

MACROSOMIA, MATERNAL BODY MASS INDEX, AND MENTAL HEALTH

**MATERNAL PRE-PREGNANCY BODY MASS INDEX, MACROSOMIA, AND
MENTAL HEALTH IN CHILDREN AND ADOLESCENTS**

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Requirements for the Degree Doctor of Philosophy**

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ABSTRACT

Objectives: To examine associations between macrosomia, maternal body mass index (BMI) during pregnancy, and psychopathology in youth, and to determine if these are due to prenatal environmental exposures or confounding variables.

Methods: Study 1 reviewed studies examining associations between macrosomia and mental health. Data from the Ontario Child Health Study (OCHS) were then used to explore these links in youth (Study 2). A second review summarized studies assessing associations between maternal pregnancy BMI and psychopathology in offspring (Study 3). Data from the Western Australia Pregnancy Cohort were then used to quantify associations between maternal pre-pregnancy BMI and child behaviour at age 1 and 2 (Study 4), and from 5-17 years of age (Study 5).

Results: Seven of the 15 studies that had examined associations between macrosomia and psychopathology supported a link. In the OCHS, youth born macrosomic had elevated externalizing scores compared those born at appropriate birth weights. Eight of 12 studies suggested that links exist between elevated maternal BMI during pregnancy and psychopathology in offspring. Maternal pre-pregnancy BMI was positively associated with offspring externalizing problems from age 2 to 17 and linked to less favourable trajectories of internalizing symptoms from 5-17. These findings persisted despite adjustment for confounders.

Conclusions: Youth born macrosomic have elevated levels of externalizing symptoms, though a more robust association was noted with maternal pre-pregnancy BMI. The data comprising this thesis suggest that associations between macrosomia/maternal BMI and

externalizing and internalizing problems in youth may be due to intrauterine exposures rather than confounding variables.

Keywords: macrosomia, high birth weight, pregnancy, mother, body mass index, overweight, obesity, mental disorders, internalizing, externalizing,

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None

LIST OF ABBREVIATIONS AND SYMBOLS

ACOG: American College of Obstetricians and Gynecologists
ACTH: Adrenocorticotrophic Hormone
ADH: Attention-deficit/hyperactivity
ADHD: Attention-deficit/hyperactivity disorder
ALSPAC: Avon Longitudinal Study of Parents and Children
ANOVA: Analysis of variance
APA: American Psychiatric Association
 β : Unstandardized regression coefficient
BMI: Body mass index
CD: Conduct disorder
CI: Confidence interval
CIHR: Canadian Institutes of Health Research
CBCL: Child Behavior Checklist
DAT: Dopamine transporter
DM: Diabetes mellitus
DNA: Deoxyribonucleic acid
DOHaD: Developmental origins of health and disease
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-IV-TR: DSM-IV – Text Revision
ES: Standardized Effect Size
GA: Gestational age
GDM: Gestational diabetes mellitus
HBW: High birth weight
HPA: Hypothalamic-pituitary-adrenal axis
IQ: Intelligence quotient
KEMH: King Edward Memorial Hospital
LBW: Low birth weight
LGA: Large for gestational age
LMP: Last menstrual period
N: Number
NOS: Newcastle Ottawa Scale
NS: Not significant
OCHS: Ontario Child Health Study
OD: Oppositional defiant
OR: Odds Ratio
p: probability
PGDM: Pre-gestational diabetes mellitus
RR: Relative risk
SA: Sympathoadrenal axis
SD: Standard deviation
SE: Standard error

SES: Socioeconomic status
SGA: Small for gestational age
SPSS: Statistical Package for the Social Sciences
TTS: Toddler Temperament Scale

DECLARATION OF ACADEMIC ACHIEVEMENT

This ‘sandwich’ thesis consists of five studies conceived of and written by the student. He developed their premises, objectives and goals, conducted their data analyses, prepared the manuscripts and made revisions in keeping with the suggestions of his co-authors. All of this work was completed between July 1st 2009 and April 1st, 2012. As such, the work contained herein meets the requirements for inclusion in the main text of this thesis. In keeping with the requirements of a ‘sandwich’ thesis, below I highlight the contributions made to each study by my co-authors.

Study 1 reviews the research that has examined links between being born at high birth weight and the risk of later psychopathology. It was co-authored by the thesis supervisor, Dr. Michael Boyle who critically reviewed the manuscript and made suggestions to improve it.

Study 2 examined associations between being born large or small for gestational age and internalizing and externalizing problems in youth born in Ontario, and was again co-authored by Dr. Boyle. He provided guidance on the study’s statistical analyses and critically reviewed the manuscript prior to its submission for publication.

Study 3, a systematic review of the literature assessing links between maternal overweight/obesity prior to/during pregnancy and psychopathology in offspring was co-authored by Dr. Valerie Taylor of the University of Toronto and by Dr. Boyle. They critically reviewed articles to determine their eligibility for inclusion in the review and made revisions to the manuscript.

Study 4 examined associations between maternal pre-pregnancy body mass index and temperamental and behavioural outcomes in offspring at 1 and 2 years of age, respectively. It was co-authored by Dr. Boyle, Dr. Monique Robinson of the University of Western Australia, and Dr. Louis Schmidt and Dr. Alison Niccols of McMaster University. Dr. Boyle, Dr. Schmidt, and Dr. Niccols reviewed the manuscript and Dr. Robinson served as a content resource for the Western Australia Pregnancy (Raine) Study Cohort, the sample upon which the work was based.

Finally, Study 5 assessed and quantified links between maternal pre-pregnancy body mass index and internalizing and externalizing problems throughout childhood and adolescence. It was co-authored by Dr. Boyle and Dr. Robinson. Dr. Boyle consulted on the statistical analysis and critically reviewed the final paper. Again, Dr. Robinson served as a resource on the Western Australia Pregnancy Cohort.

CHAPTER ONE

BACKGROUND

Psychopathology in Youth: Burden and Origins

One in five children will suffer from a psychiatric illness (Costello, Egger, & Angold, 2005; Offord et al., 1987) and up to 50% of the world's population will be diagnosed with a mental disorder at some point in their lifetime (Kessler et al., 1994). In Canada, mental illness is the number one cause of disability, costing \$51 billion per year in terms of health care and lost productivity (Lim, Jacobs, Ohinmaa, Schoflocker, & Dewa, 2008).

While most chronic health problems develop in adulthood, mental illness frequently emerges early in life. Behavioural problems may develop as early as the preschool years (Tremblay et al., 2004; Alink et al., 2006) and nearly 50% of adult psychiatric patients will have met diagnostic criteria for a mental disorder by adolescence (Kim-Cohen et al., 2003). Because brain plasticity is highest during gestation, infancy, and early childhood (Kolb, Gibb, & Robinson, 2003); detection and intervention strategies applied early on may offer the most efficient means by which the prevalence and severity of mental health problems may be reduced.

Psychopathology in Youth: Classification

Despite the fact that up to 20% of children and adolescents struggle with clinically significant emotional and behavioural problems, debate still exists as to whether psychopathology in youth is best defined categorically or dimensionally (Coghill & Sonuga-Barke, 2012). While psychiatry emerged as a discipline based on rules of

categorization that distinguished between ‘health’ and ‘illness’ (Mack, Forman, Breown, & Francis, 1994), the high prevalence of comorbidity, along with the belief that most forms of psychopathology represent an underlying continuum, bring into question this method of classification. The presence of clinical heterogeneity in individuals diagnosed as having the same disorder further challenges the usefulness of category-based systems of diagnosis (Sonuga-Barke 1998).

Dimensional approaches to defining psychopathology suggest that disorders exist “on a linear continuum of graded severity” (Clark et al., 1995; p. 145). This method of classification avoids wasting potentially useful clinical information that does not neatly fit into categorical diagnostic definitions, and in many cases, provides better fit to observed data (e.g., Gjone, Stevenson & Sundet, 1996). Dimensional approaches may also have greater statistical power and predictive validity for disorder than their categorical diagnostic counterparts (Fergusson & Horwood, 1995).

One particularly influential dimensional approach to classifying psychopathology replaced the categorical structure of mental health problems with empirically derived dimensions of disorder. Using a long list of descriptors of problem behaviours in children and employing multivariate and factor analytic statistical techniques, Achenbach derived a set of scales that spanned multiple continuous dimensions. This factor analysis of child behavioural data provided the basis for his Child Behavior Checklist (CBCL; Achenbach, 1991), and supported the existence of two broad-based dimensions of disorder in youth referred to as “internalizing” and “externalizing” (Achenbach, Conners, Quay, Verhulst, & Howell, 1989).

One benefit of using dimensional classification of disorder in children and adolescents is its flexibility in examining developmental trajectories over time. This is especially useful in youth psychopathology where multifinality (those with similar risk factors developing different psychopathological outcomes) and equifinality (different pathways leading to the same outcome) are common (Cicchetti & Rogosch, 1996).

More recent empirical data also support the hypothesis that the majority of emotional and behavioural problems in children and adolescents are best conceptualized as dimensional rather than categorical constructs. This work suggests that depression, aggression and attention deficit/hyperactivity disorder are more consistent with a dimensional than categorical explanation (e.g., Hankin, Fraley, Lahey, & Waldman, 2005; Walters, Ronen, & Rosenbaum, 2010; Haslam et al, 2006).

Psychopathology in Youth: Internalizing and Externalizing Problems

Internalizing problems are those marked by sadness, worry, physical complaints and shyness. Children with internalizing difficulties are often described as having emotional problems and/or as being over-controlled (Eisenberg et al, 2001; Hinshaw, 1987). These youth tend to deal with problems *internally* rather than acting them out externally. Common examples of categorically defined internalizing disorders include major depressive disorder, generalized anxiety disorder and social anxiety disorder. Children and adolescents suffering from internalizing problems are more likely to develop anxiety disorders and depressive disorders later in life (APA, 1994).

Externalizing problems are characterized by behaviours that are directed toward the *external* environment (Campbell, Shaw & Gilliom, 2000). These are often easily

observable and include overactivity, disobedience, aggression and delinquency. When categorically defined, externalizing disorders include the diagnoses attention-deficit/hyperactivity disorder, oppositional defiant disorder and conduct disorder. Increased levels of externalizing problems in children are associated with juvenile delinquency, violent behaviour and adult crime (Moffitt, 1993).

However, it is important to note that the dichotomization of child psychopathology into internalizing and externalizing problems is neither perfect nor complete, as children with internalizing difficulties may have a significant adverse impact on their external world and those with externalizing disorders may suffer ‘internally’ to a significant extent.

The Developmental Origins of Health and Disease and Prenatal Programming Hypotheses: Historical Background

Development is a process that involves a continuous interchange between an individual and his/her environment. The emergence of the emotional and behavioural regulation systems underlying human psychological development and function requires environmental inputs during gestation and postnatal life. However, adverse or stressful exposures, particularly those occurring in prenatal or early postnatal life, can negatively impact this development and affect the emergence of psychopathology later on.

The Developmental Origins of Health and Disease (DOHaD) hypothesis posits that environmental exposures occurring during early life (including gestation and the first two to three years after birth) can affect an organism’s physiology in persistent ways that increase their risk of developing disease later on. When the period of exposure is

restricted to gestation, later effects are often referred to as being due to ‘prenatal programming’ (Gluckman & Hanson, 2005).

Though widely regarded as a recent scientific development, data supporting the DOHaD and prenatal programming hypotheses first emerged in the early 1900s (Gliboff, 2005). At this time, the Viennese biologist Kammerer showed using midwife toads (*Alytes obstetricans*) that heritable alterations in their preferred mating sites could be influenced by environmental manipulation. In particular, his exposure of first generation toads to an unusually dry and hot environment led them to mate in water which differs from their typical land-based mating pattern. He subsequently demonstrated that this change in mating locale persisted to the sixth generation of offspring, even when environmental conditions reverted to their original state. Though his findings were challenged, he was one of the first to suggest that heritability could be altered by environmental exposures (Vargas, 2009).

Epidemiological and clinical evidence supporting the importance of early life exposures to later health and disease in humans first emerged in the 1930s. Among the most influential work in this area was done by Kermack, McKendrick and McKinlay (1934) who reported links between early childhood disadvantage and later mortality. However, it was not until the early 1970s that Dörner and colleagues in East Germany explicitly suggested that perinatal conditions could be related to specific forms of somatic pathology, namely obesity and diabetes mellitus (DM; cited in: Dörner, Rodekamp, & Plagemann, 2008). Dörner also introduced the term ‘programming’ (*die Programmierung*) as it is currently used. Around this time, Freinkel (1980) developed his

fuel-mediated teratogenesis hypothesis to explain how the maternal metabolic state present during gestation could affect the transmission of DM risk from one generation to the next. In 1980, he suggested:

Developing fetal structures may be exquisitely attuned to fine alterations in maternal fuel economy... It is suggested that concepts of teratogenesis should be expanded to include alterations occurring subsequent to organogenesis during the differentiation and proliferation of fetal cells. Such changes could cause long-range effects upon behavioral, anthropometric and metabolic functions. (p. 1024)

This work was also the first to suggest that maternal overnutrition could be harmful to development during gestation and beyond.

Using epidemiological data, Forsdahl (1977) and Wadsworth (1985) later independently suggested that intrauterine conditions could contribute to the development of cardiovascular disease. In 1985, Notkola and colleagues linked early childhood poverty to an elevated risk of heart disease, heart attack, and mortality due to these causes later in life. The next year, David Barker and colleagues published the first of a trio of papers in *The Lancet* that are probably the most influential and best-known works in the area of prenatal programming/DOHaD. This work suggested that men with the lowest birth weights had the highest rates of death in adulthood from cardiovascular disease.

Since then, the importance of the intrauterine environment to later health and disease has been demonstrated in hundreds of studies examining outcomes ranging from

obesity and diabetes to depression and schizophrenia (e.g., Dabelea & Crume, 2011; Rice, Jones, & Thaper, 2007; Cannon, Jones, & Murray, 2002).

Prenatal Programming Theory: From ‘Thrifty Phenotype’ to Developmental Plasticity

Barker’s early work led he and Nicholas Hales to hypothesize in 1992 that a fetus exposed to sub-optimal nutritional conditions in-utero might develop an energetically ‘thrifty phenotype’ and intentionally limit its growth during gestation in order increase the likelihood it would survive to birth. However, their model was not supported by the empirical data that followed, and was criticized for downplaying the importance of periconceptual circumstances, and for artificially separating the influences of prenatal and postnatal environmental factors (Gluckman, Hanson, & Buklijas, 2010).

In response to these shortcomings, Bateson (2001) and Gluckman and Hanson (2004) suggested that the mechanisms by which prenatal and early life exposures could increase the risk of later disease involved the fetus’ and newborn’s utilization of information present in their environment to predict later environmental conditions. They hypothesized that these adjustments in developmental trajectory were designed to optimize survival and so were not pathological, but rather in keeping with the normal processes of developmental plasticity. Gluckman and Hanson (2004) stressed that the early life exposures that could affect later development were of two main types: a) severe ones which clearly and grossly disrupted the developmental program (i.e., teratogens), and b) those that triggered attempts to generate predictive adaptive responses (i.e.,

developmental plasticity). These latter alterations are thought to account for prenatal programming/DOHaD phenomena and are the focus of this thesis.

The biological processes comprising developmental plasticity have a time horizon that are longer than basic homeostatic processes, but shorter than evolutionary selection. Since the energy requirements for plasticity are high, it is generally restricted to earlier phases of development. As a result, it is easier for an organism to change their phenotype earlier in its development than it is later on (Gluckman & Hanson, 2004). Evidence in humans suggests that this plasticity is highest during the period between conception and two to three postnatal years (Gluckman et al., 2010).

While developmental plasticity is thought to give the developing organism an enhanced ability to respond to environmental changes, these processes can result in adaptation or maladaptation. In order to be adaptive, the predictive responses made by the organism need to relatively accurately predict the prevailing environment present later in life. The extent to which acute changes in the intrauterine environment affect plasticity compared to more chronic cues (such as the mother's body composition at conception) is not known.

