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Infants born large for gestational age and developmental attainment in early childhood

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Abstract

Birth weight is a strong predictor of neonatal health outcomes. The majority of literature has focused on those infants born SGA. Infants born LGA have been shown to be at higher risk of immediate obstetrical complications and metabolic deficits, yet less research has focused on subsequent development. This study aims to investigate whether LGA is associated with developmental attainment and to examine the attribution of upstream factors and variables along the causal pathway. Data from the NLSCY was used. LGA was defined as a BW >90th percentile. Outcomes were poor verbal ability (scoring <15th percentile on the PPVT-R) and externalizing behaviour problems (scoring >90th percentile on any externalizing behavioural scale). A DAG guided analyses. Multivariable logistic regression was used, mediation and interaction was assessed and all analyses were stratified by sex. LGA was not associated with developmental attainment for males or females. There was no evidence supporting mediation or an interaction.

Keywords

Large for gestational age, developmental attainment, verbal ability, externalizing behaviour problem, directed acyclic graph

Abbreviations

SGA=small for gestational age, LGA=large for gestational age, NLSCY=National Longitudinal Study of Children and Youth, PPVT-R=Peabody Picture Vocabulary Test-Revised, DAG=directed acyclic graph

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List of Abbreviations

AGA	Appropriate for Gestational Age
aOR/OR	Adjusted Odds Ratio or Odds Ratio
ASD	Autism Spectrum Disorder
BMI	Body Mass Index
BW	Birth Weight
CAI	Computer Assisted Interview
CDC	Center for Disease Control and Prevention
DAG	Directed Acyclic Graph
DD	Developmental Disabilities
ECD	Early Childhood Development
GWG	Gestational Weight Gain
HBA_{1C}	Glycated Hemoglobin
HBW	High Birth Weight
HR/HRR	Hazard Ratio or Hazard Rate Ratio
IADPSG	International Association of Diabetes and Pregnancy Study Groups
IQ	Intelligence Quotient
LFS	Labor Force Survey
LGA	Large for Gestational Age
MS	Metabolic Syndrome

NLSCY	National Longitudinal Survey of Children and Youth
NS	Not significant
PMK	Person Most Knowledgeable
PPVT-R	Peabody Picture Vocabulary Test (Revised)
RDC	Research Data Center
RRR	Relative Risk Ratio
SES	Socioeconomic Status
SD	Standard Deviation
SDS	Standard Deviation Scores
SGA	Small for Gestational Age
WHO	World Health Organization
WISC	Weschler Intelligence Scale for Children

Chapter 1 – Introduction and Research Objectives

1.1 Introduction

Infant birth weight (BW), a marker of prenatal conditions, is a strong predictor of neonatal health outcomes. [1] The majority of literature has focused on infants born small for gestational age (SGA), however, it has been noted that there is a reverse J-shaped curve when examining BW and risk of adverse outcomes. This is supported by animal studies, which have shown aberrant functioning in processes associated with cognition and behaviour among rodents born large for gestational age (LGA). [2-3] While infants born LGA have been shown to have a higher risk of immediate obstetrical complications (shoulder dystocia, birth trauma and instrumental delivery) [4] and metabolic deficits (diabetes mellitus and adult obesity), less research has focused on subsequent development. [5-7] Of these studies, few have considered essential third variables or adjusted for gestational age within analysis, and most have focused on late childhood or early adolescence, ignoring a significant period of development. [8]

Development involves a series of intricate processes that begins in the early prenatal stage and, typically, results in the normal progression of the child across a variety of dimensions, including physical, mental, social and behavioural. [9-10] Developmental problems in children can range from minimal intellectual or behavioural disabilities to severe impairment, and may have lasting consequences. For example, externalizing behaviour and cognitive/verbal ability in early childhood have consistently been shown to predict future academic performance and achievement. [11-14]

It is estimated that at least one in every ten children suffers from a learning disability or cognitive delay, also proposing that this is likely an under-representation of the true value. [15] Furthermore, it has been reported that approximately 25% of Canadian children arrive at kindergarten not having met the age-appropriate developmental expectancies, while another Canadian study reported that 6.6%, 14.2% and 14.7% of children aged 2-5 demonstrated a high level of symptoms of hyperactivity/inattention, physical aggression/conduct disorder and emotional/anxiety problems, respectively. [16] Given that poor development in early childhood can have a lasting impact on future achievement, the high prevalence of these conditions is of concern.

Many risk factors have been suggested to associate with child development including social, biological, or environmental factors, however the root causes and underlying interactions are still in discussion. [17-18] The more commonly accepted risk factors are the presence of maternal depression, [17, 19-20] low maternal education, [17, 21] low socioeconomic status, and lack of parental interaction or stimulation with the child. [22-23] It has also been suggested that a sub-optimal uterine environment can have both short and long-term effects on a fetus, especially during sensitive periods of development. [9, 21]

The goal of this study is to investigate whether there is an association between infants born LGA and developmental attainment in early childhood. Moreover, the study seeks to examine potential mechanisms to further comprehend this relationship, focusing on two areas of interest. Throughout this thesis, attention will be paid to maternal diabetes and child's body mass index (BMI). Maternal diabetes is a common cause of LGA [24], and has been shown to influence behaviour and cognitive development in children. [25-26] Moreover, infants born LGA are at an increased risk for childhood obesity, [27] which has been associated with lower cognitive control [28-30] and more emotional or behavioural problems. [31-33] While the literature is vast, this thesis attempts to explore an area where an important influence may be present.

Evidence suggests that interventional strategies targeted to children with developmental problems are able to improve symptoms and aid in appropriate development, as well as improve parent-child interactions and feelings of support. [34, 35-36] Thus, understanding the impact factors on development, especially in areas that have consistently shown to predict later achievement, is of utmost importance.

1.2 Research Objectives

The goal of this study is to examine the potential association between being born large for gestational age and subsequent developmental attainment in early childhood.

The study will address two principal research questions:

1. Is there an association between being LGA at birth and developmental attainment in early childhood? In this study, developmental attainment will be operationalized using two indicators: verbal ability, measured by the Revised Peabody Picture Vocabulary Test (PPVT-R) and presence of externalizing behaviour problems, evaluated at ages 4-5. Behavioural assessments will be treated as a composite measure of externalizing behaviours, including conduct disorder/physical aggression, indirect aggression and hyperactivity/inattention.

2. To what extent are pre-natal and post-natal factors responsible for the association between being LGA at birth and developmental attainment in early childhood?
    a. Are observed associations attributed to upstream variables such as maternal diabetes, either gestational or pre-gestational?
    b. Are observed associations mediated through variables along the causal pathway such as the child's body mass index?

It is hypothesized that there will be an association between those born LGA and developmental attainment in verbal ability and externalizing behaviour, however, it is postulated that these associations will be mostly attributable to pre and post-natal factors.

Chapter 2 – Literature Review

2.1 Literature Review Search Strategy

A systematic search for the main hypothesized association (LGA to development) was conducted July 2015 searching for both published and grey literature using PubMed, EMBASE, PsycINFO, CINAHL, Cochrane Library, Web of Science, Dissertations and Theses database and with a final web search using Google Scholar advanced search. Additional searches using only the EMBASE search engine were carried out investigating the proposed mechanisms (maternal diabetes and child BMI). Bibliographies of all included studies were also searched for additional articles. The full strategy for each database and search can be seen in tables A1 and A2 of Appendix A.

The search strategy was challenging as LGA is a newer term, and is often used synonymously with other obstetrical terms such as macrosomia, although they do not describe the same occurrence. Due to this, both terms were included in the search, and compared within the following discussion. Moreover, since this body of literature is still evolving, many different facets of development were included in the search, and reviewed. Searches were restricted to those published in either English or French, and from the years 2000 to 2015. Duplicates were removed, and titles for the remaining articles were reviewed for relevance, followed by abstract and then ultimately full text.

Results from this review are as follows: LGA and development (n=18), macrosomia and development (n=13), maternal diabetes/obesity and LGA (n=37), maternal diabetes/obesity and child development (n=14), LGA and child's BMI (n=7), and child BMI and development (n=9).

2.2 Introduction and biology of LGA/macrosomia

LGA is defined as a birth weight greater than the 90th percentile for gestational age and sex, based on a reference population. In 2008, the rate of LGA in Canada was reported as 11.1 per 100 singleton live births, [37] although this is thought to likely be increasing due to the rising obesity rates. [38] Macrosomia, occasionally referred to as high birth weight (HBW), is generally defined as a birth weight greater than 4000 grams, and sometimes as greater than 4500 grams.

While the exact cause of LGA or macrosomia is not always known, in many instances, excessive fetal growth is thought to be due to congenital anomalies, maternal metabolic conditions (diabetes, obesity) or other factors. There are several anomalies that have been associated with high birth weight, including Carpenter Syndrome, Weaver Syndrome and Beckwith-Wiedemann Syndrome. Other factors, such as post-term pregnancy (>42 weeks gestation), male fetus, or prior history of larger babies have also been found to influence the size of a fetus. Also, parental stature (taller or heavier parents) may genetically predispose an infant to be constitutionally large, yet biologically normal. However, maternal obesity, extreme gestational weight gain (GWG) and maternal diabetes are most commonly associated with excessive fetal growth. One mechanism was proposed in the 1920s by Jorgen Pedersen, who suggested that high transfer of glucose from diabetic mothers to the fetus induced fetal hyperglycemia. This, in turn, caused hypertrophy of the fetal islet tissue of the pancreas, causing overproduction of insulin, fetal hyperinsulinemia, and finally excessive fetal growth. [39] This proposition has been extended to maternal obesity and excessive GWG, hypothesizing that these mothers may experience an inflammatory response and placental dysfunction, increasing insulin resistance in the fetus, and resulting in an abnormal glucose-insulin relation. [40-41]

2.3 Associations of LGA and/or macrosomia with developmental outcomes

Research investigating the association of LGA and/or macrosomia with developmental outcomes in early childhood has examined many areas, which have been categorized to behavioural outcomes, cognitive outcomes, psychological outcomes and autism spectrum disorder (ASD).

2.3.1 LGA/macrosomia and behavioural outcomes

LGA

Studies examining behavioural outcomes among those born LGA have provided compelling support. Firstly, a prospective population based cohort study from Brisbane (n=4971), examined size for gestational age and behavioural outcomes including internalizing behaviour problems (withdrawn, anxious and depressed symptoms), externalizing behaviour problems (delinquency and aggressive symptoms) and social disorders. The authors reported a positive association with LGA infants (reported as birth weight z-scores in the top quintile) being at a higher risk for social disorder symptoms (aOR: 1.57 [1.12-2.20]. A moderate increased risk was also seen for anxious and depressive symptoms; however, it was not significant. Intriguingly, adjustment for maternal anxiety and depression during pregnancy did not markedly change the relationship. This study had a significant loss to follow-up, but multiple imputation was used to assess the impact, and the authors found similar results. [42] A Korean study echoed these findings. They found that child externalizing and internalizing behaviour, as assessed by the Korean Child Behaviour Checklist, differed depending on the birth outcome, concluding that the overall score increased by up to 3.023 points (p=0.02), for each increasing level of size for gestational age. [43] The latter study had a small sample size (n=320), while both used self-reported outcome measures.

Some studies have hypothesized that maternal obesity plays a role within this association. Van Mil et al used a large population cohort (n=6015) and found that increasing birth weight standard deviation scores (SDS) was associated with less attention problems, but only up to approximately 3600 grams, in which there was no further reduction in risk. However, if the child had an obese mother, there was an evident increase in attention problems among those children with a higher BW SDS, (p-interaction=0.007). [44]

Macrosomia

There has been substantially less examination on the association between macrosomia and behavioural outcomes, although some support is still provided. Buschgens and colleagues attempted to not only examine associations between obstetrical factors and risk of externalizing behaviour problems, but to also tease out where the true hazard lies (i.e. through familial risk, environmental factors or perinatal factors). Examining a sample of Dutch pre-adolescents (n=2230), this study found that macrosomia (defined in this study as a BW >4500 grams) was a predictor for one parent-reported (aggression), and all teacher-reported behavioural problems. Authors proposed that these findings might be attributed to either adverse perinatal events or subsequent child obesity due to being born macrosomic. Main effects were also found for familial risk (as measured by parental substance abuse/dependency and parental anti-social behaviour), maternal prenatal smoking and pregnancy or labor complications. [45]

Summary

Studies examining associations between macrosomia or LGA and behavioural outcomes tended to use different definitions of the exposure, and a range of hypotheses were proposed to explain the pathway. Nonetheless, there appears to be an observable relation among LGA or macrosomic infants and behavioural deficits.

2.3.2 LGA/macrosomia and cognitive outcomes

LGA

The impact of infants born LGA on future cognitive functioning in early childhood is mixed. Examining a very specific population, Brand et al included only babies born LGA, comparing those with and without hypoglycemia. No significant differences were found using a developmental and intelligence scale, except on the reasoning subscale (mean difference: 9.3 [1.3, 17.2]). This study had a relatively small sample (n=75) and potential selection bias (only 64% of the original population was followed completely), although it was the first to examine this specific group, and authors performed analyses using multiple definitions of hypoglycemia to support their conclusions. [46] A large sample of Norwegian men (n=317 761) who had been drafted in the military was assessed using a standardized intelligence test that has been shown to correlate with the Wechsler Adult Intelligence Scale (r=0.73). They found that those at the highest BW z-score (defined in this study as >3.00 SDs above the mean) were more likely to have poor test scores (aOR: 1.22 [1.00, 1.48]). Moreover, adjustment for social factors only altered the results slightly; yet, adjustment for individual characteristics (adult height and BMI) attenuated the associations greatly (β=0.107 to β=0.102 and β=0.057 respectively). [47]

Other researchers attempted to explain this association using samples from large national databases. Paulson et al sampled U.S. children from a longitudinal cohort and found no significant differences in cognitive functioning across numerous time points (9 months, 2, 3.5 and 5.5 years; Wilks λ=0.6, p=0.615). The reference group was children whose birth weight was appropriate for gestational age (AGA), defined as 5-89th percentile, which could potentially include a high-risk sub-set of children as AGA is more frequently defined as between the 10-90th percentile. However, a second analysis was performed with AGA defined as 5-94th percentile and this demonstrated no change in their findings. That being said, the excluded cases in their analyses tended to have lower maternal education and socioeconomic status (SES), which are known to influence cognitive development. [8] Finally, in a large population cohort from Western Australia, LGA infants were more likely to have only intellectual disabilities associated with autism (aOR: 2.36 [0.93, 6.03]), although the confidence interval was quite wide, and did not reach significance after adjustment. [48] In this study, LGA was defined very comprehensively (considered sex, gestational age, parity and maternal height), however, only Caucasian and Aboriginal women were included.

Macrosomia

The literature examining macrosomia on cognition has contrasting findings. Birth weight has been shown to positively correlate with intelligence scores (Moray House Test $r=0.25$, $p=<0.001$); however, mean scores tend to decrease at a BW higher than 4500 grams. Researchers have attempted to tease out the causal pathways and mechanisms between these associations. Shenkin and colleagues examined two competing hypotheses. The first, which states that birth weight and SES independently alter cognition, while the latter speculates that the association between SES and cognition, is mediated by birth weight. It was concluded that the "mediation" hypothesis had poor fit statistics, ruling out the suggestion that birth weight is simply a marker of social deficiency. [49] Richards et al performed conditional analyses, and concluded that there may be important periods for the effect of postnatal growth in the relation of BW on cognition, with height being important in early childhood and adolescence and weight gain in late adolescence. [50-51] Associations between macrosomia and intellectual performance has also been examined among specific populations, finding that among persons diagnosed with schizophrenia, both low and high BW are associated with minor deficits in visuo-spatial reasoning, processing speed, and verbal/visual working memory. [52]

Contrasting with the majority of the other results, another study used only male siblings from a Norwegian population in an interesting study design. The authors used siblings in an attempt to disentangle social and environmental confounders that may be immeasurable. Controlling for length of pregnancy, the sibling comparison showed that men with a BW greater than 5000 grams had an intelligence quotient (IQ) score 2.2 points higher than their siblings with a BW from 4000-4499 grams. Authors concluded that the observed association between HBW and lower IQ in other studies is likely due to unmeasured confounders at the family-level. It should be noted that the results may differ for females, as this study restricted to only males. [53-54] A national survey from the U.S. reiterated this, by reporting the highest risk for developmental disabilities among those children born with the lowest birth weights. [55]

Summary

The majority of the research findings report a negative association between macrosomia or LGA and specific aspects of cognition, however, the contribution of familial, environmental or social factors are still in need of further clarity.

