x}_{mat\_age_i} \tag{1.12}$$

$$x_{education_i} = \beta_0 + \boldsymbol{\beta}_{mat\_age} \boldsymbol{x}_{mat\_age_i} \tag{1.13}$$

$$x_{income_i} = \beta_0 + \boldsymbol{\beta}_{mat\_age} \boldsymbol{x}_{mat\_age_i} \tag{1.14}$$

## 3.5.4    Analyses for Objective 3

The third objective was to assess whether breastfeeding initiation modified the direct and indirect effects of prenatal exposure to GDM on childhood BMI trajectories. This was done by repeating the analyses done for Objective 2 separately by breastfeeding, that is, whether the child was breastfed or was not breastfed.  These analyses were thus conducted for 4 different groups: females who were not breastfed, females who were breastfed, males who were not breastfed, and males who were breastfed.  To examine differences by breastfeeding initiation/non-initiation within each sex-specified group, 95% confidence intervals were produced for the following parameters: the estimated means and variances for the intercept, linear component of slope, and quadratic component of slope for BMI trajectories; the estimated coefficients for the effect of prenatal exposure to GDM on the intercept, linear component of slope and quadratic component of slope for BMI trajectories; and the estimated coefficient for the effect of prenatal exposure to GDM on birth weight for gestational age.  To compare overall differences in BMI trajectories between children who were breastfed and children who were not breastfed, 95% confidence intervals for the estimated means and variances for the intercept, linear component of slope, and quadratic component of slope were compared between breastfeeding groups. To examine modification of the effect of prenatal exposure to GDM on BMI trajectories by breastfeeding, 95% confidence intervals model-estimated coefficients for the effect of prenatal exposure to GDM on the intercept, linear component of slope, and quadratic component of slope were compared between breastfeeding groups.

Conventional methods for testing differences between groups in Mplus, such as multi-group analyses, were unavailable for the model used. This was due to the use of time scores, a technique that allows individual variation in observation times for panel data, which results in different variance/covariance matrices for each individual. As a result, Mplus software is unable to conduct multi-group analysis for models employing the use of time scores.

# 4    Results

This chapter begins with an overview of the study population characteristics, including characteristics at baseline as well as throughout NLSCY cycles (Section 4.1). The remaining sections outline results of each of the latent growth curve models (LGCMs), beginning with the unconditional LGCM (Section 4.2), followed by the unadjusted conditional LGCM examining the direct and indirect effects of prenatal exposure to GDM on childhood BMI trajectories (Section 4.3.1), the conditional LGCM adjusted for important confounding variables (Section 4.3.2), and finally the stratified conditional LGCMs examining effect modification by breastfeeding (Section 4.3.3). For all statistical tests, a significance level of $\alpha = 0.05$ is used.

## 4.1   Characteristics of the Study Population

The initial study population, which was defined as all children aged 0-1 year in cycle 1 (1994-1995) who contributed longitudinal data, consisted of 3,619 children. After exclusion of 207 twins, the final study sample included 3,412 children. Further exclusions were made automatically during latent growth curve analyses, and were due to missing values in any exogenous $x$ variables (i.e. missing values for exogenous predictors, in this case, maternal age) or missing values for all observed $y$ variables (i.e. missing BMI trajectories). These excluded cases are further described in the sections below in the results of latent growth curve analyses.

Of the 3,412 children in the study sample, 1651 (48.4%) are female and 1761 (51.6%) are male. Nearly twice as many male than female children were exposed to GDM prenatally in the study population, with 127 (7%) mothers of male children and 73 (4%) mothers of female children reporting GDM diagnosis during pregnancy. As all analyses are conducted separately by gender, study sample characteristics at baseline are also presented separately for females and males (Table 4.1). Mean age and mean BMI score at each cycle are presented in Table 4.2. Mean BMI score at each cycle by GDM exposure group is presented in Table 4.3.

Almost 20% of children (306 females and 328 males) were born into households with

less than average income adequacy, that is, households in the lowest and lower-middle income adequacy categories. Around 30% of children (497 females and 514 males) were born into households that fell in the middle category for income adequacy. Of the remaining 51% of children, approximately 38% (640 females and 676 males) were born to households classified as upper-middle income adequacy and almost 13% (208 females and 223 males) were born into households with the highest level of income adequacy.

For the vast majority (91-92%) of children included in the study, the PMK for the child was the biological mother. Average maternal age at the index pregnancy was approximately $30 \pm 5$ years for both females and males. For approximately 37% of mothers, the child included in the survey was their first child. Around 16% of mothers of both female and male children in the study sample were less than secondary school educated at the time of birth of the child included in the survey; 271 and 295 mothers of female and male children, respectively, did not complete secondary school graduation. Approximately 16% of mothers (257 mothers of female and 294 mothers of male children) in the study had completed secondary school graduation, while the remaining two-thirds of mothers completed some form of education beyond secondary school at the time of birth of the child included in the survey. Approximately 20% of mothers (338 mothers of female and 367 mothers of male children) reported ever smoking during pregnancy with the child. Finally, 23% (397) of mothers of female children and 24% (408) of mothers of male children reported never having breastfed their child while the remaining 75% in each group reported having breastfed their child at least for a short while.

## 4.2   Unconditional Latent Growth Curve Analysis

Quadratic unconditional LGCMs for females (N=1611) and males (N=1691) were estimated using maximum likelihood estimation with robust standard errors to model BMI from age 2 to 10 years. Excluded cases were those that had missing data for all variables except $x$-variables, that is, cases with missing BMI trajectories (females: N=57, males: N=52). Model results for unconditional latent growth curve analyses are summarized in Table 4.4*. Model fit for the unconditional quadratic was assessed using

the BIC values (BIC, females = 30420.626; BIC, males = 29787.174), which were lower in the quadratic unconditional LGCM than in the linear unconditional LGCM (data not shown). Significant inter-individual variability in childhood BMI trajectories was found for both females and males in terms of the intercept (females: $\boldsymbol{\sigma^2 = 4.74}$, S.E. = 0.932, $\boldsymbol{p} < 0.001$; males: $\boldsymbol{\sigma^2 = 3.45}$, S.E. = $\boldsymbol{0.681}$, $\boldsymbol{p} < 0.001$), linear component of slope (females: $\boldsymbol{\sigma^2 = 0.85}$ S.E. = $\boldsymbol{0.296}$, $\boldsymbol{p} < 0.005$; males: $\boldsymbol{\sigma^2 = 0.87}$, S.E. = $\boldsymbol{0.181}$, $\boldsymbol{p} < 0.001$), and quadratic component of slope (females: $\boldsymbol{\sigma^2 = 0.01}$ S.E. = $\boldsymbol{0.004}$, $\boldsymbol{p} < 0.05$; males: $\boldsymbol{\sigma^2 = 0.01}$, S.E. = $\boldsymbol{0.003}$, $\boldsymbol{p} < 0.001$). Significant covariance was found between the intercept and the linear component of slope ($\boldsymbol{\beta_1}$) for both males and females. Intercepts covaried significantly with the quadratic component of slope ($\boldsymbol{\beta_2}$) only for males. The average BMI trajectory for females in the study sample starts at a BMI score of 17.9 at 2 years of age, with adiposity rebound appearing to occur before the age of 6 years (Figure 4.1). The average BMI trajectory for males in the study sample has a similar starting point, with adiposity rebound occurring at around 6 years of age (Figure 4.1).

## 4.3 Conditional Latent Growth Curve Analyses

### 4.3.1 Unadjusted Direct and Indirect Pathways

Results of the conditional LGCM for the direct effect of prenatal exposure to GDM and the indirect effect through birth weight for gestational age for females (N=1555) and males (N=1619) are shown in Table 4.5 and Figure 4.2. The cases excluded from analyses were those that had missing data on predictor variables and missing BMI trajectories (females: N=113, males: N=124). For both females and males, BIC values increased from the unconditional model (BIC, females = 30420.626; BIC, males = 29787.174) to the conditional model (BIC, females = 32779.035; BIC, males = 32409.456).

From the unconditional model to the conditional model, variance in the intercept ($\alpha$) of BMI trajectories for females was reduced by 12% (unconditional: $\sigma_\alpha{}^2 = 4.74$, S.E. = 0.932, $p < 0.001$; conditional: $\sigma_\alpha{}^2 = 4.18$, S.E. = 0.892, $p < 0.001$), while variances in the linear ($\beta_1$) and quadratic ($\beta_2$) components of slope remained the same. For males,

variance of the intercept was reduced by 7% from the unconditional model to the conditional model (unconditional: $\sigma_\alpha{}^2 = 3.45$, S.E. $= 0.681$, $p < 0.001$; conditional: $\sigma_\alpha{}^2 = 3.22$, S.E. $= 0.687$, $p < 0.001$), while variances of the linear and quadratic components of slope remained approximately the same (Table 4.5).

In this model prenatal exposure to GDM ($x_{GDM_i}$) only has a significant effect on the intercept of BMI trajectories for males, reducing the model estimated BMI score at age 2 by nearly 1 point (estimated effect on intercept$= -0.929$, S.E. $= 0.354$, $p < 0.05$). The effects of prenatal exposure to GDM on the linear and quadratic components of slope for both males and females and on the intercept for females did not reach statistical significance (Table 4.5).

The Sobel test for significance of a mediation effect did not reveal a statistically significant indirect effect (through birth weight for gestational age) of prenatal exposure to GDM on any BMI trajectory parameters for females or males (Table 4.6). The p-values for the tests of the indirect effect of prenatal exposure to GDM on the intercept, linear slope, and quadratic slope for females ranged from 0.25 to 0.34. The p-values for the tests of the indirect effect of prenatal exposure to GDM on the intercept, linear slope, and quadratic slope for males ranged from 0.67 to 0.70.

## 4.3.2 Adjusted Effects of Prenatal Exposure to GDM on Childhood BMI Trajectories

Model results for the conditional LGCM of the direct effect of prenatal exposure to GDM and the indirect effect through birth weight for gestational age, adjusted for maternal age, parity, maternal highest level of education, household income adequacy, and smoking during pregnancy are shown in Table 4.7. Model results for all other covariates are provided in Appendix C. Automatically excluded cases were those for which data on exogenous variables were missing (females: N=114, males: N=128). For both females and males, BIC values increased from the unadjusted conditional model (BIC, females = 32779.035; BIC, males = 32409.456) to the adjusted conditional model (BIC, females = 47769.572; BIC, males = 48603.247).

Variance of the intercept of BMI trajectories for females was reduced by 9% from the

unadjusted to the adjusted conditional LGCM (unadjusted: $\sigma_\alpha^2 = 4.18$, S.E. $= 0.892$, $p < 0.001$; adjusted: $\sigma_\alpha^2 = 3.79$, S.E. $= 0.875$, $p < 0.001$). Also for females, variance of the linear component of slope decreased by 5% from the unadjusted to the adjusted conditional LGCM (unadjusted: $\sigma_{\beta_1}^2 = 0.848$, S.E. $= 0.314$, $p < 0.05$; adjusted: $\sigma_{\beta_1}^2 = 0.808$, S.E. $= 0.303$, $p < 0.05$). The quadratic component of slope ($\beta_2$) remained the same for females. For males, variance of the intercept of BMI trajectories decreased by 7% from the unadjusted to the adjusted conditional LGCM (unadjusted: $\sigma_\alpha^2 = 3.22$, S.E. $= 0.687$, $p < 0.001$; adjusted: $\sigma_\alpha^2 = 2.99$, S.E. $= 0.653$, $p < 0.001$). Variance of the linear component of slope was reduced by 6% from the unadjusted to the adjusted conditional LGCM (unadjusted: $\sigma_{\beta_1}^2 = 0.857$, S.E. $= 0.184$, $p < 0.001$; adjusted: $\sigma_{\beta_1}^2 = 0.805$, S.E. $= 0.179$, $p < 0.001$). Variance of the quadratic component of slope also remained approximately the same for males (Table 4.6).

The effect of prenatal exposure to GDM ($x_{GDM_i}$) on the intercept of BMI trajectories for males in the study sample remains significant in the adjusted model. The effect of prenatal exposure to GDM on the linear and quadratic components of the slope of BMI trajectories did not reach statistical significance for males or females. There was also no statistically significant effect of prenatal exposure to GDM on the intercept of BMI trajectories for females (Table 4.7). Adjusted childhood BMI trajectories for females and males with and without prenatal exposure to GDM are shown in Figure 4.2.

## 4.3.3 Modification by Breastfeeding

Effect modification of the association between prenatal exposure to GDM and childhood BMI trajectories by breastfeeding was examined using stratified conditional latent growth curve analyses adjusted for maternal age, parity, maternal highest level of education, household income adequacy, and smoking during pregnancy. Analyses were stratified by gender and breastfeeding history, resulting in four groups; females who were never breastfed, females who were breastfed, males who were never breastfed, and males who were breastfed. Model results for the adjusted conditional LGCM for each of the four groups are presented in Table 4.8 and Table 4.9. Additional model results are provided in Appendix C. The number of cases excluded in analyses due to missing data on exogenous

variables was 113 for females and 125 for males. BIC values decreased substantially with stratified models versus all previous models for both females (Never breastfed: BIC = 11625.542; Breastfed: BIC = 35576.190; Table 4.8) and males (Never breastfed: BIC = 13350.902; Breastfed: BIC = 34740.127; Table 4.9).

Residual variances of trajectory parameters changed from the overall adjusted LGCMs to the adjusted LGCMs stratified by breastfeeding initiation/non-initiation. The exception for all models was residual variances of the quadratic components of slope, which remained relatively unchanged from overall adjusted to stratified adjusted models. Variances of all trajectory parameters remained statistically significant in all models stratified by breastfeeding initiation/non-initiation except among never breastfed females.