Prenatal Programming: General Mechanisms

The most common term used to describe the environmental conditions mothers and their offspring respond to in-utero and later in life is 'stress'. During gestation, many of the 'stresses' experienced by the mother are transduced to the fetus. The stresses mothers can be exposed to during pregnancy are myriad, ranging from nutritional deprivation to intimate partner violence.

The experience of stress by the mother during gestation can lead to physiological responses in the mother, the fetus and the placenta. While the placenta has the capacity to protect the fetus from some of the maternal mediators of these responses, it is not an impermeable barrier. For example, while the placenta does metabolize a proportion of the cortisol elaborated by the mother in response to stress, the fetus is still exposed to a non-trivial amount (Gitau, Cameron, Fisk, & Glover, 1998).

Certain endogenous or exogenous substances that do not traverse the placenta still have the capacity to affect the fetus via their effects on placental physiology. Indeed, a number of the maternal mediators of stress can modify placental function (Fowden, Forhead, Coan, & Burton, 2008) and activate the fetal hypothalamic-pituitary-adrenal (HPA) axis and impact the fetus in this way as well (Lazinski, Shea, & Steiner, 2008).

The downstream biological mechanisms by which these stresses and the maternal, placental and fetal responses to them lead to predictive adaptive responses and changes in physiology are likely epigenetic in nature (Gluckman et al, 2010). Epigenetic changes are alterations of DNA that do not involve modifications of the DNA sequence itself. In humans, the whole of a cell's DNA is compacted into a structure called chromatin. The basic component of chromatin is the nucleosome. It consists of 147 base pairs of DNA wrapped twice around a core of proteins referred to as histones. The structural 'tails' of these histones project out of the core of the nucleosome and can be modified via the attachment of molecular moieties such as methyl and acetyl groups. Changes in chromatin structure resulting from the addition of these groups can actually result in phenotypic changes that are heritable. These epigenetic changes are sensitive to

nutritional states and thought to be vital to developmental plasticity. However, the phenotypic effects that result from epigenetic alterations seem to differ depending on the type of molecular change and its timing (McGowan & Szyf, 2010).

Prenatal Programming and Psychopathology

The phenotypic expression of most cases of psychiatric illness requires both a genetic predisposition and exposure to environmental stress (Zubin & Spring, 1974). Despite the fact that genetic factors play a key role in the development of psychopathology, a significant proportion of the variability in expression of psychiatric phenotypes is due to environmental exposures (Eaton, 2004). The best-known types of stresses that increase the risk of mental health problems occur in postnatal life (e.g., child abuse, parental intimate partner violence, poverty etc.). However, in the past 15 years, links have also emerged between adverse or ‘stressful’ exposures occurring during gestation and psychopathology later in life (e.g., Cannon et al, 2002; Rice et al, 2007; Schlotz & Phillips, 2009; Glover, 2011). These include reports of associations between psychopathology and exposure to elevated levels of maternal anxiety, psychosocial stressors, depression, and malnutrition during pregnancy. Interestingly, the findings comparing the end-results of models of programming that examine nutrition and other types of stress are quite similar. This may be due to the fact that over the course of evolution, predation and nutritional stress were linked and so similar signaling pathways may be responsible (Gluckman, Hanson, Cooper, & Thornburg, 2008).

Abnormal Birth Weight and Psychopathology

While myriad maternal exposures during pregnancy have the capacity to affect brain development in ways that can increase the risk of psychopathology later in life, until recently, the majority of the work done in this area had examined associations between being born at low birth weight and mental illness (Schlotz & Phillips, 2009). One reason for this is that fetal anthropometric measures such as birth weight are easily obtained and have been available in hospital charts for decades. Of considerable interest to those interested in the fetal origins of adult disease is the fact that birth weight is largely determined by the maternal uterine environment (including maternal obesity and diabetes mellitus), with relatively little influence of maternal genotype (Snow, 1989). Moreover, maintenance of normal weight in-utero is protected by a number of biological safeguards that have evolved over time. Thus, if one is born at an abnormal birth weight, it is suggestive of exposure to significant intrauterine environmental perturbation.

Low Birth Weight and Psychopathology: Findings and Limitations

To date, research on the link between birth weight and later psychopathology suggests that this association may follow a reverse J-shaped curve (Schlotz & Phillips, 2009; See Figure 1). That is, the highest risks for mental disorder occur at low birth weight, then decrease up to a point with increasing birth weight, and increase again at the very highest end of the birth weight spectrum. This pattern of association has also been noted between birth weight and a number of other human health outcomes including hypertension, cardiovascular disease and all-cause mortality (e.g., Curhan, Chertow,

Willett, Spiegelman, Colditz, Manson, Speizer, & Stampfer, 1996; Leon, Lithell, Vagero, Koupilova, Mohsen, Berglund, Lithell, & McKeigue, 1998).

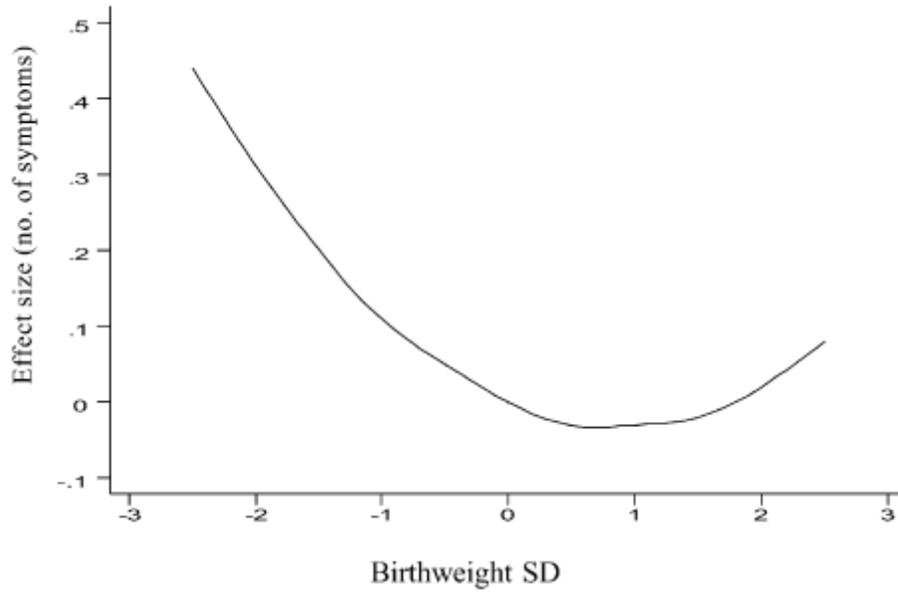


Figure 1: The reverse J-shaped curve

At this time, we will limit our discussion of birth weight and psychopathology risk to links between low birth weight (LBW) and later mental disorder as those associated with high birth weight will be reviewed in detail in Study 1 of the thesis.

Present in about 10% of live births, being born at a low birth weight (birth weight < 2500 grams), or small for gestational age (SGA; birth weight <10th percentile for gestational age) is associated with dozens of different causes (ACOG, 2000), the majority of which are known to elicit a neuroendocrine stress response from the mother and/or placenta.

The earliest noted associations between LBW and specific mental health problems focused on psychotic disorders in adults and attention-deficit/hyperactivity disorder

(ADHD) in children. Indeed, studies utilizing a wide range of observational designs suggest that being born at LBW is associated with a doubling of the risk of developing schizophrenia (Cannon et al, 2002) and ADHD (Schlotz & Phillips, 2009).

More recently, reports have begun to accumulate that suggest that LBW may also be associated with an increased risk of developing problems with depression. While the results of case-control studies that have examined associations between LBW and unipolar depression have been mixed, findings of more methodologically rigorous cohort studies generally appear to support the existence of a link (Rice et al, 2007). Recent evidence also suggests that LBW may not simply act as yet another risk factor for later depression, but that it may actually amplify the effects of traditional risk factors for depressive illness (e.g., childhood abuse, socioeconomic disadvantage; Costello, Worthman, Erkanli, & Angold, 2007). However, the very few studies that have examined the association between LBW and bipolar disorder have yielded mixed results (Scott, McNeil, Cavanagh, Cannon, & Murray, 2006).

Much less attention has focused on the link between LBW and later problems with anxiety. While a number of studies have reported outcomes for children and adolescents, this body of work has yielded a wide variety of results, with some studies providing evidence of a link (e.g., Indredavik, Vik, Heyerdahl, Kulseng, Fayers, & Brubakk, 2004) while others have failed to do so (e.g., Hille, den Ouden, Saigal, Wolke, Lamber, Whitaker, Pinto-Martin, Hoult, Meyer, Feldman, Verlooove-Vanhorick, & Paneth, 2001).

The mixed findings present in some of the literatures linking LBW and psychopathology are likely at least partly due to the presence of methodological

limitations. Because this work has been observational in nature, the most common limitation and biggest threat to causal inference is their widespread lack of adjustment for confounding variables, in particular familial psychopathology and socioeconomic disadvantage. If the genes for psychiatric disorder present in the mother or father of an infant impede fetal growth, since these are known to increase the risk of later psychopathology in offspring, associations between fetal weight and psychiatric problems in their children are more likely to be attributable to genetic risk than fetal environmental exposures. The same is true for exposure to socioeconomic disadvantage.

Studies of the links between low birth weight and later psychopathology have also largely ignored the potential mediators of these associations. Mediating variables are intermediate in a putative causal pathway, serving to transfer risk from exposure to outcome. Mediators must be subject to change (malleable), influenced by the exposure, and exert a causal influence on outcome. Failing to examine such variables can lead to erroneous claims of direct or causal associations between predictors (e.g., LBW) and outcomes (e.g., psychopathology). Examples of potential mediators between LBW and mental health problems include cognitive limitations and ill-health in childhood.

Additional methodological limitations in these studies further prevent a clear understanding of the true nature of the relationship between the intrauterine environment and psychopathology later in life. One major problem is that no study has been specifically designed to examine associations between birth weight and psychiatric illness. As a result, the data supporting this link is based mainly upon secondary data analysis of large cohorts utilizing assessment scales that are chosen because they are

quick and easy to administer rather than for their psychometric soundness. Moreover, the heavy reliance of many studies in this area on hospital discharge records results in the dichotomization of continuous symptom data and a decrease in study power which can lead to the trivialization of significant and meaningful associations. The inability of many of these studies to adequately capture those suffering from the majority of psychiatric disorders (i.e., those for which hospitalization is not required), and questions about the reliability and validity of diagnostic labels applied during inpatient admissions also limits the findings of this work.

An additional difficulty posed by the study of child and adolescent psychiatric outcomes is the issue of determining the most efficient and accurate means of assessing psychopathology. Indeed, the presentation of emotional and behavioural problems in youth can vary across settings and so interpretations can be affected by a number of factors inherent to the individual, their parents and other informants (De Los Reyes, & Kazdin, 2005). The measurement of these constructs is thus optimized via the utilization of self, parent *and* teacher-reports. Therefore, the widespread use of single informants in studies done to date, though cost-effective, may also contribute to the heterogeneity seen in their results.

Finally, other than for ADHD, relatively little research has examined links between prenatal exposures/LBW and psychopathology in children and adolescents. The few studies that have been done in this age group have utilized highly selected groups of individuals or examined outcomes cross-sectionally.

Prenatal Programming and Psychopathology: Putative Mechanisms

In what physiologic systems might the above exposures act through epigenetic mechanisms to increase the risk of psychopathology specifically, later in life? While this is an area of active research, none have been definitively proven to be responsible for these changes. Hypothesized culprits include the growth and thyroid hormone axes, as well as the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (Schlotz & Phillips, 2009). In fact, persisting alterations in the fetal sympathoadrenal (SA) system, which consists of both the sympathetic nervous system and HPA axis, has been one of the most frequently implicated mediators of adverse fetal environmental exposures. Certainly it makes evolutionary sense for this system to be fine tuned in-utero as a lower threshold for activation and strengthened responses can increase the likelihood of survival in offspring born into a dangerous or stressful environment. Unfortunately, if the environment to which a fetus is exposed postnatally is excessively stressful or fails to match that which is predicted, such adaptive responses may not be possible or the alterations made in response to them may not be adaptive at all (Gluckman et al., 2010).

Prenatal Programming and Psychopathology: Beyond Low Birth Weight

Given the myriad causes of LBW, the lack of a proven causal link between it and later psychopathology, and the practical difficulties associated with therapeutically increasing birth weight, it may be limited not only in its pathophysiological implications, but also as a potential target for preventive intervention. As a result, factors known to be useful markers of intrauterine environmental exposures, that have relatively few risk factors for them, and that may be amenable to intervention are important targets of study.

Being born at a high birth weight (>4000g or >4500g) or large for gestational age (>90th or 95th percentile for gestational age) is such a marker. Also known as macrosomia, it has relatively few risk factors (i.e., maternal pre-pregnancy obesity, excess maternal weight gain in pregnancy, maternal diabetes mellitus, genetic overgrowth syndromes), and most of these may be amenable to prevention or treatment in women of childbearing age (ACOG, 2000).

The five studies that comprise this thesis represent the work I have done to examine these associations. This is based on the proposed *hypothetical* model below (Figure 2) which illustrates the ways in which birth weight may be linked to psychopathology. It shows that birth weight and mental illness may be directly related, due to an increased risk of another process that subsequently increases the risk of psychopathology (i.e., mediated) or accounted for by confounding variables.

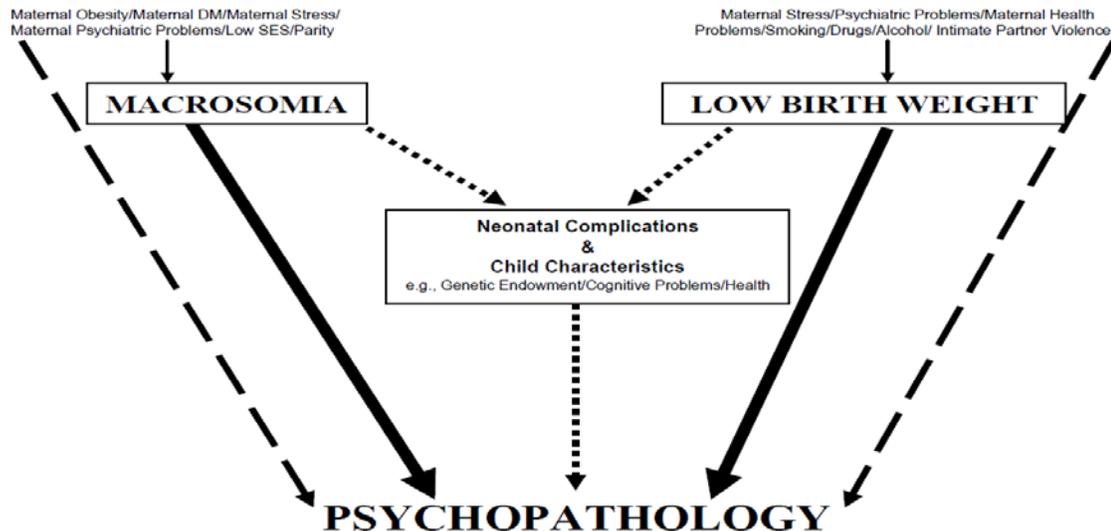


Figure 2. Schematic diagram of the proposed pathways from pre-pregnancy environment, pregnancy conditions and fetal anthropometric abnormalities to postnatal environment and the development of psychopathology.

- ▶ : Direct 'Causal' Pathway
-▶ : Mediated Pathway
- - - - -▶ : Confounded Pathway

‘Sandwich’ Thesis Overview

Each of the thesis’ five studies corresponds to a manuscript that is already published or is currently under review. Study 1 reviews the literature that has examined associations between being born macrosomic and the risk of psychopathology later in life. It highlights the fact that the links between macrosomia and youth mental health are not well understood and that the work conducted to date has been affected by a number of shortcomings. These include the use of inconsistent and/or limited definitions of macrosomia, a failure to utilize multiple informants in the assessment of psychopathology in youth, the infrequent examination of the mediators of these associations, and the fact that statistical adjustment for known confounders is relatively rare. The findings of this review provided the impetus for the conduct of Study 2 of the thesis which examined associations between being born large or small for gestational age and internalizing and externalizing psychopathology in a sample of 2923 youth aged 4-16 years. While we found that being born large and small for gestational age was associated with an increased risk of externalizing psychopathology as reported by parents, teachers, and the children and adolescents themselves, the effect size was small.