2.3.3 LGA/macrosomia and psychological outcomes

LGA

In general, research is mixed on whether being born LGA has an impact on psychological outcomes. Using a Canadian sample of 1118 (n=147 LGA), Van Lieshout found that children born LGA had significantly higher scores only on a self-reported externalizing scale (aOR: 1.39 [1.01, 2.78]), even after adjustment for familial history of psychopathology and socioeconomic disadvantage. Examination of parent-reported and teacher-reported externalizing scores remained in the same direction, but did not reach significance. Both the exposure, outcome and psychiatric history were self-reported potentially inducing bias, and LGA was defined as a BW >95th percentile which may only consider the most severe cases. [56-57] Using a 1966 birth cohort, the risk of schizophrenia at 31 and 34 years of age among those born LGA (BW >90th percentile) was evaluated. An increased overall risk for schizophrenia was seen (aOR: 2.7 [1.2-6.4]), but after stratification by sex, it only remained significant for males (aOR: 2.8 [1.1-7.2]), and at 34 years of age, the association was no longer significant (aOR: 2.1 [0.9-5.0]). [58-59]

Chudal et al found no suggestion that LGA infants, defined as a BW >90th percentile, were at an increased risk for bi-polar disorder in early childhood (aOR: 0.83 [0.47-1.46]), although, LGA cases and controls accounted for only 2.8 and 3.9% of the entire sample respectively. [60]

Macrosomia

There are also mixed findings when examining macrosomia and associations with psychological outcomes in children, in both high-risk children and in the general population. Wegelius et al found that in a population of individuals with psychotic disorders, macrosomia (defined in this study as >4000 g) was associated with more severe symptoms of bizarre behaviour ($p<0.001$), affective flattening ($p=0.01$) and attention deficits ($p=0.01$). [61] Another study by Wegelius investigated susceptibility of a schizophrenia diagnosis among individuals with high familial risk (i.e. at least two siblings had been diagnosed with schizophrenia, or the individual came from a region with a high prevalence of schizophrenia). A significant association was found between macrosomia (defined in this study as >4000 g) and schizophrenia (hazard rate ratio or HRR: 1.68 [1.13, 2.50]), but not primary psychotic disorders (HRR: 1.18 [0.84, 1.65]). [62] While both studies used a comprehensive diagnosis approach, the population came from an older cohort (births between 1940-1976), and is likely not representative of the current population.

Examining males conscripted into the military, an increased risk of schizophrenia was found among individuals with a BW greater than 4000 grams (hazard ratio or HR: 3.34 [1.77, 6.30]), but not for increased birth length (HR: 1.43 [0.66, 3.10]). Interestingly, there was no statistical interaction between birth weight and future height in respect to its association with schizophrenia (p=0.23) suggesting minimal contribution of postnatal growth. [63] Cases were obtained solely based on hospital admissions and similar to above, the sample came from an older cohort (births between 1973 and 1980).

Further studies have examined associations among a sample that is more representative of the general population. Herva et al found that there was no significant association between birth weight and physician diagnosed depression in adulthood. However, a positive association was found for self-reported depression assessed by the Hopkins Symptoms Checklist among females who had a BW over 4500 grams (aOR: 2.02 [1.20, 3.39]). The relationship was not significant when macrosomia was defined as 4000-4999 grams, or as ≥5000 grams. [7]

Summary

There are mixed findings when examining the association between both macrosomia and LGA with psychological outcomes, suggesting that the exact nature of this association is not well understood. Many studies have commented on the potential implication of maternal diabetes, [63] labor complications due to macrosomia and LGA or fetal hypoxia, [58, 61-62] however, these factors have not been effectively included in many analyses. Moreover, many of the studies were from much older cohorts, potentially limiting their applicability to the current population. [7, 61-63]

2.3.4 LGA/macrosomia and autism spectrum disorder

LGA

Mixed evidence has been found as to whether there is an association between LGA and ASD. Moore et al, Abel et al and Hultman et al all reported an increased risk of ASD in LGA infants (aOR 1.16 [1.08-1.26], aOR 1.49 [1.26-1.76] and OR 1.6 [1.0-2.6] respectively), with the former reporting it to be protective in preterm births, yet a risk factor in term births. Comparably, Abel and colleagues reported that the risk was greatest among children born at term gestation, and that excessive fetal growth was more often associated with autism associated with intellectual disability than without ($p<0.004$). Explanations of the potential protective nature of preterm births were not given, but it was speculated that labor complications due to LGA may be an important factor. Moore and Hultman both did not adjust for familial history of psychological disorders, and Hultman's study had a disproportionate number of males in their cases, however, all studies used recent birth cohorts. [64-66] A systematic review, which examined fetal ultrasound measurements and developmental outcomes concluded that being LGA, as based on ultrasound measurements of estimated fetal weight, increased risk of ASD, but not any other outcome, and that the greatest risk for the adverse outcomes reviewed was among those infants with the lowest estimated fetal weight. [67]

In contrast, using Nordic populations, Larsson et al, Haglund & Kallen, and Eaton et al concluded that being LGA had no association with ASD risk (aOR: 0.90 [0.67-1.22], aOR: 0.3 [0.0-1.9] and RR: 0.64 respectively). Of interest, Eaton et al found that the most predictive variable for psychopathology in childhood was the interaction of birth weight with speed of post-natal growth, supporting the suggestion that growth in early life is an important factor in relation to future development. [68-70]

Macrosomia

Literature suggests there is no effect of macrosomia and risk for ASD diagnosis. A systematic review and meta-analysis examined literature from 2007 forward investigating perinatal and neonatal factors on ASD risk. Authors found that macrosomia (defined in this study as >4000 g) was not significantly associated with the outcome (summary effect estimate: 1.13 [0.95, 1.35]), and authors concluded that there was little evidence to suggest that elevated BW plays a role in risk for autism. That being said, publication bias was probable, according to results from Egger's test ($p<0.05$). [71]

Summary

Due to the contradictory results, no conclusions can be definitively drawn in regards to LGA status and risk for ASD diagnosis. Differential diagnostic criteria were used, and it appears that the results may vary depending on where the study sample was drawn, as the refuting studies sampled from psychiatric hospitals or registries, while the studies in support used youth or birth cohorts. It does appear that macrosomia has no association with ASD risk, although, publication bias within the meta-analysis is possible.

2.4 Mechanisms linking LGA to later development in childhood

The exact causal pathway between being born LGA and child development is still unclear, as delivery complications, social and biological factors have all been thought to play some role. However, numerous researchers have commented on the potential implications of maternal diabetes or obesity [63] and postnatal growth [45,47,70] when examining this association. Moreover, maternal diabetes and obesity are common risk factors for LGA, [72] which in turn, is known to increase risk for childhood obesity, [73] and both of these factors have been shown to be independently associated with future development in children. [25-26, 73]

The following section will discuss these two pathways that are hypothesized to be involved in the association between infants born LGA and developmental attainment in early childhood.

2.4.1 Maternal diabetes or obesity

In Canada, adults with obesity or diabetes has been increasing over the years. [74-75] While both are known to increase risk for LGA, [72] there is also evidence that glucose distress or maternal metabolic conditions can result in developmental disparities in children. [25-26]

One aspect of this study will attempt to answer if being LGA has a different effect on developmental attainment depending on the presence or absence of maternal diabetes.

Maternal diabetes/obesity is associated with LGA/macrosomia

There has been an abundance of literature examining associations between maternal diabetes or obesity and being LGA, with the majority demonstrating support. The bulk of the literature has examined macrosomic infants, which will only be summarized briefly. While one study found no independent association, [76] the majority have reported independent relations between maternal obesity, gestational weight gain, or diabetes and risk for macrosomia. [72, 77-87] In women with pre-existing or gestational diabetes, maternal obesity or GWG is found to further increase risk by up to 3-fold. [88-89] Additionally, abnormal glycemic control, as measured by glycated hemoglobin (HbA_{1C}) was found to be a predictor of macrosomia. [82, 90]

Similar to macrosomia, many studies have reported a positive association between maternal obesity or diabetes and being born LGA. Three retrospective cohorts from Asia have concluded that maternal obesity is linked to LGA infants, with a meta-analysis reporting enhanced risk of up to 2-fold (aOR: 1.53 [1.44, 1.63) and aOR: 2.08 [1.95, 2.23] for overweight and obese women respectively). [91-93] Other geographic regions, such as the United States, [94] Turkey, [95] and Denmark, [96] have supported these findings. Again, excessive GWG appeared to strengthen the association for overweight women by further increasing risk (aOR: 2.99 [1.92, 4.65]). [97]

Gestational diabetes has also been reported as an independent risk factor for LGA births. A systematic review evaluated untreated gestational diabetes, based on World Health Organization (WHO) and International Association of Diabetes and Pregnancy Study Groups (IADPSG) standards, and risk for adverse perinatal outcomes. Eight studies were retrieved, concluding an increased risk for LGA births using both WHO and IADPSG guidelines (RR: 1.53 [1.39, 1.69] and RR: 1.71 [1.38, 2.13] respectively). [98-99]

Discussion is still ongoing in regards to which of these risk factors has the predominant influence. A study conducted in Florida studied the independent effects of maternal obesity, GWG, and gestational diabetes and found that while they each increased risk for LGA births, excessive GWG was the most impactful, [100] while a Swedish study concluded that the highest risk is in fact seen in mothers with obesity and type 1 diabetes (aOR: 13.27 [11.27, 15.59]).[99] These results were echoed by a prospective study done in China.[101-102] Heude et al found that while maternal obesity was related to LGA, once women with gestational diabetes and hypertension were removed, the odds for LGA was weakened for women with obesity (OR: 3.23 [1.86, 5.60] to OR: 2.57 [1.29, 5.13]), yet strengthened for the association between GWG and risk of LGA.[103] Maternal pre-pregnancy BMI, GWG and diabetes status were all independent risk factors for LGA among a racially diverse population, however their joint effect caused a substantial increase in risk for LGA births among Non-Hispanic Whites, Non-Hispanic Blacks, Hispanic women, but not for Asian women, in which the odds ratio remained relatively stable, signifying possible racial disparities.[104]

The role of glycemic control as a predictive measure for LGA has also been well established, with the literature showing an increased rate of LGA infants among women with an impaired glucose tolerance test.[105] Moreover, if left untreated during pregnancy, there is a 7-fold increase in risk for LGA as found by a prospective study from Sweden (OR: 7.3 [4.1, 12.7]).[106] Conversely, no difference was found in a cross-sectional study from Thailand examining women treated with diet versus insulin, and prevalence of LGA births (p=0.15).[107] Pursuing further into the biochemistry of glycemic control, it has been found that third trimester HbA_{1C} was an independent risk factor for LGA (p=0.006) in women with type 1 and type 2 diabetes, and abnormal HbA_{1C} prior to delivery resulted in higher odds of having LGA infants (aOR: 3.1 [1.3, 7.6]). No discernible trend was found in women with gestational diabetes (p=0.12).[108-110]

Is maternal diabetes/obesity associated with future development?

Literature is mixed regarding the effect of maternal diabetes or obesity on development in children. Examining the Stanford Binet Intelligence Test, it was reported that, after adjustment, a non-linear association was found between maternal BMI and IQ in children; specifically, IQ was 2.5 (-4.5, -0.6) points and 3.2 (-5.6, -0.8) points lower for women with a BMI of 32 and 34 respectively. However, this cohort was initially designed to address the effect of substance abuse on development, and the study is mostly comprised of single, low-income individuals. GWG was not significantly associated with any aspect of cognitive development, but authors suggested that it may be important if considered in conjunction with maternal BMI. [111] This was supported by a perinatal health study from the U.S., which examined IQ using the Wechsler Intelligence Scale at age 7, and the Stanford Binet IQ test at age 4. They found reduced scores for children whose mother was overweight (BMI $\geq$30) (adjusted β=-2.0 [-3.5, -0.5]), which were altered depending on severity of GWG. [112]

Other researchers have concluded that any association is very modest, or negligible. A population cohort study compared European countries, and found that after adjustment, associations between scores on the Bayley Scale of Infant Development and maternal obesity attenuated markedly to virtually null. [113] Results from a national prospective cohort from the U.K., expressed similar results. Using principal components analysis to achieve an overall cognitive ability measure, authors reported that a 10-point increase in maternal BMI was associated with a decrease in cognitive ability by only one tenth of a standard deviation. [114]

Maternal obesity has also been associated with behavioural development in children. A national study found that children of class II/III obese mothers had higher risk for emotional (aOR: 1.94 [1.05, 3.58]), peer relationship problems (aOR: 1.83 [1.09, 3.09]), a diagnosis of attention deficit disorder/attention deficit hyperactivity disorder (aOR: 3.76 [1.41, 10.05]), current use of speech/language therapy (aOR: 1.87 [1.12, 3.15]) and current use of psychological services (aOR: 2.24 [1.03, 4.85]). These results were supported in direction by obese/overweight status, but did not reach significance. [115] Antoniou et al supported this with a twin study from the UK, but showed very modest effects. Authors reported an increase of only 0.008 standard deviations (SDs) in aggressive behaviour (p=0.02) and 0.09 SDs in overall externalizing behaviour (p=0.02) for children who have overweight or obese mothers (BMI ≥25), and found no significance for any other sub-set of externalizing behaviours or any sub-set of internalizing behaviours. Timing of these assessments has been suggested as influential, however, associations have been found for children as young as two years old. [116]

While the exact mechanisms are still under consideration, it has been postulated that maternal obesity leads to an increase in pregnancy complications, which may be the true leading factor to developmental deficits. [111-112] Alternatively, inflammation, hormonal dysfunction (such as leptin and insulin) or nutritional scarcities (such as folic acid or Vitamin D) are more common in women who are obese, and are associated with neurodevelopmental processes. [111-113]

There is also inconsistent literature regarding the association between presence of maternal diabetes and child development. Using the Wechsler Intelligence Scale for Children (WISC), studies from the U.K. found that there were no significant differences in overall IQ for children born to mothers with type 1 diabetes, however, these children performed worse on two sub-tests (digit span, $p<0.01$ and working memory, $p=0.04$), although the sample size was very small (n=40). [117] Upon examining both pre-gestational and gestational diabetes, authors found that any type of glucose distress resulted in lower scores for intelligence, readiness for school and educational attainment. [118] There have also been suggestions that the onset and duration of compromised glucose levels may influence development. Examining women with pre-gestational and gestational diabetes, an inverse relation was found between overall intelligence score and fasting glucose, HbA_{1C} levels and b-hydroxybutyrate levels, all markers for glucose distress. [119] A negative correlation has also been reported between motor tests scores in children and severity of maternal hyperglycemia [120] while a study from Mexico concluded that mothers who were hospitalized during pregnancy for poor glucose control had children with lower average IQ scores ($p=0.009$). [119] A Canadian study examined infants of mothers with gestational diabetes on language impairment and receptive vocabulary. They found a four to twelve-word difference at 18 months and up to ten-word difference at 30 months, but no difference at age 42 and 60 months. Interestingly, maternal education acted as a moderator of the effect of gestational diabetes on a language composite score, ($p=0.03$), suggesting the positive influences of the child's post-natal environment. [121] Finally, in an ongoing cohort from California, associations were explored between perinatal factors and developmental disabilities (DD) in children, defined by a score of <70 on the Mullen Scales of Early Learning, or the Vineland Adaptive Behaviour Scale. After adjustment, it was found that maternal diabetes (either type 2 or gestational) was associated with higher risk of DD in the child (aOR: 2.33 [1.08, 5.05]). [122]

Conflicting with other findings, a study conducted in Spain found that maternal obesity and diabetes actually resulted in higher cognitive and language functioning in children at 6 months of age, however the study acknowledged its low power and sample size (n=331), concluding that findings should be interpreted with caution. [123]

2.4.2 Child's body mass index

It is widely accepted that infants with obesity are at risk for various somatic conditions such as diabetes, high blood pressure, high cholesterol and cardiovascular disease. [124] An increase in the prevalence of childhood obesity has caused researchers to meticulously examine risk factors, and short or long-term consequences. Literature supports an association between LGA and subsequent obesity; however, new research has begun to describe the potential consequent effect of obesity on development. [73]

LGA/macrosomia is associated with the child's body mass index

Recently, researchers have examined the effect of birth weight on childhood obesity, with most studies providing support. Infants that are macrosomic (defined in this study as a BW >4000 grams) are more likely to have a BMI greater than the 85th percentile at age 2 (aOR: 1.88 [1.38, 2.58]), even after adjusting for socioeconomic and other birth factors.[73] Four studies conducted in the United States also supported this finding. The first study found that increasing BW percentiles resulted in a heightened risk of obesity at ages two to five (aOR: 2.48 [1.001, 6.146]). LGA was defined using a program that considers gestational age, sex, and maternal height and weight, though the population was mostly African Americans, and single mothers with low education and income. [125] Pham et al concluded that LGA was associated with childhood obesity (aOR: 1.8 [1.4, 2.3]). [126] Gillman and colleagues supported this, finding that after adjustment for maternal BMI and activity, social, and nutritional factors, LGA status still moderately increased the risk for future obesity (aOR: 1.3 [1.1, 1.5]). [127] Other researchers examined metabolic syndrome (MS) as a whole, as defined by having two or more of the following symptoms: obesity, high blood pressure, glucose intolerance or dyslipidemia. Again, the risk of MS increased in infants born LGA (HR: 2.19 [1.23, 3.82]). [128] Authors also examined the cumulative hazard of developing a metabolic syndrome over time by graphing the risk according to size for gestational age (LGA or AGA) for each group (gestational diabetes, or control). There were no differences in the risk of developing MS over time in the control group (p=0.56), but there was in the diabetic group (p=0.004). [128]

While those infants born SGA are known to experience "catch-up" growth, the occurrence of LGA infants and "catch-down" growth have been studied less comprehensively. Using a sample from the Generation R Study, authors studied the effect of being born LGA on risk of obesity, as defined by the International Obesity Taskforce cut-offs. It was found that while LGA children experience "catch-down" growth, their mean head circumference, length and weight are consistently different compared to normal weight children. Moreover, after adjusting for parity, maternal BMI and social factors, post-natal growth patterns acted as a modifier with the risk of overweight or obesity for LGA infants with and without "catch-down" growth being 1.39 (0.75, 2.59) and 12.46 (6.07, 25.58) respectively. It should be noted that LGA was defined as greater than the 95th percentile, which may include only the most severe cases. [129]

Is a child's body mass index associated with future development?