For females, residual variance of the intercept of BMI trajectories decreased by almost 32% from the overall adjusted LGCM to the adjusted LGCM for never breastfed females (overall females: $\sigma_\alpha{}^2 = 3.79$, S.E. = 0.875, $p < 0.001$; never breastfed females: $\sigma_\alpha{}^2 = 2.59$, S.E. = 1.478, $p > 0.05$). Residual variance for the linear component of slope decreased by 30% from the overall LGCM for females to the LGCM for never breastfed females (overall females: $\sigma_{\beta_1}{}^2 = 0.808$, S.E. = 0.303, $p < 0.05$; never breastfed females: $\sigma_{\beta_1}{}^2 = 0.563$, S.E. = 0.414, $p > 0.05$). In the adjusted LGCM for breastfed females, residual variance of the intercept of BMI trajectories increased by 10% from the overall adjusted LGCM (overall females: $\sigma_\alpha{}^2 = 3.79$, S.E. = 0.875, $p < 0.001$; breastfed females: $\sigma_\alpha{}^2 = 4.18$, S.E. = 1.056, $p < 0.001$). Residual variance of the linear component of slope also increased for breastfed females by 15% from the overall LGCM for females to the LGCM for breastfed females (overall females: $\sigma_{\beta_1}{}^2 = 0.805$, S.E. = 0.179, $p < 0.001$; breastfed females: $\sigma_{\beta_1}{}^2 = 0.927$, S.E. = 0.374, $p < 0.05$).

In the adjusted LGCM for never breastfed males, residual variance of the intercept of BMI trajectories decreased by almost 12% from the overall adjusted LGCM (overall males: $\sigma_\alpha{}^2 = 2.99$, S.E. = 0.653, $p < 0.001$; never breastfed males: $\sigma_\alpha{}^2 = 2.64$, S.E. = 1.210, $p < 0.05$). Residual variances for the linear component of slope increased by almost 49% from the overall LGCM for males to the LGCM for never breastfed males (overall males: $\sigma_{\beta_1}{}^2 = 0.805$, S.E. = 0.179, $p < 0.001$; never breastfed males: $\sigma_{\beta_1}{}^2 =$

1.197, S.E. $= 0.438$, $p < 0.05$). In the adjusted LGCM for breastfed males, residual variance of the intercept of BMI trajectories decreased by 8% from the overall adjusted LGCM (overall males: $\sigma_\alpha{}^2 = 2.99$, S.E. $= 0.653$, $p < 0.001$; breastfed males: $\sigma_\alpha{}^2 = 2.74$, S.E. $= 0.716$, $p < 0.001$). Residual variances for the linear component of slope also decreased for breastfed males by almost 24% from the overall LGCM for males to the LGCM for breastfed males (overall males: $\sigma_{\beta_1}{}^2 = 0.805$, S.E. $= 0.179$, $p < 0.001$; never breastfed males: $\sigma_{\beta_1}{}^2 = 0.615$, S.E. $= 0.181$, $p < 0.005$).

BMI trajectories for children exposed and unexposed to GDM prenatally in each of the four groups are shown in Figure 4.3. Prenatal exposure to GDM ($x_{GDM_i}$) only had a statistically significant effect on the intercept ($\alpha$) of BMI trajectories for males who were never breastfed (Table 4.9). The effect of prenatal exposure to GDM on other parameters of BMI trajectories for the three other groups did not reach statistical significance (Table 4.8 and Table 4.9). Differences in the effect of prenatal exposure to GDM on BMI trajectories between children who were and were not breastfed were examined using 95% confidence intervals for model estimates of the effect of prenatal exposure to GDM on trajectory parameters (Table 4.10). Confidence intervals for each parameter estimate overlapped between breastfeeding groups, indicating no statistically significant modification of the effect of prenatal exposure to GDM on BMI trajectories by breastfeeding history.

**Table 4.1.** Baseline characteristics of study the population.

| Characteristic | Females (N= 1651) | | Males (N=1761) | |
|---|---|---|---|---|
| | N | Value | N | Value |
| **Maternal** | | | | |
| Age at pregnancy – Yr (S.D.) | 1517 | 30.6 (5.0) | 1611 | 30.4 (5.0) |
| Parity - % | | | | |
| *Primiparous* | 608 | 36.8 | 658 | 37.4 |
| *Multiparous* | 920 | 55.7 | 932 | 52.9 |
| Highest level of education obtained - % | | | | |
| *Elementary school* | 38 | 2.3 | 62 | 3.5 |
| *Some secondary school* | 233 | 14.1 | 233 | 13.2 |
| *Secondary school graduation* | 257 | 15.6 | 294 | 16.7 |
| *Other beyond high school* | 12 | 0.7 | 5 | 0.3 |
| *Some trade school* | 121 | 7.3 | 157 | 8.9 |
| *Some community college* | 273 | 16.5 | 207 | 11.8 |
| *Some university* | 93 | 5.6 | 85 | 4.8 |
| *Diploma/certificate trade school* | 147 | 8.9 | 194 | 11.0 |
| *Diploma/certificate community college* | 184 | 11.1 | 185 | 10.5 |
| *Bachelor degree* | 248 | 15.0 | 263 | 14.9 |
| *Masters, degree in medicine, doctorate* | 40 | 2.4 | 72 | 4.1 |
| **Household** | | | | |
| Income adequacy for household size - % | | | | |
| *Lowest* | 67 | 4.1 | 73 | 4.1 |
| *Lower middle* | 239 | 14.5 | 275 | 15.6 |
| *Middle* | 497 | 29.7 | 514 | 29.2 |
| *Upper middle* | 640 | 38.8 | 676 | 38.4 |
| *Highest* | 208 | 12.6 | 223 | 12.7 |
| **Pregnancy** | | | | |
| GDM diagnosis - % | | | | |
| *Yes* | 73 | 4.4 | 127 | 7.2 |
| *No* | 1441 | 87.3 | 1489 | 84.6 |
| Smoked during pregnancy - % | | | | |
| *Yes* | 338 | 20.5 | 367 | 20.8 |
| *No* | 1177 | 72.3 | 1249 | 75.7 |
| **At birth** | | | | |
| Weight – kg (S.D.) | 1636 | 3.36 (0.55) | 1748 | 3.52 (0.56) |
| Length – m (S.D.) | 1496 | 0.51 (0.04) | 1631 | 0.52 (0.04) |
| Gestational age – wk (S.D.) | 1638 | 39.1 (1.68) | 1758 | 39.2 (1.73) |
| Birth weight for gestational age z-score | 1636 | 0.19 (1.10) | 1748 | 0.26 (1.03) |
| **During infancy** | | | | |
| Breast fed - % | | | | |
| *Yes* | 1238 | 75.0 | 1321 | 75.0 |
| *No* | 397 | 24.0 | 408 | 23.2 |

**Table 4.2.** Mean age in months and BMI score for each cycle.

| Characteristic | Females | | Males | |
|---|---|---|---|---|
| | N | Value | N | Value |
| Age – months (S.D.) | | | | |
| *Cycle 2* | 1651 | 35.7 (6.5) | 1761 | 35.8 (6.5) |
| *Cycle 3* | 1538 | 58.3 (6.6) | 1615 | 58.3 (6.7) |
| *Cycle 4* | 1400 | 84.7 (6.9) | 1463 | 84.5 (7.2) |
| *Cycle 5* | 1359 | 105.2 (6.6) | 1412 | 105.3 (6.8) |
| *Cycle 6* | 1249 | 133.3 (6.6) | 1285 | 133.2 (6.7) |
| | | | | |
| BMI – score (S.D.) | | | | |
| *Cycle 2* | 1351 | 17.5 (2.77) | 1408 | 17.6 (2.45) |
| *Cycle 3* | 1267 | 16.8 (2.82) | 1240 | 16.9 (2.50) |
| *Cycle 4* | 1156 | 17.0 (3.34) | 1142 | 16.9 (2.96) |
| *Cycle 5* | 1152 | 17.6 (3.61) | 1195 | 17.9 (3.64) |
| *Cycle 6* | 1067 | 18.6 (3.46) | 1077 | 19.2 (3.99) |

**Table 4.3.** Mean BMI score at each cycle by exposure group.

| Exposure Group | Females | | Males | |
|---|---|---|---|---|
| | N | BMI Score | N | BMI Score |
| GDM – "No" | | | | |
| *Cycle 2* | 1210 | 17.6 | 1243 | 17.7 |
| *Cycle 3* | 1130 | 16.9 | 1083 | 16.9 |
| *Cycle 4* | 1028 | 17.0 | 1003 | 16.9 |
| *Cycle 5* | 1032 | 17.7 | 1032 | 17.8 |
| *Cycle 6* | 945 | 18.7 | 917 | 19.1 |
| | | | | |
| GDM – "Yes" | | | | |
| *Cycle 2* | 65 | 16.5 | 96 | 16.8 |
| *Cycle 3* | 64 | 16.1 | 101 | 16.0 |
| *Cycle 4* | 63 | 16.3 | 89 | 16.8 |
| *Cycle 5* | 44 | 17.4 | 93 | 18.3 |
| *Cycle 6* | 48 | 18.5 | 86 | 19.8 |
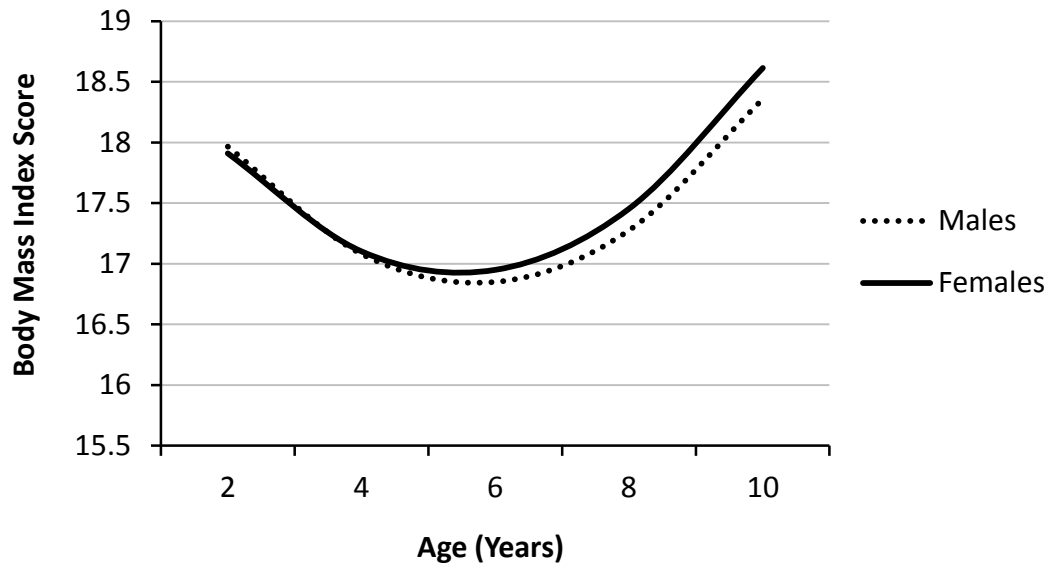
**Figure 4.1.** Unconditional latent growth curve model of childhood BMI trajectories from age 2 to 10 years.

**Table 4.4.** Results of Unconditional LGCM by gender.

| | Females (N= 1611) | | | Males (N=1691) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| **Intercepts** | | | | | | |
| $\alpha$ (intercept) | 17.91 (0.176) | 101.81 | 0.000 | 17.97 (0.138) | 129.95 | 0.000 |
| $\beta_1$ (linear slope) | -0.57 (0.103) | -5.51 | 0.000 | -0.61 (0.085) | -7.14 | 0.000 |
| $\beta_2$ (quadratic slope) | 0.08 (0.013) | 6.47 | 0.000 | 0.09 (0.010) | 8.819 | 0.000 |
| | | | | | | |
| **Covariances** | | | | | | |
| $\alpha$ with $\beta_1$ | -0.99 (0.478) | -2.07 | 0.039 | -0.86 (0.348) | -2.46 | 0.014 |
| $\alpha$ with $\beta_2$ | 0.07 (0.049) | 1.40 | 0.161 | 0.08 (0.037) | 2.09 | 0.037 |
| $\beta_1$ with $\beta_2$ | -0.08 (0.033) | -2.48 | 0.013 | -0.10 (0.020) | -4.75 | 0.000 |
| | | | | | | |
| **Residual Variances** | | | | | | |
| $\alpha$ (intercept) | 4.74 (0.932) | 5.08 | 0.000 | 3.45 (0.681) | 5.07 | 0.000 |
| $\beta_1$ (linear slope) | 0.85 (0.296) | 2.88 | 0.004 | 0.87 (0.181) | 4.80 | 0.000 |
| $\beta_2$ (quadratic slope) | 0.01 (0.004) | 2.40 | 0.016 | 0.01 (0.003) | 5.13 | 0.000 |
| BMI at 2 Yr | 2.85 (0.842) | 3.38 | 0.001 | 2.46 (0.674) | 3.65 | 0.000 |
| BMI at 4 Yr | 4.69 (0.472) | 9.93 | 0.000 | 3.90 (0.321) | 12.17 | 0.000 |
| BMI at 6 Yr | 6.17 (0.963) | 6.41 | 0.000 | 4.41 (0.512) | 8.61 | 0.000 |
| BMI at 8 Yr | 7.85 (0.747) | 4.49 | 0.000 | 7.01 (1.187) | 5.90 | 0.000 |
| BMI at 10 Yr | 4.57 (1.791) | 2.55 | 0.011 | 3.90 (1.635) | 2.39 | 0.017 |
| | | | | | | |
| **Model Fit Measures** | | | | | | |
| *Loglikelihood (Null Value)* | -15147.544 | | | -14830.406 | | |
| *BIC* | 30420.626 | | | 29787.174 | | |
| *Sample-size adjusted BIC* | 30366.620 | | | 29733.167 | | |

**Table 4.5.** Conditional LGCM for the direct effect of prenatal exposure to GDM and indirect effect through birth weight for gestational age. Model results by gender.