In response to this, I hypothesized that the link between macrosomia and behaviour problems might actually be due to one of macrosomia’s antecedent risk factors, rather than macrosomia itself. I posited that macrosomia was simply a marker of the true association between increased maternal pre-pregnancy BMI or gestational diabetes mellitus (GDM) and behaviour problems, rather than a cause. However, since the prevalence of screening for GDM varied widely in the late 1980s when the Western

Australia Pregnancy Cohort was assembled (Hunter, Doery, & Miranda, 1990), I was concerned about the presence of large numbers of diabetic women in the ‘non-diabetic’ group. Given the potential for this to mute the strength of the association between GDM and psychopathology in offspring combined with the fact that the continuum of overweight and obesity is now the most common complication of pregnancy in the developed world (Guelinckx, Devlieger, Beckers, & Vansant, 2008), I chose to examine links between maternal pre-pregnancy BMI and child and adolescent psychopathology. To set the stage for this work, I completed Study 3 of the thesis, a systematic review of published research that had examined these associations. This work showed that no studies had assessed the link between maternal BMI and child outcomes prior to 3 years of age, and none had quantified them longitudinally. Moreover, only two had adjusted for both a familial risk of psychopathology and socioeconomic disadvantage, important confounders of these associations.

Study 4 of the thesis assessed when these associations first emerged and addressed two of the aforementioned shortcomings of the literature in this area by examining associations at 1 and 2 years of age and by adjusting for the confounders of this association. This work utilized the 2900 members of the Western Australia Pregnancy Cohort to examine links between maternal pre-pregnancy body mass index and temperament at 1 year of age, and with behaviour problems at 2 years. It showed that a positive association between maternal BMI and externalizing behaviour in offspring first becomes apparent at 2 years of age.

Given this observation, I then set out to determine in Study 5 if this link persists throughout childhood and adolescence. I found that the statistically significant, positive association between maternal pre-pregnancy BMI and externalizing problems continued throughout childhood and adolescence and persisted despite adjustment for confounders. However, there was also a statistically significant interaction between maternal BMI and time, such that associations between increasing maternal BMI and elevated levels of internalizing problems emerged at 8 years and increased in strength through age 17.

As can be seen, the studies that comprise this thesis are inter-related. For example, while Study 1 (Review of Macrosomia and Psychopathology) provides the rationale and context for Study 2 (Macrosomia and Psychopathology in the OCHS Cohort), it was not published at the time Study 2 was submitted. As a result, a brief duplication of some of its material in the introduction section of Study 2 was unavoidable.

As Study 3 (Review of Maternal BMI and Psychopathology) provides the background and premise for Studies 4 (BMI and early child outcomes) and 5 (BMI and child/adolescent outcomes), as these latter two works were published as standalone pieces, there is some overlap between Study 3 and their introduction and discussion sections of Studies 4 and 5. Finally, as Studies 4 and 5 utilize the same cohort and attempt to address research questions using similar methods, the methods sections of these studies do contain some duplication.

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CHAPTER TWO

STUDY 1

TITLE: Is Bigger Better? Macrosomia and Psychopathology Later in Life

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CONTEXT AND IMPLICATIONS OF THIS STUDY: This first study of the ‘sandwich’ thesis reviews the literature examining associations between being born macrosomic and later psychopathology. As the background section of this thesis suggests, birth weight can provide a reasonable index for intrauterine environmental exposures. However, most of the work linking birth weight and mental disorders has focused on LBW and assigned infants born at the high end of the birth weight spectrum to control groups. This may have prevented the detection of meaningful associations between HBW and mental health problems later in life.

This work is the first review of the literature in this area and highlights the methodological and substantive shortcomings of previously conducted studies. It also provides direction to the field on how it should proceed so that future studies can accurately address the question of whether macrosomia is a legitimate risk factor for psychopathology later in life.

The review shows that this is a relatively neglected area of study with significant methodological shortcomings, but that macrosomia has promise as a potential risk factor for later mental health problems. However, it does indicate that closer attention should be paid to methodological issues in order for an accurate assessment of this association to be made, and provides guidance to future researchers in this area on how this can be done.

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Abstract

Evidence suggests that a curvilinear relationship may exist between birth weight and later psychopathology. Increases in the prevalence of macrosomia and of two of its risk factors (maternal pre-pregnancy obesity and diabetes mellitus) and their amenability to intervention argue for a critical review of the association between macrosomia and mental illness. Of the nine studies in adults and six studies in youth that have examined associations between macrosomia and psychiatric disorders, seven have provided evidence suggestive of a link. Significant methodological variability and an inability to adjust for important confounders limit the findings of these studies. As a result, it remains unclear if individuals born macrosomic are at increased risk for psychopathology later in life. Future work should attempt to examine a broader range of psychiatric outcomes, use validated measures, include data on putative confounders and utilize genetically sensitive designs to assess associations between macrosomia, its precursors and later psychological and emotional functioning.

Introduction

As early as the mid-1950s, it has been suggested that suboptimal intrauterine environments can affect brain development in ways that may increase the risk for psychiatric disorder later in life (1). Given that the majority of the neuroanatomical mediators of cognition and emotion form in-utero (2), it is reasonable to expect that exposure to physiological and psychological stresses in gestation could increase one's risk for psychopathology.

Understanding the impact of prenatal factors on the risk of developing psychiatric problems is important for two reasons. One, identification of causal risk factors could provide the scope for prediction and primary and secondary preventive interventions. Two, an understanding of the prenatal factors relevant to the etiology of psychiatric disorders can inform hypotheses regarding the pathophysiologies of these syndromes and guide the development of therapeutics.

Most of the research that has examined the relationship between prenatal environments and psychopathology in humans has focused on those born at low birth weight (LBW). However, increases in the prevalence of macrosomia (being born large for gestational age or at high birth weight) and two of its major risk factors, maternal pre-pregnancy obesity and diabetes mellitus (DM; 3-5), and the ease of identification and amenability to intervention of these risk factors argue for a critical examination of the association between macrosomia and later mental health problems. Emerging research suggests that an increased susceptibility to psychopathology may not be restricted to infants born small. Reverse J-shaped associations have been observed between birth

weight and a number of disorders including DM (6). Despite this, few studies have examined associations between macrosomia and psychopathology. Most research that has examined the relationship between LBW and psychopathology has relegated macrosomic infants to control groups, possibly underestimating the strength of the association with LBW and masking possible links to macrosomia.

Interest in the association between LBW and later pathology is based on the fact that LBW reflects a stressful intrauterine milieu. However, macrosomia may also be a marker of exposure to intrauterine stress. In animal models, crowding stress (7) and adrenocorticotrophic hormone (ACTH) administration (8) in late gestation are associated with increased birth weight. Macrosomia is also associated with an elevated risk of complications at birth including a higher incidence of obstetric trauma and maternal hemorrhage (9) which are also associated with an increased risk of certain forms of psychopathology (10). Pre-pregnancy obesity and DM, can be marked by increased levels of pro-inflammatory cytokines (11) and oxidative stress (12), states that are also associated with an elevated risk of certain types of psychiatric disorders (eg. 13,14). While multiple studies have reported *associations* between LBW and later psychopathology (10,15), the development of primary preventive efforts targeting the prenatal period require that *causal* relationships be demonstrated (16). Unfortunately, the presence of residual confounders such as the familial risk of psychopathology and the post-natally persisting suboptimal psychosocial environments have undermined the demonstration of causality in studies of LBW. Such confounders are also relevant to work that examines macrosomia.

In this paper, we will review the studies that have contained data on the association between macrosomia and later mental illness. Subsequently, we explore the pathways through which macrosomia and its antecedents could increase the risk of later psychopathology and make recommendations for studies aimed at clarifying empirically the strength and nature of this association, should it exist.

Methods

Studies for this review were identified using MEDLINE, EMBASE and PsycINFO searched from their inceptions to September 15th, 2010 using the terms [(fetal macrosomia OR large for gestational age OR high birth weight) AND (mental disorders ‘OR’ mental disease)]. A targeted search of recent reviews of the prenatal programming of psychiatric disorders (10,15,17-19) was also conducted and studies in the reference lists of these papers were checked. Studies that reported data on all types of psychopathology in those born macrosomic were eligible and reviewed.

Results

Table 1 summarizes the 15 studies (20-34) that have examined associations between macrosomia and psychopathology and includes information on study design, findings and limitations. Nine of these studies reported outcomes in adults (20-28) and six in youth (29-34). Seven of these suggested that macrosomia is a significant predictor of later psychiatric disorder – five were studies of adults (20, 24-27) and two, youth (33, 34). However, those that reported positive results were not unequivocal.

Table 1. Published Data Reporting on Associations Between Macrosomia and Psychopathology

Reference	Sample	Design	Macro-somia Def'n	Reference Group	Outcome (Means of Assessment)	Findings (Support/Refute; Risk, 95% CI)	Limitations
ADULTS							
Hultman et al, 1997 (20)	Consecutively admitted inpatients vs. Matched Controls 82 cases, 164 controls	Case-Control	HBW for length (≥ 1 SD)	NBW for Length	Schizophrenia (Inpatient psychiatrist diagnosis)	Support OR=4.42 (1.97-9.91)	Sampling: Hospitalization data only Control of Error: No examination of familial risk of psychopathology or post-natal environment
Hultman et al, 1999 (21)	Linked birth and psychiatric registries 167 Cases, 835 Controls	Historical Cohort	LGA (≥ 2 SD) PI ($\geq 95^{\text{th}}$ %ile)	AGA PI (6^{th} - 94^{th} %ile)	Schizophrenia (Inpatient psychiatrist diagnosis)	Refute OR=0.5 (0.2-1.6) OR=1.0 (0.4-2.2)	Sampling: Hospitalization data only, followed to 22 years old, 3 cases ≥ 4500 g Measurement: HBW cut-off used Control of Error: No examination of familial risk of psychopathology or post-natal environment
Dalman et al, 1999 (22)	Linked birth and psychiatric registries (up to age 22) 507 516	Historical Cohort	≥ 4500 g	4000-4499g	Schizophrenia (Inpatient psychiatrist diagnosis)	Refute RR=0.7 (0.3-1.8)	Sampling: Hospitalization data only, followed to 22 years old, 5 cases

	eligible, 238 cases						≥4500g Control of Error: No examination of post-natal environment
Gunnell et al, 2003 (35) & 2005 (23)	Linked birth and psychiatric registries 719 476 eligible, 736 cases	Historical Cohort	≥4000 g	3500-3999g	Schizophrenia (Inpatient psychiatrist diagnosis)	Refute HR=1.02 (0.62-1.69)	Sampling: Hospitalization data only, followed up to 27 years old, 19 cases ≥4000 g
Bersani et al, 2007 (24)	40 consecutively admitted male psychiatric clinic patients and 73 of their brothers	Case-Control	≥4000 g	3001-3999g	Schizophrenia (Psychiatrist Diagnosis)	Support OR=4.52 (1.00-20.48)	Sampling: Males only, small sample
Cheung, 2002 (25)	5567 Members of the 1970 British Cohort Study	Birth Cohort	≥1.5 SD above the mean	Mean Birth Weight 3380 g	Psychological symptoms (At age 26; Malaise Inventory)	Mixed (Supported when based on continuous outcome data but not when outcome categorized)	Sampling: Sample attrition Measurement: Implications of outcome used unclear Control of Error: No examination of familial risk of psychopathology
Colman et al, 2007 (26)	Members of 1946 British Birth Cohort (sample	Birth Cohort	≥4500 g	<4500 g	Symptoms of Anxiety and Depression over the lifespan (A variety of	Support (No OR reported in paper)	Sampling: Sample attrition Measurement: Use of multiple

	size varied by age)				measures were used, depending on age)		scales; psychometric properties not reported Reporting: Exact nature of relationship and magnitude not described in paper Control of Error: No examination of familial risk of psychopathology
Herva et al, 2008 (27)	8339 members of the 1966 North Finland Birth Cohort	Birth Cohort	4500-4999 g $P \geq 95^{\text{th}}$ percentile	3000-3499g 50-75 th %ile	Depression (At age 31; Hopkins Symptom Checklist)	Mixed (Supports in females but not males; on HSC, not when reported as physician diagnosed.) OR=2.02 (1.20-3.39) OR=1.53 (1.05-2.22)	Sampling: Sample attrition
Favaro et al, 2006 (28)	Cases (N=187) and controls (N=540) sampled from a birth cohort of Italian women with case sample augmented by the addition of eating	Case-Control	>4000 g	2500-4000g	Anorexia or Bulimia Nervosa (Structured Clinical Interview for the DSM)	Refute Anorexia OR=1.3 (0.5-3.3) Bulimia OR=0.6 (0.2-2.7)	Sampling: Some ascertainment bias in the collection of cases Control of Error: No examination of familial risk of psychopathology or post-natal environment

	disorders clinic patients						
YOUTH							
Eaton et al, 2001 (29)	Linked birth and psychiatric registries yielding 3325 cases and 102 905 controls	Historical Cohort	>4000g and LGA	3000-4000g and AGA	Adolescent Psychiatric Inpatients (Various diagnoses up to age 15; Inpatient Psychiatrist diagnosis)	Refute Autism: RR=1.07 (0.5-2.1) MR: RR=1.1 (0.6-1.9) Asperger's: RR=1.1 (0.6-1.9) Learning Disorder: RR=0.97 (0.7-1.4) Eating Disorder: RR=0.28 (0.0-2.1)	Sampling: Hospitalization data only Control of Error: No examination of familial risk of psychopathology or post-natal environment
Hultman et al, 2002 (30)	Linked birth and psychiatric registries yielding 408 cases and 2040 controls	Historical Cohort	≥4500g LGA (>2 SD above mean)	2500-4499g AGA	Autism (By age 10; Inpatient psychiatrist diagnosis)	Refute Unadj OR=1.5 (0.9-2.5) Unadj OR=1.7 (1.0-2.7) Adj OR=1.6 (0.9-2.8)	Sampling: Hospitalization data only, restricted to those under age 10 Control of Error: No examination of familial risk of psychopathology or post-natal environment
Larsson et al, 2005 (31)	Linked birth and psychiatric registries yielding 698 cases and 17450 controls	Historical Cohort	>4500g >90 th %ile for GA	3001-3500g 10 th -90 th %ile	Autism (Inpatient psychiatrist diagnosis)	Refuted for both definitions RR=0.99 (0.59-1.67) RR=0.90 (0.67-1.22)	Sampling: Mainly Hospitalization data Control of Error: No examination of familial risk of psychopathology
Linnett et al, 2005 (32)	Linked birth and psychiatric registries yielding	Historical Cohort	>4000g	3000-3999g	Hyperkinetic disorder (Psychiatrist diagnosis)	Refute RR=1.0 (0.9-1.3)	Sampling: Mainly Hospitalization data

	834 cases and 20100 controls						
Buschgens et al, 2009 (33)	2230 Dutch pre-adolescents	Cohort	>4500 g	2501-4499 g	Externalizing symptoms (hyperactive/impulsive, aggression, delinquency at age 10-12 using CBCL (parent), TCP (teacher))	Support (Continuous outcomes examined only; slightly different pattern of risk present depending on informant) β Values Parent-Rated (CBCL) Inattention: NS Aggression: 0.06 Delinquency: NS Teacher-Rated (TPC) Inattention: 0.07 Hyperactivity/Impulsivity: 0.09 Aggression: 0.08 Delinquency: 0.09	Control of Error: No adjustment for SES
Alati et al, 2009 (34)	Prospective birth cohort of 4971 Australian Children	Birth Cohort	Highest BW Quintile	Middle Quintile	Social problems, internalizing and externalizing symptoms at age 14 (CBCL Youth Self Report)	Mixed (Support for social problems but not for internalizing or externalizing symptoms) β Values Anxious/Depressive: 0.39 (-0.01-0.78) Social Problems: 0.21 (0.02-0.41)	Measurement: Self-report only

CI=Confidence Interval
 BW=Birth Weight
 LBW=Low Birth Weight
 HBW=High Birth Weight
 PI=Ponderal Index (A variably defined index of infant mass over length)
 LGA=Large for gestational age
 AGA=Appropriate for gestational age
 SD=Standard Deviation
 OR=Odds Ratio
 HR=Hazard Ratio
 RR=Relative Risk
 CBCL=Child Behavior Checklist
 TCP=Teacher's Checklist of Psychopathology
 NS=Not significant
 SES=Socioeconomic Status

Six studies examined associations between being born macrosomic and schizophrenia (20-25) and all but two of these (20, 24) were based on linked birth and psychiatric hospitalization registries. The two (20, 24) that supported an association used a case-control design, included a relatively small number of cases and failed to adjust for parental diagnosis of psychotic disorder. Another study (35) that reported a positive association between macrosomia and schizophrenia in males who were followed up to age 22 (23) failed to report a link when follow-up was extended to age 27.