Literature has provided mixed findings regarding the effect of a child's BMI on development. Research examining this association has begun to provide evidence that a higher BMI is related to worse school performance, compared to their normal weight counterparts. [130] Moreover, studies have shown that adolescents with obesity consider themselves inferior at school; however, there is less focus on these associations in early childhood. [131] A national study from the U.S. examined academic performance in kindergarten students using reading and math test scores. They found that males who were overweight, given by a BMI $\geq$95th percentile for their age and sex, did not perform differently on the reading test ($p=0.088$), but scored 1.22 points lower on the math test ($p=0.001$) compared to non-overweight males. There were no significant differences among females for either test. However, the longitudinal analysis suggested that after controlling for socio-economic factors, there were no significant differences in test scores between overweight and normal weight children. [131] A prospective study from Illinois found that children with higher BMI and higher levels of fat exhibited lower accuracy on the NoGo Task ($p=0.03$). However, there was no association found for the Go Task, a similar test that requires less cognitive control suggesting that the negative relation between BMI and cognitive performance is detected only in tasks that require higher cognitive ability. Authors also reported a negative relation between BMI and whole body fat with academic achievement. [132-133]

Examining the association between childhood obesity and behavioural problems, a national prospective study in the U.K. found that boys with obesity, aged 5, were at a higher risk for conduct disorder (relative risk ratio or RRR: 1.1 [1.1, 2.7]) hyperactivity/inattention (RRR: 1.9 [1.3, 2.1]) and peer relationship problems (RRR: 2.3 [1.4, 3.9]). An increased risk for girls was only found for peer relationship problems. [134] This was substantiated with a longitudinal cohort which reported that externalizing behavioural problems is associated with a higher BMI in children as young as 2, and remains into early adolescence, although the effect size was small. [130] Furthermore, high BMI has been found to be positively associated with some dimensions of impulsivity (positive and negative urgency $p=0.039$ and $p=0.002$ respectively). [135]

Although many studies have supported an association, others have refuted it, or provided inconclusive deductions. A sample of Portuguese children showed no difference in academic performance across BMI groups for females, and a slight increase in performance for overweight males, however this was not statistically significant. [136] Using cross-sectional data from the U.S., it was found that, after adjustment for numerous factors, BMI percentile was not significantly associated with achievement scores in a primarily African American population, but socioeconomic status ($p=0.0001$) and race ($p=0.0001$) was. [137] Gunstad and colleagues examined the effect of BMI on numerous cognitive tasks, such as attention, verbal recall, intellectual function, motor skills and language. After adjusting for age and estimated base intellectual function, no difference was found across the BMI groups ($\lambda=0.96$, $p=0.26$). [138] Finally, two cohort studies from the Netherlands concluded that no association existed between BMI and delinquent behaviour or psychopathology. [130, 139]

2.5 Sex differences examined within the literature

The literature cited tends to examine the association between being born LGA and development separately for boys and girls, [7, 49] or adjusts for child sex within the analysis, [5, 8, 43, 47, 50] as combining them may discount important differences.

To begin, it has been suggested that male fetuses are more likely to be born macrosomic or LGA, compared to females. [140-141] In the 2005-2007 national census, Statistics Canada reported 56 827 (CI: 56 387, 57 270) male LGA births, and 55 490 (CI: 55 056, 55 927) females LGA births. [142] Females also tend to have a higher average score on the PPVT-R compared to males, [143] and have been shown to perform better in school and on tests measuring academic readiness. [144-145] Males have been shown to exhibit more externalizing behaviours, such as physical aggression, [146] and hyperactive behaviour. [147] Finally, it has been suggested that males and females experience social cues and health determinants differently, and have differential susceptibilities to social and biological factors. [148-149]

Therefore, the reviewed literature warrants the need for stratified analysis within this project, allowing us to examine the sex-specific effect of being born LGA and subsequent developmental attainment in early childhood.

2.6 Gaps in the literature

Although there is an emerging body of literature that examines infants born LGA or macrosomic and subsequent development, there are still gaps present.

One area requiring more attention is the impact of being LGA and development in early childhood, such as at age 5 or younger. The majority of literature has focused on late childhood or early adolescence, failing to address the critical period of development, or during the transition from home life to school. Moreover, the mechanisms behind this association are still not well understood, and the extent to which ancestral factors or variables along the causal pathway contribute to this association still requires further clarification. This ties in to the lack of studies considering post-natal stimulation or parent-child interactions. It is well known that these factors play into child development in some fashion, yet many studies have not been able to assess it due to lack of available data. Finally, the body of literature currently has mixed results, and further research is required to provide more evidence as to whether a true association exists or not.

The literature supports the hypothesis that maternal diabetes and childhood obesity may play a role, however, the association between LGA and development is weaker, specifically in the early childhood. This study aims to examine specific pathways in relation to the association between being born LGA and developmental attainment in early childhood. Further comprehension of these mechanisms is of utmost importance and can provide insight into the long-term consequences of early experiences, assisting in the implementation of interventional strategies.

Chapter 3 – Analytic Framework

3.1 Analytic model (Directed Acyclic Graph)

A directed acyclic graph (DAG) is an important tool in identifying causal associations, and provides a visual summary of hypothesized relationships among the variables, based on a priori knowledge and an extensive literature search. The DAG can also aid in analytic planning and can be used as a tool to identify confounders, especially when the relationships are quite complex. [150] This diagram includes all considered variables, along with arrows pointing from one variable to another indicating an association, in attempts to characterize underlying relations that may be important to the research question. [151]

The DAG used for this thesis is illustrated in Figure 3.1, and demonstrates the predictors and explanatory variables that are involved in the pathway between being born LGA and developmental attainment in early childhood. A simplified version, as can be seen in Figure 3.2, illustrates only the variables that are available for analysis within the chosen database. Moreover, some components of the DAG are bolded to show changes within original text and what is available within the dataset. For example, maternal substance abuse during pregnancy is represented in the original DAG, however; only maternal alcohol use and smoking during pregnancy were available in the selected database. This has been bolded in the simplified diagram (Figure 3.2) to reflect this change.

The direct relationship between the exposure and outcome can be seen in Figure 3.2, through the bolded arrow. In addition, the paths with the dashed arrows represent the proposed mechanisms thought to explain this association; i.e. through the presence of maternal diabetes or a child’s BMI.

3.2 Confounding variables

3.2.1 Confounders

In observational studies, the detected effect of an exposure on an outcome may be misleading due to confounding variables. Failure to address confounders may lead to erroneous relationships or introduce bias, thus, investigation of variables that are associated with the exposure and may contribute to childhood developmental attainment is a critical step of this study. [151] The following review summarizes all the variables that were considered in this DAG, based on a review of the literature.

Pre-natal factors

Parity

Numerous studies have adjusted for parity within their analyses, [42, 47] as the number of babies a mother has previously had, has been shown to influence birth weight, with some studies reporting a dose-response relationship between parity and size for gestational age. Results from an Ontario cohort demonstrated an increase in risk for multiparous women (OR: 2.24 [2.02, 2.49]) when parity $\geq$5), while another Canadian study stated an increase in risk of almost 50% upon increasing parity (OR: 1.49 [1.22, 1.82]). [152-153]

Moreover, parity or birth order, has been found to be associated with child development, however, the mechanisms are still unclear. Heiland found that first-borns fare modestly better on the PPVT-R, while other studies have reported no association. [154] On the other hand, it has been suggested that birth order has an indirect effect on child development via breastfeeding practices or parent-child interactions, as parents have been shown to become more lenient in following health guidelines, and provide less quality home stimulation for higher birth order children. [155]

Maternal age

Maternal age has been associated with a number of obstetric complications, including HBW or LGA status. Researchers have reported a relative risk of 1.40 (1.25, 1.58) for extreme LGA infants among women that were 40 years of age or older, yet other authors have negated any association. [156] More commonly, this association is thought to be due to the fact that older women tend to be multiparous, which is a commonly cited risk factor for LGA births. [156-158]

An association between maternal age and development has also been established. Eide and colleagues demonstrated that maternal age was positively associated with intelligence. [47] However, the majority of the literature has suggested that an independent effect is improbable, and that maternal age likely impacts development through social factors, [159-160] or through adverse peripartum events, such as birth trauma or instrumental delivery. [161]

Maternal social factors

The direct association of maternal social factors with LGA is difficult to interpret. Very few studies have examined main effects, and of those, the results are quite contradictory. Even so, it is thought that social factors impacts BW through either maternal behaviour during pregnancy, or associated characteristics of the mother, such as maternal age and parity. [162]

There is still debate over which aspect of familial environment has the largest impact on development, and through what mechanisms, however a Canadian study concluded that parental low income and maternal education status were both significant predictors for poor development as measured by the PPVT-R and a motor/social development scale (OR: 1.58 [1.09, 2.31] and OR: 1.98 [1.25, 3.15]) respectively). [17] Disrupted marriage has also been shown to negatively influence emotional and cognitive development in children.[163-164] Alternatively, it has been thought that social factors influences development through mediating factors such as through quality of the home environment, parental stimulation, or differences in breastfeeding practices. [159, 165-166]

Ethnicity/Race

Maternal race may have an impact on an infant being born LGA. Birth weight differences across ethnic or racial groups have been identified in numerous studies. [48, 167] Some researchers have suggested that social disparities account for 10% of the birth weight distribution among racial groups. A critical component of the association between race and BW could also be due to differences in social factors and maternal characteristics. [167]

Maternal race and immigrant status have also been found to be associated with poor development in children. Two Canadian studies using the National Longitudinal Survey of Children and Youth (NLSCY) found that maternal immigrant status is a strong predictor of poor development in motor or social skills and verbal intelligence, and consistently increased risk among all age groups (aOR: 2.73 [1.10, 1.70] for all ages combined). [17, 168] Using nationally representative data from children born in 2001, it was found that children in an ethnic minority group scored lower on cognitive tests and positive behavioural scales. The effects seemed to worsen over time, with increasing deviations between 9 and 24 months of age. [169] An indirect effect on developmental attainment is also possible, due to racial disparities in breastfeeding practices. [170]

Maternal substance abuse

In this framework, maternal substance abuse has no direct impact on LGA status, however, there are known social and racial disparities among women who abuse substances during pregnancy, which may constitute an indirect association to LGA. [171-172]

Maternal substance use has been associated with poor development. Both nicotine and alcohol exposure in utero are associated with attention and impulsivity problems in childhood. While the association is not as strong for cognitive development, there is still evidence that substance abuse during pregnancy can worsen executive or cognitive functioning in childhood, as seen through lower IQ scores, and inferior performances on achievement tests. [173]

Maternal diabetes

The presence of maternal diabetes is one of the most common causes of babies being born LGA. [24] Both pre-existing and gestational diabetes are reported as a significant risk factor for LGA births, with studies stating an increased risk from as low as 2-fold to as high as almost 14-fold. [98-99]

Maternal diabetes has also been found to be an independent predictor for child development. It has been reported that a mother with any kind of glucose distress may have children with lower scores on intelligence tests, and who feel less prepared for school entry. [119, 117] Infants of mothers who had gestational diabetes have been found to have up to a 12-word difference in language ability at age 18 months, while another study reported a higher risk for developmental disabilities among these children. [121-122] It could also be postulated that there is an indirect effect of diabetes to child development through differential breastfeeding practices. [174-175]

Post-natal factors

Breastfeeding

Breastfeeding is highly recommended by many health organizations, for its known benefits to both the mother and child, including child development. A large cluster-randomized trial found that exclusive breastfeeding resulted in a 7.5-point increase in verbal IQ, 2.9-point increase in performance IQ and 5.9-point increase for overall IQ. [175] Longer duration of breastfeeding has also been associated with fewer parent-reported behavioural problems in children. [176] These findings were echoed by a longitudinal study from the United States that found an increase in emotional problems and conduct disorders among children who were breastfed less than 6 months, however, after adjustment, it was no longer significant. [177] However, a systematic review concluded that much of the reported influence of breastfeeding on child development is likely due to confounding. [178]

An indirect causal pathway may also exist. Two separate reviews both concluded that breastfeeding reduces the risk of childhood obesity. The first review, also a meta-analysis, demonstrated a decrease in risk by over 20% (aOR: 0.78 [0.71, 0.85]), while the latter concluded some attenuation after adjustment for confounders, but still established breastfeeding as protective. [179-180]

Child stimulation/Parent-child interactions

Very few studies have been able to include a measure of child stimulation, or parent-child interaction when examining the effect of being born LGA on future development. [50]

That being said, an environment that promotes learning has been reliably shown to predict a child's cognitive ability. [180] A Canadian study using NLSCY data found that parenting practices (such as hostile parenting and lack of positive interactions) negatively associated with a child's development. [17] A longitudinal study that spanned two decades established that cognitive stimulation at age four (measured by number of books and presence of educational toys) and parental stimulation at age four (measured by nurturance and supportiveness of the parent) predicted brain development fifteen years later. [181] Parent-child interactions have also been found to predict child behavioural problems, with ineffective parenting, such as rigidity, coercion and hostility acting as strong predictors of externalizing and internalizing behaviour in children. [182-183] Finally, one study reported that the majority of the variance in child development is almost exclusively due to disparities in parental behaviour and home environment. [155]

Maternal depression

While maternal depression has been linked to social factors, such as low income and lack of partner support, [184] it has recently been reported that low-income women with gestational diabetes had nearly double the risk of experiencing perinatal depression (OR:

1.85 [1.45, 2.36]). The associations in other groups are still not well examined, however, a prospective study found that type 2 diabetes increases the risk of clinical depression (RR: 1.29 [1.18, 1.40]). [19,184-185]

Maternal depression is considered a risk factor for child behavioural and cognitive development. Mothers who are depressed have been shown to engage in inferior interactions with their children, have ineffective mood regulation, and do not respond as efficiently to their child's needs. [184] Using a longitudinal approach, Hay et al found that children of depressed mothers had lower IQ scores, attention problems and were more likely to require additional educational resources. [186]

3.3 Mediator Variables

3.3.1 Mediation

Consideration of mediator variables is an important step when examining causal pathways, specifically when attempting to understand underlying mechanisms. In this context, a mediator lies on the causal pathway if it falls between being LGA and developmental attainment. [187]

Peri-partum events

Being LGA has been found to result in a higher risk for shoulder dystocia, birth trauma, and higher risk for cesarean section or an instrumental delivery ($p<0.001$). [4]

It has been mentioned in prior research that adverse peri-partum events may act as a mediator along the examined pathway. [58, 65] Literature suggests that labor complications may increase risk for poor development, however the findings are mixed, and the majority of the articles are old. Studies that have examined instrumental delivery on child cognition have found contradicting evidence, with some stating that these children have lower overall test scores, [188-189] while others contest any association. [190]

It has also been reported that among LGA infants, lower motor and developmental function scores were reported if they experienced an instrumental or cesarean delivery, however is still not definite whether these differences are due to obstetric complications, or other factors, [188, 191] as some researchers have speculated that the anesthetic used during cesarean delivery may be a contributing factor. [192-193] Although the research is quite conflicting, there is reason to believe that birth trauma or method of delivery may have some bearing on future developmental attainment.