| | Females (N= 1555) | | | Males (N=1619) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| Regression Weights | | | | | | |
| $\alpha$ (intercept) ON $x_{GDM_i}$ | -0.855 (0.536) | -1.594 | 0.111 | -0.929 (0.354) | -2.627 | 0.009 |
| $\alpha$ (intercept) ON $x_{bwt_i}$ | 0.208 (0.106) | 1.966 | 0.049 | 0.234 (0.089) | 2.620 | 0.009 |
| $\beta_1$ (linear slope) ON $x_{GDM_i}$ | 0.042 (0.222) | 0.188 | 0.851 | 0.199 (0.259) | 0.769 | 0.442 |
| $\beta_1$ (linear slope) ON $x_{bwt_i}$ | -0.075 (0.058) | -1.289 | 0.197 | -0.063 (0.060) | -1.041 | 0.298 |
| $\beta_2$ (quadratic slope) ON $x_{GDM_i}$ | 0.005 (0.028) | 0.195 | 0.845 | 0.000 (0.035) | 0.005 | 0.996 |
| $\beta_2$ (quadratic slope) ON $x_{bwt_i}$ | 0.011 (0.007) | 1.493 | 0.135 | 0.007 (0.008) | 0.861 | 0.389 |
| $x_{bwt_i}$ ON $x_{GDM_i}$ | 0.294 (0.205) | 1.437 | 0.151 | 0.082 (0.188) | 0.433 | 0.665 |
| | | | | | | |
| Residual Variances | | | | | | |
| $\alpha$ (intercept) | 4.181 (0.892) | 4.689 | 0.000 | 3.216 (0.687) | 4.683 | 0.000 |
| $\beta_1$ (linear slope) | 0.848 (0.314) | 2.704 | 0.007 | 0.857 (0.184) | 4.654 | 0.000 |
| $\beta_2$ (quadratic slope) | 0.011 (0.004) | 2.450 | 0.014 | 0.013 (0.003) | 5.055 | 0.000 |
| | | | | | | |
| Model Fit Measures | | | | | | |
| Loglikelihood (Null Value) | | -16293.977 | | | -16108.664 | |
| BIC | | 32779.035 | | | 32409.456 | |
| Sample-size adjusted BIC | | 32696.439 | | | 32326.859 | |

**Table 4.6.** Results of the Sobel test for the indirect effect through birth weight for gestational age of prenatal exposure to GDM on childhood BMI trajectory parameters.

| Trajectory Parameter | Females | Males |
|---|---|---|
| Intercept | | |
| *Sobel test statistic* | 1.158 | 0.430 |
| *p-value* | 0.247 | 0.667 |
| Slope (Linear) | | |
| *Sobel test statistic* | -0.960 | -0.403 |
| *p-value* | 0.337 | 0.687 |
| Slope (Quadratic) | | |
| *Sobel test statistic* | 1.059 | 0.390 |
| *p-value* | 0.289 | 0.696 |

**Table 4.7.** Conditional LGCM for the direct effect of prenatal exposure to GDM and indirect effect through birth weight for gestational age, adjusted for maternal age, parity, smoking during pregnancy, household income adequacy, and maternal highest level of education. Model results by gender

| | Females (N= 1555) | | | Males (N=1619) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| **Regression Weights** | | | | | | |
| $\alpha$ (intercept) ON $x_{GDM_i}$ | -0.901 (0.471) | -1.914 | 0.056 | -0.933 (0.381) | -2.449 | 0.014 |
| $\alpha$ (intercept) ON $x_{bwt_i}$ | 0.213 (0.105) | 2.025 | 0.043 | 0.259 (0.100) | 2.573 | 0.010 |
| $\beta_1$ (linear slope) ON $x_{GDM_i}$ | 0.060 (0.218) | 0.274 | 0.784 | 0.144 (0.258) | 0.558 | 0.577 |
| $\beta_1$ (linear slope) ON $x_{bwt_i}$ | -0.082 (0.060) | -1.381 | 0.167 | -0.045 (0.059) | -0.769 | 0.442 |
| $\beta_2$ (quadratic slope) ON $x_{GDM_i}$ | -0.002 (0.028) | -0.074 | 0.941 | -0.008 (0.033) | -0.238 | 0.812 |
| $\beta_2$ (quadratic slope) ON $x_{bwt_i}$ | 0.013 (0.008) | 1.767 | 0.077 | 0.007 (0.007) | 0.883 | 0.377 |
| $x_{bwt_i}$ ON $x_{GDM_i}$ | 0.357 (0.162) | 2.200 | 0.028 | 0.165 (0.164) | 1.003 | 0.316 |
| **Residual Variances** | | | | | | |
| $\alpha$ (intercept) | 3.789 (0.875) | 4.332 | 0.000 | 2.988 (0.653) | 4.576 | 0.000 |
| $\beta_1$ (linear slope) | 0.808 (0.303) | 2.667 | 0.008 | 0.805 (0.179) | 4.491 | 0.000 |
| $\beta_2$ (quadratic slope) | 0.011 (0.004) | 2.455 | 0.014 | 0.012 (0.003) | 4.570 | 0.000 |
| **Model Fit Measures** | | | | | | |
| Loglikelihood (Null Value) | | -23623.888 | | | -24039.382 | |
| BIC | | 47769.572 | | | 48603.247 | |
| Sample-size adjusted BIC | | 47544.022 | | | 48377.693 | |
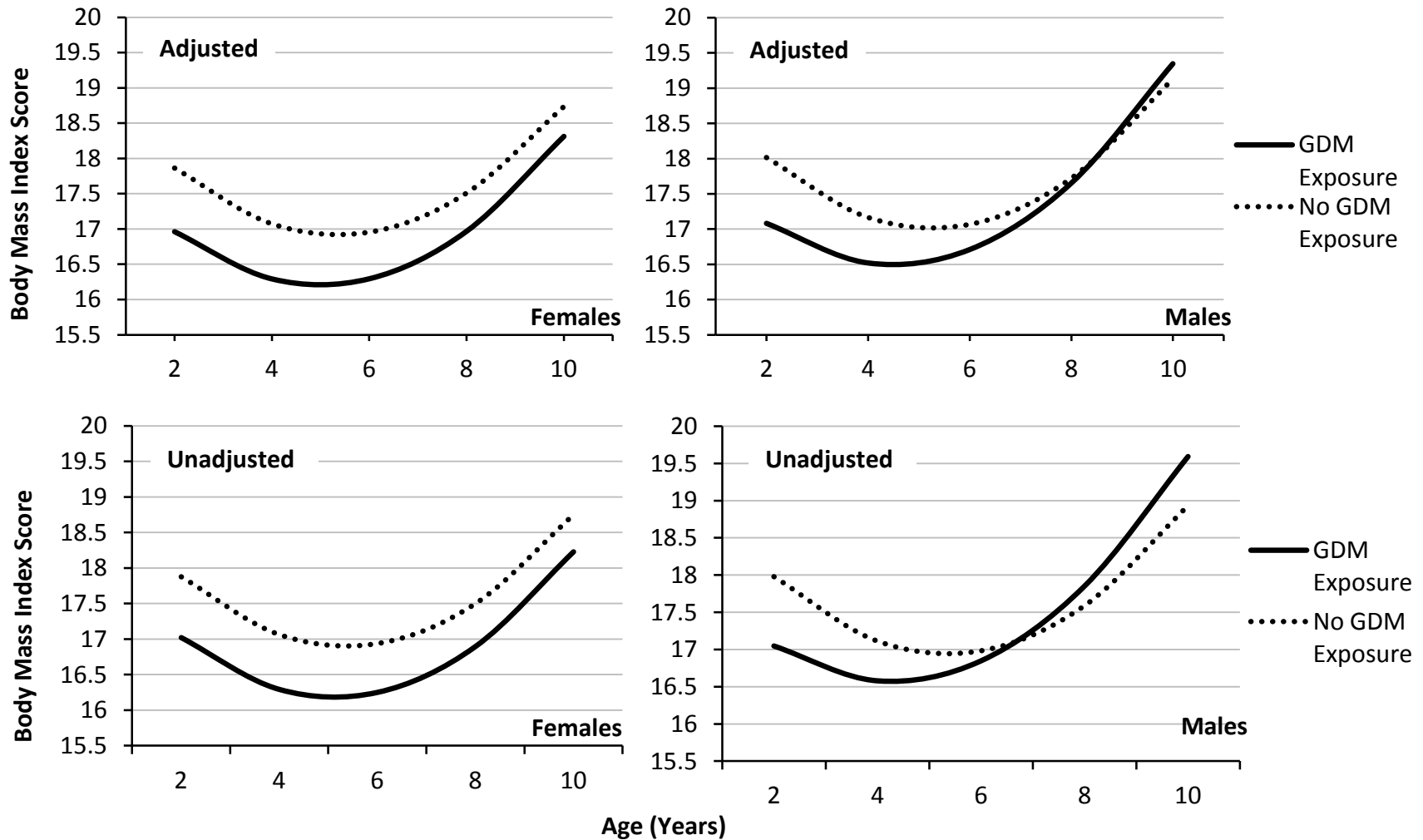
**Figure 4.2**. Results of analyses for Objectives 1 and 2. Unadjusted and adjusted latent growth curve models (LGCMs) of early childhood BMI trajectories for children with and without prenatal exposure to GDM. Model results by gender. Note: adjusted LGCMs are controlled for maternal age, parity, smoking during pregnancy, household income adequacy, and maternal education.

**Table 4.8.** Results of Objective 3 conditional LGCM by breastfeeding for females.

| | Never Breastfed (N= 390) | | | Breastfed (N=1152) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| **Regression Weights** | | | | | | |
| $\alpha$ (intercept) ON $x_{GDM_i}$ | -0.627 (0.726) | -0.864 | 0.388 | -1.042 (0.586) | -1.777 | 0.075 |
| $\alpha$ (intercept) ON $x_{bwt_i}$ | 0.219 (0.222) | 0.984 | 0.325 | 0.217 (0.117) | 1.846 | 0.065 |
| $\beta_1$ (linear slope) ON $x_{GDM_i}$ | 0.171 (0.315) | 0.542 | 0.588 | 0.154 (0.291) | 0.528 | 0.597 |
| $\beta_1$ (linear slope) ON $x_{bwt_i}$ | -0.130 (0.104) | -1.249 | 0.212 | -0.085 (0.070) | -1.207 | 0.228 |
| $\beta_2$ (quadratic slope) ON $x_{GDM_i}$ | -0.008 (0.041) | -0.198 | 0.843 | -0.016 (0.034) | -0.482 | 0.630 |
| $\beta_2$ (quadratic slope) ON $x_{bwt_i}$ | 0.019 (0.012) | 1.591 | 0.112 | 0.014 (0.009) | 1.573 | 0.116 |
| $x_{bwt_i}$ ON $x_{GDM_i}$ | 0.589 (0.249) | 2.364 | 0.018 | 0.317 (0.207) | 1.527 | 0.127 |
| **Residual Variances** | | | | | | |
| $\alpha$ (intercept) | 2.592 (1.478) | 1.754 | 0.079 | 4.181 (1.056) | 3.959 | 0.000 |
| $\beta_1$ (linear slope) | 0.563 (0.414) | 1.361 | 0.174 | 0.927 (0.374) | 2.480 | 0.013 |
| $\beta_2$ (quadratic slope) | 0.010 (0.006) | 1.636 | 0.102 | 0.012 (0.005) | 2.150 | 0.032 |
| **Model Fit Measures** | | | | | | |
| *Loglikelihood (Null Value)* | | -5600.973 | | | -17717.095 | |
| *BIC* | | 11625.542 | | | 35934.687 | |
| *Sample-size adjusted BIC* | | 11400.263 | | | 35709.169 | |

**Table 4.9.** Results of Objective 3 conditional LGCM by breastfeeding for males.

| | Never Breastfed (N= 428) | | | Breastfed (N=1169) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| **Regression Weights** | | | | | | |
| $\alpha$ (intercept) ON $x_{GDM_i}$ | -1.529 (0.534) | -2.864 | 0.004 | -0.510 (0.382) | -1.333 | 0.183 |
| $\alpha$ (intercept) ON $x_{bwt_i}$ | 0.199 (0.184) | 1.077 | 0.281 | 0.247 (0.115) | 2.154 | 0.031 |
| $\beta_1$ (linear slope) ON $x_{GDM_i}$ | 0.259 (0.338) | 0.768 | 0.443 | -0.080 (0.232) | -0.345 | 0.730 |
| $\beta_1$ (linear slope) ON $x_{bwt_i}$ | -0.229 (0.127) | -1.797 | 0.072 | 0.027 (0.062) | 0.439 | 0.660 |
| $\beta_2$ (quadratic slope) ON $x_{GDM_i}$ | -0.010 (0.044) | -0.238 | 0.812 | 0.009 (0.027) | 0.330 | 0.741 |
| $\beta_2$ (quadratic slope) ON $x_{bwt_i}$ | 0.042 (0.017) | 2.529 | 0.011 | -0.006 (0.008) | -0.798 | 0.425 |
| $x_{bwt_i}$ ON $x_{GDM_i}$ | -0.125 (0.249) | -0.503 | 0.615 | 0.416 (0.151) | 2.765 | 0.006 |
| **Residual Variances** | | | | | | |
| $\alpha$ (intercept) | 2.637 (1.210) | 2.180 | 0.029 | 2.741 (0.716) | 3.826 | 0.000 |
| $\beta_1$ (linear slope) | 1.197 (0.438) | 2.732 | 0.006 | 0.615 (0.181) | 3.408 | 0.001 |
| $\beta_2$ (quadratic slope) | 0.020 (0.007) | 2.823 | 0.005 | 0.009 (0.003) | 3.541 | 0.000 |
| **Model Fit Measures** | | | | | | |
| Loglikelihood (Null Value) | | -6460.352 | | | -17119.295 | |
| BIC | | 13350.902 | | | 34740.127 | |
| Sample-size adjusted BIC | | 13125.591 | | | 34514.607 | |