Studies of associations between macrosomia and more common psychiatric outcomes such as depression in adults are less common. Data on two population-based birth cohorts (26, 27) found positive associations between high birth weight and elevated symptoms of depression in adulthood but the former was only positive for females and only when defined using a psychometric scale, not when assessed by self-report of a physician diagnosis. Cheung reported on the link between birth weight for gestational age and psychological symptoms assessed by the Malaise inventory in a British birth cohort (25). In this study, more symptoms were reported among individuals born less than 0.5 standard deviations (SD) and more than 1.5 SD above the mean but only when these were reported on a continuous rather than a dichotomous scale.

Studies examining associations between macrosomia and psychopathology in children and adolescents are rarer. Three of these studies (29-31) used linked birth and hospitalization data to explore the association between macrosomia and autism. None reported an association. Another examined the link between perinatal variables and hyperkinetic disorder (ADHD) in 834 cases and 20 100 register-based controls and found

no link with macrosomia (32). However, two population-based studies of adolescents reported that macrosomia was a significant predictor of emotional and behavioural problems. In one study, significant associations were noted between being born >4500g and 5 out of 7 parent and teacher-rated externalizing scales (e.g., inattention, hyperactivity-impulsivity, aggression and delinquency) in 10-12 year old Dutch youth (33). A study of 14-year old Australians reported that those born at weights greater than the 80th percentile for gestational age had significantly increased levels of self-reported social problems and a trend toward elevated levels of internalizing (depressive/anxiety symptoms) and externalizing problems, though these latter two scales did not reach statistical significance (34).

Six studies defined macrosomia as being born at 4500 g or more (22, 26, 27, 30, 31, 33) and four used ≥ 4000 g as a cut-off (23, 24, 28, 29, 32). The remainder (21, 25, 34) defined macrosomia according to the distribution of birth weights in that study or incorporated gestational age into their definition. Studies by Hultman and colleagues' (30) and Larsson et al (31) examined both birth weight and birth weight adjusted for gestational age as predictors of psychopathology. The birth weights to which macrosomic infants were compared varied but the most common definition was 2500-4499 g. Absence of a common definition of macrosomia and normal birth weight complicates comparisons between and synthesis of studies in this area. The way in which psychopathology was defined and measured was also highly variable. Seven studies relied on inpatient hospitalization data to define diagnosis (20, 21-23, 29-31) and three used outpatient diagnoses (24, 28, 32). Five studies used scales to define disorder (25-27, 33, 34).

Unfortunately, a number of studies failed to adjust for putative confounders of the link between macrosomia and mental illness. Only seven (20, 21, 26, 28, 29-31) attempted to adjust for familial risk of psychopathology or the presence of maternal mental illness in pregnancy, and six failed to adjust for post-natal environmental confounders (20-22, 28-30).

While significant variability existed in the criteria used to classify macrosomia, there was no apparent link between the definition used and positive or negative findings. However, the outcomes examined, the ways in which they were measured, and the means of identifying and selecting cases did influence the likelihood of observing significant associations. Studies that used hospital referrals and classified disorder according to inpatient discharge diagnoses were less likely to report a link than studies that selected their cases from general population samples containing all possible individuals with disorder (25-27, 33, 34). Interestingly, these five studies not only all reported positive results, but also used scales to measure mental illness as opposed to psychiatrist-derived discharge diagnoses. Moreover, studies of disorders less likely to result in hospitalization (eg. depression vs. schizophrenia) were more likely to report a positive association. However, studies of disorders more likely to require hospitalization most frequently used inpatient discharge data and so it is difficult to determine if these associations are due to true etiological links or study-specific methodological features.

Discussion

It is not yet possible to come to firm conclusions about the association between macrosomia and psychopathology at the present time given the current mixed findings and methodological and clinical heterogeneity inherent in these studies. Contributing to this heterogeneity are variability in the disorders assessed, developmental stages examined, sample sizes and sampling frames available, measurement tools and the variables available to address confounding.

The rarity of and difficulties associated with recruiting and retaining individuals with illnesses such as schizophrenia and bipolar I disorder in general population cohorts frequently necessitates the use of hospital records based on inpatient stays for sampling. Unfortunately, such registry-based strategies exclude individuals who are not hospitalized. While this may not greatly affect the representativeness of populations of individuals with the above conditions, utilization of inpatient data alone will miss the majority of sufferers of most depressive and anxiety disorders. While sampling through the general population produces more representative samples of individuals suffering from these problems, they are not without limits. Such studies can be affected adversely by high rates of attrition (25-27), the psychometric properties of their measures (34) and missing data. Unfortunately, while case-control studies may be an efficient way to examine rare disorders, they are more susceptible to bias than cohort studies given their separate sampling of cases and controls and, in many cases the retrospective measurement of predictors. Only through further attempts to replicate the above findings in studies with sensitivity to these limitations will we be able to truly determine if macrosomia is a significant predictor of later mental disorders.

Current approaches to classifying macrosomia may also undermine efforts to study its effects. At present, there is no consensus on its optimal definition and the appropriate reference group for predicting psychopathology. Defining macrosomia in a variety of ways and contrasting the predictive power of these cut-offs may benefit studies in this area. Variability in the quality of assessment data also poses problems for the interpretation of the above studies. Unfortunately, some failed to report on the psychometric properties of these measures, raising concerns about the attenuating effects of random measurement error.

Perhaps the biggest threat to establishing valid associations between macrosomia and psychopathology arises from the failure to control for potential confounders of the association, namely the familial risk of mental illness and the persisting effects of adverse psychosocial environments. Of the positive studies, only two (33, 34) of seven adjusted for familial risk of psychopathology and three (25, 26, 34) controlled for postnatal psychosocial disadvantage. Studies that fail to adjust for these confounders may overestimate the strength of the association between macrosomia and psychopathology and further place into question the validity of the link. Disentangling genetic and environmental confounders in studies of prenatal programming is complicated; not only are maternal genes passed on to the fetus but they also shape pre and postnatal environments. The use of genetically sensitive study designs may help us to better assess the relative contributions of these factors.

Certainly it appears that individuals born macrosomic are exposed to a suboptimal intrauterine milieu that may in fact be stressful. However, it is not clear if this is sufficient

to produce psychopathology. If prenatal factors are responsible for this increase in risk, it is clear that our current understanding of the mechanisms underlying it is not well developed. Indeed, it is possible that the aforementioned increases in pro-inflammatory cytokines and oxidative stress accompanying maternal diabetes and obesity could play a role. However, hormonal (eg. cortisol, estrogen, insulin) and dietary (increased glucose, folate deficiency) factors could also be involved.

It is also conceivable that macrosomia could affect the risk of psychopathology via postnatal mediating factors known to be associated with both macrosomia and psychopathology including problems with obesity and physical health in childhood (6). These illnesses or individuals' struggles with them could contribute to or be responsible for observed links. For example, it is known that macrosomic infants are more likely to become obese adolescents, and that such individuals are at elevated risk of bullying others and of being bullied themselves (36). It is also conceivable that macrosomia increases the risk of psychiatric problems through its putative effects on cognition (37,38), personality and/or stress sensitivity (39,40) or health though this has not yet been studied.

Even if stronger evidence of associations between macrosomia and mental disorders existed, it would still be unclear if this relation is causal or if macrosomia is merely a *marker* of putative upstream causal factors of later psychiatric problems including maternal obesity, weight gain during pregnancy and/or diabetes mellitus. Unfortunately, data on these predictors have either been lacking or ignored in studies examining the links between macrosomia and psychopathology. A limited number of studies have examined maternal obesity and DM for their association with psychological

problems in the offspring of these gestations but none have taken macrosomia into account. A small number of studies suggest that individuals exposed to diabetic pregnancy are more likely to develop schizophrenia (10), ADHD (41) and anorexia nervosa (28). Moreover, some work also suggests that maternal pre-pregnancy obesity is associated with offspring emotion regulation problems (42), ADHD symptoms (43), and perhaps even an increased risk of schizophrenia (44). It is not clear whether these links are mediated by intrauterine biological exposures, maladaptive maternal psychological characteristics that may put some women at risk for obesity in the first place, as well as affect their offspring postnatally (45), genetic factors, or a combination of the three. This is certainly an area in need of further study.

Summary and Conclusions

Despite theoretical arguments for expecting associations between macrosomia and later psychopathology, studies examining this link have produced mixed findings, which may reflect their vulnerability to a number of definitional and methodological limitations. To address these limitations, future studies might focus on the use of genetically sensitive designs, or, in their absence and depending on the outcome of interest, registry or population-based cohorts that contain adequately sized samples, incorporate measures of gestational age, perform assessments across development and use multiple informants and optimal measures of psychopathology.

If a link between macrosomia and psychiatric disorders is confirmed, work could then focus on identifying those at risk and on assessing the genetic and other biological antecedents (i.e. maternal pre-pregnancy obesity, weight gain during pregnancy and

maternal diabetes mellitus), mediators and moderators of these links, and on modeling the trajectories of these individuals over time. Animal models of macrosomia, maternal obesity and DM are powerful tools that have the potential to elucidate the putative mechanisms by which these exposures could increase risk. While a considerable challenge, given the increasing prevalence of macrosomia and its risk factors, the demonstration of causal associations between it and psychiatric illness may be an important goal and could provide realizable targets for the prevention of mental disorders.

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CHAPTER THREE

STUDY 2

TITLE: Being Born Large or Small for Gestational Age and Externalizing and Internalizing Problems in a Cohort of Canadian Youth

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CONTEXT AND IMPLICATIONS OF THIS STUDY: Study 2 of the thesis builds on the previous review by addressing the need for more studies of the link between macrosomia and later mental health and incorporates the suggestions of the Study 1 into its assessment of the association. In particular, it addresses the shortcomings of existing studies in this area by assessing mental health in children and adolescents, utilizing a general population sample, and collecting data from multiple informants using a well-validated measure of psychopathology. It also attempts to isolate the association between macrosomia and mental health by taking into account the known confounders of this link.

This work supports prior studies that suggest that an association does exist between macrosomia and externalizing problems in youth. It also extends this work by examining outcomes throughout childhood and adolescence and by utilizing multiple informants and a validated outcome assessment. Moreover, that this association persists despite adjustment for confounders and mediators suggests that a direct association might exist between macrosomia and externalizing problems in youth. However, the size of this effect was small. While this may be due to the presence of measurement and informant issues, on a population level, reducing the prevalence of macrosomia might have some

potential for reducing externalizing behaviour in children and adolescents. Nevertheless, more work is required before interventions should be undertaken for this purpose.

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Abstract

Objective: To determine if youth born large (LGA, birth weight >95th percentile) or small (SGA, <5th percentile) for gestational age are at increased risk of developing symptoms of externalizing and internalizing problems.

Method: Data on 4 to 16 year old members of the Ontario Child Health Study were used to examine associations between LGA, SGA and psychopathology. This sample consisted of 2923 youth on whom parent, teacher and self-reported levels of internalizing and externalizing symptoms were available and whose caregivers retrospectively reported birth weight and gestational age. Psychopathology was assessed using DSM-oriented scales derived from the Child Behavior Checklist (CBCL).

Results: Multilevel linear regression analyses revealed that after adjustment for parental psychopathology, socioeconomic disadvantage, sex, age, maternal age, birth order, and child health and school performance; youth born LGA had higher scores on the self-reported externalizing scale (1.39, 95% CI, 0.01 to 2.78), but not the internalizing scale, compared to those born at an appropriate weight for gestational age (10th-90th percentile). Parent and teacher ratings generally supported these findings in direction but did not reach statistical significance. Youth and parents reported increased levels of externalizing and internalizing symptoms in those born SGA, but these were not statistically significant.

Conclusions: Youth born >95th percentile for gestational age manifest increased levels of externalizing symptoms. Given increasing rates of macrosomic births, further study is warranted to replicate and determine the clinical significance of these findings, the

contribution of the antecedents of LGA to this risk and the extent to which this association is causal.

Introduction

Nearly 1 in 5 children suffer from an emotional or behavioural problem¹ and almost 50% of adults with psychiatric illness met diagnostic criteria for mental disorders in childhood². The experience of mental illness can result in great suffering for the individual and their families, as well as enormous costs for health care systems and society as a whole. Given these costs, an important goal of research should be the identification of preventable risk factors that are causally related to mental disorders.

The majority of the neuroanatomical and neurochemical mediators of cognition and emotion develop in-utero, suggesting that the intrauterine environment can affect brain development in ways that increase one's risk for psychopathology later in life³. Indeed, the presence of suboptimal or stressful intrauterine environments, as are coarsely represented by being born at a low birth weight (LBW, <2500g), are associated with an increased risk of chronic disease across the lifespan⁴.

The identification of intrauterine exposures or perinatal markers of risk for mental disorders can aid in our understanding of the causes and pathophysiology of these conditions. However, this is predicated on the fact that *intrauterine* factors are causally linked to later psychopathology, an assertion that is complicated by the presence of factors that could confound their associations with later psychiatric problems including familial or genetic risk for psychopathology and suboptimal psychosocial environments present pre and postnatally.

Research to date generally supports the existence of an association between being born small and later psychopathology⁴⁻⁶. However, being born small is not the only anthropometric abnormality at birth that may be associated with later pathology. The reverse J-shaped relationship reported between birth weight and disorders such as diabetes mellitus (DM⁷) suggests that infants born large may also be at risk.

Why might individuals who are born macrosomic (LGA or >4500g) be more likely to develop psychopathology? One, it can be argued that a number of maternal conditions leading to high birth weight are themselves stressful. Certain risk factors for macrosomia (e.g. pre-pregnancy obesity and DM) are associated with increased levels of pro-inflammatory cytokines⁸ and oxidative stress⁹, which themselves may be involved in the pathogenesis of certain forms of psychopathology¹⁰. Two, complications of pregnancy and delivery are more common in those born large¹¹ and may play a role in the development of certain psychiatric disorders⁶. Three, macrosomia is linked to a number of postnatal conditions that may increase the risk of psychological problems later in life, including obesity¹². Finally, macrosomia might also increase this risk via its putative effects on cognition¹³.

Despite increasing rates of macrosomia¹⁴, only six reports have considered the putative link between macrosomia and psychopathology in youth¹⁵⁻²⁰. Two studies examined associations between high birth weight/LGA and autism^{18,19} while another one focused on hyperkinetic disorder¹⁷. The remaining studies assessed associations between macrosomia and a variety of emotional and behavioural problems. The two studies that did demonstrate a link used general population samples and assessed disorder using

problem checklists. One reported a link between being born in the top 20% of birth weights for gestational age and youth-reported social problems in 14-year olds¹⁵; and the other, between being born >4500g and externalizing symptoms in a group of Dutch 10 to 12-year olds¹⁶.