Childhood obesity

Research has shown a significant association between being born LGA and childhood obesity. After consideration of numerous third variables such as social, nutritional, activity related and maternal BMI, studies found that being born LGA still moderately increased risk for obesity (aOR: 1.3 [1.1, 1.5]). [127]

A child's BMI in early age may also be associated with cognitive and behavioural development later in life. It was found that a higher BMI is related to worse school performance, compared to their normal weight counterparts. [130] Moreover, studies have shown that adolescents with obesity consider themselves inferior at school; however, there is less focus on these associations in early childhood. [131] Moreover, a longitudinal cohort study from U.S. provided further support by reporting that externalizing behavioural problems is associated with a higher BMI in children as young as two. [130]

3.4 Minimally Sufficient Set

Researchers attempt to estimate the unbiased association between an exposure (X) on an outcome (Y), through meticulous consideration of confounders. A traditional approach to confounding is to merely "adjust" for that variable within regression analysis, however, research suggests this may unintentionally lead to the introduction of conditional associations or collider bias. [195]

Greenland and colleagues define a sufficient set as a set of confounders that adequately reduces or removes bias, while a minimally sufficient set means no further variable can be removed from the original set without resulting in an insufficient set. Researchers may be inclined to adjust for more variables than those included in the minimally sufficient set to remain consistent with prior literature, however, this may introduce bias, and can create an effect where none exists or obscure a true effect. [194] For example, adjusting for a mediator can bias results towards the null, while conditioning on a collider (a variable in which it is the outcome of two or more other variables) can distort the association between the two parent variables. Moreover, in doing so, this may open a backdoor path (a path that connects the outcome and exposure regardless of direction) and thus result in a biased estimate. Particularly in the instances where the mechanisms are still unclear, adjustment for a minimal set of confounders can be highly valuable. [195]

The majority of the literature reviewing DAGs and selection of confounders using causal diagrams have concluded that it is an invaluable tool for confounder selection in analyses, can aid in statistical interpretation and also provides a common language and framework when discussing with colleagues. [196] However, it should also be mentioned that the greatest limitation in the development of a DAG is the assumption that the proposed associations are correct, in that it is only as strong as the underlying evidence used to create it. [197]

According to the framework provided by Greenland and colleagues, to reduce bias, the use of a minimally sufficient set is optimal, meaning statistical adjustment is only made for as few variables as required. A six step approach was furthered by Shrier and colleagues working off of Greenland and Pearls' original concepts to test the set of chosen confounders. The six steps are discussed below.

1. Ensure the confounders chosen to reduce bias are not descendants of the exposure. This ensures that the selected set are confounders in the traditional sense, and that they do not fall along the causal pathway.

2. Delete all variables that are non-ancestors of the exposure, the outcome and the selected set of confounders. An ancestor is a variable that causes another variable either directly or indirectly. This ensures that all remaining variables are conditioned on, or have their descendants conditioned on.

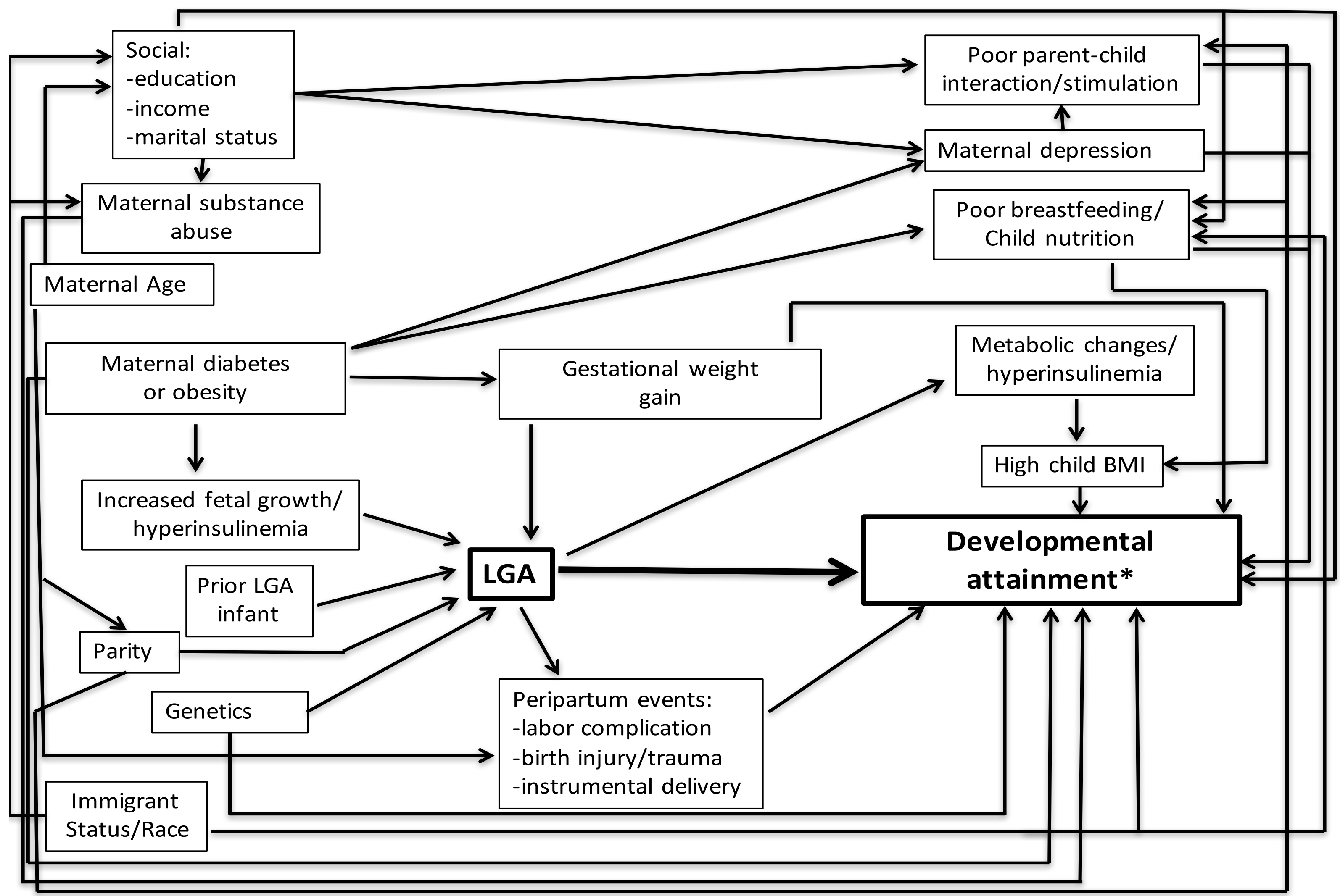
3. Delete all lines coming from the exposure, simplifying the DAG, and again ensuring no selected variables fall on the causal pathway.

4. Connect all parent variables that share a common child variable, as adjustment for the common child creates a conditional association. This allows for a visual representation of all conditional associations that can occur.

5. Remove all arrowheads from the lines, simplifying the DAG further as the directions were only necessary for the first four steps.

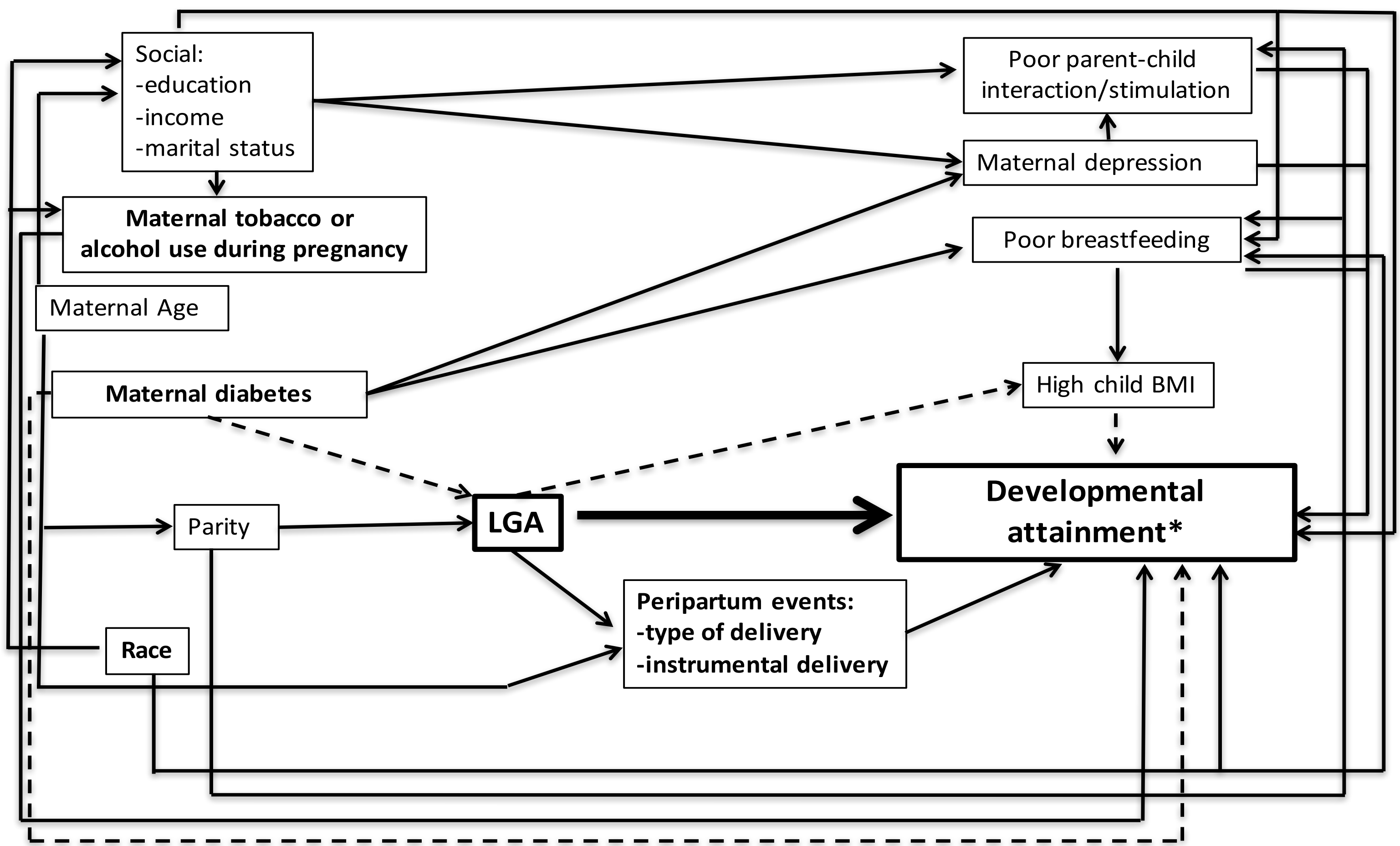
6. Delete all lines between the selected set of confounders and all other variables, allowing for a visual representation of regression techniques.

If the exposure variable is not connected to the outcome after the six steps are complete, then the set of chosen confounders will effectively minimize bias. A critical analysis of the DAG was done using the reviewed variables, and following the approach, it was found that adjustment should only be made for maternal diabetes and parity. [198]



*Developmental attainment refers to verbal ability (measured by the PPVT-R) and externalizing behaviour problems (measured as a composite outcome)

Figure 3.1 – Directed acyclic graph representing the hypothesized mechanisms behind being born large for gestational age and developmental attainment in early childhood



*Developmental attainment refers to verbal ability (measured by the PPVT-R) and externalizing behaviour problems (measured as a composite outcome)

Figure 3.2 – A simplified directed acyclic graph representing the main mechanisms that will be studied in this project, as well as demonstrating changes, which reflect the availability of questions within the database

Chapter 4 – Methods

4.1 Data Source and Access

The data source for this study was the National Longitudinal Survey of Children and Youth; a biennial survey conducted in Canada, which began in 1994, and currently, has 8 completed cycles (most recent is the 2008/2009 cycle). Each cycle has a longitudinal and cross-sectional component. The NLSCY follows the development of children from birth to early adulthood, collecting data on their health and healthcare utilization, social environment, as well as information on their parents or guardians. Furthermore, data was also obtained pertaining to characteristics of the family, the neighborhood and the child's school and recreational experiences. The objective of the NLSCY is to determine the prevalence of risk and protective factors for children, examining their impact on child's cognitive, emotional and physical development. The ultimate goal of the NLSCY is to aid in policy and program development targeted at benefiting the children and youth.

A written proposal was submitted to Social Sciences and Humanities Research Council to be granted access to Statistics Canada Research Data Centre (RDC) at The University of Western Ontario. Upon acceptance, training and a security clearance was undergone by the main researcher. A microdata research contract was signed to become a deemed employee of Statistics Canada, and an oath of office and secrecy was taken. All analyses were completed at the RDC, and were reviewed by RDC analysts to ensure that survey weights were used, minimum cell counts were met, and to screen for any breeches of confidentiality, based on both indirect identifiers and sensitive variables.

4.2 Sampling Strategy and Data Collection

Children were drawn from respondent households sampled by the Labor Force Survey (LFS), a monthly survey that collects information on labor market data, and is redesigned every 10 years (in 1994 and 2004) to maintain an accurate representation of the Canadian population. The LFS targets all non-institutionalized civilians aged 15 and over, living in Canada, excluding residents of Yukon, Nunavut, Northwest Territories, Indian Reserves or Crown lands, and children whose parents are members of the Canadian Armed Forces.

The LFS uses a stratified, multi-stage design along with probability sampling. Provinces are first divided into economic regions and employment insurance economic regions, in which the primary stratification is an intersection of these two regions. These regions are then classified into rural, remote or urban areas using census definitions. Urban areas are further classified into apartment frames or area frames. Where necessary, the urban area frame is stratified to regular, high-income and low population density strata. Finally, households in the final strata are divided into clusters, a sample of the clusters is taken, and a final sample of dwellings is taken from each cluster. The number of dwelling samples is dependent on the type of stratum; for example, the urban apartment frame allows 5 dwellings per cluster while the rural area allows for 10 dwellings per cluster.

The survey is performed using a combination of computer assisted interviews (CAI) and paper questionnaires. The CAI can be further classified as computer assisted personal interviewing, which is done in person and computer assisted telephone interviewing, which is done over the phone. The use of computer technology allowed for computer-generated edits to be used, such as review screens, range edits or flow-screen edits. All interviewers are trained extensively in survey administration using classroom training resources and self-guided materials. The NLSCY is offered in both official languages. Further information in regards to sampling and methodology undergone by the NLSCY is published elsewhere. [199]

4.3 Study Sample

The NLSCY consists of two components; the longitudinal sample, children aged 0-11 sampled from the first cycle, and the Early Childhood Development (ECD) component. The latter was a new cohort of children aged 0-1 that were added at each cycle, and followed for at least three consecutive cycles to examine their development in early life. A maximum of one child per household could be selected for the ECD component beginning in cycle 5. Prior to this, an exception was made for twins. Each cycle also gathers a top-up sample of new children aged 2-5 years old, to effectively represent the changing population. [199]

This study used the ECD cohort from cycles 6, 7 and 8. In cycle 6, there were 4684 respondents in the ECD cohort, of which 4650 and 3852 returned and responded for cycles 7 and 8, respectively. Some children were not surveyed as they had passed away, moved elsewhere or had not responded for numerous cycles in a row. The response rates were 81.3%, 83.0% and 76.9% for cycle 6, 7 and 8 respectively. [199]

In this study, any child who entered the survey in cycle 6 at ages 0-1, and remained in cycles 7 and 8, were eligible for inclusion. The respondent, known as the person most knowledgeable (PMK), must have been the biological mother, to increase accuracy of pregnancy outcome reporting. Finally, mothers who had a multiple pregnancy, and children who were small for gestational age were excluded.

A detailed list of all variables and how they were coded for analysis in the current study can be seen in Table 4.1, with bolded categories representing the response selected as the reference group.

4.4 Outcome Measures

The outcome of interest is developmental attainment at ages 4-5 (cycle 8). This will be measured in two ways: with the Revised Peabody Picture Vocabulary Test for verbal ability, and using behavioural scales to assess externalizing behaviour problems.

4.4.1 Verbal ability (PPVT-R)

The PPVT-R was developed at the University of Hawaii to measure receptive or hearing vocabulary, and for the purpose of the NLSCY, was used to gauge school readiness and verbal ability for children aged 4 to 5. During the assessment, the child would look at a series of pictures, and identify the correct one that matched the word the interviewer said aloud. The NLSCY offers the scores in both raw and standardized forms, in which the latter has a norm sample based from the previous records from cycles 1 to 5 of the NLSCY. In cycle 8, the response rate for the PPVT-R was 83.9%. [199]

Overall, the PPVT-R is accepted as a measure of intelligence and scholastic aptitude in children. The original test, normed to an American population, had a median split-half reliability of 0.80 and a median test-retest reliability of 0.78. This test has also been shown to have good stability, with a test-retest reliability of 0.89, when given across a span of 11 months. The PPVT-R has also been found to have moderate validity, [198] and is known to correlate well with the WISC-III (r=0.75 for vocabulary score, r=0.76 for verbal IQ and r=0.60 for full scale IQ). Moreover, this test correlates with measures of achievement, such as the Revised Wide Range Achievement Test and the Comprehensive Tests of Basic Skills. [200-201]

Consistent with other literature, poor verbal ability was defined as scoring equal to, or less, than the 15th percentile on the age-standardized score for the PPVT-R, creating a dichotomous variable (poor verbal ability or appropriate verbal ability). [17]

4.4.2 Externalizing Behaviour Problems

To examine externalizing behaviour problems, a composite outcome was created. The NLSCY sampled pre-existing scales to measure externalizing behaviour in children, with minor modifications. However, to ensure the psychometric properties of the scale were still sound in this context, a factor analysis was done to confirm the constructs. Scores were produced and reliability measures were also reported. Further details on this process are published elsewhere. [199]

Consistent with other literature, an externalizing behaviour problem in children was defined as scoring in the top 10th percentile on any of the three scales used. [202] A case would be defined as such if the child scored in the top 10th percentile on at least one of the three externalizing behaviour scales examined (hyperactivity/inattention, conduct disorder/physical aggression or indirect aggression). These scales have acceptable reliability with the NLSCY reporting Cronbach's alphas of 0.809, 0.774 and 0.632 for hyperactivity, physical aggression and indirect aggression respectively. [199]

4.5 Exposure Variable

4.5.1 Large for gestational age

Being born large for gestational age was the primary exposure within this study. Size for gestational age was derived using the mother's reports of the infant's birth weight in kilograms, and gestational age which was a derived variable from mother's report of how many days she gave birth before or after her due date. Size for gestational age was determined using sex-specific Canadian standards established by Kramer. The final variable was coded as either small for gestational age (<10^{th} percentile), appropriate for gestational age (between the 10^{th} and 90^{th} percentile), or large for gestational age (>90^{th} percentile). Infants that were identified as SGA were excluded from the study as they pose their own individual risks, and decreased power when performing analysis. Appropriate for gestational age was used as the reference group. [203]

Size for gestational age was chosen over a classification of macrosomia (birth weight >4000 grams) as without consideration of gestational age, misclassification may occur. A cross-tabulation confirmed this, however, as per RDC regulations, the output could not be released.