**Table 4.10.** Confidence intervals of Objective 3 LGCM estimates for comparison between breastfeeding groups.

| | Females - Est. (95% CI) | | Males - Est. (95% CI) | |
|---|---|---|---|---|
| | **Never Breastfed** | **Breastfed** | **Never Breastfed** | **Breastfed** |
| **Intercepts** | | | | |
| $\alpha$ *(intercept)* | 18.438 (17.910,18.966) | 17.699 (17.326,18.072) | 18.356 (17.867,18.846) | 17.910 (17.564,18.256) |
| $\beta_1$ *(linear slope)* | -0.528 (-0.842,-0.214) | -0.561 (-0.810,-0.311) | -0.712 (-1.076,-0.348) | -0.600 (-0.795,-0.406) |
| $\beta_2$ *(quadratic slope)* | 0.080 (0.043,0.118) | 0.082 (0.050,0.115) | 0.106 (0.057,0.155) | 0.093 (0.071,0.115) |
| **Residual Variances** | | | | |
| $\alpha$ *(intercept)* | 2.592 (-0.305,5.489) | 4.181 (2.111,6.251) | 2.637 (0.266,5.007) | 2.741 (1.337,4.146) |
| $\beta_1$ *(linear slope)* | 0.563 (-0.248,1.375) | 0.927 (0.194,1.659) | 1.197 (0.338,2.056) | 0.615 (0.261,0.969) |
| $\beta_2$ *(quadratic slope)* | 0.010 (-0.002,0.022) | 0.012 (0.001,0.022) | 0.020 (0.006,0.033) | 0.009 (0.004,0.014) |
| **Regression Weights** | | | | |
| $\alpha$ *(intercept)* ON $x_{GDM_i}$ | -0.627 (-2.049,0.795) | -1.042 (-2.191,0.107) | -1.529 (-2.575,- 0.482) | -0.510 (-1.259,0.240) |
| $\beta_1$ *(linear slope)* ON $x_{GDM_i}$ | 0.171 (-0.447,0.789) | 0.154 (-0.417,0.724) | 0.259 (-0.402,0.921) | -0.080 (-0.535,0.375) |
| $\beta_2$ *(quadratic slope)* ON $x_{GDM_i}$ | -0.008 (-0.089,0.072) | -0.016 (-0.083,0.050) | -0.010 (-0.096,0.075) | 0.009 (-0.043,0.061) |
| $x_{bwt_i}$ ON $x_{GDM_i}$ | 0.589 (0.100,1.077) | 0.317 (-0.090,0.723) | -0.125 (-0.613,0.363) | 0.416 (0.121,0.711) |
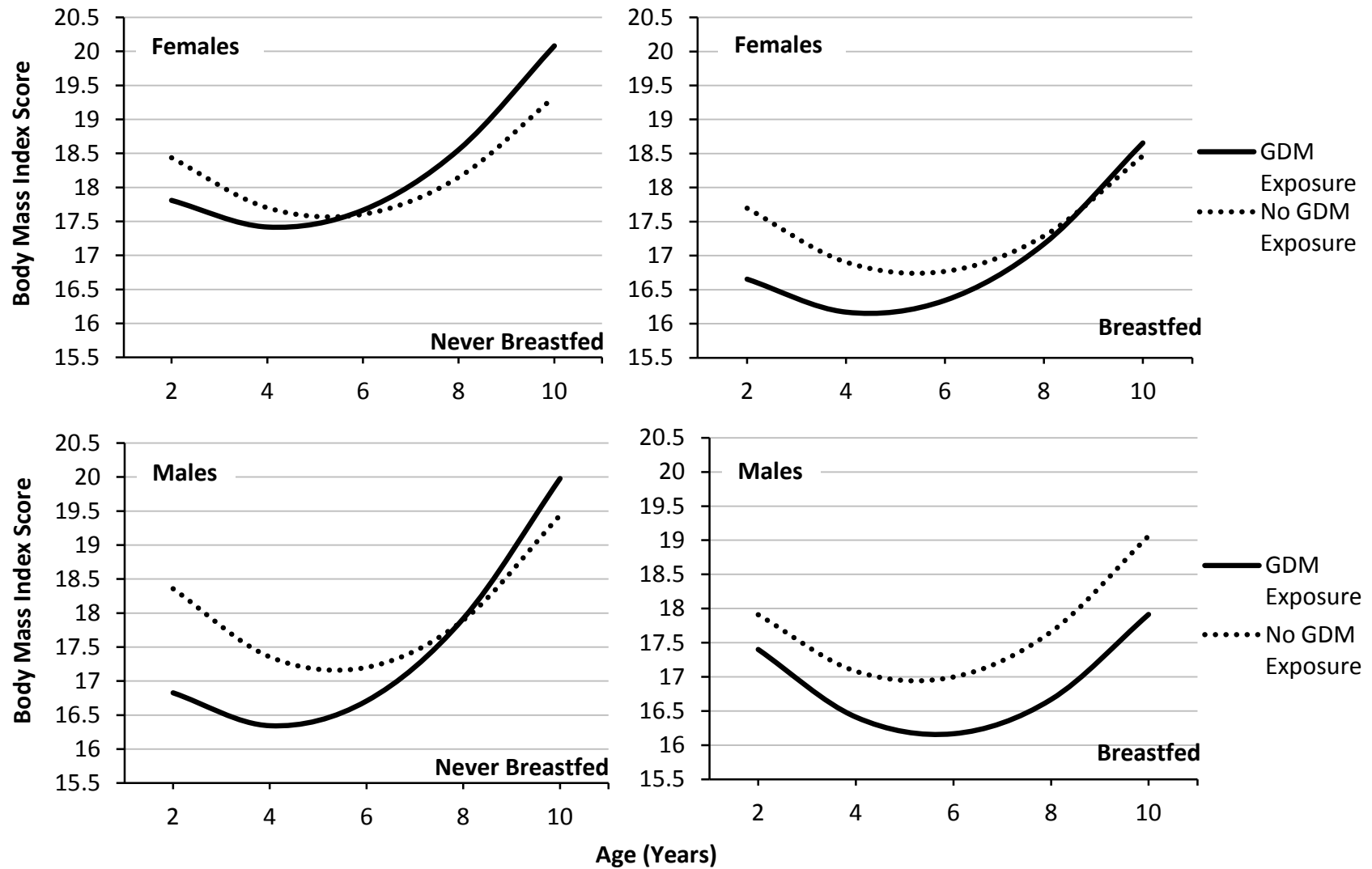
**Figure 4.3.** Results of analyses for Objective 3. Latent growth curve models (LGCMs) of early childhood BMI trajectories for children with and without prenatal exposure to GDM stratified by breastfeeding history. Model results by gender. Note: LGCMs are controlled for maternal age, parity, smoking during pregnancy, household income adequacy, and maternal education.

# 5    Discussion

This chapter presents discussions of the findings of the current study. Section 5.1 outlines the main research findings, discussing the significance of study results in context of the research objectives and the overall body of literature examining the association between maternal IGT during pregnancy and childhood overweight and obesity. This is followed by Section 5.2, which presents a discussion of the possible reasons for the statistically non-significant findings in the study. Section 5.3 discusses the limitations of this study and Section 5.4 discusses the study strengths. Finally, Section 5.5 provides a summary of the conclusions of the study and recommendations for further research.

This study's aim was to examine the association between GDM and early childhood BMI trajectories. The main prediction was that prenatal exposure to GDM is associated with BMI trajectories that exhibit unhealthy changes in child weight for height and the potential for overweight and obesity risk. Specific objectives of the study were to model early childhood BMI trajectories and examine the direct and indirect effects of prenatal exposure to GDM, adjusting for important confounding factors, as well as to explore breastfeeding as a potential effect modifier and protective factor.

## 5.1   Overview of Research Findings

### 5.1.1    Early Childhood BMI Trajectories

As expected, BMI data for both female and male children in the study population fit a quadratic model of growth from the ages of 2 to 10 years. Childhood BMI trajectories exhibited an initial decline from the age of 2 years before steadily inclining through the age of 10 years for both females and males.  The timing of adiposity rebound, that is the point of renewed incline in BMI, occurred earlier on average in females compared to males in the study sample (Figure 4.1). Overall, according to the model, adiposity rebound appeared to occur between the ages of 5 and 6 years for females and males in the sample. This is consistent with the literature on timing of adiposity rebound, which states that minimum BMI during childhood occurs at 5 to 6 years of age.[65]  Also according to the modelled trajectories, females on average had higher BMI between the ages of 6 and

10 years than males in the study population (Figure 4.1).

## 5.1.2    Inter-Individual Variability

An important post hoc consideration is how much inter-individual variation was seen in trajectories. The amount of residual variance in trajectory parameters comparing one model to the next reveals important information about how representative an average trajectory is for the population being described. Indeed, the main advantage of latent growth curve analyses is the ability to simultaneously consider individual- and group-level patterns in longitudinal data.

At the outset, the study population showed significant variance in all BMI trajectory parameters (intercept, linear slope, and quadratic slope), which provided justification for further analyses. The addition of prenatal exposure to GDM as a predictor of BMI trajectories explained 12% and 7% of the variance in the intercepts of BMI trajectories for females and males, respectively, and explained none of the variance in slopes. Significant residual variance in all trajectory parameters remained in this model. As this first model was unadjusted, the large residual variance is explained by the inter-individual variability remaining due to the omission of other important predictors of childhood BMI trajectories. Some of these other predictors, considered to be confounding or control variables, were added in the second model. This second model explained a further 9% and 7% of the variance in the intercepts and an additional 5% and 6% of the variance in the linear component of slope of BMI trajectories for females and males, respectively. Since residual variances decreased from the first to the second model, it can be concluded that the proposed predictors accounted for some of the inter-individual variability in BMI trajectories. Still, residual variances in all trajectory parameters remained significant in the adjusted model, reflecting further unexplained inter-individual variability.

In the third model, stratified for females and males by breastfeeding initiation/non-initiation, interesting changes in variance of trajectory parameters occurred. Among never breastfed females, residual variances in the intercept and linear component of slope were reduced considerably, while residual variances were increased for the same parameters

among breastfed females comparing stratified to unstratified models. This suggests that the average adjusted BMI trajectory better represents never breastfed females than it does the overall study population of females. Conversely, the average adjusted BMI trajectory for females is less representative of the change in BMI among breastfed females in the study population. Among males who were never breastfed, residual variance in the intercept is decreased while variance in the linear component of slope is dramatically increased. This indicates that while the starting point of the average adjusted BMI trajectory may well represent never breastfed males at age 2 years in the study population, the slope of the average trajectory is much less representative. The variances of the intercept and linear component of slope of BMI trajectories for breastfed males are reduced from the unstratified adjusted model, indicating the average adjusted BMI trajectory better represents breastfed males in the study population than overall study population of males.

## 5.1.3 Effects of Prenatal Exposure to GDM on the Shape of Early Childhood BMI Trajectories

### 5.1.3.1 Overall Effects

Overall, the results of the current study do not support the existence of a statistically significant effect of prenatal exposure to GDM on early childhood BMI trajectories in the population studied. The one finding that did reach statistical significance was the effect of prenatal exposure to GDM on BMI at age 2 years among males. Exposure to GDM *in utero* was associated with a significant decrease in BMI at age 2 years among males. This opposes the original hypothesis that prenatal exposure to GDM is associated with higher initial BMI due to over-nutrition and fetal overgrowth. Although these results would seem to suggest a potential protective effect of prenatal exposure to GDM on early infant weight, the literature does not support such an association. Instead this finding may reflect adverse pregnancy outcomes associated with GDM that result in low early infancy weight gain, such as spontaneous preterm birth[172] and gestational hypertension.[143]

Despite that results were predominantly non-significant, a recurring pattern emerged from the model-estimated values of the effect of prenatal exposure to GDM on childhood

BMI trajectories. In both unadjusted and adjusted analyses, prenatal exposure to GDM appears to be associated with lower BMI at age 2 years followed by an increased rate of incline in BMI between the ages of 6 and 10 years for females and males (Figure 4.2). Although this overall pattern was neither statistically significant nor consistent with the hypothesized effect of intrauterine exposure to GDM on childhood BMI trajectories, it is a pattern that mirrors those described in the literature to be predictive of poor health outcomes.[8 58 59 61 64-67] Indeed, this particular pattern mirrors that of catch-up growth, described in the literature as initially low weight followed by accelerated early weight gain associated with obesity risk and later metabolic disease.[8 58 59 67]

The goal of studies attempting to identify early life risk factors for child obesity, such as intrauterine exposure to GDM, is ultimately to reveal predictors for patterns of childhood growth associated with increased risk of later metabolic disease. Indeed, this was the intent of the current study. Previous studies that have described patterns in childhood growth very similar to those seen in the current study have shown these growth patterns to be predictive of adolescent obesity,[59] adult diabetes,[58 67] and CHD.[8 58] These studies all found that the greatest metabolic risk was associated with early growth patterns that began with lower than average BMI at birth[8 58] through age 2 years[58 59 67] followed by higher than average BMI beyond the ages of 6 to 12 years.[8 58 59 67] In all of these cases it is the combination of low initial BMI with a period of accelerated or catch-up growth resulting in higher than average BMI that is most strongly predictive of later obesity or metabolic disease. Indeed, Eriksson and colleagues[8] demonstrated an interaction between the two factors, showing that lower than average BMI at birth plus rapid childhood weight gain is associated with higher risk of death from CHD than either low BMI at birth followed by normal weight gain or normal BMI at birth followed by rapid childhood weight gain.

Despite the non-significant findings for the overall effect of prenatal exposure to GDM on the shape of childhood BMI trajectories in the current study, some studies suggest the patterns of infant and childhood weight gain described above can be seen among offspring of mothers with GDM. In terms of initial BMI, GDM is more often associated with higher and not lower than average birth weight.[119] However, treatment for GDM has

been shown to reduce rates of high birth weight.[82] One study even found that the offspring of mothers with obstetrically managed GDM had lower than average BMI during the first two years, which was followed by accelerated weight gain throughout early childhood.[84] This study also compared mothers with GDM who were treated during pregnancy to mothers with untreated mild IGT and revealed steeper weight gain among offspring of mothers with GDM beyond the age of 5 years compared to offspring of mothers with mild IGT.[84] Thus, it is theoretically possible that children born to mothers with well-managed GDM follow this pattern of low initial BMI and subsequent accelerated childhood weight gain.

## 5.1.3.2    Indirect Effect through Birth Weight for Gestational Age

The data do not support a causal model for the effect of intrauterine exposure to GDM on early childhood BMI trajectories in which birth weight is an important mediator.  Indeed, tests for the indirect effect of prenatal exposure to GDM through birth weight for gestational age on BMI trajectory parameters did not reach statistical significance. This goes against the hypothesis and suggests that the effect of prenatal exposure to GDM on early childhood BMI trajectories is not mediated by birth weight for gestational age. However, given that the current study did not reveal a statistically significant direct effect of prenatal exposure to GDM on childhood BMI trajectories, it is not surprising that the indirect effect was also not found to be statistically significant. A more detailed discussion of the reasons for this study's non-significant findings is provided in Section 5.2.