Between-study variability in measurement and control of error limits the usefulness of these reports. Moreover, all six studies used different definitions of macrosomia. Some used thresholds based on birth weight alone while others took gender and gestational age into account. Neglecting gestational age when defining macrosomia can lead to an underrepresentation of females and those born at term or pre-term but large. In addition, only one of these studies adjusted for important confounders that include familial risk of psychopathology and stressful psychosocial environments¹⁵. Few of these studies have contained data from more than one informant, let alone from the child, parent and teacher.

Given the limited information on the relationship between macrosomia and psychopathology and our interest in the effects of perinatal factors on youth mental health, the objectives of this study are to: 1) examine the link between being born LGA or SGA and internalizing and externalizing symptoms in a sample of 4-16 year olds born between 1967 and 1979 and living in the province of Ontario, Canada; 2) determine if these associations are due to LGA/SGA or putative confounders of these associations (familial risk for psychopathology and psychosocial disadvantage); and 3) determine if these links persist despite adjustment for possible mediators of the association including school performance and physical health problems.

Methods

Sample and Study Design

Data come from the Ontario Child Health Study (OCHS²¹), a population-based survey designed to estimate the prevalence of emotional and behavioural disorders in a provincially representative sample of 4-16 year old youth born between January 1, 1966 and January 1, 1979. A probability sample of households was enlisted using the 1981 Canada Census to represent 97% of the population. In order to increase study power, those who were 4-12 years old in the 1983 wave of the study (and who were between 8 and 16 at the OCHS follow-up in 1987) had their ratings from both 1983 and 1987 included. Consent was provided verbally prior to the acquisition of information from parents, teachers and youth and written consent was provided so that information on participants could be shared with investigators. All study procedures were approved by the Research Ethics Board at McMaster University.

Variables

Predictor Variables (LGA and SGA). In 1983, caregivers (95% mothers) retrospectively reported youth birth weights and gestational age (GA). To estimate GA, caregivers were asked if the child was born more than 1 week before or after the estimated date of delivery. A negative response led youth to be considered born at ‘term’ and assigned a GA of 40 weeks (the modal gestational age of Canadian infants²²). With a positive response, caregivers were asked to estimate the numbers of weeks before or after the due date the youth was born. Mothers can retrospectively provide relatively accurate reports on birth weight²³ and gestational age²⁴ compared to medical records.

Using Canadian references²², a z-score for each youth's birth weight for gestational age was calculated based on their sex. Those born at a birth weight appropriate for gestational age (AGA; between the 10th and 90th percentile) comprised the reference group to which others were compared. In this study, we examined 2 definitions of LGA (90th-95th and >95th percentile), as research has suggested that some infants born large may be at decreased risk for psychopathology, while larger infants (e.g. >93rd percentile of birth weight for GA²⁵ and >4500g²⁶) may be at increased risk. Canadian norms place the 95th percentile of birth weight for gestational age at term at 4212g for females and 4382g for males and the 90th percentile at 4034g for females and 4200g for males. Two definitions of SGA were also used (5th-10th percentile and <5th percentile). The 5th percentile corresponds to 2814g for term females and 2927g for males and the 10th 2955g for term females and 3029 g for males.

Outcome Variables (Internalizing and Externalizing Problems). The CBCL was used to assess psychopathology in children and adolescents and internalizing and externalizing scales were created from this instrument using the items demonstrated by Achenbach, Dumenci and Rescorla²⁷ to map well onto the criteria used to define DSM-IV diagnoses. This resulted in the creation of scales representing affective problems, anxiety problems, attention deficit hyperactivity (ADH) problems, oppositional defiant (OD) problems and conduct (CD) problems. Our internalizing scale summed the scores of the affective and anxiety scales for each respondent (youth, parent and teacher) separately and our externalizing scale was made up of the sum of the scores for each respondent on the ADH, OD and CD scales. The internal reliability of the youth, parent and teacher-

reported internalizing scales were 0.88, 0.88 and 0.88, respectively; and 0.85, 0.88 and 0.94 for corresponding externalizing scales.

Covariates. The putative confounder familial psychiatric history was defined by a self-reported lifetime history of treated psychiatric problems in either parent. To supplement this definition of familial risk, we also included maternal self ratings on the negative dimension of the Bradburn Affect Balance Scale²⁸, and whether or not either parent had a history of arrest. The other confounder was a measure of socioeconomic disadvantage that was comprised of 5 indicators: single parent status, one or both parents supported financially by social assistance, youth's family lives below the poverty line, youth lives with family in a rental dwelling and youth's family resides in subsidized housing. Each item was scored 0 = absent or 1 = present, summed together, and treated as a continuous variable. We also adjusted for maternal age, child sex, age and birth order (with the last child born to that mother serving as the reference) reported by the caregiver. Although measured concurrently to childhood internalizing and externalizing scales, we examined childhood health problems and school performance as potential mediators. The presence of childhood health problems was coded: 0 = none, 1 = one or more, according to the number of these problems reported by their caregiver. As there were no formal assessments of cognitive ability available in the OCHS, we used teacher assessments of school performance to represent this construct. We utilized parent reports of school performance when teacher ratings were not available. These were labeled: 1 = far below grade, 2 = below grade, 3 = average school performance, 4 = above grade and 5 = far above grade. This variable was also treated as continuous. Missing values for the above

covariates were assumed to be missing at random and imputed using the expectation-maximization algorithm. All covariates were used to estimate the others' missing values. Given the low prevalence of missing data in the predictors or outcomes, multiple imputation was not conducted.

Data Analysis

The goal of our analysis was to determine if being born LGA or SGA predicted levels of internalizing and externalizing symptoms in youth. The use of CBCL assessments completed in both 1983 and 1987 for some individuals (those aged 4-12 in 1983) led to a 3-level data hierarchy of repeated assessments (level 1), nested within individuals (level 2), nested within households, and required the use multilevel linear regression to adjust for the non-independence of responses. The statistical software MLwiN²⁹ was used to conduct analyses. Fixed effects regression parameters derived using this method are the major focus of this work and are interpreted in the same way beta coefficients are in ordinary least squares regression analyses.

The objective of the analysis was to model psychopathology as a function of birth weight for gestational age and selected covariates. Model 1 disaggregates response variability within respondents (repeated measures), between respondents (with families) and between families (and is the null model). Model 2 includes 4 dummy codes indicating LGA (90th-95th, >95th percentile) and SGA (5th-10th, <5th percentile). Model 3 adjusted for our confounders and other covariates (parental psychiatric illness requiring treatment, maternal Bradburn negative scale score, past parental arrest, socioeconomic disadvantage, maternal age and child sex, age and birth order) and model 4 adjusted for putative

mediators (youth health problems and poor school performance) in addition to the variables included in model 3. Since health problems and school performance were assessed at the same time as our outcomes of interest, we adjusted for them rather than conducting formal mediational analyses. All statistical tests were 2-tailed.

Given the dearth of studies reporting on associations between macrosomia and later psychopathology, its increasing prevalence, and its potential importance on a population scale, we report results without correction for multiple comparisons in order to avoid missing potentially meaningful links (i.e. to avoid false negatives or type II errors)³⁰. The existence of measurement error in both the classification of macrosomia and informant ratings and threat of lack of agreement among different informants³¹ increased our concern that these factors could create a bias toward the null hypothesis and further contributed to our decision to forego adjusting type I error for multiple comparisons.

We also calculated and reported a standardized effect sizes (produced by dividing the value of the fixed effect regression parameter by its standard deviation) in order to allow readers to assess the relevance of any weak but potentially important effects³².

Results

Table 1 contains the characteristics of the sample. It consisted of 2923 youth living in 1869 households and whose parents provided birth weight, gestational age and outcome data. Self-ratings were only requested of youth aged 12-16 (n=1118), while parents and teachers reported on youth of all ages (complete data was available for 2923 and 2154 participants respectively). Given that 1983 and 1987 ratings were included,

there were 2012, 4500, and 3589 discrete ratings by youth, parents and teachers, respectively. One hundred forty seven youth were born >95th and 145 <5th percentile of birth weight for gestational age.

Table 1: Number of Respondents and Sample Characteristics

Families		1869
Children		2923
Parent-Ratings (N)	1983	2923
	1987	1577
Teacher-Ratings (N)	1983	2154
	1987	1435
Youth-Ratings (12-16 Year-olds only) (N)	1983	1118
	1987	894
Males (%)		51.1%
LGA>95 th ile (N)		147
LGA 90 th -95 th %ile (N)		146
AGA (N)		2337
SGA 5 th -10 th %ile (N)		148
SGA <5 th %ile (N)		145
Mean Age (Years)		10.1 (3.7)
Mean Maternal Age (At Reporting)		37.0 (7.3)
Mean Socioeconomic Disadvantage		0.64 (1.12)
Parents Ever Treated for Psychiatric Problems (%)		416 (22.3%)
Mean Bradburn Affect Scale Score (Negative Dimension)		2.4 (1.8)
Parent(s) Ever Arrested (%)		110 (5.9%)
Youth Health Problems (%)		504 (17.2%)
Modal School Performance Rating		3.3 (1.0)

In our unadjusted model, significant associations were noted between being born >95th percentile and externalizing symptoms for both youth and parent-report but not teacher-report. Among those born <5th percentile, only parent-reported externalizing symptoms were increased. After adjustment for confounders, youth and parent-reported externalizing symptoms demonstrated a significant association with being born >95th percentile for gestational age.

Being born >95th percentile was a significant predictor of only youth-reported externalizing symptoms after adjustment for all confounders and mediators (Effect Size (ES)=0.20; see Table 2). Parent (ES=0.11) and teacher (ES=0.01) ratings supported this finding in direction but did not reach statistical significance. Youth born in the 90th-95th percentile manifested significantly *lower* levels of parent reported externalizing (ES=-0.15) and internalizing (ES=-0.12) pathology than those born AGA in the fully adjusted model. Teacher and youth reports supported these findings in direction but did not reach statistical significance.

Table 2: Average Differences (Standard Error) Between Youth Born LGA (>95th or 90th-95th Percentile) Compared to Those Born AGA (10th-90th Percentile) for Externalizing and Internalizing Symptom Scores

		Model 2 (Unadjusted)		Model 3 (Adjusted for Confounders)		Model 4 (Adjusted for All Covariates Including Mediators)	
		>95 th	90 th -95 th	>95 th	90 th -95 th	>95 th	90 th -95 th
Youth Report	Externalizing ES	1.8 (0.7)*	0 (0.7)	1.6 (0.7)*	0 (0.7)	1.4 (0.7)*	-0.1 (0.7)
	Internalizing ES	0.8 (0.9)	1.1 (0.9)	1.0 (0.8)	1.4 (0.8)	0.8 (0.8)	1.3 (0.8)
Parent Report	Externalizing ES	1.0 (0.5)*	-0.9(0.4)*	0.9 (0.4)*	-0.8 (0.4)*	0.7 (0.4)	-0.9 (0.4)*
	Internalizing ES	0.4 (0.4)	-1.0 (0.4)*	0.5 (0.4)	-0.7 (0.4)	0.5 (0.4)	-0.8 (0.4)*
Teacher Report	Externalizing ES	1.4 (0.9)	0.1 (0.9)	0.6 (0.9)	0 (0.8)	0.2 (0.8)	-0.5 (0.8)
	Internalizing ES	-0.1 (0.5)	-0.1 (0.4)	-0.2 (0.5)	0 (0.4)	-0.4 (0.4)	-0.2 (0.4)

ES=Standardized effect size (Calculated by dividing the value of the fixed effect regression parameter by the standard deviation)

*p<0.05

Youth born <5th percentile for gestational age manifested significantly higher levels of parent-reported externalizing symptoms, even after adjustment for confounders (ES=0.13), but not after the putative mediators of the association were taken into account.

Increased levels of youth and parent-reported externalizing and internalizing symptoms were seen in youth born <5th percentile but these were not statistically significant. No elevation was noted in those born between the 5th and 10th percentile (See Table 3).

Table 3: Average Differences (Standard Error) Between Youth Born SGA (5th-10th or <5th Percentile) Compared to Those Born AGA (10th-90th Percentile) for Externalizing and Internalizing Symptom Scores

		Model 2 (Unadjusted)		Model 3 (Adjusted for Confounders)		Model 4 (Adjusted for All Covariates Including Mediators)	
		<5 th %ile	5 th -10 th %ile	<5 th %ile	5 th -10 th %ile	<5 th %ile	5 th -10 th %ile
Youth Report	Externalizing ES	1.2 (0.7) 0.17	0.1 (0.7) 0.01	1.0 (0.7) 0.14	-0.2(0.7) -0.03	0.9 (0.6) 0.13	-0.2 (0.7) -0.03
	Internalizing ES	1.4 (0.8) 0.16	-0.8 (0.8) -0.10	1.2 (0.8) 0.15	-0.5(0.8) -0.07	1.2 (0.8) 0.14	-0.6 (0.8) -0.07
Parent Report	Externalizing ES	1.0 (0.4)* 0.16	0.2(0.4) 0.04	0.8 (0.4)* 0.13	0 (0.4) 0	0.8 (0.4) 0.12	0(0.4) 0
	Internalizing ES	0.5 (0.4) 0.08	0(0.4) 0	0.3 (0.4) 0.05	0 (0.4) 0	0.3 (0.4) 0.05	0 (0.4) 0
Teacher Report	Externalizing ES	0.4 (0.9) 0.04	1.1 (0.9) 0.10	0 (0.9) 0	0.4 (0.8) 0.04	-0.4 (0.8) -0.04	0.2 (0.8) 0.02
	Internalizing ES	0.4 (0.4) 0.07	0.6 (0.4) 0.10	0.1 (0.4) 0.03	0.5 (0.4) 0.09	0 (0.4) 0	0.4 (0.4) 0.07

ES=Standardized effect size (Calculated by dividing the value of the fixed effect regression parameter by the standard deviation)

*p<0.05

Discussion

In this provincially representative cohort of youth aged 4-16 years, we found that children and adolescents with birth weights above the 95th percentile for gestational age manifested higher self-reported levels of externalizing symptoms relative to those born AGA even after adjustment for confounders and potential mediators of the association. While we did not find statistically significant increases in levels of externalizing symptoms in the fully adjusted models among parent and teacher ratings for youth born this large, they were in the same direction as youth reports. According to their parents,

youth born between the 90th and 95th percentiles of birth weight for GA may actually manifest significantly *lower* levels of externalizing symptoms than those born AGA, a finding that was supported by youth and teacher-reports but that did not reach statistical significance. This is in keeping with some literature that suggests that there may be a small protective effect in infants born large, but not ‘too large’^{25,26}. Finally, after adjustment for confounders and mediators in this cohort, youth born in the lowest 5% of birth weight for gestational age manifested increased levels of self and parent-reported internalizing and externalizing pathology but these were not statistically significant.

To date, little has been published on the mental health of those born macrosomic and only two studies have reported significant associations with problems in youth^{15,16}. In a study of 4971 14-year old Australians, Alati and colleagues¹⁵ found that children born in the highest quintile of birth weight for gestational age and assessed with the CBCL were at increased risk for social problems, and, while not statistically significant, there was some suggestion that they also had higher levels of externalizing and internalizing problems than those born in the middle quintile. Buschgens and colleagues recently reported the presence of associations between being born >4500g and externalizing symptoms in 2230 10-12 year old youth using parent and teacher reports also based on the CBCL¹⁶. Compared to those born between 2500 and 4500 grams, individuals born macrosomic had higher levels of teacher-rated delinquent, aggressive, and ADHD symptoms and parent-rated symptoms of aggression. Despite adjustment for putative confounders, our results are relatively consistent in both children and adolescents across multiple informants. This suggests that youth born macrosomic may be at

increased risk of developing externalizing problems and that this may be related to intrauterine or early postnatal factors associated with macrosomia.