4.6 Confounding Variables

<u>Pre-natal factors</u>

Maternal age and parity were both reported by the mother. For analysis purposes, maternal age was divided by 10 (to facilitate interpretation of the odds ratio) and parity was categorized to 1, 2 or ≥3 live births.

Maternal social factors comprised of maternal education, maternal income and marital status. Maternal education was obtained from a 5-category variable, but due to scarce cells, the responses were collapsed resulting in 3 categories: “less than secondary school or secondary school graduate”, “some post-secondary school” and “college, university or other”, with the latter acting as the reference group.

Marital status was self-reported and again, for analysis, categories were collapsed due to small cell sizes, resulting in “married”, “living common-law”, “widowed, separated, divorced or single” response options, with married women as the reference group.

Income status was created from two separate variables. The PMK’s self-reported total household income was compared to income cut-offs provided by the NLSCY, which are based on size of area of residence and number of people living in the household. If the individual fell below the income cut-off, he/she was coded as “low income” and otherwise coded as “not low income”.

Mothers were also asked to describe their race and country of birth. Answers were collapsed to “White” or “other” and “Canada” or “other” respectively, with White and Canadian women acting as the reference groups. Due to infrequent response rate, this study was not able to include questions about a respondent’s immigrant status.

Substance abuse during pregnancy was obtained from two variables. The PMK was asked about her use of tobacco and alcohol during pregnancy. Responses were collapsed to either “yes” or “no”. Mothers were asked “Do you have any of the following long-term condition: diabetes?” and “During this pregnancy with this child, did you suffer from any of the following: pregnancy diabetes?”. Both response categories were “yes” and “no”, where “no” was treated as the reference group. Due to a small number of cases, these two variables were combined to create a single variable, which demonstrated presence of either type of diabetes (whether pre-existing or pregnancy related).

Post-natal factors

Information on breastfeeding was obtained from the mother’s response to “Did you breastfeed your child even if only for a short time?” and “For how long did you breastfeed this child?”. The original variable had 9 levels, however, for this analysis, these two variables were combined to create one single variable that represented the mother’s breastfeeding practices. Response categories were “no breastfeeding or breastfed up to 4 weeks”, “breastfed 5 weeks to 6 months” and “breastfed greater than 6 months”, with the latter serving as the reference group. These categories were chosen to correspond with WHO breastfeeding recommendations and systematic reviews which utilized the same categories. [204]

Child stimulation was measured using the mother’s reports to the following question, “How often do you or your spouse get a chance to do the following with this child? Tell stories to him”. Responses were re-categorized to “rarely or never, or a few times per month”, “once a week or a few times per week”, and “daily”, which was assigned as the reference group. Originally, factor analysis was going to be used to obtain an overall level of parental stimulation, but due to a high rate of non-response on other questions assessing types of child stimulation, this was not performed.

The NLSCY had developed scales that were designed to measure certain parenting practices and maternal depressive symptoms. To ensure the initial factor structure was maintained in the new sample, evaluation of each was undertaken. Firstly, a factor analysis was performed to determine the constructs of each scale, which allowed for scoring based on the results accounting for positive and negative loading. Finally, reliability measures, such as Cronbach's alpha, were produced for each. Additional information on how the analysis was carried out for each scale is published elsewhere. [199]

Three parenting scales were considered in this analysis, including positive interactions, ineffective parenting and rational parenting, where the final scores ranged from 0 to 20, 0 to 28 and 0 to 16 respectively. High scores indicate positive interactions with the child, hostility/ineffective parenting, and punitive/aversive parenting respectively. All three scales were left as continuous variables.

A shortened version of the Center for Epidemiology Studies Depression Scale was developed for the purpose of the NLSCY, and was used to gather information about the mental health of the respondent. The final derived scale was left as a continuous variable, and ranged from 0 to 36 with higher scores indicating depressive symptoms. Due to a large number of missing responses, post-partum depression could not be examined.

4.7 Mediator Variables

4.7.1 Child BMI

Children's height and weight were reported by the PMK in response to the following questions "What is the child's weight in kilograms and grams?" and "What is the child's height in meters and centimeters (without shoes on)?" Percentile ranges proposed by the Centers for Disease Control and Prevention (CDC), which are age and sex specific, were applied to the derived BMI variable. Categories were collapsed resulting in three response options; underweight (<5th percentile), normal weight (5-<85th percentile) and overweight or obese (≥85th percentile), with normal weight as the reference group. The NLSCY offers BMI classifications using the CDC and Cole method, though, for the purpose of this analysis, the CDC method was chosen. A Canadian study comparing different BMI classifications demonstrated that these tools provide similar estimates. [205] However, when classifying children's BMI, the use of specific percentiles, and the use of national standards, as opposed to internationally derived cut-offs have been argued as more effective. [206] Moreover, the CDC method uses one-month age intervals, as opposed to 6 month intervals used by the Cole method. This allows for a more comprehensive classification, specifically since the children in this study are close in age.

4.7.2 Peri-partum events

Peri-partum events were considered by three different questions. First, the PMK was asked, "was the child born headfirst?", to which she could answer "yes" or "no". This question was later removed, as the percentage of children not born headfirst was too low. Secondly, the PMK answered "Was the delivery vaginal or cesarean?" and "For the delivery, were any birthing aids used?". The response categories were dichotomized to either "forceps or cupping glass" and "none" with the latter as the reference group.

4.8 Data Analysis

All statistical analyses (including application of inclusion/exclusion criteria, merging of the data files and final analysis) were performed using SAS® 9.3, SAS Institute Inc., Cary, NC.

4.8.1 Statistical Analysis

Surveys weights present the average number of children each respondent represents, and is calculated by the inverse of the probability of selection, adjusted for non-response and post-stratification (sex, age and province). Longitudinal standardized funnel weights were applied to all statistical analyses. Moreover, to account for the complex design (which includes stratification and clustering), the bootstrapping method was used to increase accuracy of variance estimation, and special SAS procedures developed for surveys were utilized. All analyses were also stratified by sex.

Influential observations may have a substantial effect on parameter estimates or fit statistics. A preliminary review of these observations was done be comparing weighted and unweighted regression estimates. In accordance with guidelines provided by Statistics Canada, influential observations were assessed using the DFBeta criteria. Any observations with a high DFBeta value (>2) were removed from regression analysis to assess for large changes in parameter estimates (a change >10%). Within this analysis, no large DFBetas values were found suggesting that no single observation was causing instability in the parameter estimates. [207]

4.8.2 Missing Data Analysis

Examination of the baseline characteristics of those included in the final sample and those without follow-up information in cycle 8 were carried out to assess any differences. Chi-square tests and t-tests were used to compare categorical and continuous variables respectively. Again, funnel weights were applied and the bootstrapping method was used.

4.8.3 Univariate and univariable analyses

Primary analysis of the variables included examination of their frequency or mean distributions. Cross-tabulations of each variable with the outcome, stratified by sex, were subsequently performed to assess cell count. Inadequate frequencies resulted in collapsing of one or more categories based on requirements illustrated by Statistics Canada (must have an unweighted cell count greater than 5).

Univariable associations between each variable and the outcome were examined using logistic regression, stratified by sex, with longitudinal funnel weights and bootstrapping variance estimation applied.

4.8.4 Multivariable analyses

In order to estimate the association between being LGA and developmental attainment (objective 1), multivariable logistic regression was used. Similar to the above analysis, the regression analyses were stratified by sex, with longitudinal funnel weights and bootstrapping variance estimation applied.

A multivariable model was fitted which included the main hypothesized predictor (LGA) and a minimally sufficient set of confounders dictated by the conceptual model and the Greenland framework. [194] Two separate models were fitted for males and females, examining verbal ability and externalizing behaviour problems separately.

4.8.5 Interaction Analysis

In order to address objective 2a, an interaction term (maternal diabetes*LGA) was added into all of the final regression models.

Multivariable logistic regression, with bootstrapping variance estimation and longitudinal weights, was used to test the interaction term for the two outcomes individually, and again, stratified by sex.

4.8.6 Mediation Analysis

In order to address objective 2b, mediation was tested following the criteria proposed by Baron and Kenney:

1. Demonstrate that being LGA is associated with developmental attainment, establishing that there is an effect to be mediated.
2. Demonstrate an association between being LGA and a child's BMI, the proposed mediator.
3. Demonstrate that child's BMI is associated with developmental attainment, even while controlling for the child's LGA status.

If the association between LGA on developmental attainment, while controlling for a child's BMI, is zero, this provides support for full mediation, while if it has been reduced in absolute size and is non-zero, partial mediation is supported. [208-209]

For step 1 and 3, logistic regression was used, while for step 2, multinomial regression was used since BMI has a three-level response category. Again, the bootstrapping method was used, longitudinal weights were applied, and analyses were stratified by sex.

4.8.7 Sensitivity Analysis

Due to the unique method of confounder selection, a sensitivity analysis was performed with consideration of all confounders included in the DAG to examine if similar results would be found. Models were built with block-wise entry of variables according to conceptual categories utilized throughout this thesis (pre-natal factors and post-natal factors). Backwards elimination was performed at each step using a p-value of less than 0.20 to retain variables. After all variables had been added and assessed, a final p-value of less than 0.05 was used to build the final model. The main exposure (LGA) was forced into each of the models regardless of statistical significance.

Multivariable logistic regression, along with the bootstrapping method and longitudinal funnel weights applied were used. Models were built for each outcome separately, and again, stratified by sex.

Table 4.1 – Description of the original variables from the NLSCY, and recoding for use in this study [210-212]

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Exposure				
Size for gestational age	6	What is the birth weight of your child in kg? How many days before or past your due date did you deliver? (Derived variable)	Open	Created a binary variable using sex-specific reference points **Appropriate for gestational age** Large for gestational age
Outcome				
PPVT-R	8	N/A	N/A	Created a binary variable from the standardized score, separately for boys and girls: Poor verbal ability $\leq 15^{th}$ percentile **Appropriate verbal ability >15th percentile**
Hyperactivity	8	How often would you say this child: a) can't sit still or is restless b) is easily distracted, has trouble sticking to any activity? c) can't concentrate, can't pay attention for long? d) is impulsive, acts without thinking? e) has difficulty waiting for his turn in games or groups? f) cannot settle on anything for more than a few moments g) is inattentive?	Never or not true Sometimes or somewhat true Often or very true	Drew questions from Montreal Longitudinal Study Final score: 0-15, high score indicates hyperactivity and attentive problems Continuous

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Physical aggression	8	How often would you say this child: a) gets into many fights? b) when somebody accidentally hurts him, he reacts with anger and fighting? c) physically attacks people? d) threatens people? e) bullies or is mean to others? f) kicks, bites or hits other children?	Never or not true Sometimes or somewhat true Often or very true	Drew questions from Montreal Longitudinal Study and Ontario Child Health Survey Final score: 0-12, high score indicates conduct disorder and aggressive behaviour Continuous
Indirect aggression	8	How often would you say this child, when mad at someone: a) tries to get others to dislike that person? b) becomes friends with another as revenge? c) says bad things behind the others back? d) says to others, let's not be with him? e) tells that person's secrets to a third person	Never or not true Sometimes or somewhat true Often or very true	Drew questions from a research group in Finland Final score: 0-10, high score indicates behaviours associated with indirect aggression Continuous
Externalizing Behaviour	8	See above	See above	Created a binary variable from final scores, separately for boys and girls Composite outcome (must have scored in top 10th percentile on any one of the scales) Externalizing behavioural problem >90th percentile **No externalizing behaviour problem ≤90th percentile**

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Pre-natal Factors				
Parity	6	How many babies have you had?	Open	Creating a categorical variable **1** 2 ≥3
Maternal age	6	Age of biological mother at birth of child	Open	Rescaled to original value/10 for analysis Continuous
Marital status	7	Marital status	Married Living Common-law Widowed Separated Divorced Single	Re-categorized due to cell size **Married** Living common-law Widowed, separated, divorced or single
Maternal education	7	Highest level of schooling obtained	Less than secondary Secondary graduation Some post-secondary College, University Other	Re-categorized due to cell size Less than secondary, or secondary graduation Some post-secondary **College, University or Other**
Income	7	What is the best estimate of your total household income from all sources in the past 12 months, that is the total income from all household members? Derived income cut-off based on size of area of residence, and number of people living in household	Open	Created binary variable by comparing income to derived cut-offs provided by the NLSCY Low income (fell below cutoff) **Not low income** (fell above cutoff)

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Maternal race	7	How would you describe your race or color?	White Chinese, South Asian, Black, Native/Aboriginal, Arab/West Asian, Asian, Filipino, South East Asian, Latin American, Japanese, Korean or Other	Re-categorized due to cell size **White** Other
Country of birth	7	In what country were you born?	Canada China, France, Germany, Greece, Guyana, Hong Kong, Hungary, India, Italy, Jamaica, Netherlands, Philippines, Poland, Portugal, U.K., U.S., Vietnam or Other	Re-categorized due to cell size **Canada** Other
Maternal smoking	6	Did you smoke during your pregnancy with this child?	Yes No	Yes **No**
Maternal alcohol use	6	How frequently did you consume alcohol during your pregnancy with this child?	Never Less than once a month 1-3 times a month once a week 2-3 times a week 4-6 times a week every day	Re-categorized to create a binary variable Yes (any alcohol use) **No (no alcohol use)**
Maternal diabetes	6	Do you have any of the following long-term condition: diabetes? During this pregnancy with this child, dud you suffer from any of the following: pregnancy diabetes?	Yes No	Combined into one variable representing any type of diabetes Yes **No**

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Post-natal factors				
Breastfeeding	7	Did you breastfeed your child even if only for a short time? For how long did you breastfeed this child?	Yes No Less than 1 week, 1-4 weeks, 5-8 weeks, 9-12 weeks, 3-6 months, 7-9 months, 10-12 months, 13-16 months, more than 16 months	Combined two questions to create one BF variable No BF, or BF up to 4 weeks BF 5 weeks to 6 months **BF greater than months**
Child stimulation	7	How often do you or your spouse get a chance to do the following with this child? Tell stories to him	Rarely or never Few times per month Once a week Few times per week Daily	Re-categorized due to cell size Rarely, never, few times a month Once a week, few times per week **Daily**
Parenting (Positive Interaction)	7	How often do you: a) praise this child by saying something like ‘good for you’ or ‘what a nice thing you did’ or ‘that’s good going’? b) and this child talk or play with each other, focusing attention on each other for 5 minutes or more, just for fun? c) and this child laugh together? d) do something special with this child that he enjoys? e) play sports, hobbies or games with this child?	Never About once a week or less A few times per week 1-2 times per day Many times each day	Questions provided by Dr. M. Boyle. Adaptation of the Parent Practices Scale of Strayhorn and Weidman. Final score: 0-20, with a high score indicating positive interactions Continuous

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Parenting (ineffective)	7	How often do you: a) get annoyed with this child for saying or doing something that he is not supposed to? b) get angry when you punish this child? c) think the kind of punishment you give this child depends on your mood? d) feel you are having problems managing this child in general? e) have to discipline this child repeatedly for the same thing? of all the times that you talk to this child about his behaviour, f) what proportion is disapproval? g) what proportion is praise? (R)	Never Less than half the time Half the time More than half the time All the time The questions with a "R" after them indicate that they were reversed for scoring	Questions provided by Dr. M. Boyle. Adaptation of the Parent Practices Scale of Strayhorn and Weidman. Finale score: 0-28, with a higher score indicating hostility and ineffective parenting practices Continuous
Parenting (rational)	7	How often, do you as his parent, do each of the following when this child breaks the rules or does things that he is not supposed to: a) raise your voice, scold or yell at him b) use physical punishment c) calmly discuss the problem (R) d) describe alternative ways of behaving that are acceptable (R)	Never Rarely Sometimes Often Always The questions with a "R" after them indicate that they were reversed for scoring	Questions provided by Dr. M. Boyle. Adaptation of the Parent Practices Scale of Strayhorn and Weidman. Finale score: 0-16, with a higher score indicating punitive and aversive parenting practices Continuous

Variable	Cycle	Original Question	Original Response Categories	Recode and Comments (Bold=reference group)
Maternal depression	7	How often have you felt or behaved this way during the past week?: a) I did not feel like eating b) I felt that I could not shake off the blues, even with help from my friends c) I had trouble keeping my mind on what I was doing d) I felt depressed e) I felt that everything I did was an effort f) my sleep was restless g) I felt lonely h) I had crying spells i) I felt that people disliked me j) I felt hopeful about the future (R) k) I was happy (R) l) I enjoyed life (R)	Rarely or none of the time Some or a little of the time Occasionally or a moderate amount of the time Most or all of the time The questions with a "R" after them indicate that they were reversed for scoring	Shortened version of the depression scale from the CES-D Final score: 0-36, with higher score indicating more depressive symptoms Continuous
Mediators				
Child's BMI	7	What is the child's weight in kilograms and grams? What is the child's height in meters and centimeters (without shoes on)?	Derived variable from the NLSCY using the two questions. CDC percentiles applied.	Sex and age specific cut-offs were applied Underweight (<5th %ile) **Normal weight (5-<85th %ile)** Overweight or obese (≥85th %ile)
Peri-partum events	6	Was the delivery vaginal or cesarean? For delivery, were any birthing aids used?	Vaginal Cesarean None Forceps Cupping Glass	**Vaginal** Cesarean Re-categorized due to cell size **None** Forceps or Cupping Glass

Chapter 5 – Results

5.1 Sample Characteristics

The selection of the final study sample can be seen in Figure 5.1. There were 4684, 4650 and 3852 individuals selected for inclusion in each of the early development cohorts for cycles 6, 7 and 8 respectively. After applying the inclusion criteria that the PMK was the biological mother, the birth was singleton, and that the child must have entered in cycle 6 as a 0-1 year-old, 3794 respondents remained. Finally, respondents must have answered in all three cycles (n=1676 excluded) and infants that were born SGA were excluded (n=125). Of these, there were 1685 children (52% males) who had outcome information in cycle 8, comprising the final study sample.