One factor that may have influenced results of the indirect effect is the chosen measure of birth weight. The current study assessed the indirect effect of prenatal exposure to GDM on BMI trajectories through birth weight in grams adjusted for gestational age. Some studies have reported that BMI at birth, that is birth weight adjusted for birth length, is a better predictor of later risk of cardiovascular disease than birth weight, even when birth weight is adjusted for gestational age.[8] [173] Since BMI at birth can predict later cardiovascular health, it is possible that it may also predict the childhood growth patterns that are also predictive of cardiovascular and metabolic health. Thus, BMI at birth may have been a better choice as a mediator for the effect of prenatal exposure to GDM on

BMI trajectories than birth weight for gestational age.

## 5.1.4    Effects of Breastfeeding

Previous studies have suggested that breastfeeding may have protective effects against the development of childhood obesity.[46 99 102-108 110 174]  In this study, stratified analyses examining the potential modifying effects of breastfeeding revealed no statistically significant modification of the effects of prenatal exposure to GDM on early childhood BMI trajectories. Indeed, the differences in the model-estimated effect of prenatal exposure to GDM on BMI trajectories between breastfeeding groups were found to be non-significant. Possible reasons for these non-significant findings are discussed in Section 5.2. The remainder of the current subsection discusses the patterns that emerged from model-estimated values of the effects of prenatal exposure to GDM and breastfeeding on BMI trajectories in context of the pertaining literature. Although the results were not statistically significant, the shapes of modelled BMI trajectories in the stratified analyses reflect patterns in early childhood weight gain associated both with prenatal exposure to GDM and breastfeeding that mirror patterns predicted in initial hypotheses as well as those described in the literature.

## 5.1.4.1    Breastfeeding as a Protective Factor against Childhood Obesity Risk

Although there were no statistically significant differences between breastfeeding groups, the values of model estimates mirror patterns in past studies that have shown breastfeeding is associated with lower BMI in infancy,[99 101 106 174] early childhood,[46 104 105 108] and later childhood.[102 103 110] Overall, regardless of whether or not children were born to mothers who had GDM, breastfeeding appears to be associated with overall lower BMI throughout childhood. This is consistent with studies that have shown that breastfeeding is associated with less early infancy weight gain[99 101 106 174] as well as reduced BMI throughout childhood.[46 102-105 108 110]

### 5.1.4.2 Breastfeeding as a Modifier for the Association between Intrauterine Exposure to GDM and Childhood BMI Trajectories

The results of the current study do not support breastfeeding as a modifier of the effect of prenatal exposure to GDM on childhood BMI trajectories. However, it may be interesting to note that model-estimated values of the effect of intrauterine exposure to GDM on BMI trajectories appear markedly different depending on breastfeeding status. Never breastfed females who were exposed to GDM *in utero* have an estimated BMI trajectory that appears initially low with early and rapid catch-up growth resulting in a rate of incline in BMI that surpasses the rate of their non-exposed counterparts between the ages of 6 and 10 years (Figure 4.3; Top left). Conversely, ever breastfed females who were exposed to GDM *in utero* have a BMI trajectory that begins similarly low but rises more steadily between the ages of 4 and 10 years (Figure 4.3; Top right). In the breastfed group, females with prenatal exposure to GDM marginally surpass BMI of their non-exposed counterparts only by the age of 10 years. Thus, breastfeeding appears to be associated with an attenuation of the effects of prenatal exposure to GDM on the initial level and rate of incline of BMI trajectories among females. Other studies have reported an association between breastfeeding and slower infancy and early childhood weight gain.[101 106] These studies have shown that never breastfed infants experience accelerated weight gain in the first few years of life while breastfed infants exhibit less weight gain during the same period.[101 106] Although these studies describe very early weight gain (birth to age 2[106] and birth to age 3 years[101]), there is reason to believe breastfeeding may have an important influence on later childhood weight trajectories. Indeed one study demonstrated that among 3 to 6 year-olds, breastfeeding was associated with better appetite regulation and higher responsiveness to satiation,[100] which, continuing into later childhood, may explain more gradually inclining BMI.

The pattern seen among males in the study sample appears even more pronounced. The estimated BMI trajectory for never breastfed males who were exposed to GDM *in utero* begins significantly lower than that of non-exposed males in the same group with very early and rapid catch-up growth between the ages of 4 and 10 years (Figure 4.3; Bottom left). Never breastfed males who were exposed to GDM prenatally eventually surpass

BMI of their non-exposed counterparts by the age of 10 years. Although the pattern in BMI trajectories among never breastfed males shares similarities to the pattern seen among never breastfed females in the study, the pattern among breastfed males is markedly different. Comparing never breastfed to breastfed females, initial BMI is decreased among those exposed to GDM *in utero* and is followed by a steep incline in BMI until the age of 10 years. However, comparing never breastfed to breastfed males, initial BMI appears to increase among those exposed to GDM prenatally followed by a rate of incline in BMI throughout childhood similar to non-exposed breastfed males (Figure 4.3; Bottom right). Breastfed males who were exposed to GDM *in utero* also appear to experience later adiposity rebound (AR at 6 years) than both never breastfed males exposed to GDM (AR at 4 years) and breastfed males not exposed to GDM (AR between 4 and 6 years).

Although these findings are not statistically significant and interpretations must be drawn with caution, they do follow a pattern consistent with studies that have shown both that breastfeeding is associated with lower childhood BMI[46 102-105 108 110 175] and that it is most strongly associated with reduction of obesity risk among children with pre-existing risk factors.[107 108 112] A study by Buyken and colleagues[107] that examined the association between breastfeeding and percent body fat trajectories in early childhood found a significant protective effect of breastfeeding in males with overweight mothers but not in males with normal weight mothers. Furthermore, this study proposed an interaction effect between maternal overweight and breastfeeding.[107] This suggests that the particular risk profiles of children may modify and, in some cases, enhance the protective effect of breastfeeding. If this concept is applied to the interpretation of results in the current study, it would suggest that breastfeeding may be a particularly effective strategy to prevent adverse childhood weight outcomes associated with prenatal exposure to GDM for males.

## 5.2   Non-Significant Study Findings

The objective of the current study was to examine the impact of prenatal exposure to GDM on early childhood BMI trajectories with the hypotheses that exposure to GDM would be associated with initially high BMI as well as high rising BMI throughout

childhood. It was also hypothesized that breastfeeding would attenuate this association, as previous studies have shown that breastfeeding has protective effects against the development of overweight and obesity. However, the results of the analyses were mainly non-significant. Model results for the estimated effect of prenatal exposure to GDM on childhood BMI trajectories either did not reach statistical significance or did not support the hypotheses. Results of models examining effect modification by breastfeeding also did not reach statistical significance. There are a number of possible reasons that the study findings differed from expectations. This subsection focuses on issues related to the study design that may have contributed to these non-significant study findings.

## 5.2.1    Identification of Exposure

One issue that may have contributed to the overall non-significant study findings is the possibility of only partial identification of the exposure of interest. In the current study the exposure of interest was GDM, which was measured by maternal report of diabetes diagnosis during pregnancy. Although studies have reported GDM as a risk factor for various adverse child weight outcomes, many of these studies were able to identify GDM diagnosis through data from clinical measures such as oral glucose tolerance test (OGTT) results[75-77 83 84 91-93] and average daily glycemia.[76] While some studies have also used maternal report to identify GDM in study populations,[81 176] this measure certainly contains less information about the actual exposure to the fetus than clinical measures. Indeed, self-reported GDM diagnosis does not per se provide information about the degree to which blood sugar levels are managed throughout pregnancy or the chosen method of blood sugar management. These variables undoubtedly alter the amount of fetal exposure to a hyperglycemic prenatal environment. In current clinical practice, patients with GDM are often given intensive treatment to manage blood sugar levels during pregnancy.[177-180] Thus, it is possible that mothers in the NLSCY study population truly represented a group with well managed glycemia during pregnancy due to intensive obstetric care.

A related issue to the insufficient identification of the exposure of interest due to the unavailable information on actual maternal glycemia during pregnancy is that the study population likely included those with undiagnosed gestational hyperglycemia. Indeed,

insulin resistance is common even in normal pregnancy,[180] and many women experience levels of gestational hyperglycemia that do not meet diagnostic criteria for GDM.[181] Few studies have examined the effect of treatment for mild gestational hyperglycemia[181] and many women with mild hyperglycemia during pregnancy may not receive proper treatment to manage blood glucose levels.

In the current study population, there may have been individuals that did not meet the criteria for GDM diagnosis, but nevertheless experienced a significant level of hyperglycemia during pregnancy. However, these cases would not have self reported pregnancy diabetes in the NLSCY because of a lack of clinical diagnosis. This group would thus represent a truly at-risk population of children exposed to a hyperglycemic prenatal environment due to potentially untreated maternal hyperglycemia during gestation. The data used in the current study did not contain any further measures of maternal glucose tolerance during pregnancy beyond the question of whether or not mothers were diagnosed with GDM. Therefore, an important portion of the population at risk was not captured in the current study. This may have contributed to the non-significant study findings, as the unexposed population likely contained many cases in which children were in fact exposed to undiagnosed maternal hyperglycemia *in utero*. If this is the case, the model estimates of the impact of prenatal exposure to GDM on childhood BMI trajectories were based on differences between two groups that each contained similar cases, which would inevitably result in null findings. Furthermore, the finding that males exposed to GDM *in utero* had significantly lower initial BMI than unexposed males may only reflect the difference in outcomes of pregnancies that consistently involved treatment for blood glucose management versus pregnancies that did not.

## 5.2.2    Obstetric Management of GDM

To further complicate matters, the treatment of GDM is not necessarily standardized since management strategies used in practice are not all evidence-based in terms of both efficacy and minimization of adverse perinatal outcomes.[177-180] For example, although dietary counselling is the first line of treatment for many cases of GDM,[177] nutritional guidelines to achieve and maintain appropriate glycemic control are not evidence-based

due to limited research available on specific nutritional recommendations.[180] Furthermore, women diagnosed with GDM can range in level of hyperglycemia from levels that would constitute diabetes diagnosis outside of pregnancy to levels that do not cause symptoms but have adverse effects on the fetus.[180] In clinical practice, treatment options for GDM vary according to blood glucose levels, but decisions are based more on expert opinion and usual practice rather than research evidence.[177] Thus, there may be wide variation in terms of level and duration of hyperglycemia during pregnancy even among women diagnosed with GDM and receiving treatment.

A Cochrane review[178] of studies examining the perinatal outcomes associated with various GDM management strategies found that treatment with insulin is associated with a higher risk of labour induction and Caesarean section than treatment with oral hypoglycemic medication.[178] Pregnancy complications such as these may explain why the current study found prenatal exposure to GDM to be associated with childhood BMI trajectories that are initially lower than those of children who were not exposed to GDM.

In summary, the study findings for the association between prenatal exposure to GDM and childhood BMI trajectories differed from expectations due, in part, to the inability to define the exposure group in terms of the actual exposure. Indeed, data on maternal GDM diagnosis did not provide enough information about prenatal exposure to maternal hyperglycemia to conclude all children in the exposure group were similarly exposed. Further, intensive obstetric care and potentially tight control of blood glucose levels during pregnancy may have ensured that the group of children defined by GDM exposure actually had less exposure to maternal hyperglycemia *in utero* than others in the study population.

## 5.3   Study Limitations

### 5.3.1   Self-Reported Data

The inherent limitations of self-reported data reflect one of the main drawbacks of the current study. Indeed, as previously discussed, self-reported GDM diagnosis does not contain enough information to comment on level of fetal exposure to maternal hyperglycemia. Information on child height and weight used to calculate BMI was also

reported and not measured directly in the NLSCY. Self-report of these physical measures limit the accuracy of analyses using these data. However, the focus of the current study was on the shape of childhood BMI trajectories. Assuming that inaccuracies in maternal report of child height and weight were relatively consistent throughout cycles, this limitation has minimal influence on the interpretation of study findings. The accuracy of maternal report of birth weight and gestational age may have influenced study results given that recall of these measures likely varied with the age of the child at the time of the interview.

## 5.3.2    Sample Size and Attrition

The inability to detect statistically significant effects of prenatal exposure to GDM on childhood BMI trajectories may be due, in part, to small sample sizes and attrition. Indeed, the numbers of females and males exposed to GDM in the study sample were small to begin with, only 73 and 127, respectively.  These numbers were further reduced in analyses stratified by breastfeeding history. The large rates of attrition in the longitudinal cohort of the NLSCY also limit the power to detect significant effects. Indeed, as cycles progressed there was greater attrition. Thus, estimates for the linear and quadratic components of slope of BMI trajectories were based on progressively fewer cases over time.

## 5.3.3    Maternal Characteristics

The current study is limited by the information available in the NLSCY on maternal characteristics.  One of the most important maternal characteristics that was not captured by the survey is maternal pre-pregnancy BMI. Indeed, studies have shown that maternal BMI is a strong predictor of birth weight as well as childhood weight status, with higher pre-pregnancy BMI being associated with higher risk of childhood overweight and obesity.[182] [183] Furthermore, as previously discussed, high pre-pregnancy BMI is associated with higher risk of GDM,[130] and thus most studies examining the association between GDM and child weight status control for maternal BMI.  Although this information was unavailable for the current study, the NLSCY provides the only nationally representative Canadian data currently available to examine childhood BMI

longitudinally. While proxy variables for maternal overweight were used in adjusted analyses, there is nevertheless the possibility that patterns seen in the study results may reflect the impact of maternal BMI, and not prenatal exposure to GDM, on childhood BMI trajectories.

As mentioned previously, GDM is difficult to ascertain in population studies using self-reported diagnosis. The methodological issue with self-reported GDM already discussed is that it may truly reflect previously undiagnosed diabetes mellitus (DM).[151] Although this did not pose a threat to the current study for reasons already discussed, other methodological issues in assessing GDM diagnosis complicate the interpretation of study results. In a review of studies on the prevalence of GDM, Ferrara[151] discusses one prevailing issue with assessing GDM trends in populations which has been that OGTT for GDM that use different criteria for interpretation arrive at different diagnoses. Therefore, self-reported GDM diagnosis may not have captured all cases of GDM in the study population, as there may have been cases in which GDM was undiagnosed due to the use of different diagnostic criteria.