In our adjusted models, the observed associations between externalizing problems and macrosomia were consistent in direction for all informants but statistically significant only for youth and parent ratings. Three factors likely contribute to this: the relatively small effect sizes, the presence of measurement error in both the classification of macrosomia and informant ratings, and inherent differences (lack of agreement) in the perspectives of these informants³².

Despite the fact that there were statistical trends suggestive of associations between SGA and emotional and behavioural problems in this cohort, none were statistically significant after adjusting for all covariates. These results are at odds with some but not all studies of the association between being born small and later mental health problems. In addition to the potential contribution of measurement error, since birth weights corresponding to the 5th percentile in term infants in Canada are 2927g for males and 2814g for females, it is possible that this birth weight threshold is too high and that in order to predict psychopathology, one must examine infants born SGA and/or <2500g. It is also possible that sampling at age 4-16 led to an underrepresentation of individuals born at very or extremely low birth weights, biasing our results toward the null hypothesis. Since more pathology is sometimes seen in small infants who develop in less enriched environments^{33,34}, it is possible that the presence of universal healthcare in Canada serves to buffer these vulnerable individuals from this risk. This is a finding that warrants future study.

The OCHS was not specifically designed to examine associations between prenatal exposures and later psychopathology. Birth weight and gestational age had to be assessed retrospectively and, despite the clinical relevance of the scales used in this study, we are not able to tell if children born macrosomic are at increased risk for any specific disorder in childhood or adolescence. Our measures of child health do not include information on severity and persistence, limiting our ability to investigate the role that these conditions might have in linking macrosomia to psychopathology. Furthermore, there are constraints in our ability to control for familial risk, as we relied mainly on parent-reported treatment to assess parental psychiatric risk. As a result, the pattern of effects observed in this study are suggestive of an association between macrosomia and psychopathology. However, at present time we are not able to definitively conclude that this association is causal and it is clear that our findings require replication.

Despite its limitations, our study has a number of strengths including its use of a representative general population sample and the utilization of well-established and standardized measures of psychopathology completed by multiple informants. Moreover, the use of accepted birth weight cutoffs that are gender specific and capture large and small infants across the gestational age range reduces the likelihood that certain groups are under-represented. We also attempted to control for the familial or genetic risk of psychopathology and persisting postnatal psychosocial disadvantage in an attempt to isolate intrauterine effects.

This cohort's relative lack of detailed obstetric data leads to additional uncertainty as to whether the observed link between being born >95th percentile for GA and

externalizing symptoms is due to LGA and its accompanying intrauterine, delivery and postnatal biochemical complications, or if LGA (>95th) is merely a *marker* of putative upstream causal factors such as maternal obesity and/or diabetes mellitus. Obesity and diabetes in pregnancy are themselves associated with increased levels of emotional and behavioural problems in offspring^{35,36} and these women are also at higher risk of manifesting maladaptive personality traits³⁷ and developing postpartum depression³⁸. Indeed, further study is required to determine if it is these antecedents of macrosomia that are actually responsible for links to externalizing problems in youth.

Conclusions

The present work suggests that infants born >95th percentile for gestational age may be at increased risk for developing externalizing symptoms in childhood and adolescence and that this may be due to intrauterine factors. While the effect size of this finding is small (i.e., 0.20), given that rates of macrosomic births appear to be on the rise, reducing the number of infants born large via the provision of treatments for pregnant obese and diabetic women at a population level may provide meaningful benefits to their offspring. In view of the methodological limitations of our study, the suggestive findings bear replication in future work. These studies should be prospective in nature, attempt to use genetically sensitive designs and assess outcomes using multiple informants and optimal measures of psychopathology across the lifespan to determine if the reported associations are robust, causal and have the potential for prevention.

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CHAPTER FOUR

STUDY 3

TITLE: Pre-Pregnancy and Pregnancy Obesity and Neurodevelopmental Outcomes in Offspring: A Systematic Review

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CONTEXT AND IMPLICATIONS OF THIS STUDY: The impetus for Study 3 of the thesis was the finding of a small but significant association between macrosomia and externalizing symptoms in youth in Study 2 and the possibility that upstream factors present in the mother might account for the observed link.

Examining associations between the risk factors for macrosomia and psychopathology in offspring provide the potential to: a) more clearly understand the specific nature of the link between macrosomia and psychopathology (i.e., whether it is better conceptualized as a marker or as a cause of psychopathology), b) better elucidate the pathophysiological mechanisms underlying the link, and c) provide more specific information on what steps would need to be taken to understand the preventive implications of prior findings.

For reasons outlined in the Introduction section of the thesis, I chose to examine associations between maternal pre-pregnancy/pregnancy BMI and psychopathology in offspring rather than assessing the risk posed by GDM. In order to better understand the link between maternal adiposity and offspring mental disorders, I systematically reviewed the literature in this area.

This study objectively and replicably summarized this growing area of literature, highlights the shortcomings of existing studies, and identified existing knowledge gaps. In particular, it suggests the relative shortage of studies in this area in general and the specific dearth of research examining mental health outcomes in infants, children and adolescents. It showed that most of the studies done in this area had failed to adequately control for error (i.e., confounders) and so even after reviewing this literature, it remained unclear if maternal body mass index prior to and during pregnancy and its accompanying intrauterine environment is causally linked to psychopathology in offspring.

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CONFLICTS OF INTEREST: None

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Abstract

Maternal obesity in pregnancy is associated with a number of adverse outcomes for mother and her offspring both perinatally and later in life. This includes recent evidence that suggests that obesity in pregnancy may be associated with central nervous system problems in the fetus and newborn. Here, we systematically review studies that have explored associations between maternal overweight and obesity in pregnancy and cognitive, behavioural and emotional problems in offspring. The twelve studies eligible for this review examined a wide range of outcomes across the lifespan and eight provided evidence of a link. These data suggest that the offspring of obese pregnancies may be at increased risk of cognitive problems and symptoms of attention deficit hyperactivity disorder in childhood, eating disorders in adolescence and psychotic disorders in adulthood. Given the limitations of existing data, these findings warrant further study, particularly in light of the current worldwide obesity epidemic.

Introduction

The last 20 years have seen an exponential increase in rates of overweight and obesity around the world (1, 2). Women of childbearing age have not been spared in this epidemic and approximately one third of American (2) and one fifth of British (3) women are obese. Obesity prevalence among women aged 12-44 in the United States doubled between 1976 and 2004 and the number having a body mass index (BMI) ≥ 40 tripled (4). In the decade following 1993, a 70% increase in pre-pregnancy obesity was reported in a study of 9 U.S. states (5).

Coinciding temporally with this epidemic has been an increasing interest in how exposures in pregnancy can affect the long-term health and development of the offspring of these gestations. The process by which persistent physiological alterations in offspring result from intrauterine conditions is referred to as prenatal programming (6). Indeed, a large number of studies that attest to the importance of the intrauterine environment suggest that it can ‘program’ or affect later risk of obesity (7), hypertension (8) and even depression (9) in offspring independent of genetic and socioeconomic confounders.

The presence of maternal obesity in pregnancy creates an intrauterine environment that is suboptimal for both the mother and her fetus and is a major modifiable contributor to adverse maternal and child health outcomes. Pre-pregnancy obesity is a risk factor for diabetes mellitus, hypertension, thromboembolic disease and asthma in pregnancy (10). At delivery, obese women are 20% more likely than normal weight women to suffer perinatal haemorrhage and three times more likely to develop an infection (11). They are less likely to breastfeed (12) and are more prone to lactation delay and failure than normal

weight women (13). Obese mothers are also twice as likely to give birth to macrosomic infants who themselves have higher rates of birth trauma and perinatal asphyxia (14). In the longer term, pre-pregnancy obesity is associated with a number of adverse health outcomes for the mother including cardiovascular and metabolic disease (11) and the offspring of these pregnancies appear more likely to be obese (7) and suffer from the metabolic syndrome (15).

The cardiovascular and endocrine systems may not be the only ones whose functioning is affected or ‘programmed’ by obesity in pregnancy. In fact, a recent systematic review suggests that infants born to mothers who were obese were at increased risk of central nervous system (CNS) developmental problems including neural tube defects, spina bifida and hydrocephaly (16).

If maternal obesity does adversely affect neurodevelopmental outcomes in offspring later in life, it is not clear if this occurs via a direct programming effect or if obesity simply serves as a marker of the actual pre or postnatal causal factors. The prenatal programming hypothesis would posit that the intrauterine exposures accompanying maternal obesity would alone be sufficient to produce long term adverse effects on offspring neurodevelopment. Such an effect could occur via the dysregulation of maternal hormonal or immune systems, or even nutrient excesses. Alternatively, pregnancy obesity could be linked to neurodevelopmental outcomes via a number of indirect or non-causal pathways. For example, obesity in pregnancy might simply be a marker of problems known to affect overweight mothers and that also influence fetal neurodevelopment such as folate (17) or vitamin D deficiency (18). Pregnancy exposures

common to obese women including increased rates of diabetes mellitus (DM) (10), exposure to traumatic events in pregnancy and/or perinatal depression could also be responsible (19). Moreover, the effects of pregnancy obesity on the offspring's cognitive, emotional and behavioural development might not be due to prenatal exposures but rather mediated postnatally by obstetric complications or child health problems such as obesity or DM. Finally, genetic and/or environmental confounders might be responsible for observed associations. Maternal cognitive problems (20), maladaptive personality traits (21), frank psychiatric disorder (22) or even exposure to poverty (23) might not only increase a mother's risk of obesity, but also affect the risk of fetal neurodevelopmental problems independent of the intrauterine state associated with maternal obesity.

Given the potential for maternal obesity during pregnancy to affect CNS development coupled with the fact that it may be a modifiable risk factor for CNS problems makes this area particularly worthy of study. As a result, we systematically reviewed extant studies to determine if the offspring of women who were overweight or obese prior to or during pregnancy had higher rates of neurodevelopmental problems in childhood, adolescence and adulthood than those born to mothers with a BMI in the normal range. We anticipated that the offspring of women who were overweight and obese would manifest higher levels of problems than those born to women with normal BMIs.

Methods

We searched MEDLINE and EMBASE from their respective inceptions to September 22nd, 2010 for studies in all languages that have examined the association

between maternal overweight and obesity, weight gain during pregnancy and neurodevelopmental outcomes in the offspring of these gestations. While we examined the predictive value of maternal overweight; obesity ($BMI \geq 30$) was our main predictor of interest. The following search strategy was utilized for MEDLINE: [(pregnan* OR pre-pregnancy body mass index) AND (exp body mass index OR exp obesity OR exp overweight)] AND (exp mental disorders OR behav* OR exp brain diseases OR cognit* OR neuropsych* OR executive function* OR development* OR exp human development OR exp child development OR exp developmental disabilities OR exp personality development OR exp learning disorders OR math* OR arithmetic OR exp reading OR spelling OR exp dyslexia OR exp schools OR academic OR exp communication disorders OR exp psychomotor disorders OR exp perceptual disorders). This search was limited to studies on humans. Our EMBASE search utilized the same strategy, using the same keywords and equivalent medical subject heading terms in that database. This is available upon request.

Only studies that examined BMI or weight gain as a predictor of the study's main outcomes were eligible. These studies could examine any cognitive, psychological, behavioural, emotional or psychiatric outcome assessed after 1 month of age.

All reviewers evaluated the titles and abstracts yielded by our search to determine whether articles met eligibility criteria. They also hand searched the reference section of each relevant article from the initial screening for relevant studies. Studies were chosen for full text review if it was deemed that there was any possibility that the article was

eligible. All reviewers independently assessed all studies identified from this step and planned to resolve disagreements through discussion, though this did not occur.

Adjusted estimates of the association between maternal obesity and the study outcome were the main outcomes considered. We also extracted data on sample size, study design and the obesity definition used as well as study limitations. Study quality was assessed using the Newcastle Ottawa Scale (24). This scale is scored on a points system and case-control and cohort studies can earn a maximum score of 9 based on selection, comparability and exposure criteria.

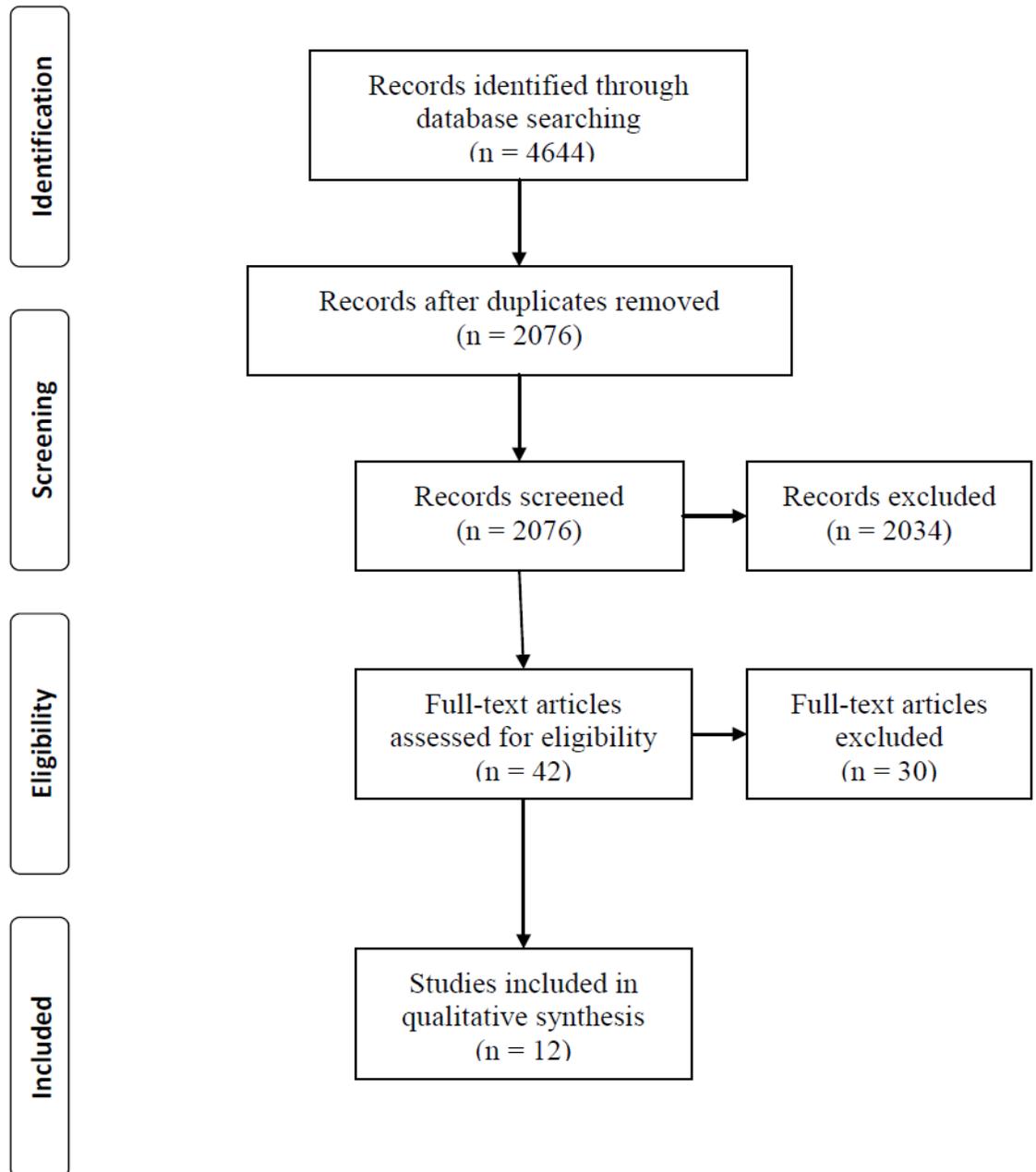
We classified study findings in terms of whether or not they provided evidence in support of our *a priori* hypothesis of an association between maternal obesity and an increased risk of neurodevelopmental problems. We used the following headings to summarize study findings with respect to this hypothesis: **SUPPORT**: clear evidence of an association between maternal obesity and offspring outcome; **MIXED**: some but inconsistent evidence of an association between maternal obesity and offspring outcome, or a clear association limited by major methodological limitations; and **NO SUPPORT**: no evidence of an association between maternal obesity and neurodevelopmental outcome. Given the heterogeneity of the eligible study outcomes and the relatively low number of studies for each of these categories, a decision was made not to meta-analyze the results of eligible studies.