The characteristics of the final study sample can be seen in Table 5.1. The prevalence of poor verbal ability as measured by the PPVT-R was 17.7% for boys and 18.7% for girls, while 21.1% of boys and 16.2% of girls had an externalizing behaviour problem. In this sample, 18.5% of the children were born large for gestational age (18.7% and 18.2% for boys and girls respectively). After applying age and sex-specific percentile cut-offs developed for children, the prevalence of overweight/obesity was 37.0% and 33.8% for boys and girls respectively. Finally, only 6.2% of mothers in the sample stated that they had either gestational or pre-existing diabetes.

5.2 Missing data analysis

The results of the missing data analysis can be seen in Table B1 of Appendix B. Comparison was made between the final study sample (n=1685), and those individuals that were excluded due to missing outcome information (n=328). Differences were found among mean age at recruitment for the child, maternal education, maternal age, maternal smoking and maternal diabetes status. Overall, children and mothers in the final study sample were slightly older. Moreover, the study sample included women with a higher level of education and higher rate of maternal diabetes, and a lower rate of smoking.

5.3 Results pertaining to objective 1: "Is there an association between being LGA at birth and developmental attainment in early childhood?"

Results can be found below for verbal ability and externalizing behaviour problems. As will be demonstrated, there was no association found between being born LGA and subsequent developmental attainment in early childhood, for either boys or girls.

5.3.1 Verbal ability (PPVT-R)

Girls

Univariable associations are presented in Table 5.2. The main effect of interest (LGA) was not statistically significant. While not of direct interest to this study, a brief discussion will be made in regards to the significant univariable associations. Having a mother who was widowed, separated, divorced or single and living in a low income household increased risk for poor verbal ability (OR: 3.494 [1.336, 9.143] and OR: 3.599 [1.584, 8.176] respectively) compared to having a mother who is married, or living in a household with adequate income. Moreover, a parity of 3 or more (OR: 2.856 [1.248, 6.534]), racial identity other than white (OR: 4.188 [1.687, 10.394]), low parental stimulation as indicated by reading practices (OR: 2.698 [1.408, 5.169]) and shorter duration of breastfeeding (OR: 3.474 [1.699, 7.228]) all increased risk for poor verbal ability measured by the PPVT-R compared to girls of mothers with a lower parity, those who are White and read more often to their child and those who breastfed for a longer duration.

Multivariable analysis, controlling only for a minimally sufficient set of confounders as described in section 3.4, is presented in Table 5.4. The main effect of interest (LGA) was not statistically significant. Similarly, maternal diabetes had no association with poor verbal ability. Parity did retain a multivariable association. A child whose mother has had 3 or more previous children was found to be at an increased risk of poor verbal ability (aOR: 2.832 [1.216, 6.599]) compared to a child whose mother has had only one previous child.

Boys

Univariable associations are presented in Table 5.2. The main effect of interest (LGA) was not statistically significant. While not of direct interest to this study, a brief discussion will be made in regards to the significant univariable associations. Having a mother who fell below the income cut-off (OR: 3.393 [1.563, 7.368) and who had only secondary school education (OR: 3.100 [1.612, 5.958]) increased risk for poor verbal ability as measured by the PPVT-R, compared to children of mothers who had adequate income and a higher level of education. Furthermore, boys of mothers with a high parity (OR: 2.227 [1.077, 4.604]) and who scored higher on a depression scale (OR: 1.066 [1.005, 1.130]) increased risk compared to low parity mothers and those with a lower depression score. Finally, low parental stimulation as indicated by frequency of reading to the child also increased risk (OR: 3.259 [1.424, 7.461]) compared to parents who read to their child more frequently.

Multivariable analysis, controlling only for a minimally sufficient set of confounders is presented in Table 5.4. The main effect of interest (LGA) was not significant. Similarly, maternal diabetes had no association with poor verbal ability. Again, parity did retain a multivariable association. A child whose mother has had 3 or more previous children was found to be at an increased risk (aOR: 2.180 [1.031, 4.066]) compared to a child whose mother has had only one previous child.

5.3.2 Externalizing Behaviour Problems

Girls

Univariable associations are shown in Table 5.3 The main effect of interest (LGA) was not statistically significant. While not of direct interest to this study, a brief discussion will be made in regards to the significant univariable associations. Having a mother with maternal diabetes (OR: 3.268 [1.339, 7.977]) and who consumed alcohol during pregnancy (OR: 1.878 [1.014, 3.481]) both increased risk of externalizing behaviour problems compared to girls of mothers without diabetes and those who consumed no alcohol while pregnant. Furthermore, a high score on a maternal depression scale (OR: 1.069 [1.016, 1.124]) and ineffective or punitive parenting practices moderately increased risk (OR: 1.183 [1.090, 1.281] and OR: 1.215 [1.063, 1.388] respectively), while positive parental interactions decreased risk (OR: 0.862 [0.755, 0.984]).

Multivariable analysis, controlling only for a minimally sufficient set of confounders is presented in Table 5.5. The main effect of interest (LGA) was not significant. Maternal diabetes status was associated with increased risk of externalizing behaviour problems (aOR: 2.868 [1.068, 7.706]), compared to girls whose mothers did not have maternal diabetes.

Boys

Univariable analyses are presented in Table 5.5. The main effect of interest (LGA) was not statistically significant. While not of direct interest to this study, a brief discussion will be made in regards to the significant univariable associations. Having mothers who smoked during pregnancy increased risk for externalizing behaviour problems compared to boys of mothers who did not smoke (OR: 2.333 [1.270, 4.287]). Moreover, a higher maternal score on a depression scale (OR: 1.060 [1.012, 1.109]), ineffective parenting (OR: 1.235 [1.145, 1.332]) and punitive parenting (OR: 1.288 [1.163, 1.427]) increased risk for externalizing behaviour problem.

Multivariable analysis, controlling for only the minimum set of confounders, is presented in Table 5.5. There were no statistically significant associations.

5.4 Results pertaining to objective 2: "to what extent are pre-natal and post-natal factors responsible for any association between being LGA at birth and developmental attainment in early childhood?"

5.4.1 Interaction Analyses

To assess objective 2a (attribution of maternal diabetes), an interaction term (maternal diabetes*large for gestational age) was added to all multivariable logistic regression models. No evidence was found to suggest that the presence of maternal diabetes changed the association between being LGA and subsequent developmental attainment (all p-interaction values >0.8).

5.4.2 Mediation Analyses

To assess objective 2b (attribution of child's BMI), mediation was tested. Although there were no main associations between LGA and developmental attainment for boys or girls on either outcome, some authors have suggested that mediation should still be tested. It is thought that an indirect association between the exposure and outcome is still possible, even in the absence of a main effect. That being said, mediation was tested using the Baron and Kenney method, and the results were unchanged. All models were statistically insignificant, so the results are not shown. No evidence for mediation was found.

5.4.3 Sensitivity Analysis

To assess if similar results would be found if all confounders were considered as opposed to a minimally sufficient set, sensitivity analyses were performed using a series of block-wise entry and backwards elimination processes. Final results can be seen in Tables C1, C2, C3 and C4 of Appendix C. Results were unchanged even after consideration of all confounders, as the main effect (LGA) remained statistically insignificant in all models for both boys and girls, and on both outcomes.

Table 5.1 – Baseline characteristics of boys and girls at ages 0-3 (Cycles 6 and 7)

Characteristic	Girls (n=803) n(%) or mean (SD)	Boys (n=882) n(%) or mean (SD)	All (n=1685) n(%) or mean (SD)
Exposure			
Size for gestational age			
Appropriate for gestational age	657 (81.8)	717 (81.3)	1374 (81.5)
Large for gestational age	146 (18.2)	165 (18.7)	311 (18.5)
Outcome			
Mean standardized PPVT-R Score	102.58 (16.03)	101.11 (15.71)	101.82 (15.88)
Verbal ability			
Poor	150 (18.7)	156 (17.7)	N/A
Appropriate	653 (81.3)	726 (82.3)	
Externalizing behaviour problem			
Top 10th percentile	130 (16.2)	186 (21.1)	N/A
≤90th percentile	673 (83.8)	696 (78.9)	
Pre-natal factors			
Parity			
1	309 (41.8)	342 (41.2)	651 (41.4)
2	244 (33.0)	316 (38.0)	560 (35.6)
≥3	187 (25.2)	173 (20.8)	360 (23.0)
Mean maternal age at birth	29.53 (5.29)	29.55 (5.46)	29.54 (5.38)
Marital status			
Married	519 (64.7)	598 (67.7)	1117 (66.3)
Living common-law	154 (19.2)	160 (18.2)	314 (18.7)
Widowed, separated, divorced or single	130 (16.1)	124 (14.1)	254 (15.0)
Maternal level of education			
<Secondary or secondary graduation	142 (18.8)	165 (19.4)	307 (19.2)
Some post-secondary	89 (11.9)	100 (11.8)	189 (11.8)
College, University or other	521 (69.3)	583 (68.8)	1104 (69.0)
Income status			
Not low income	648 (80.7)	747 (84.7)	1395 (82.8)
Low income	155 (19.3)	135 (15.3)	290 (17.2)

Characteristic	**Girls (n=803) n(%) or mean (SD)**	**Boys (n=882) n(%) or mean (SD)**	**All (n=1685) n(%) or mean (SD)**
Maternal race			
White	653 (87.2)	740 (87.3)	1393 (87.3)
Other	95 (12.8)	108 (12.7)	203 (12.7)
Maternal country of birth			
Canada	622 (82.8)	740 (87.4)	1362 (85.2)
Other	129 (17.2)	108 (12.6)	237 (14.8)
Smoking during pregnancy			
Yes	102 (12.8)	98 (11.2)	200 (12.0)
No	694 (87.2)	773 (88.8)	1467 (88.0)
Alcohol use during pregnancy			
Yes	124 (15.5)	147 (16.9)	271 (16.2)
No	672 (84.5)	724 (83.1)	1396 (83.8)
Maternal diabetes			
Yes	40 (5.00)	65 (7.4)	105 (6.2)
No	763 (95.00)	817 (92.6)	1580 (93.8)
Post-natal factors			
Breastfeeding practices			
Never or up to 4 weeks	112 (16.2)	128 (16.1)	240 (16.2)
5 weeks to 6 months	221 (31.9)	268 (33.9)	489 (32.9)
Greater than 6 months	360 (51.9)	396 (50.0)	755 (50.9)
How often do you read to this child?			
Rarely, never or a few times a month	73 (9.1)	71 (8.1)	144 (8.5)
Once a week or a few times a week	183 (22.8)	243 (27.6)	426 (25.3)
Daily	547 (68.1)	568 (64.3)	1115 (66.2)
Mean parenting scores			
Positive interactions (0-20)	16.62 (2.89)	16.56 (2.25)	16.59 (2.27)
Ineffective parenting (0-28)	8.60 (3.52)	8.99 (3.28)	8.80 (3.40)
Rational parenting (0-16)	3.94 (2.08)	4.22 (2.04)	4.09 (2.07)
Mean maternal depression score (0-36)	4.03 (4.67)	4.16 (4.95)	4.10 (4.81)

Characteristic	Girls (n=803) n(%) or mean (SD)	Boys (n=882) n(%) or mean (SD)	All (n=1685) n(%) or mean (SD)
Mediators			
Child's BMI – CDC Method			
Underweight (<5th percentile)	74 (15.4)	85 (15.0)	159 (15.2)
Normal weight (5 - <85th percentile)	243 (50.8)	270 (48.0)	513 (49.3)
Overweight or Obese (≥85th percentile)	162 (33.8)	208 (37.0)	370 (35.5)
Type of delivery			
Vaginal	601 (74.8)	669 (75.9)	1270 (75.4)
Cesarean	202 (25.2)	213 (24.1)	415 (24.6)
Delivery aid			
None	522 (86.9)	546 (81.9)	1068 (84.3)
Forceps or suction cup	79 (13.1)	120 (18.1)	199 (15.7)

*Frequencies were rounded to the nearest whole number

Table 5.2 – Unadjusted odds ratios (95% CI) for poor verbal ability as measured by the PPVT-R, for boys and girls aged 4-5

	Boys OR (95% CI)	Girls OR (95% CI)
Size for gestational age		
AGA	Ref	Ref
LGA	0.847 (0.394, 1.818)	1.080 (0.434, 2.690)
Parity		
1	Ref	Ref
2	1.367 (0.735, 2.542)	1.125 (0.456, 2.780)
>3	2.227 (1.077, 4.604)	2.856 (1.248, 6.534)
Marital Status		
Married	NS	Ref
Living common law		1.987 (0.954, 4.139)
Widow, separated, divorced, single		3.494 (1.336, 9.143)
Maternal level of education		
<Secondary or secondary graduation	3.100 (1.612, 5.958)	1.601 (0.622, 4.120)
Some post-secondary	2.040 (1.050, 3.964)	2.029 (0.730, 5.640)
College, University or Other	Ref	Ref
Income Status		
Low income	3.393 (1.563, 7.368)	3.599 (1.584, 8.176)
Not low income	Ref	Ref
Maternal race		
White	NS	Ref
Other		4.188 (1.687, 10.394)
Maternal country of birth		
Canada	NS	Ref
Other		2.011 (0.864, 4.681)
Breastfeeding		
Never or up to 4 weeks	NS	1.907 (0.524, 6.936)
5 weeks to 6 months		3.474 (1.669, 7.228)
Greater than 6 months		Ref
How often do you read to this child?		
Rarely, never or a few times a month	3.259 (1.424, 7.461)	2.224 (0.767, 6.446)
Once a week or a few times a week	2.815 (1.443, 5.495)	2.698 (1.408, 5.169)
Daily	Ref	Ref
Parenting Practices		
Positive interaction	NS	NS
Ineffective		NS
Rational		1.121 (0.957, 1.314)
Maternal depressive symptoms	1.066 (1.005, 1.130)	NS
Delivery Aid		
None	Ref	NS
Forceps or suction Cup	0.518 (0.197, 1.361)	

Only results with a p<0.2 are displayed in this table (except for the exposure variable), however, other variables that were examined include maternal diabetes, child's BMI, smoking during pregnancy, alcohol use during pregnancy, maternal age at birth, and type of delivery.
NS = not significant at p<0.2 level

Table 5.3 – Unadjusted odds ratios (95% CI) for externalizing behaviour problems, for boys and girls aged 4-5