Finally, in terms of the limitations in available maternal data, the NLSCY did not contain information to isolate those who did not have a GDM diagnosis but had DM prior to pregnancy. Therefore, the unexposed group in the study population may have contained individuals born to women with DM. This poses the problem that children born to women with DM are not likely to have the same level of obesity risk as children born to women with normal glucose tolerance. Indeed, many studies either treat offspring of diabetic mothers separately from offspring of nondiabetic mothers and offspring of mothers with GDM[75 78 87 88 93] or exclude this group entirely when examining the effect of prenatal exposure to GDM on child weight status.[81 83 86 92]

## 5.3.4 Breastfeeding and Early Nutrition

Due to the small sample sizes, it was not feasible to divide breastfeeding categories any further than the two categories defined by breastfeeding initiation. However, many studies have shown that, once initiated, the duration and consistency of breastfeeding has important and varied effects on later childhood growth.[46 99 101 105-110] Thus, group defined

in this study as having ever been breastfed is a less homogenous group than those who were never breastfed, which likely lead to the non-significant model results among breastfed children. Also the data did not contain information on early nutrition, and in particular, the timing of introduction of solid foods, which also has important impacts on child weight and weight gain.[111]

## 5.4   Study Strengths

The current study is one of the first to investigate the child obesity problem in Canada by assessing prenatal predictors of BMI trajectories for a large, nationally representative, longitudinal sample of Canadian children using LGCM. Robust population-level data produced through the strong sampling design of the NLSCY were analyzed in this study with an equally strong statistical technique designed to handle longitudinal data.  Despite non-significant findings, this thesis provides a framework for future research on childhood growth trajectories that can be used with improved datasets, variables, and theoretical models. This section details the strengths of the current study in terms of the analytic approach and dataset and discusses the importance of this study as a foundation for future pediatric overweight and obesity research.

### 5.4.1   Analytic Approach

One of the major strengths of this study is the analytic approach to assessing prenatal exposure to GDM as a predictor of child weight. While many studies have examined the relationship between exposure to GDM *in utero* and child weight status measured at a single point in time, the current study examined the impact of this exposure on trajectories of growth.  As discussed previously, the analysis of longitudinal patterns of growth provides greater insight into child health than analyses of weight status alone by revealing timing of developmental events, early growth patterns, and rates of growth.[8 61 64-66] Studies that examine weight status at a single point in childhood or adolescence omit important information on the patterns and rates of growth from infancy that have been shown to be predictive of future health status.  The current study allowed observation of the impact of prenatal exposure to GDM on BMI in infancy, timing of adiposity rebound, and the rate of incline in BMI throughout early childhood.   While each of these

characteristics of early growth has been shown to have important implications for later overweight and obesity, it is the combination of these characteristics that conveys the most meaning when evaluating the risk of obesity and future metabolic disease. Indeed, these observations, considered together as growth patterns, provide the very best insight into child health.

The statistical technique chosen for this thesis is the best method currently available to analyze these complex growth patterns. Indeed, LGCM is an advanced statistical technique that allows repeated observations to be treated not just as multiple related data points to be assessed on the individual and group levels, but as a single continuous phenomenon for each individual. It is for this reason that this was the most appropriate analytic approach to address the research questions in this thesis. As LGCM is based in structural equation modelling (SEM), this permitted designing a causal model that could simultaneously address direct and indirect effects of the exposure of interest on BMI trajectories while also adjusting for other upstream predictors. Indeed, SEM-based causal models take into account the timing of impact of different predictors as well as relationships between them, resulting in a more realistic theoretical framework.

The explicit treatment of missing data in analyses reflects another one of this study's analytical strengths. Indeed, missing data is a persistent issue with panel data due to the inevitability of attrition in longitudinal data collection. The statistical software used to conduct analyses in this study, Mplus,[162] was designed for longitudinal data analysis and offers a number of options for missing data adjustment. As described previously, missing data were adjusted using FIML estimation, which is a method that has been shown to outperform other missing data methods in terms of efficiency and bias.[165] While other methods to deal with missing data in SEM-based analyses involve atheoretical deletion of cases with missing values (e.g. listwise deletion, pairwise deletion), FIML is based in theory and uses all available observed data to adjust for missing values and produce unbiased parameter estimates in MAR data conditions.[165]

## 5.4.2    Dataset

This study used a large dataset that contained population level data that was collected

using a strong, complex sampling design, as described in Section 3.1.2. This sampling design resulted in a nationally representative sample population, and thus the use of this dataset in the current study ensured study results would be relevant and generalizable to the Canadian pediatric population.

### 5.4.3    Groundwork for Future Research

As more studies begin to utilize longitudinal data to assess early-life predictors of childhood overweight and obesity, there will likely be more research conducted with the objective of examining rates and patterns of childhood growth. As more longitudinal childhood health data become available, there will also be more opportunities to conduct this type of analysis. Currently, few studies have used LGCM in the context of pediatric obesity research. However, the growing interest in how patterns of childhood growth predict later weight and health outcomes will necessitate more research using this analytic technique. Since the use of growth curve modelling using latent variables is relatively novel in epidemiological research, studies such as this one will help to lay the groundwork for future childhood obesity research. Indeed, future studies can utilize the framework of the current study to address similar research questions by using new datasets, linking current datasets to hospital records containing more accurate maternal and child health information, and improving on the theoretical model as new variables become available.

## 5.5   Conclusions and Recommendations

This study took an analytic technique for longitudinal data not commonly used in child obesity research to assess important prenatal risk factors for childhood BMI. With the epidemic of childhood obesity and the ever-growing prevalence of obesity-related metabolic disorders among children, the focus of pediatric obesity research has been shifting to causal mechanisms for obesity present earlier and earlier in development. The current study sought to examine prenatal contributions to the development of childhood overweight and obesity by looking at the effects of prenatal exposure to gestational diabetes mellitus on childhood BMI trajectories. Although the study findings did not reach statistical significance, interesting patterns emerged from the estimated models that

may warrant further investigation. Future research in this area must use data that contains complete maternal pre-pregnancy information and a study design that also accounts for postnatal factors in order to arrive at conclusions that have potential clinical and therapeutic value. Nevertheless, this study highlights the fact that early childhood growth is complex and studies that attempt to assess predictors of unhealthy childhood growth should examine child weight outcomes in context of this complexity.

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# Appendices

Appendix A: Summary of previous studies examining the association between maternal impaired glucose tolerance (IGT) and weight status of offspring.

| Author(s) /Year | Study Information | Population Characteristics | Sample Size | Measure of Maternal IGT | Child Weight Outcome/ Measure | Measure of Association | Estimate of Association between Maternal IGT and Child Weight Outcome |
|---|---|---|---|---|---|---|---|
| Boersch-mann et al. [75] /2010 | Germany – Prospective German GDM offspring study (GDM study) and BABYDIAB study (1989-2000) | Children born to mothers with GDM (OGDM), mothers with type I diabetes (OT1D), and nondiabetic mothers (ONDM) followed from <1 to 14 years of age | 1,420 | 75-gram Oral Glucose Tolerance Test (OGTT; from GDM study)/ Type I diabetes status (from BABYDIAB study) | Overweight at age 2, 8, and 11 years (BMI $\geq 90^{th}$ percentile)/ weight and height measured by physicians at clinic visits | Percent increase in obesity prevalence due to GDM exposure | Increase in overweight at age 2, 8, 11 comparing OGDM to OT1D and ONDM: 31.1%, 15.8%, 15.5% (p = 0.05) |
| Buzinaro et al.[76] /2008 | Brazil - Obstetrics Hospital of the Faculty of Medicine of Botucatu (HCFMB) Obstetric Service (1988-1999) | Pregnant women who participated in previous HCFMB studies and their children | 73 | Normal, hyperglyc-emic, or GDM defined by OGTT & daily glycemia (American Diabetes Society & Brazilian Guidelines on Dyslipidemia) | Weight at birth and overweight in adolescence (BMI $\geq 85^{th}$ percentile)/ Neonatal questionnaire and anthropomet-ric measures | Comparison between groups using ANOVA and Goodman test | Birth weight: Higher in offspring of GDM mothers 3667 ± 527 g) than hyperglycemic and control mothers (3282 ± 401 and 3167 ± 565 g) p<0.05

Overweight: More offspring of GDM mothers overweight compared to control (52.2% vs 14.8%) p<0.05 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Catalano et al. [77] /1995 | United States (Vermont) - Longitudinal study of carbohydrate metabolism before and during early and late gestation (1984-1990) | Healthy, non-obese, non-smoking women with *either* normal glucose levels prior to pregnancy and GDM/abnormal glucose tolerance during pregnancy *or* normal throughout | 16 | GDM diagnosis *or* at least one abnormal glucose tolerance test score | Neonatal growth/ birth weight, fat mass | Coefficient of determin-ation ($R^2$) (Maternal insulin sensitivity before/ during pregnancy) | Birth weight and insulin sensitivity <u>during</u> pregnancy: $R^2 = 0.48$*<br><br>Fat mass and insulin sensitivity <u>before</u> pregnancy: $R^2 = 0.46$*<br><br>*Adjusted for significant independent variables |
| Cho et al.[78] /2000 | United States – The Diabetes in Pregnancy Center (Northwestern University) longitudinal study of maternal metabolism (1977-1983) | Offspring of mothers with GDM or pregestational diabetes (PGDM) and offspring of control mothers with no abnormal glucose tolerance during pregnancy | 179 | GDM or PGDM diagnosis | BMI at ages 10 to 16/ measured height and weight | Difference in average BMI score comparing offspring of GDM/PGDM mothers with control mothers | Average BMI* in OGDM/OPGDM: 22.5 ± 5.6 Average BMI* in offspring of control mothers: 20.5 ± 4.0 (p<0.005) *Controlled for age and sex* |
| Crume et al. [15] /2011 | United States (Colorado) – Exploring Perinatal Outcomes in Children (EPOCH) Study (1992-2002) | Singleton children aged 6 to 13 exposed to GDM and random sample not exposed to GDM | 461 | GDM status (positive/ negative) from health insurance company perinatal database | Adiposity, fat distribution/ BMI, waist girth, skinfold thickness, MRI measured by researchers | Average difference (measures) comparing GDM to no GDM | BMI: 1.3 kg/m$^2$ higher (p=0.02) Waist: 4.2 cm larger (p=0.004) Visceral, subcutaneous, and central fat: higher (p=0.01) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dabelea et al. [79] /2000 | United States (Arizona) – Longitudinal study of diabetes and related complications (1965) | Pima Indian families with two or more non-diabetic children; ≥1 child born prior to maternal diabetes diagnosis and ≥1 child born after (same father) | 183 | Diabetes diagnosed with 75-gram OGTT according to WHO (1985) criteria (Medical history) | BMI at age 13/ recorded height and weight | Mean difference in BMI between siblings exposed to diabetes and unexposed | BMI at age 13: 2.6 kg/m$^2$ (95% CI: 0.9-4.3 kg/m$^2$) higher comparing siblings exposed to maternal diabetes to siblings unexposed to it (controlled for sibship) |
| Deierlein et al. [80] /2011 | United States – Pregnancy Infection and Nutrition (PIN) study (2001-2008) | Pregnant women receiving prenatal care from University of North Carolina Hospitals who delivered live, singleton infants | 263 | Blood glucose concentra-tion categories: <100, 100-<130, ≥130 mg/dL | Overweight at age 3 years (BMI≥85$^{th}$ percentile)/ height and weight measured by PIN staff | Risk ratio for overweight comparing offspring of mothers with ≥130 versus <100 mg/dL | 2.34 [95% CI: 1.25-4.38] adjusted for maternal education, race, prenatal smoking, prepregnancy BMI, and maternal height |
| Gillman et al. [81] /2003 | United States – Growing Up Today Study (1996)/Nurses' Health Study II | Children of female registered nurses aged 9-14 years; Important exclusions: Mothers with pre-existing diabetes, children with diabetes | 14,881 | Maternal report of diabetes diagnosed during index pregnancy (GDM) | Overweight at age 9-14 years (BMI > age- and sex-specific 95$^{th}$ percentile)/ child self-reported height, weight | Odds Ratio of overweight comparing GDM to no GDM | 1.4 [95% CI 1.0–1.9] – unadjusted<br><br>1.2 [95% CI 0.8–1.7] – adjusted for birth weight and maternal BMI |

| Gillman et al. [82] /2010 | Australia – Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)/ Children, Youth and Women's Health Service (CYWHS) | Mothers with mild GDM who participated in ACHOIS trial and their singleton children aged 4-5 years who were linked to CYWHS surveillance data | 199 | Random assignment to Routine care versus treatment for mild GDM (through ACHOIS trial) | Macrosomia at birth *and* BMI ≥ age- and sex-specific 85th percentile at age 4-5 years/ recorded height and weight measures by CYWHS | Percent/ BMI Z-score difference between routine and treatment groups | Macrosomia at birth: 21.9% in routine care group (n=105) and 5.3% in treatment group (n=94)  BMI at age 4-5 years: no significant difference between groups | |
|---|---|---|---|---|---|---|---|---|
| Hillier et al. [83] /2007 | United States – Kaiser-Permanente Hawaii (KPH) and Kaiser Permanente Northwest (KPNW) Membership databases | Singleton births at KPH/KPNW between 1995 and 2000; Important exclusions: Mothers with pre-existing diabetes | 9,439 | Most recent GDM screening test result from KPH/KPNW medical records | Overweight at age 5-7 years (weight ≥ 85th and 95th age- and sex-specific percentiles) /measured weight in records | Odds ratio of overweight comparing higher 3 quartiles of glucose challenge test scores to lowest quartile | 1.28 (95% CI 1.02-1.60) comparing highest quartile of GCT score to lowest | |
| Lee et al. [84] /2007 | Korea – Il-Shin Christian General Hospital; Ajou, Seoul National, and Pochon Cha University Hospitals | Women with diagnosed GDM or impaired glucose tolerance (IGT) and their children recruited in the hospital study | 298 | GDM or IGT determined by 50 g glucose challenge test followed by 3h OGTT | BMI from measured height and weight for children aged 3 to 5 years | Comparison of mean BMI between offspring of GDM versus IGT mothers | BMI at age ≥5 years: OGDM: 16.9 kg/m$^2$ (95% CI, 16.2–17.4) OIGT: 15.2 kg/m$^2$ (95% CI, 14.3–16.1) p<0.01 No significant differences between groups at ages 3 and 4 years | |