Results

Our initial search identified 1713 potentially eligible studies in MEDLINE and 2931 in EMBASE (Figure 1). Forty-two full text articles were examined. Upon review,

12 articles remained (25-36). Of these 12, two examined associations between increased maternal BMI and childhood IQ (25, 26), two reported on fetal alcohol syndrome (27, 28), two examining ADHD in children (29,30), (one of which also contained data on negative emotionality (30)); four contained data on schizophrenia and related psychoses in adulthood (31-34) and two examined eating disorders (35,36). One of the eating disorders studies also contained data on depressive/anxiety problems in adolescents diagnosed by a healthcare professional (36). The other used maternal weight gain during pregnancy as a predictor of anorexia and bulimia nervosa (35). A summary of both the methodological issues and the substantive results of these studies can be found in Table 1. Of note, four additional studies either only examined BMI either as a confounder or covariate and did not provide adjusted estimates of its effect on neurodevelopmental outcomes (37-40) and were not eligible. Seven studies used pre-pregnancy BMI as their predictor (25-28, 30-32), one examined maternal BMI in the first trimester (29), two in the second (34, 36) and one in the third (33). Only three studies examined pregnancy weight gain (25, 29, 35).

Figure 1: Maternal Obesity in Pregnancy and Neurodevelopmental Outcomes in Offspring: Flow Diagram



Sample sizes in these studies ranged from 169 to 21090 mother-offspring pairs. Five were case-control studies and seven contained data from prospective birth cohorts.

Of the 12 studies examined, five provided clear support for an association between maternal obesity and neurodevelopmental problems. One of these examined childhood IQ (33), one looked at attention deficit hyperactivity disorder (ADHD) in children (29), two focused on schizophrenia in adults (32, 34) and one examined eating disorders in adolescence (36). Three studies provided mixed support of a link according to our classification system; one for childhood IQ (27), one for ADHD (30; which also suggested that negative emotionality was also increased in the offspring of mothers with pre-pregnancy obesity), and one of schizophrenia (31). Of the remaining four studies; two on fetal alcohol syndrome (27, 28), one on schizophrenia (33) and one examining eating disorders in adults (35) did not support the presence of a link.

Of the 12 studies reviewed, six attempted to control for a familial or genetic risk of the outcome in mothers (25, 30-34) and seven attempted to adjust for potential postnatal socioeconomic confounders that are likely to have been present prenatally (25, 26, 30, 31, 35, 36). All three of the studies that adjusted for both types of confounders (25, 30, 31) provided some support for an association between maternal obesity and poorer neurodevelopmental outcome. No study adjusted for the presence of maternal DM or other perinatal factors such as macrosomia or birth complications. None of the reviewed studies examined the role postnatal factors might have played in mediating the association between pregnancy obesity and offspring outcomes. The sampling frames of eligible studies were extremely variable, ranging from geographically limited high-risk groups to multinational birth cohorts.

Five out of the seven studies that examined pre-pregnancy obesity, one that assessed BMI in the first trimester and both studies that examined it in the second trimester found BMI to be a significant predictor of neurodevelopmental problems in offspring. However, despite the fact that the only study that assessed BMI in the third trimester failed to support a link, and Kawai and colleagues’ data (34) suggested that increased second trimester BMI was more deleterious than third, heterogeneity in the studies examined precludes firm conclusions from being made regarding the presence of a sensitive period of exposure to maternal obesity.

Table 1: Studies Reporting Data on Maternal Obesity or Weight Gain During Pregnancy and Offspring Cognitive and Psychiatric Outcomes

Reference	Sample	Design	Predictor/ Exposure	Study Objectives/ Outcomes	Findings	Limitations (Sampling, Measurement, Control of Error) Newcastle- Ottawa Scale (NOS) Score
IQ						
Neggers et al, 2003 (25)	Mother children pairs (Average age ~5 years) (N=355) Born in 1985-1989	Sample from a prospective cohort of low income African American children whose mothers were selected because of low plasma	Pre-pregnancy BMI self-reported by mother at ~23 wks after LMP BMI analyzed as a continuous and categorical measure Reference Group for	To assess the association between maternal pre-pregnancy BMI and maternal weight gain in pregnancy and psychomotor development Overall, verbal and nonverbal IQ	SUPPORT Each increase of 1 unit in maternal BMI associated with significantly reduced IQ and nonverbal IQ Overall IQ scores of offspring of obese women were 4.7 points	Sampling: Highly selected, small and disadvantaged sample (low SES, low mean maternal and child IQ, low zinc level). High rate of attrition Measurement: Retrospective maternal self-report of weight

		zinc levels (USA)	Categorical Analyses: BMI=19.8-26 Overweight: 26.1-29 Obese >29 Pregnancy weight gain also analyzed as a continuous variable		lower and nonverbal scores 5.6 points lower than those who's mothers had normal BMI	at ~23 weeks GA Control of Error: No adjustment for maternal PGDM or GDM NOS=7
Heikura et al, 2008 (26)	2 Finnish Birth Cohorts (1966; N=12058 and 1986; N=9032) at ~11.5 years old	Cohort Study (Finland)	Pre-pregnancy BMI self-reported retrospectively at 25 wks after LMP Reference Group BMI: 20-25 Thin: <20 Overweight: 25-30 Obese: ≥30	To investigate maternal sociodemographic and health factors assessed during pregnancy for their association with intellectual disability IQ<70 (Intellectual disability)	MIXED 1966 Obese: OR=1.3, 95%CI 0.5-3.1 1986 Obese: OR=3.6, 95%CI 2.0-6.6	Measurement: Retrospective maternal self-report of weight at ~25 weeks GA Height also self-reported by some mothers Control of Error: Did not adjust for maternal or paternal IQ No adjustment for maternal PGDM or GDM NOS=7
FETAL ALCOHOL SYNDROME						
May et al, 2005 (27)	6 year olds (53 cases and 116 controls) Born in 1993	Case-Control (South Africa's Western Cape Province)	Pre-Pregnancy BMI (self-reported retrospectively 7 years after pregnancy)	To describe risk factors for FAS Fetal Alcohol Syndrome (diagnosed by dysmorphologists)	NO SUPPORT Unadjusted t-test showed that BMI was significantly lower in mothers of Fetal alcohol syndrome children (24.9)	Sampling: case and control mothers differed in a number of important ways including SES, education etc. Generalizability of results may be limited.

					than control mothers (27.5), p=0.019	Measurement: Retrospective maternal self-report of weight and height 7 yrs after delivery, alcohol intake etc. Possible social desirability bias Control of Error: Did not appear to control for important confounders (eg. maternal fetal alcohol spectrum disorder, GDM or PGDM) NOS=5
May et al, 2008 (28)	6 year olds (72 cases and 134 controls) Born in 1996	Case-Control (South Africa's Western Cape Province)	Pre-Pregnancy BMI (self-reported retrospectively 7 years after pregnancy)	To describe risk factors for FAS Fetal Alcohol Syndrome (diagnosed by dysmorphologists)	NO SUPPORT Unadjusted ANOVA showed that BMI was significantly lower in mothers of fetal alcohol syndrome children (22.5) than control mothers (27.4), p=0.001	Same as May et al, 2005 NOS=5
ADHD (Children)						
Rodriguez et al, 2008 (29)	7-12 year olds (N=12556) Born	3 Prospective Birth Cohorts (Scandinavi	BMI from medical records at ~10 weeks after LMP	To examine the association between BMI and/or weight gain and core symptoms of	SUPPORT Overweight (BMI>26): OR=1.43, 95%CI 1.12-	Measurement: Weight assessed at 10 wks after LMP was called 'pre-

	1978-1987	a)	Reference Group: BMI=19-26 Overweight : BMI>26 Pregnancy Weight Gain	ADHD in school-age offspring Top 10%ile of ADHD Symptom Scores (Teacher Rated)	1.83) Each Unit increase in BMI: OR=1.04, 95%CI 1.02-1.07) For women with high BMI, weight gain further increased odds (OR=1.24, 95%CI 1.07-1.44)	pregnancy weight' Only single informant; unknown clinical relevance of scale of scale cutoff selected Control of Error: No adjustment for familial risk of ADHD No adjustment for maternal PGDM or GDM NOS=8
Rodriguez, 2010 (30)	5 year olds (N=1714) Born 1999-2000	Prospective Birth Cohort (Sweden)	Pre-Pregnancy BMI from the Swedish Medical Birth Register Reference Group: BMI=20-25 Overweight (BMI 25-30) Obese (BMI≥30)	To assess the association between maternal pre-pregnancy obesity and risk for ADHD symptoms in children. Top 15%ile of ADHD, Negative emotionality symptom scores (Mother and Teacher-rated)	MIXED <u>Parent Report:</u> No increased odds for any outcome <u>Teacher Report:</u> <i>Overweight</i> Inattention: OR=2.00, 95%CI 1.20-3.35 Hyperactivity: NS Negative Emotionality: OR=1.81, 95%CI 1.22-2.69 <i>Obese</i> Inattention: OR=2.09, 95%CI 1.19-4.82 Hyperactivity: NS	Sampling: High rate of attrition Measurement: Unclear if Height and Weight are self-reported or assessed by medical professionals. Unclear when this was assessed Unknown clinical relevance of scale cutoff selected Outcomes: Overweight at risk but not obese, results positive only for certain symptoms with specific

					Negative Emotionality: NS	informants No adjustment for maternal PGDM or GDM NOS=7
PSYCHOSES						
Jones et al, 1998 (31)	Participa nts up to 28 years old (n=1057 8) Born in 1966	Prospective Birth Cohort (Finland)	Pre- pregnancy BMI reported retrospectively by mother at 24-28 wks GA BMI>29 Reference Group: BMI=19-29	To determine if abnormalities of pregnancy, delivery and the neonatal period are associated with adult-onset schizophrenia Schizophrenia (Psychiatrist diagnosed)	MIXED BMI>29 OR=2.1, 95%CI 0.9-4.6	Measurement: Retrospective maternal self- report of weight and height at 24-28 weeks GA Control of Error: No adjustment for familial risk of schizophrenia No adjustment for maternal PGDM or GDM NOS= 6
Schaefer et al, 2000 (32)	30-38 year olds (63 cases and 6570 controls) Born 1959- 1967	Case- Control study of participants in a Prospective US Birth Cohort of those born between 1959 and 1967	BMI measured at study enrolment by healthcare personnel Pre- Pregnancy Obesity (BMI>30) Reference Group: BMI=20-27	To examine the relation between maternal pre- pregnant BMI and schizophrenia spectrum disorders Schizophrenia and Spectrum Disorders (Psychiatrist Diagnosed)	SUPPORT Schizophrenia and Spectrum Obese: RR=2.9, 95%CI 1.3-6.6 Schizophrenia Alone: RR=2.7, 95%CI 0.95- 7.8	Sampling: High rate of attrition Measurement: Unclear GA at study enrolment Control of Error: No adjustment for maternal PGDM or GDM NOS=9
Wahlbeck et al, 2001 (33)	Individua ls born between 1924 and	Prospective Birth Cohort (Finland)	Late Pregnancy BMI from birth records	To assess the influence of maternal body size, infant size at	NO SUPPORT *BMI of obese mothers used as reference	Sampling: High rate of attrition Did not assess if prediction improved by

	1933 (N=7086)		Reference Group: BMI>30	birth and childhood growth on schizophrenia risk Schizophrenia (Inpatient discharge diagnosis)	group. Those with BMI less than 30 were at increased odds (OR=3.06, 95%CI 1.12-8.38) relative to those born >30 In continuous analyses, each decrease of 1 unit in maternal BMI increased odds of schizophrenia by 9% (OR=1.09, 95%CI 1.02-1.17)	inclusion of quadratic term (ie. did not rule out a J-shaped relation between BMI and schizophrenia) Measurement: Timing of weight and height measures of women not defined Control of Error: No adjustment for maternal PGDM or GDM, SES or familial risk of schizophrenia NOS=6
Kawai et al, 2004 (34)	~20 year olds (Cases: n=52, Controls: n=6570) Born on or after 1966	Case-Control Study (Japan)	BMI measured at first and last antenatal care visits by clinic personnel BMI as a continuous measure in early (GA=-18.5 wks) and late (GA=-38.3 wks) pregnancy	To assess associations between maternal antenatal factors and schizophrenia in offspring Schizophrenia (Psychiatrist diagnosed)	SUPPORT For every 1 unit increase in early pregnancy BMI, odds of schizophrenia increased 24% (OR=1.24, 95%CI 1.02-1.50) For every 1 unit increase in late pregnancy BMI, odd of schizophrenia increased 19% (OR=1.19; p<0.05)	Sampling: Case-control study, relatively young sample Control of Error: No adjustment for SES, maternal mental illness during pregnancy other than psychoses No adjustment for maternal PGDM or GDM (No mothers in study had PGDM or GDM) NOS=4
EATING DISORDERS						

Favaro et al, 2006 (35)	Females born between 1971 and 1979 (187 cases and 554 controls)	Case-control study of females born on 2 wards in Italy. Cases supplemented by patients from eating disorder clinics (Italy)	Pregnancy Weight Gain from hospital records Reference Group: 7-15 kg >15 kg	To explore the role of obstetric complications in the development of eating disorders Anorexia and Bulimia Nervosa (Psychiatrist diagnosed)	NO SUPPORT Anorexia: OR=0.8, 95%CI 0.4-1.7 Bulimia: OR=0.9, 95%CI 0.4-2.3	Sampling: Some ascertainment bias in the collection of cases Weight gain standards applied to all women regardless of their pre-pregnancy BMI Control of Error: No examination of familial risk of eating disorders No adjustment for maternal PGDM or GDM NOS= 5
Allen et al, 2009 (36)	14 year old males and females born between 1989 and 1991 N=1597	Cohort (Australia)	Maternal BMI self-reported at 16 wks after LMP	Eating Disorder Cases (assessed using a 24 item scale adapted from the Child Eating Disorder Examination and Eating Disorder Examination Questionnaire)	SUPPORT Each increase of 1 unit in maternal BMI increased odds of eating disorder caseness by 11% (OR=1.10, 95%CI 1.05-1.16) Each increase of 1 unit in maternal BMI increased odds of a diagnosed depressive/anxiety disorder by 7% (OR=1.07, 95%CI 1.03-1.11)	Sampling: High sample attrition Measurement: Maternal weight was retrospectively self-reported Control of Error: No adjustment for parental eating disorders No adjustment for maternal PGDM or GDM NOS=6

Abbreviations

ADHD: Attention deficit hyperactivity disorder
ANOVA: Analysis of variance
BMI: Body mass index
CI: Confidence Interval
DM: Diabetes mellitus
GA: Gestational age
GDM: Gestational Diabetes Mellitus
IQ: Intelligence quotient
LMP: Last menstrual period
N: Number of mother-offspring pairs
NOS: Newcastle Ottawa Scale
NS: Not significant
OR: Odds Ratio
PGDM: Pre-gestational diabetes mellitus
RR: Relative risk
SES: Socioeconomic status

Overall, no particular study design, sample characteristics or obesity definitions seemed to predict significant associations. Moreover, no conclusions can be made with respect to the existence of a dose-response effect for maternal obesity on neurodevelopmental outcomes.

Discussion

Despite the fact that relatively few studies have examined associations between maternal obesity prior to and during pregnancy and neurodevelopmental outcomes in offspring, some evidence suggests that it may be associated with an increased risk of certain cognitive and psychiatric problems across the lifespan. The results of the studies that comprise this body of evidence are inconsistent however, and it is not possible to definitively conclude that maternal obesity negatively impacts neurodevelopment in humans at present time. More work needs to be done to determine if obesity prenatally programs or is causally related to adverse neurodevelopmental outcomes in offspring.