	Boys OR (95% CI)	Girls OR (95% CI)
Size for gestational age		
AGA	Ref	Ref
LGA	0.973 (0.529, 1.792)	1.113 (0.497, 2.490)
Marital Status		
Married	Ref	Ref
Living common law	1.537 (0.809, 2.923)	1.390 (0.667, 2.895)
Widow, separated, divorced, single	1.191 (0.582, 2.439)	0.529 (0.235, 1.191)
Income Status		
Low income	1.871 (0.957, 3.657)	0.511 (0.247, 1.057)
Not low income	Ref	Ref
Smoking during pregnancy		
Yes	2.333 (1.270, 4.287)	1.924 (0.989, 3.744)
No	Ref	Ref
Alcohol use during pregnancy		
Yes	NS	1.878 (1.014, 3.481)
No		Ref
Maternal Diabetes		
Yes	NS	3.268 (1.339, 7.977)
No		Ref
How often do you read to this child?		
Rarely, never or a few times a month	1.549 (0.680, 3.530)	2.470 (0.826, 7.388)
Once a week or a few times a week	1.462 (0.865, 2.472)	1.412 (0.785, 2.540)
Daily	Ref	Ref
Parenting Practices		
Positive interaction	0.921 (0.823, 1.030)	0.862 (0.755, 0.984)
Ineffective	1.235 (1.145, 1.332)	1.183 (1.090, 1.281)
Rational	1.288 (1.163, 1.427)	1.215 (1.063, 1.388)
Maternal depressive symptoms	1.060 (1.012, 1.109)	1.069 (1.016, 1.124)
Child's BMI – CDC Method		
Underweight (<5th percentile)	1.491 (0.573, 3.881)	NS
Normal weight (5-<85th percentile)	Ref	
Overweight or Obese (≥85th percentile)	0.570 (0.304, 1.068)	
Type of delivery		
Vaginal	Ref	NS
C-section	0.801 (0.452, 1.420)	
Delivery Aid		
None	Ref	NS
Forceps or suction Cup	1.553 (0.805, 2.995)	

Only results with a p<0.2 are displayed in this table (except for the exposure variable), however, other variables that were examined include maternal level of education, maternal age at birth, parity, maternal race, maternal country of birth, type of delivery, and breastfeeding practices.
NS = not significant at p<0.2 level

Table 5.4 – Adjusted odds ratios (95% CI) for poor verbal ability as measured by the PPVT-R for boys and girls aged 4-5, adjusted for a minimally sufficient set

	Unadjusted ORs (95%CI)	**Adjusted ORs (95%CI)**
GIRLS		
Size for gestational age		
AGA	Ref	Ref
LGA	1.080 (0.434, 2.690)	1.106 (0.397, 3.078)
Maternal diabetes		
Yes	1.176 (0.287, 4.817)	1.107 (0.258, 4.740)
No	Ref	Ref
Parity		
1	Ref	Ref
2	1.125 (0.456, 2.780)	1.119 (0.460, 2.724)
≥3	2.856 (1.248, 6.534)*	2.832 (1.216, 6.599)*
BOYS		
Size for gestational age		
AGA	Ref	Ref
LGA	0.847 (0.394, 1.818)	0.649 (0.294, 1.432)
Maternal diabetes		
Yes	2.057 (0.591, 7.154)	2.084 (0.557, 7.795)
No	Ref	Ref
Parity		
1	Ref	Ref
2	1.367 (0.735, 2.542)	1.391 (0.755, 2.565)
≥3	2.227 (1.077, 4.604)*	2.180 (1.031, 4.606)*

* $p<0.05$

Table 5.5 – Adjusted odds ratios (95% CI) for externalizing behaviour problems for boys and girls aged 4-5, adjusted for a minimally sufficient set

	Unadjusted ORs (95%CI)	Adjusted ORs (95%CI)
GIRLS		
Size for gestational age		
AGA	Ref	Ref
LGA	1.113 (0.497, 2.490)	0.973 (0.409, 2.319)
Maternal diabetes		
Yes	3.268 (1.339, 7.977)*	2.868 (1.068, 7.706)*
No	Ref	Ref
Parity		
1	Ref	Ref
2	1.011 (0.576, 1.776)	0.992 (0.561, 1.752)
≥3	1.169 (0.553, 2.475)	1.086 (0.500, 2.358)
BOYS		
Size for gestational age		
AGA	Ref	Ref
LGA	0.973 (0.529, 1.792)	0.975 (0.530, 1.794)
Maternal diabetes		
Yes	1.305 (0.430, 3.957)	1.277 (0.427, 3.817)
No	Ref	Ref
Parity		
1	Ref	Ref
2	0.829 (0.495, 1.390)	0.822 (0.489, 1.383)
≥3	1.014 (0.516, 1.992)	0.992 (0.522, 1.888)

* $p<0.05$

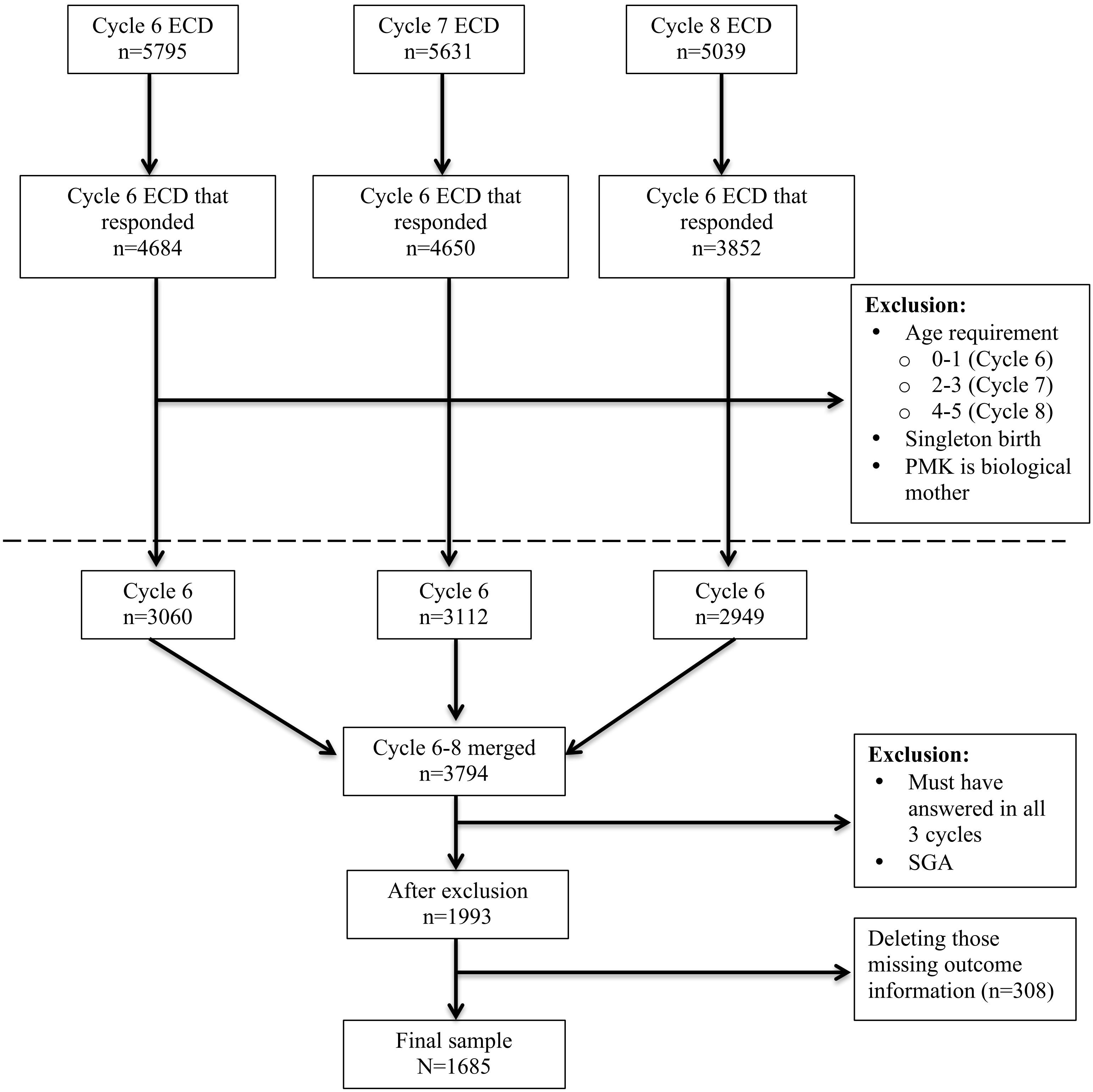


Figure 5.1 – Flowchart demonstrating selection of the final study sample

*Above the dotted line pertains to sampling characteristics of the NLSCY, and below the dotted line pertains to the selection of the final sample included in this study

Chapter 6 – Discussion

6.1 Summary and Study Contribution

This study found no evidence to suggest that LGA is associated with either verbal ability or externalizing behaviour problems in children aged four to five. No evidence was found to support the hypothesized mediation via child's BMI or mechanisms via maternal diabetes.

Contributing to the current literature, this project is one of the few that focuses on children at a young age, and during the transition from home to the school environment. [8, 42, 44, 46] Research has argued the importance of building an adequate foundation in early life, as many dimensions of development, such as motor, vocabulary, emotional and logic, have been shown to establish themselves within the first six years of age. That being said, the contributing variables may differ in early or late childhood, and thus examination of early life events is essential. [213-215]

This study also explicitly studied LGA, while many other studies solely examined macrosomia. [7, 45, 49-55, 61-63, 71] Using birth weight alone may result in misclassification, especially in post-term pregnancies. For example, according to Canadian standards, a BW between 3249 and 4528 grams for a male infant born at 43 weeks would fall within the AGA classification (between the 10^{th} and 90^{th} percentile). [176] Consideration of gestational age allowed for a more conservative and accurate view on the relation between size at birth and subsequent developmental attainment.

Finally, this study contributed a negative finding to set of mixed literature, providing further evidence as to whether a true association exists or not.

6.2 Interpretation of Findings

6.2.1 Results pertaining to objective 1: "Is there an association between being LGA at birth and developmental attainment in early childhood?"

Verbal ability and externalizing behaviour problems

This study found no association between LGA and poor verbal ability or externalizing behaviour problems for either boys or girls. These results are similar to prior findings, [48, 59-60, 67-70] specifically with Paulson's study, who used similar statistical techniques in respect to the study design. [8] That being said, it also contradicts other findings, which concluded that an association does exist, on at least one of the measured dimensions of development. [42-44, 46-47, 56, 58, 64-66]

There are several explanations that could justify why no association was found. First, these results may reflect an actual null association between the studied exposure and outcomes. Secondly, it is possible that not enough time had passed to identify a true association or to have lasting effects. Some researchers argue that aggression or behavioural deficits in children are difficult to assess in early ages as atypical behaviour is often regarded as "children growing up", [215] while other studies state that it is challenging to obtain an accurate portrayal of a child's cognitive ability prior to the age of six. [216] Thirdly, an association may exist between LGA and developmental attainment, but not on the dimensions measured. This study focused on two very specific aspects of development, and it is conceivable that other dimensions would have significant findings. Finally, it could also be speculated that the studies which found positive findings overestimated their results by either classifying LGA as >95th percentile, by using a simple birth weight cut-off or by not considering study designs within their analyses.

Nevertheless, this study found that higher parity increases risk for poor verbal ability, which is consistent with other literature. [152-153] It has been suggested that this may be due to resource dilution, hypothesizing that parents offer less time, physical resources, financial resources or less quality stimulation as they have more children. [154] Another suggestion is that there may be maternal differences during pregnancy and the post-partum period as higher parity moms tend to be more lenient in following guidelines. [155] Maternal diabetes was also found to increase risk for presentation of externalizing behaviours in girls. Very few studies have examined this specific relation, however, other literature has shown an increase in over-activity and attention-seeking behaviours in children of diabetic mothers. It is thought that abnormal glucose levels may alter fetal development, or that poor development may be a result of perinatal complications due to maternal diabetes. [122, 217-218]

6.2.2 Results pertaining to objective 2: "to what extent are pre-natal and post-natal factors responsible for the association between being LGA at birth and developmental attainment in early childhood?"

Interaction Hypothesis

There was also no evidence to support an interaction between maternal diabetes and being LGA. To our knowledge, this is the first study to examine this interaction within this context. The number of women with maternal diabetes was quite low, and it is possible that this study was not powered to assess the interaction. [219] Further, it could be speculated that by combining pre-gestational and gestational diabetes, we may be masking differences between the two.

Mediation Hypothesis

To follow a conservative approach, mediation analyses were performed even though there were no observable associations between the exposure and outcomes, and thus no "effect to be mediated". No evidence was found to support that a child's BMI acts as a mediator within the association of LGA to developmental attainment. LGA is known to increase risk for childhood obesity, [125-128] and research demonstrates that obesity has a negative impact on cognition and behaviour in children. [130-133, 134] Studies examining this association found that postnatal growth had a modest, yet negative effect on cognition and verbal ability in children. [47, 50-51] Nonetheless, it is possible that in this study, the detrimental effects of childhood obesity could not reach clinical significance at such an early age. While the CDC method for BMI classification states that it can be used in children aged 0-19, [199] other researchers suggest that it is difficult to label obesity in early age due to changes in BMI of young children. Typically, a child's BMI will increase at birth till approximately age one, where it will then decrease, followed by a second rise in BMI, termed the adiposity rebound, which commonly occurs between ages three and seven. [220] Finally, the response rate for BMI was low, which may have affected the ability to identify a true association.

6.3 Study Strengths

The primary strength of this study is the use of a large nationally representative database. Moreover, this survey was created specifically to examine early development of children, and because of that, had vast information on their birth information, environment, lifestyle, parents or guardians, as well as important complex concepts that were quantified with validated scales. This allowed for consideration of confounders that others studies were not able to include.

Secondly, an extensive literature search was performed examining all variables that may be associated with the exposure and outcome. A DAG was created based on the literature, and allowed for a selection of confounders a priori. The DAG also allows for a clear depiction of the study's assumed causal relations derived from the literature, and provides a simplified depiction of whether new associations will be created if adjustment is made for a certain variable. [221] Additionally, a minimally sufficient set of confounders was used in analysis, which has been shown to reduce bias. By adjusting for all "known confounders", the researcher may unintentionally incorporate others forms of bias, such as conditional associations or collider bias. [198]

Next, this study also carefully considered the complex study design used by the NLSCY, and incorporated appropriate statistical techniques. To allow for the complex design, which included stratification and clustering, longitudinal statistical weights, in conjunction with a replicate based variance estimation process (bootstrapping) was used. This allows for a more conservative approach to parameter and variance estimation. This is especially important if there are significant results that are very close to the rejection threshold. Failure to include these statistical techniques may result in underestimation of standard errors and biased parameter estimates. [222-223]

Also, the outcomes selected for this study had sound psychometric properties. Most studies have an "acceptable" range for a Cronbach's alpha from 0.70-0.90. [224] For externalizing behaviours, the scales have Cronbach's alpha of 0.809 and 0.774 for hyperactivity and physical aggression respectively, while indirect aggression fell just below the acceptable range with a value of 0.632. Moreover, to ensure the initial factor structure was maintained in the new sample, evaluation of each scale was undertaken. [199] Also, the PPVT-R has been shown to correlate well with many dimensions of the WISC-III (r=0.75 for vocabulary score, r=0.76 for verbal IQ and r=0.60 for full scale IQ), [199] and the original test, normed to an American population, had a median split-half reliability of 0.80 and a median test-retest reliability of 0.78. [200]

Finally, this study stratified all models by child sex. Other studies, which have failed to do so may be discounting important differences, [140] as males and females are thought to experience and respond to social cues and health determinants differently. [148]

6.4 Study Limitations

There are limitations within this study that are worth discussing. To begin, the longitudinal nature of this study required information from all 3 cycles of the ECD cohort, and as a result, a large number of children had to be excluded (n=1676). Also, of those that responded in all 3 cycles, some were missing outcome information and had to be excluded (n=308). A loss of sample size may have influenced the statistical power of this study to detect significant effects. [225]

As per many pre-designed surveys, researchers are limited to the questions and variables that are available to them, as well as the categorizations provided. While we had an abundance of valuable information, we were not able to obtain information on immigration status or post-partum depression due to low response rate. Also, no information was available in regards to parental stature, or maternal weight gain during pregnancy. [220]

Moreover, survey respondents may answer inaccurately to sensitive questions, in order to conform to socially acceptable behaviours. Research has shown that respondents are more likely to either not respond at all, or underreport negative behaviours. [226-227] In this case, the PMK may have been less likely to account for negative behaviours of their child.

Additionally, since the majority of the questionnaire is self-reported, recall bias may have affected the accuracy and completeness of this information. For example, studies have shown that parents tend to inaccurately report their child's height and weight, which may have affected the derived BMI. [228] However, at least for the exposure, maternal reports of birthing information, such as infant birth weight and type of delivery have been shown to be accurate. [229]

6.5 Conclusions and Future Directions

This study finds no evidence to support an association between being born large for gestational age and developmental attainment in either males or females on the two specific dimensions of verbal ability and externalizing behaviour problems. Furthermore, no evidence was found to support the hypothesized mechanisms of maternal diabetes or child's BMI.

Further research is needed into other dimensions of development. This study looked at two specific facets, however, the literature review that was performed supported research in many other areas, such as internalizing behaviour, impulsivity or psychopathology.

Additionally, further examination is needed into the mechanisms that may be driving this association, if any. Building a model where LGA falls as a mediator between maternal diabetes or parity and developmental attainment may be quite interesting, especially the latter, since parity was found to increase risk or poor verbal ability for both boys and girls. [154-155] It would also be useful to perform a full longitudinal analysis to assess mechanisms in early childhood, as well as late childhood, and any differences that may present themselves over time. This would provide a unique insight to the attribution of post-natal environmental variables.