| Lindsay et al.[85] /2000 | United States – (Arizona) Epidemiological survey of Gila River Indian Community (1955-1994) | Pima and Tohono O'odham Indian women between with Type 2 diabetes (DM), no diabetes (NDM), and prediabetes (PDM) | 2096 | Pre-pregnancy diabetes diagnosis (DM), or diabetes arising within 10 years (PDM) | Birth weight and BMI from 5 to 30 years of age/ hospital records and research examinations | Comparison of birth weight and age- and sex-adjusted BMI between offspring of DM, NDM, and PDM | Birth weight significantly higher in ODM: ODM 3724 ± 52 g, OPDM 3,541 ± 41 g, ONDM 3,408 ± 11 g; p< 0.05 BMI significantly higher comparing ODM to both ONDM and OPDM from age 5 to 19 years |
|---|---|---|---|---|---|---|---|
| Pettit et al.[86] /1985 | United States – (Arizona) Gila River Indian Community of Arizona and Sacaton/Phoenix Indian Health Service hospitals | Pima Indian women with no previous diabetes diagnosis and their offspring with recorded pregnancies between 1965 and 1984 | 1049 | Pregestation-al diabetes (PGDM), normal GT (<140 mg/dL blood glucose), or abnormal GT (≥140 mg/dL blood glucose) | Percent desirable weight at age 5-19 years/ child weight divided by the 50th percentile sex- and age-specific weight for height | Comparison of percent desirable weight between offspring of mothers in three blood glucose groups | Significantly higher percent desirable weight at ages 5-9 and 10-14 years comparing offspring of mothers with abnormal GT or PGDM to offspring of mothers with normal GT, controlling for maternal obesity |
| Plage-mann et al.[41] /1997 | Germany (Berlin) – Department of Neonatology of the Clinic of Obstetrics and Gynaecology in Berlin-Kaulsdorf | Children born between 1980 and 1990 to diabetic mothers with available developmental data | 317 | Insulin dependent diabetes mellitus (IDM) and GDM | Birth weight and size and BMI at age 1 to 9 years/ recorded data, measures taken during study | Percent SGA, AGA, LGA, overweight, and obese | No significant differences between IDM and GDM groups, but both groups showed high frequency of high birth weight and LGA in infancy and overweight, and obesity in childhood |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Silver-man et al. [87] /1993 | United States (Illinois) – Prospective longitudinal study using Diabetes in Pregnancy Center (1977-1983) | Pregnant women with GDM, pregestational diabetes (PGDM), or no diabetes and their offspring | 242 | GDM or pregestation-al diabetes (PGDM) diagnosis | Birth weight *and* BMI from age 3 months to 8 years/ measures taken during study | Comparison of BMI growth curves to national standards | Offspring of GDM/PGDM women higher BMI from age 6 to 9 compared to national standards with average BMI at 90th percentile of general population |
| Silver-man et al. [88] /1998 | United States (Illinois) – Prospective longitudinal study Diabetes in Pregnancy Center (1977-1983) | Pregnant women with GDM, pregestational diabetes (PGDM), or non-diabetic and their offspring | ? | GDM or PGDM diagnosis and amniotic fluid insulin (AFI) concentra-tion | BMI from infancy to age 17 years/ Yearly height/weight measures | Mean BMI at age 14-17 in children of GDM/PGDM versus control women | Mean BMI at age 14-17 years in children of GDM/PGDM women: 24.6 ± 5.8 kg/m$^2$ (versus control at 20.9 ± 3.4 kg/m$^2$; p<0.001) |
| Tallarigo et al.[89] /1986 | Italy – National Research Council Clinical Physiology Institute, Obstetrical clinic (1981-1983) | Pregnant women tested at the obstetrical clinic and given an oral glucose tolerance test (OGTT) | 249 | Three levels of maternal plasma glucose at third trimester: <100 mg/dl, 100-119 mg/dl, and 120-164 mg/dl | Macrosomia at birth | Test for linear trend between maternal plasma glucose level and frequency of macrosomia | Percent macrosomia: <100 mg/dl: 9.9%, 100-119 mg/dl: 15.5%, 120-164 mg/dl: 27.5%   p<0.01 |

| Tam et al. [90] /2010 | China (Hong Kong) – 15-year follow-up study of cardio-metabolic risks in adolescents (originally recruited in 1992-1994) | Adolescents aged 15 years who were part of an cohort of children born to women with GDM and age-matched controls who were examined at 8 years of age in a previous study | 129 | In utero hyperinsulin-emia measured by C-peptide *and* insulin levels in umbilical cord blood | Overweight (age- and sex-specific BMI ≥90th percentile)/ Height and weight at age 15 measured during study | Odds Ratio of overweight at age 15 comparing those exposed/un-exposed to hyperinsulin-emia *in utero* (measured two ways) | *In utero* hyperinsulinemia measured by Cord blood insulin level: 7.66 (95% CI 1.32-44.5) Cord blood C-peptide level: 10.8 (95% CI 1.69-69.2) [*both adjusting for birth weight, maternal BMI, maternal GDM status and Tanner stage*] | |
|---|---|---|---|---|---|---|---|---|
| Villa-Caballero et al. [176] /2009 | United States (California) - Randomized community intervention for healthy eating and physical activity | Children in grades K to 2 and their mothers recruited for healthy eating/physical activity study (predominantly Latino) | 725 | Maternal report of diabetes diagnosis and GDM during index pregnancy | Child BMI and overweight status (age- and sex-specific BMI and CDC BMI cut-offs)/ Measured weight and height collected in original study | Odds Ratio of normal weight comparing children whose mothers had GDM to children whose mothers did not have GDM | Children of mothers with GDM had OR of 0.32 of being normal weight, adjusted for age, education, employment status, and marital status (p<0.05) | |

| Vohr et al.[91] /1997 | United States (Rhode Island) - Prospective study, Women and Infants' Hospital (1991-1993) | Mothers diagnosed with GDM or not (control) during index pregnancy and their LGA and AGA infants seen at birth then at age 1 year | 192 | GDM diagnosed with criteria: 1-h 50-gram glucose test ≥130mg/dl, then two abnormal 100-gram OGTT | Weight at age 1 year/ weight measures based on gestational age and sex, anthropometr-ic measures | Multiple regression for independent effect | LGA infants of GDM mothers compared to all other infants: BMI, waist girth, abdominal skin folds at age 1 higher than all other groups (p<0.001) |
|---|---|---|---|---|---|---|---|
| Wright et al.[92] /2009 | United States (Massachusetts) – Project Viva, prospective prebirth cohort study (recruited 1999-2002) Note: Only women with GDM received counselling to manage blood sugar | Pregnant women (singleton pregnancy) and their children Exclusions: history of previous Type I or II DM or polycystic ovary syndrome with IGT | 1238 | GDM, IGT, or normal glucose tolerance based on fasting and non-fasting OGTT results | Adiposity at age 3/ age- and sex-specific BMI, subscapular and triceps skinfold thickness | Multivariable linear regression of child BMI and skinfolds on maternal glucose tolerance during pregnancy | Adiposity assessed by BMI: no statistically significant impact of maternal glucose tolerance

Adiposity assessed by skinfolds: Children of GDM mothers had skinfolds 1.31mm thicker than other groups (95% CI: 0.08-2.55; p<0.04) |
| Wroblew ska-Seniuk et al.[93] /2009 | Poland (Poznan) – Clinical Hospital of Obstetrics and Gynecology medical records | Children born at the Clinical Hospital of Obstetrics and Gynecology with mothers who had PGDM, GDM, or normal glucose tolerance during pregnancy | 185 | PGDM, GDM, or normal glucose tolerance during pregnancy from hospital records | Obesity and/or overweight in childhood (3-9 years)/ age- and sex-specific BMI z-score measured continuously | Differences in BMI z-scores between groups | BMI z-scores higher in children born to mothers with GDM (0.81 ± 1.01) than to mothers with PGDM (-0.04 ± 1.42) and control mothers (0.07 ± 1.28) |

# Appendix B: Description of Latent Growth Curve Analysis.

## Latent Growth Curve Modelling: Explanation and Theory

From a theoretical perspective, latent growth curve modelling (LGCM) is an analytic tool used to test hypotheses about unobserved phenomena that are manifest in observed measures. As previously mentioned, LGCM is most effective for the analysis of repeated measures from multiwave panel data.[160] The underlying or "latent" phenomenon is theorized to have a similar shape to the curves produced by the repeated measures. [160] However, the observed trajectories are limited by the number of recorded observations and thus only provide snapshots of the underlying continuous latent trajectories. [160]

## Unconditional Models

The first figure below depicts the LGCM used in the current study minus any explanatory variables and is therefore the unconditional version of the model (Figure B1). The boxes, $y_1$ through $y_5$, represent the observed scores at each data collection point. In the current study, these boxes reflect BMI at ages 2, 4, 6, 8, and 10 years. The circles represent the growth factors of the latent trajectory and indicate the intercept ($\alpha$) and the linear slope ($\beta_1$) and quadratic slope ($\beta_2$) components of the latent trajectory. The intercept and slope growth factors are continuous latent variables that serve as the parameters of the latent group-level (average) trajectory to be estimated. In the current study, there was an a priori expectation that trajectories would have a quadratic shape since BMI typically declines after the age of 2 years before beginning a steady incline throughout childhood.[64] Thus, two latent variables describe slope in the current model, whereas a linear model would only have a single latent variable for slope.

In the unconditional model, the observed repeated measures ($y_1$ through $y_5$) are related to the continuous latent variables through the following trajectory equation:

$$y_{it} = \alpha_i + \lambda_t \beta_{1i} + \lambda_t^2 \beta_{2i} + \epsilon_{it} \tag{1}$$

where $y_{it}$ represents the value of the observed measure for the $i$th individual at time $t$, $\lambda_t$ is a constant fixed to values 0, 1, 2, 3, and 4 for the linear component of the slope of the

trajectory, and $\lambda_t^2$ are simply these values squared for the quadratic component of slope. The symbol $\epsilon it$ indicates the random error for each individual observed measure ($i$) at each time point ($t$).

The intercept $\alpha_i$ is a constant for each individual and thus has a fixed effect on each of the measures $y_{it}$, indicated by fixed factor "loadings" of 1.0 from the latent variable $\alpha$ to each of the observed measures $y_1$ to $y_5$ (Figure B1). The individually-varying linear and quadratic growth factors $\beta_{1i}$ and $\beta_{2i}$ also have fixed factor loadings, $\lambda_t$ and $\lambda_t^2$ respectively, since the model imposes a quadratic shape on the data (Figure B1). The three random latent variables $\alpha_i$, $\beta_{1i}$, and $\beta_{2i}$, can be further described by the following three expressions:

$$\alpha_i = \mu_\alpha + \zeta_{\alpha i} \tag{1.1}$$

$$\beta_{1i} = \mu_{\beta_1} + \zeta_{\beta_1 i} \tag{1.2}$$

$$\beta_{2i} = \mu_{\beta_2} + \zeta_{\beta_2 i} \tag{1.3}$$

where $\mu_\alpha$, $\mu_{\beta 1}$, and $\mu_{\beta 2}$ are means of all individual intercept and slope variables and $\zeta_{\alpha i}$, $\zeta_{\beta 1 i}$, and $\zeta_{\beta 2 i}$ are the individual disturbances or deviations from those means. It is these deviations that form the central focus of the analysis and upon which hypotheses are made.
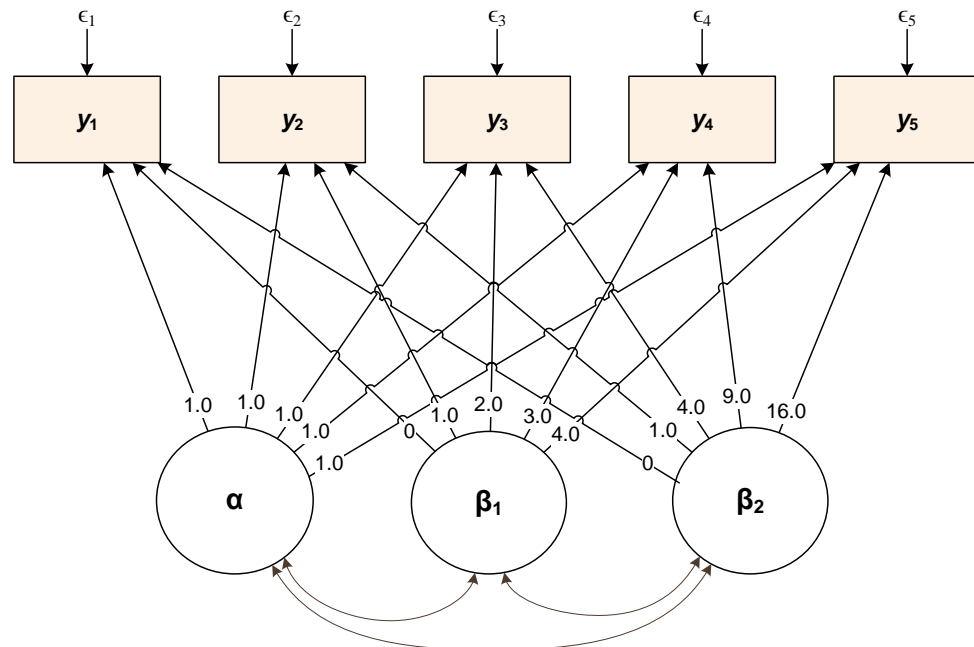


**Figure B1.** Unconditional quadratic latent growth curve model.

The majority of the assumptions of the unconditional LGCM also hold true for the conditional model. The first is that the mean of the random errors for all individuals and time points, or $E(\epsilon_{it})$, is equal to zero. Next, it is assumed that all the intercept and slope latent variables, $\alpha_i$, $\beta_{1i}$, and $\beta_{2i}$, are uncorrelated with the random error $\epsilon_{it}$ for all individuals. That is, these variables are assumed not to reflect the disturbance caused by random error. It is further assumed that errors within an individual are uncorrelated over time and that errors between individuals are also uncorrelated.
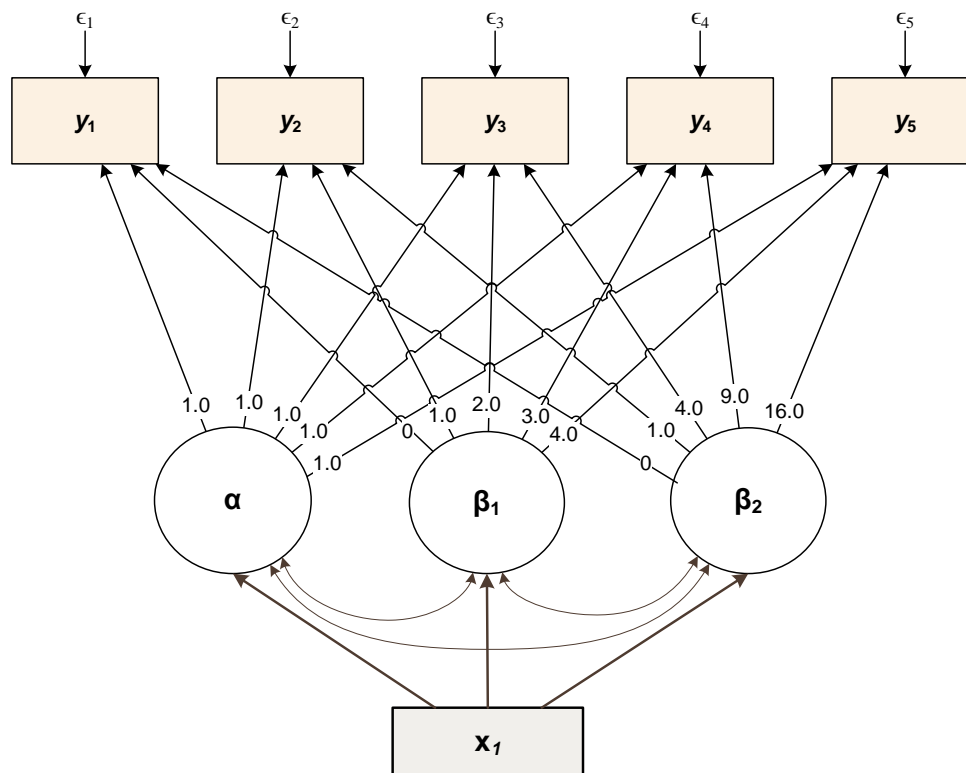
## Conditional Models

In Figure B2 a time-invariant explanatory variable, or covariate, $x_1$ has been added to the original model turning the unconditional LGCM into a conditional LGCM. The covariate is time-invariant since it is a variable whose effect on the latent trajectory does not vary with time. In the current study, the main time-invariant predictor of interest was prenatal exposure to GDM, however a more complex conditional model was also used to control for the effects of other time-invariant covariates described in Section 2.1.2 (Figure 2.2). In a conditional LGCM, added covariates predict the continuous latent trajectory variables and thus have a direct impact on the variables $\alpha_i$, $\beta_{1i}$, and $\beta_{2i}$ and an indirect impact on the observed variables $y_1$ to $y_5$ (Figure B2). Therefore, the trajectory equation (1) remains the same for the conditional model, but the expressions (1.2, 1.3, and 1.4) for the latent variables $\alpha_i$, $\beta_{1i}$, and $\beta_{2i}$ change as follows (for a simple conditional LGCM with covariate $x_1$):

$$\alpha_i = \mu_\alpha + \boldsymbol{\gamma_{\alpha_1}}\boldsymbol{x_{1_i}} + \zeta_{\alpha i} \tag{1.4}$$

$$\beta_{1i} = \mu_{\beta_1} + \boldsymbol{\gamma_{\beta_1}}\boldsymbol{x_{1_i}} + \zeta_{\beta_1 i} \tag{1.5}$$

$$\beta_{2i} = \mu_{\beta_2} + \boldsymbol{\gamma_{\beta_2}}\boldsymbol{x_{1_i}} + \zeta_{\beta_2 i} \tag{1.6}$$

where $x_{1i}$ is the value of the covariate for each individual and $\gamma_{\alpha 1}$, $\gamma_{\beta 1}$, and $\gamma_{\beta 2}$ are the coefficients for the covariate in each of the intercept and slope equations. The values of these coefficients are the primary outputs of interest from the conditional latent growth curve analysis.

**Figure B2.** Conditional quadratic latent growth curve model

## Advantages of Latent Growth Curve Modelling

Latent growth curve modelling has a number of advantages. First, unlike other techniques for longitudinal data analysis, it does not make the assumption that there is no measurement error.[160] Indeed, as pictured in Figures B1 and B2, latent growth curve analysis incorporates time-specific measurement error into the model ($\epsilon_n$). Second, it provides group-level and individual-level information by producing estimates of the mean (group-level) and variance (individual variation) for all parameter estimates. Latent growth curve analysis also allows variances of the latent intercept ($\alpha_i$) and slope ($\beta_1$ and $\beta_2$) variables to be correlated, that is, it allows for covariance. This provides a more realistic representation of a longitudinal outcome, since initial levels are likely to correlate with the rate of change over time of the outcome.

# Appendix C: Additional Model Results.

**Table C1.** Model results for the effects of all other covariates in the conditional LGCM by gender.

| | Females (N= 1555) | | | Males (N=1619) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| Regression Weights | | | | | | |
| $\alpha$ (intercept) ON $x_{mat\_age_i}$ | -0.075 (0.025) | -3.038 | 0.002 | -0.031 (0.020) | -1.527 | 0.127 |
| $\alpha$ (intercept) ON $x_{parity_i}$ | 0.872 (0.238) | 3.658 | 0.000 | 0.236 (0.208) | 1.136 | 0.256 |
| $\alpha$ (intercept) ON $x_{smoke_i}$ | 0.693 (0.272) | 2.554 | 0.011 | 0.338 (0.268) | 1.262 | 0.207 |
| $\alpha$ (intercept) ON $x_{income_i}$ | 0.211(0.125) | 1.692 | 0.091 | -0.005 (0.123) | -0.041 | 0.967 |
| $\alpha$ (intercept) ON $x_{education_i}$ | -0.029 (0.038) | -0.775 | 0.438 | -0.019 (0.034) | -0.553 | 0.581 |
| | | | | | | |
| $\beta_1$ (linear slope) ON $x_{mat\_age_i}$ | 0.017 (0.015) | 1.120 | 0.263 | 0.013 (0.014) | 0.933 | 0.351 |
| $\beta_1$ (linear slope) ON $x_{parity_i}$ | -0.133 (0.164) | -0.816 | 0.415 | 0.005 (0.128) | 0.043 | 0.966 |
| $\beta_1$ (linear slope) ON $x_{smoke_i}$ | -0.170 (0.168) | -1.011 | 0.312 | 0.079 (0.161) | 0.490 | 0.624 |
| $\beta_1$ (linear slope) ON $x_{income_i}$ | -0.144 (0.105) | -1.366 | 0.172 | -0.050 (0.073) | -0.680 | 0.496 |
| $\beta_1$ (linear slope) ON $x_{education_i}$ | -0.022 (0.026) | -0.836 | 0.403 | 0.004 (0.024) | 0.165 | 0.869 |
| | | | | | | |
| $\beta_2$ (quadratic slope) ON $x_{mat\_age_i}$ | -0.001 (0.002) | -0.545 | 0.586 | -0.002 (0.002) | -1.010 | 0.313 |
| $\beta_2$ (quadratic slope) ON $x_{parity_i}$ | 0.011 (0.021) | 0.554 | 0.580 | 0.002 (0.016) | 0.104 | 0.917 |
| $\beta_2$ (quadratic slope) ON $x_{smoke_i}$ | 0.028 (0.021) | 1.341 | 0.180 | -0.015 (0.021) | -0.708 | 0.479 |
| $\beta_2$ (quadratic slope) ON $x_{income_i}$ | 0.013 (0.014) | 0.886 | 0.376 | -0.002 (0.009) | -0.247 | 0.805 |
| $\beta_2$ (quadratic slope) ON $x_{education_i}$ | 0.002 (0.003) | 0.517 | 0.605 | -0.002 (0.003) | -0.582 | 0.560 |

**Table C2.** Model results for the effects of all other covariates in the conditional LGCM by breastfeeding for females.

| | Never Breastfed (N= 390) | | | Breastfed (N=1152) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| Regression Weights | | | | | | |
| $\alpha$ (intercept) ON $x_{mat\_age_i}$ | -0.126 (0.048) | -2.631 | 0.009 | -0.061 (0.028) | -2.185 | 0.029 |
| $\alpha$ (intercept) ON $x_{parity_i}$ | 1.335 (0.463) | 2.884 | 0.004 | 0.789 (0.275) | 2.864 | 0.004 |
| $\alpha$ (intercept) ON $x_{smoke_i}$ | 1.128 (0.338) | 0.768 | 0.443 | 0.445 (0.298) | 1.495 | 0.135 |
| $\alpha$ (intercept) ON $x_{income_i}$ | 0.075 (0.271) | 0.277 | 0.782 | 0.189 (0.142) | 1.329 | 0.184 |
| $\alpha$ (intercept) ON $x_{education_i}$ | 0.078 (0.095) | 0.826 | 0.409 | -0.044 (0.043) | -1.020 | 0.308 |
| | | | | | | |
| $\beta_1$ (linear slope) ON $x_{mat\_age_i}$ | 0.066 (0.028) | 2.391 | 0.017 | 0.003 (0.018) | 0.165 | 0.869 |
| $\beta_1$ (linear slope) ON $x_{parity_i}$ | -0.548 (0.271) | -2.020 | 0.043 | -0.016 (0.197) | -0.083 | 0.933 |
| $\beta_1$ (linear slope) ON $x_{smoke_i}$ | -0.247 (0.266) | -0.926 | 0.354 | -0.084 (0.197) | -0.425 | 0.671 |
| $\beta_1$ (linear slope) ON $x_{income_i}$ | -0.220 (0.163) | -1.346 | 0.178 | -0.114 (0.125) | -0.917 | 0.359 |
| $\beta_1$ (linear slope) ON $x_{education_i}$ | 0.014 (0.045) | 0.299 | 0.765 | -0.038 (0.032) | -1.187 | 0.235 |
| | | | | | | |
| $\beta_2$ (quadratic slope) ON $x_{mat\_age_i}$ | -0.006 (0.003) | -1.843 | 0.065 | 0.000 (0.002) | 0.068 | 0.946 |
| $\beta_2$ (quadratic slope) ON $x_{parity_i}$ | 0.052 (0.030) | 1.731 | 0.083 | -0.002 (0.025) | -0.065 | 0.948 |
| $\beta_2$ (quadratic slope) ON $x_{smoke_i}$ | 0.035 (0.030) | 1.181 | 0.238 | 0.017 (0.025) | 0.698 | 0.485 |
| $\beta_2$ (quadratic slope) ON $x_{income_i}$ | 0.023 (0.018) | 1.336 | 0.182 | 0.009 (0.017) | 0.532 | 0.595 |
| $\beta_2$ (quadratic slope) ON $x_{education_i}$ | -0.004 (0.005) | -0.705 | 0.481 | 0.005 (0.004) | 1.132 | 0.258 |

**Table C3.** Model results for the effects of all other covariates in the conditional LGCM by breastfeeding for males.

| | Never Breastfed (N= 428) | | | Breastfed (N=1169) | | |
|---|---|---|---|---|---|---|
| | Est. (S.E.) | Est./S.E. | p-value | Est. (S.E.) | Est./S.E. | p-value |
| Regression Weights | | | | | | |
| $\alpha$ (intercept) ON $x_{mat\_age_i}$ | 0.023 (0.035) | 0.664 | 0.507 | -0.056 (0.024) | -2.368 | 0.018 |
| $\alpha$ (intercept) ON $x_{parity_i}$ | -0.245 (0.352) | -0.697 | 0.486 | 0.451 (0.239) | 1.885 | 0.059 |
| $\alpha$ (intercept) ON $x_{smoke_i}$ | 0.287 (0.389) | 0.737 | 0.461 | 0.328 (0.349) | 0.941 | 0.347 |
| $\alpha$ (intercept) ON $x_{income_i}$ | -0.420 (0.194) | -2.161 | 0.031 | 0.099 (0.145) | 0.681 | 0.496 |
| $\alpha$ (intercept) ON $x_{education_i}$ | 0.082 (0.067) | 1.228 | 0.220 | -0.030 (0.041) | -0.719 | 0.472 |
| | | | | | | |
| $\beta_1$ (linear slope) ON $x_{mat\_age_i}$ | -0.023 (0.028) | -0.827 | 0.408 | 0.029 (0.016) | 1.838 | 0.066 |
| $\beta_1$ (linear slope) ON $x_{parity_i}$ | 0.348 (0.256) | 1.356 | 0.175 | -0.139 (0.143) | -0.976 | 0.329 |
| $\beta_1$ (linear slope) ON $x_{smoke_i}$ | -0.201 (0.277) | -0.727 | 0.467 | 0.163 (0.182) | 0.897 | 0.370 |
| $\beta_1$ (linear slope) ON $x_{income_i}$ | 0.196 (0.143) | 1.369 | 0.171 | -0.108 (0.081) | -1.328 | 0.184 |
| $\beta_1$ (linear slope) ON $x_{education_i}$ | -0.025 (0.047) | -0.526 | 0.599 | 0.013 (0.029) | 0.441 | 0.659 |
| | | | | | | |
| $\beta_2$ (quadratic slope) ON $x_{mat\_age_i}$ | 0.004 (0.004) | 1.113 | 0.266 | -0.004 (0.002) | -1.976 | 0.048 |
| $\beta_2$ (quadratic slope) ON $x_{parity_i}$ | -0.037 (0.034) | -1.084 | 0.278 | 0.020 (0.017) | 1.194 | 0.232 |
| $\beta_2$ (quadratic slope) ON $x_{smoke_i}$ | 0.012 (0.036) | 0.333 | 0.739 | -0.017 (0.022) | -0.748 | 0.454 |
| $\beta_2$ (quadratic slope) ON $x_{income_i}$ | -0.027 (0.018) | -1.515 | 0.130 | 0.004 (0.010) | 0.427 | 0.670 |
| $\beta_2$ (quadratic slope) ON $x_{education_i}$ | 0.000 (0.006) | 0.075 | 0.941 | -0.003 (0.003) | -0.765 | 0.444 |

# Curriculum Vitae

| | |
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