Finally, a more comprehensive approach into defining size for gestational age may be of interest to target children who are most at risk. For example, researchers could compare moderate (>90th percentile) and extreme (>95th percentile) LGA, or infants who are truly LGA versus those that are constitutionally large.

Ongoing identification of risk factors for poor development is important in the improvement of primary prevention and as well to understand the underlying mechanisms driving the association. Research has demonstrated that early childhood development programs show both immediate and long-term benefits for the child, and can lower future public expenditures (welfare, grade repetition costs, etc.). [35-36, 230-231] There is likely no single path from biological, social or environmental variables to poor development, thus, continuing examination into numerous variable and pathways is paramount.

Although this study failed to find an association between being born large for gestational age and developmental attainment on these dimensions, it nevertheless provides valuable insight into mechanisms, and contributes a negative finding to a pool of mixed literature.

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APPENDICES

Appendix A: Search strategies

Table A1 – Literature search strategy for main association (LGA to childhood development)

#	Search Term	Articles retrieved*
	PubMed	
1	Fetal macrosomia	n=2798
2	"large for gestational age" OR macrosomi* OR "large-for-gestational-age" OR "high birth weight" OR "birth weight greater than 4000 grams" (n=5106)	n=5106
3	1 OR 2	n=5106
4	exp Child Development OR exp Mental Disorders Diagnosed in Childhood OR exp child behavior (n=5720)	n=5720
5	"child development*" OR "mental disorder diagnosed in childhood" OR "attention deficit disorder" OR "attention deficit hyperactive* disorder" OR "child behaviour disorder" OR "child behaviour disorder" OR "child development disorder" OR "autism" OR "autis*" OR "asperger syndrome" OR "communication disorder" OR "learning disorder" OR "developmental disabilit*" OR "motor skill disorder" OR "schizophreni*" OR "child behaviour" OR "child behavior" OR "infant behaviour" OR "infant behavior" OR "impulse control disorder" OR "psychosocial disorder" OR ADHD OR "cognitive disorder*"	n=161438
6	4 OR 5	n=165061
7	3 AND 6	n=99
	EMBASE	
1	Large for gestational age/	n=1531
2	("large for gestational age" or macrosomi* or "large-for-gestational-age" or "high birth weight" or "birth weight greater than 4000 grams").mp	n=8739
3	1 OR 2	n=8739
4	Child Development/ or developmental disorder/ or exp autism/ or child behavior/ or exp behavior disorder/	n=470167
5	("child development*" or "mental disorder diagnosed in childhood" or "attention deficit disorder" or "attention deficit hyperactive* disorder" or "child behaviour disorder" or "child behaviour disorder" or "child development disorder" or "autism" or "autis*" or "asperger syndrome" or "communication disorder" or "learning disorder" or "developmental disabilit*" or "motor skill disorder" or "schizophreni*" or "child behaviour" or "child behavior" or "infant behaviour" or "infant behavior" or "impulse control disorder" or "psychosocial disorder" or ADHD or "cognitive disorder*").mp	n=378538

6	4 OR 5	n=658190
7	3 AND 6	n=200
	PSYCInfo	
S1	"large for gestational age" OR macrosomi* OR "large-for-gestational-age" OR "high birth weight" OR "birth weight greater than 4000 grams"	n=155
S2	Childhood development OR pervasive developmental disorders OR behavior disorders OR cognitive development	n=605220
S3	"child development*" OR "mental disorder diagnosed in childhood" OR "attention deficit disorder" OR "attention deficit hyperactive* disorder" OR "child behaviour disorder" OR "child behaviour disorder" OR "child development disorder" OR "autism" OR "autis*" OR "asperger syndrome" OR "communication disorder" OR "learning disorder" OR "developmental disabilit*" OR "motor skill disorder" OR "schizophreni*" OR "child behaviour" OR "child behavior" OR "infant behaviour" OR "infant behavior" OR "impulse control disorder" OR "psychosocial disorder" OR ADHD OR "cognitive disorder*"	n=267279
S4	S2 or S3	n=763864
S5	S1 and S4	n=62
	CINAHL	
S1	(MH “Infant, Large for Gestational Age”)	n=139
S2	“large for gestational age" OR macrosomi* OR "large-for-gestational-age" OR "high birth weight" OR "birth weight greater than 4000 grams"	n=1037
S3	S1 OR S2	n=1037
S4	(MH exp "Mental disorders diagnosed in childhood") OR (MH exp "child behavior") OR (MH "child development") OR (MH "infant development")	n=13915
S5	“child development*” OR “mental disorder diagnosed in childhood” OR “attention deficit disorder” OR “attention deficit hyperactive* disorder” OR “child behaviour disorder” OR “child behaviour disorder” OR “child development disorder” OR “autism” OR “autis*” OR “asperger syndrome” OR “communication disorder” OR “learning disorder” OR “developmental disabilit*” OR “motor skill disorder” OR “schizophreni*” OR “child behaviour” OR “child behavior” OR “infant behaviour” OR “infant behavior” OR “impulse control disorder” OR “psychosocial disorder” OR ADHD OR “cognitive disorder*”	n=53835
S6	S4 OR S5	n=53835
S7	S3 AND S6	n=21

For the remainder of the databases (Cochrane Library (n=2), Web of Science (n=42) and The Dissertations and Theses database (n=7) and Google Scholar (n=0)), a search was done using only the keywords, which are the terms in quotations.
*These numbers reflect the retrieved articles prior to exclusion of outdated articles, those not in English or French, and those that are not relevant.

Table A2 – Literature search strategy for mechanisms associating LGA and childhood development using EMBASE

#	**Search Term**	**Articles retrieved***
	EMBASE	
1	Child, Preschool/ or Child/	n=1689437
2	Child development/ OR developmental disorder/ OR child behaviour/ OR behaviour disorder/ OR cognition/	n= 313906
3	Large for gestational age/ or Macrosomia/	n= 5813
4	Maternal diabetes mellitus/ OR Pregnancy diabetes mellitus/ OR Maternal obesity/	n=25878
5	Childhood obesity/	n=5866
6	1 AND 2	n=78115
7	4 AND 6	n=88
8	4 AND 3	n=2853
9	5 AND 6	n=194
10	5 AND 3	n=68

*These numbers reflect the retrieved articles prior to exclusion of outdated articles, those not in English or French, and those that are not relevant.

Appendix B: Missing Data Analysis

Table B1 – Comparing the study sample to those without follow-up information (excluded due to missing outcome)

Characteristic	Study sample N=1685 n(%)	Missing outcome N=328 n(%)	Test Statistic T-test or Chi^2 p-value
Mean age at recruitment (months)	14.25	13.05	p=0.0133
Size for gestational age			
AGA	1374 (81.5)	269 (82.2)	p=0.8425
LGA	311 (18.5)	59 (17.8)	
Maternal diabetes			
Yes	105 (6.2)	9 (2.7)	p= 0.0461
No	1580 (93.8)	319 (97.3)	
Child's BMI	16.92	17.54	p= 0.0781
Child's BMI – CDC Method			
Underweight	159 (15.2)	26 (13.6)	p=0.5703
Normal weight	513 (49.3)	86 (45.0)	
Overweight or Obese	370 (35.5)	79 (41.4)	
Marital status			
Married	1117 (66.3)	229 (70.0)	p=0.3940
Living common-law	314 (18.7)	47 (14.2)	
Widow, separated, divorced or single	254 (15.0)	52 (15.8)	
Income status			
Low income	290 (17.2)	72 (21.9)	p=0.1762
Not low income	1395 (82.8)	256 (78.1)	
Maternal level of education			
<Secondary or secondary grad	307 (19.2)	78 (25.6)	p=0.0117
Some post-secondary	189 (11.8)	54 (18.0)	
College/University/Other	1104 (69.0)	169 (56.4)	
Smoking during pregnancy			
Yes	200 (12.0)	66 (20.3)	p=0.0065
No	1467 (88.0)	258 (79.7)	
Alcohol use during pregnancy			
Yes	271 (16.2)	49 (15.1)	p=0.7499

No	1396 (83.8)	275 (84.9)	
Maternal age at birth	29.54	28.51	p=0.0348
Parity			
1	651 (41.4)	105 (36.1)	p=0.4167
2	560 (35.6)	109 (37.5)	
>3	360 (23.0)	77 (26.4)	
Maternal race			
White	1393 (87.3)	242 (80.8)	p= 0.0774
Other	203 (12.7)	58 (19.2)	
Maternal country of birth			
Canada	1362 (85.2)	240 (80.3)	p=0.1901
Other	237 (14.8)	59 (19.7)	
Type of delivery			
Vaginal	1270 (75.4)	245 (74.8)	p= 0.8699
Cesarean	415 (24.6)	83 (25.2)	
Delivery Aid			
None	1068 (84.3)	210 (86.0)	p= 0.6531
Forceps or suction cup	199 (15.7)	34 (14.0)	
Maternal depression score	4.10	4.36	p=0.6332
Parenting Scales			
Positive Interaction	16.59	16.59	p=0.9817
Ineffective parenting	8.80	8.13	p=0.0821
Rational parenting	4.09	3.86	p=0.2854
How often do you read to this child?			
Rarely, never or a few times a month	144 (8.5)	26 (7.8)	p= 0.8576
Once a week or a few times a week	426 (25.3)	89 (27.2)	
Daily	1115 (66.2)	213 (65)	
Breastfeeding practices			
Never or less than 4 weeks	240 (16.2)	60 (22.0)	p= 0.1239
5 weeks to 6 months	489 (32.9)	99 (36.2)	
Greater than 6 months	755 (50.9)	115 (41.8)	

*Frequencies were rounded to the nearest whole number

Appendix C: Sensitivity Analysis

Table C1 – Adjusted odds ratios (95 CI%) for poor verbal ability as measured by the PPVT-R for girls aged 4-5, adjusted for all available confounders using block-wise entry and backwards elimination

Variable	Block 1 (pre-natal) R^2= 0.1283 Adjusted R^2= 0.2147	Block 2 (post-natal) R^2= 0.1479 Adjusted R^2= 0.2451	Final model ($p<0.05$) R^2= 0.1342 Adjusted R^2= 0.224
Size for gestational age			
AGA	Ref	Ref	Ref
LGA	1.042 (0.413, 2.628)	1.273 (0.489, 3.315)	1.155 (0.491, 2.717)
PRE-NATAL			
Marital Status			
Married	Ref	-----	-----
Living common law	2.074 (0.975, 4.412) *		
Widow, separated, divorced, single	3.141 (0.948, 10.409) *		
Country of birth			
Canada	-----	-----	-----
Other			
Race			
White	Ref	Ref	Ref
Other	2.868 (1.117, 7.361) **	2.783 (0.992, 7.804) *	2.911 (1.134, 7.740) **
Education			
<Secondary or secondary grad	-----	-----	-----
Some post-secondary			
College/University/Other			
LICO			
Low income	2.132 (0.893, 5.090) *	4.502 (1.758, 11.526) **	4.277 (1.903, 9.611) **
Not low income	Ref	Ref	Ref
Parity			
1	Ref		
2	1.241 (0.540, 2.848)	-----	-----
≥ 3	2.535 (0.991, 6.484) *		
POST-NATAL			
Breastfeeding			
No or <4 weeks	------	1.717 (0.391, 7.545)	1.903 (0.558, 6.493)
5 weeks to 6 months		3.165 (1.486, 6.744) **	3.553 (1.683, 7.499) **
>6 months		Ref	Ref
Reading			
Rarely/never/few times a month	-------	1.779 (0.244, 12.970)	-----
Once a week/few times a week		2.258 (1.090, 4.680) **	
Daily		Ref	
Parenting (rationality)	-------	-----	-----

*$p<0.2$, **$p<0.05$

Table C2 – Adjusted odds ratios (95 CI%) for externalizing behaviour problems for girls aged 4-5, adjusted for all available confounders using block-wise entry and backwards elimination

Variable	Block 1 (pre-natal) R^2= 0.0464 Adjusted R^2= 0.0795	Block 2 (post-natal) R^2= 0.1158 Adjusted R^2= 0.1976	Final model (p<0.05) R^2= 0.0863 Adjusted R^2= 0.1470
Size for gestational age			
AGA	Ref	Ref	Ref
LGA	1.144 (0.482, 2.716)	1.351 (0.543, 3.362)	1.239 (0.524, 2.930)
PRE-NATAL			
Marital Status			
Married	Ref	Ref	Ref
Living common law	1.340 (0.648, 2.770)	1.523 (0.733, 3.161)	1.605 (0.768, 3.355)
Widow, separated, divorced, single	0.307 (0.113, 0.832) **	0.217 (0.067, 0.704) **	0.218 (0.070, 0.676) **
Diabetes			
Yes	2.444 (0.861, 6.939) *	2.806 (0.905, 8.708) *	-----
No	Ref	Ref	
Smoking during pregnancy			
Yes	2.380 (1.133, 4.998) **	2.530 (1.103, 5.802) **	3.332 (1.601, 6.936) **
No	Ref	Ref	Ref
Alcohol use during pregnancy			
Yes	1.886 (0.998, 3.566) *	2.079 (1.017, 4.247) **	-----
No	Ref	Ref	
POST-NATAL			
Reading			
Rarely/never/few times a month	-----	-----	-----
Once a week/few times a week			
Daily			
Maternal depression	-----	1.049 (0.986, 1.116) *	-----
Parenting (positive interactions)	-----	0.884 (0.762, 1.026) *	-----
Parenting (ineffective)	-----	1.232 (1.131, 1.343) **	1.235 (1.135, 1.343) **
Parenting (rationality)	-----	-----	-----

*p<0.2, **p<0.05

Table C3 – Adjusted odds ratios (95 CI%) for poor verbal ability as measured by the PPVT-R for boys aged 4-5, adjusted for all available confounders using block-wise entry and backwards elimination

Variable	Block 1 (pre-natal) R^2= 0.059 Adjusted R^2= 0.1005	Block 2 (post-natal) R^2= 0.0696 Adjusted R^2= 0.1187	Final model (p<0.05) R^2= 0.0539 Adjusted R^2= 0.0926
Size for gestational age			
AGA	Ref	Ref	Ref
LGA	0.703 (0.302, 1.636)	0.724 (0.324, 1.621)	0.834 (0.372, 1.873)
PRE-NATAL			
Marital Status			
Married	Ref	-----	-----
Living common law	1.960 (1.028, 3.740) **		
Widow, separated, divorced, single	1.492 (0.409, 5.449)		
Education			
<Secondary or secondary grad	2.885 (1.448, 5.746) **	3.061 (1.538, 6.090) **	3.006 (1.515, 5.963) **
Some post-secondary	2.180 (1.181, 5.575) **	2.071 (1.048, 4.094) **	1.929 (0.982, 3.789) *
College/University/Other	Ref	Ref	Ref
LICO			
Low income	-----	-----	-----
Not low income			
Parity			
1	Ref	Ref	-----
2	1.742 (0.828, 3.666) *	1.561 (0.800, 3.046) *	
≥ 3	2.566 (1.181, 5.575) **	2.258 (1.076, 4.739) **	
POST-NATAL			
Reading			
Rarely/never/few times a month	-----	3.203 (1.353, 7.581) **	3.085 (1.296, 7.341) **
Once a week/few times a week		1.951 (0.973, 3.909) *	1.931 (0.980, 3.805) **
Daily		Ref	Ref
Maternal depression	-----	-----	-----

*p<0.2, **p<0.05

Table C4 – Adjusted odds ratios (95 CI%) for externalizing behaviour problems for boys aged 4-5, adjusted for all available confounders using block-wise entry and backwards elimination

Variable	Block 1 (pre-natal) R^2= 0.0145 Adjusted R^2= 0.0226	Block 2 (post-natal) R^2= 0.1024 Adjusted R^2= 0.1591	Final model (p<0.05) R^2= 0.1024 Adjusted R^2= 0.1591
Size for gestational age			
AGA	Ref	Ref	Ref
LGA	1.057 (0.571, 0.1959)	1.242 (0.655, 2.355)	1.242 (0.655, 2.355)
PRE-NATAL			
Marital Status Married Living common law Widow, separated, divorced, single	-----	-----	-----
Smoking while pregnant			
Yes	2.348 (1.276, 4.320) **	2.119 (1.087, 4.128) **	2.119 (1.087, 4.128) **
No	Ref	Ref	Ref
POST-NATAL			
Reading Rarely/never/few times a month Once a week/few times a week Daily	-----	-----	-----
Maternal depression	-----	1.051 (1.001, 1.103) **	1.051 (1.001, 1.103) **
Parenting (positive interactions)	-----	-----	-----
Parenting (ineffective)	-----	1.175 (1.077, 1.282) **	1.175 (1.077, 1.282) **
Parenting (rationality)	-----	1.145 (1.012, 1.295) **	1.145 (1.012, 1.295) **

*p<0.2, **p<0.05

Curriculum Vitae

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