The finding that the offspring of these gestations may be at increased risk of reduced intelligence quotient (IQ) and symptoms of ADHD in childhood, eating disorders

in adolescence and perhaps even non-affective psychotic disorders as adults warrants further study, particularly in light of the current worldwide obesity epidemic. If maternal obesity is causally related to these outcomes, given the ever-increasing number of obese women of childbearing age seen around the world, the prevention and treatment of obesity might lead to significant health gains for these women and their offspring.

While methodologically limited, two studies supported the existence of an association between maternal pre and early pregnancy obesity and intellectual disability in their children. In one of these studies, Heikura and colleagues (26) examined associations between pre-pregnancy BMI and intellectual disability in youth. They found that maternal obesity was a predictor of intellectual disability in those born in 1986 (OR=3.6, 95%CI 2.0-6.6) but not those born in 1966 (OR=1.3, 95%CI 0.5-3.1). This finding raises the possibility that pre-pregnancy obesity does not directly program low IQ, but that the observed association is due to unmeasured confounders. Unfortunately, these authors were not able to determine if a linear association existed between increasing BMI and decreasing IQ. Moreover, while the percentage of women with BMI>30 was similar in both 1966 and 1986, the fact that all of these women were combined into a single group raises the possibility that there may have been a greater proportion at the more extreme high end of the BMI spectrum in 1986 than in 1966. It is not clear if such era specific effects are present for psychiatric outcomes.

Two studies by Rodriguez and colleagues also suggest that a link may exist between pre-pregnancy overweight and obesity and symptoms of ADHD in children (29, 30). In both studies, teacher ratings of the offspring of obese mothers had increased

levels of ADHD symptoms in childhood. However, in the latter study, parent reports of childhood ADHD symptoms and negative emotionality (i.e., sadness, fear and anger) failed to support a link. While this could mean that the effect is small or even absent, in light of the low to moderate associations seen between parent and teacher ratings of childrens' ADHD symptoms (41), one cannot conclusively rule out a link. That parental ADHD was adjusted for in their most recent study provides tantalizing preliminary evidence that maternal obesity could prenatally program offspring ADHD. Future research should attempt to replicate these findings and extend the follow-up of these individuals to determine the adolescent and adult impact of this exposure.

The association between increasing maternal BMI and the risk of eating disorders in 14-year old Australian youth was another notable finding, but was limited by the fact that the authors were not able to adjust for eating pathology in the parents of these individuals (36). Therefore, while it is possible that there may be a direct intrauterine effect of obesity on this outcome, the effects could also be mediated via the impact of weight on the interactions between mothers, fathers, and their children around eating and weight perception.

The studies contained in this review also suggest that there may be an effect of maternal obesity on the later risk of schizophrenia. Evidence of an association was seen in 3 of 4 studies that have examined this outcome, including one that adjusted for both maternal risk of psychosis and SES (32). In another study, the authors reported that early gestation obesity had a larger effect than obesity that occurred later in pregnancy on risk,

raising the possibility that either the timing or cumulative amount of exposure to obesity in pregnancy is relevant (34).

Even though all three studies that adjusted for both potential familial and environmental confounders reported evidence of associations between maternal obesity and neurodevelopmental problems, it does not necessarily follow that these effects are due to intrauterine programming. Confounders such as a familial risk of cognitive/psychiatric problems and low SES may not only act individually to increase risk but are also likely to interact with one another or even be correlated. This complex interplay complicates the interpretations of studies in this area, even when both are measured and considered in statistical analyses. This complexity is increased further by the elevated risk observed among obese individuals for certain maladaptive personality characteristics (21), high anxiety and problems with decision making (42). These problems could contribute to the development of emotional and behavioural problems in offspring via their impact on rearing practices and in order to provide adequate control over error, they should be considered in these studies in addition to clinical diagnoses of specific psychiatric syndromes. Future studies would benefit from the utilization of genetically sensitive designs or the examination of subsequent pregnancies within the same mother-partner pair to attempt to separate the relative contributions of these genetic and environmental influences.

Seven of the 12 eligible studies (25-29, 31, 36) utilized retrospective maternal self-reports of weight and four (26-28, 31), of height. In general, when self-reported, height tends to be overestimated and weight and BMI underestimated compared to direct

measurement (43). Previous studies suggest that this discrepancy in BMI may be particularly pronounced for obese individuals (44). While the true impact of this bias is not known, it is possible that some of the eligible studies have underestimated the size of the association between maternal BMI and neurodevelopmental outcomes in offspring.

To date, relatively little attention has been paid to the biochemical mechanisms that might underlie observed associations. The intrauterine milieu of obese pregnancy is complex but increased levels of estrogen (45), cortisol (46), free fatty acids (47), pro-inflammatory cytokines (48), and oxidative stress (49) might play a role. Postnatal mediating factors such as obstetric complications, later childhood weight and health problems, or even sympathetic nervous system overactivity (50) could also be involved. Decrements in IQ and emotion regulation problems in children might also be mediators of the link between maternal obesity and later risk of psychopathology.

Potential postnatal maternal mediators of the association between obesity in pregnancy and offspring neurodevelopmental problems could include the increased risk of depression seen in the postpartum period (19) and beyond (51), the maladaptive personality characteristics (21) of some obese women, problems with breastfeeding (12), and perhaps even increased levels of stress (52) and stress sensitivity (53). The children of obese women could also be affected by the increased levels of discrimination their mothers face both in the community and in the workplace (54).

Future studies in the area of maternal obesity in pregnancy and neurodevelopmental problems in offspring should focus on obtaining unbiased risk estimates by using direct measurements of height and weight if possible, examining a

broad range of outcomes across the lifespan, utilizing generalizable samples and validated assessments of outcome and adjusting for putative confounders. Such work would also benefit from an examination of putative sensitive periods and the potential biochemical mediators or causes of the association. These could include the assessment of genetic variants germane to risk pathways and their interaction with maternal obesity and its associated biochemical sequelae. These data would provide us with important clues as to the pathophysiology of the neurodevelopmental outcomes of interest and potentially guide the development of novel therapeutic agents. Case-control studies and data from existing pregnancy and birth cohorts could be used to rapidly test the above hypotheses.

A clear demonstration of causal effects requires the use of experimental approaches. Researchers conducting experimental studies in humans aimed at examining strategies designed to reduce pre-pregnancy obesity and to help women reach and maintain healthy weights during pregnancy could consider monitoring cognitive and temperamental outcomes in infants and toddlers and, if resources exist, emotional and behavioural functioning in the youth offspring of treatment and control groups. However, these studies would need to be adequately powered to examine outcomes in offspring if they are to advance our current knowledge. If human data accumulate and support a link, animal studies could be used to develop a better understanding of the mechanisms underlying this association.

Given the increasing prevalence of maternal obesity, demonstrating that causal associations exist between it and neurodevelopmental outcomes in offspring is an

important goal and could provide realizable targets for the primary prevention of cognitive and psychiatric problems. Certainly, more data are needed before obesity treatments can be touted as beneficial to offspring neurodevelopment.

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CHAPTER FIVE

STUDY 4

TITLE: Maternal Pre-Pregnancy Body Mass Index and Offspring Temperament and Behavior at 1 and 2 Years of Age

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CONTEXT AND IMPLICATIONS OF THIS STUDY: Study 4 of the thesis builds on the previous review by focusing on the need for more studies of the link between maternal BMI prior to pregnancy and by addressing the complete absence of work examining outcomes prior to three years of age. It also utilizes a large sample, and collects behavioural data using validated measures. Finally, the study attempts to determine if observed associations are likely to be due to fetal exposure to increased maternal body mass prior to and during pregnancy by adjusting for both a familial history of mental disorder as well as socioeconomic disadvantage.

As a result, this work represents the first study to provide evidence that an association between maternal pre-pregnancy BMI and externalizing behaviour in offspring exists prior to the age of 3 years. It also demonstrates that these problems first emerge around 24 months of age and suggests that they may be due to the intrauterine environment accompanying increased BMI in pregnancy rather than being due to the confounders of this association. While more work is needed to definitively demonstrate that such associations are causal, this study's results combine with those summarized in

Study 3 to suggest that exposure to increased maternal BMI in pregnancy might ‘program’ an increased risk of externalizing problems in young children.

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ABSTRACT

OBJECTIVE: To determine if maternal pre-pregnancy body mass index (BMI) is associated with elevated levels of temperamental difficulties and behavior problems in offspring at 1 and 2 years of age, respectively.

PATIENTS AND METHODS: Data for this study came from the Western Australian Pregnancy (Raine) Cohort of 2900 mothers and their infants. Mothers rated child temperament using the Toddler Temperament Scale (TTS) at age 1 and child behavior with the Child Behavior Checklist (CBCL) at age 2. The association between maternal pre-pregnancy BMI and temperament type (eg. easy versus intermediate-low, intermediate-high, slow-to-warm-up and difficult) was examined using multinomial logistic regression. Links between maternal BMI and CBCL internalizing and externalizing scales were quantified using linear regression. Analyses of both outcomes were adjusted for socioeconomic status and other known confounding variables.

RESULTS: After adjusting for confounders, pre-pregnancy BMI was not associated with an increased risk of difficult, slow-to-warm-up, intermediate-high or intermediate-low temperament in offspring at 1 year of age, but was positively associated with externalizing behavior problem scores ($\beta=0.131$, 95% CI 0.013 to 0.249) at age 2.

CONCLUSIONS: Associations between increasing maternal pre-pregnancy BMI and elevated levels of externalizing behaviors may emerge as early as 2 years of age. Additional research is required to replicate these findings and to determine if the association between the intrauterine conditions accompanying increased maternal body mass index and behavior problems in offspring is causal.

Introduction

Maternal obesity is the most common complication of pregnancy in the developed world, affecting up to 40% of women.¹ Despite widespread knowledge of its adverse effects on maternal and fetal health, rates of pre-pregnancy obesity have continued to increase.²

The intrauterine environment associated with obesity is suboptimal for fetal development. Infants born to obese women have a higher risk of congenital anomalies, including neural tube defects³ and are more likely to develop obesity⁴ and asthma⁵ later in life. A recent systematic review that examined associations between maternal overweight/obesity prior to and during pregnancy and neurodevelopmental problems in offspring found that eight of the 12 studies completed to date supported the presence of a link.⁶ This review included three of four studies of schizophrenia, one of two studies of eating disorders, two of the three cohorts that examined cognitive function, and both studies of attention-deficit/hyperactivity disorder (ADHD). One subsequently published study⁷ examined cognitive and behavioral outcomes in children and noted links between maternal pre-pregnancy overweight and offspring behavior problems in the Dutch Generation R cohort but not in the Avon Longitudinal Study of Parents and Children (ALSPAC). A recent case-control study also suggested that the risk of autism spectrum disorders and developmental delay were increased in women who were obese during pregnancy.⁸

Of the studies that have examined associations between maternal pre-pregnancy and pregnancy overweight and obesity and emotional and behavioral outcomes in

children, none have exclusively assessed outcomes prior to 3 years of age. Previous work has also generally failed to clarify whether links between increasing pre-pregnancy BMI and neurodevelopmental outcomes in offspring are likely to be due to the intrauterine environment associated with overweight and obesity in pregnancy or the confounders of these associations.⁶ Because maternal psychopathology (e.g., ADHD, depression)⁹ and socioeconomic disadvantage¹⁰ may be risk factors for obesity, as well as for internalizing and externalizing problems¹¹ in offspring, these factors must be taken into account when examining the role maternal pregnancy BMI might play in the development of these difficulties. Despite this, only two studies have adjusted for a maternal history of psychopathology in addition to socioeconomic status^{12,13} and only one of these involved children.¹³ While both reported associations that persisted despite adjustment, the scarcity of research that controls for all relevant confounders limits what risks can be attributed to increasing BMI in pregnancy (i.e., programming) versus confounding factors.

Given the already high rates of maternal pre-pregnancy obesity seen around the world and the vital importance of early development to health and success in school and life, we set out to determine if associations exist between maternal pre-pregnancy body mass index (BMI) and child temperament and behavior at 1 and 2 years of age, respectively, and if these persist despite adjustment for known confounding variables.

PATIENTS AND METHODS

Sample

Data for this work come from the Western Australian Pregnancy (Raine) Study Cohort, a sample of 2900 women recruited at 16-20 weeks of gestation from the public antenatal

clinics at the King Edward Memorial Hospital (KEMH) in Perth, Australia and nearby private clinics between May 1989 and November 1991. To be eligible, women had to speak English and plan to live in Western Australia after the delivery of their infant. Ninety percent of women approached agreed to participate.¹⁴ Participating mothers were more likely to be teenagers and never-married than women in Western Australia's general population.¹⁵ These women had a total of 2868 live born children. Of these, 2310 and 1990 provided assessments of their children's temperament and behavior at age 1 and 2 years, respectively. This Raine Study only planned to follow up 70% of the original sample at the 2 year visit owing to resource limitations. Informed consent was obtained at enrolment and at both follow-up visits. The study protocol was approved by the Human Ethics Committee at KEMH and/or Princess Margaret Hospital for Children in Perth.

Predictors (Maternal Pre-Pregnancy Body Mass Index)

At the time of study enrolment, maternal height was measured by study staff and women were asked to estimate their pre-pregnancy weight. If they were unable to provide their pre-pregnancy weight, their measured weight at enrolment was substituted (N=146). Pre-pregnancy BMI was calculated by dividing their weight in kilograms by their height in metres squared. We utilized BMI as a continuous variable rather than examining it as a categorical predictor so as to make use of all of the data present and to optimize statistical power. As a BMI < 16 defines extreme thinness/emaciation, those who reported a pre-pregnancy BMI < 16 (N=83) were excluded from the study, since it is unlikely that these women would be able to conceive.

Outcomes

Temperament. Temperament was assessed by maternal report at 1 year of age using the Australian Revision of the Toddler Temperament Scale (TTS).^{16,17} This measure is a validated, 97-item questionnaire that utilizes a 6-point Likert scale with options ranging from “almost never” to “almost always”. The TTS produces scores on nine dimensions of temperament: activity, rhythm, approach-withdrawal, adaptability, intensity, threshold of responsiveness, mood, distractibility, and persistence/attention span. Higher scores on a particular dimension represent more problematic behavior or poorer functioning. Based on these dimension scores, standard algorithms¹⁸ were used to classify children as fitting into one of five temperament categories (easy, difficult, slow-to-warm-up, intermediate-low, and intermediate-high). Children with difficult temperament children are defined as those with low rhythmicity, approach and adaptability, and high intensity and negative mood. Children with easy temperament are the opposite. The child scored as slow-to-warm-up is low in activity, approach, and adaptability, negative in mood, variable in rhythmicity and mild in intensity. Children in the intermediate-low category children are closer to those with easy temperament while those deemed intermediate-high tend to behave more like children in the difficult temperament group.

Behavior. Child behavior was rated at 2 years of age by maternal report using the Child Behavior Checklist for Ages 2-3.¹⁹ This questionnaire is a 99-item, empirically validated measure of child behavior that consists of six syndrome scales (social withdrawal, depressed, sleep problems, somatic problems, aggressive behavior and destructive behavior) which can be aggregated into broader internalizing and externalizing scales.

The internalizing scale reflects emotional difficulties and consists of the withdrawal, depressed and somatic problems subscales. The externalizing scale reflects behavioral problems and consists of the aggression and destructive subscales. We examined internalizing and externalizing scale raw scores as outcomes in order to capture the full breadth of behavioral variability present in these children. These scales have good test-retest reliability and internal consistency.¹⁹

Confounding Variables

The lifetime presence of maternal psychopathology was defined by an answer in the affirmative to the following question asked at 8, 10, 14 and 17 year-old Raine Cohort follow-ups: “have you ever been treated for an emotional or mental health problem?” (0 = never, 1 = ever). This definition was supplemented by the inclusion of variables assessing alcohol intake and smoking during pregnancy. The number of cigarettes smoked per day during the first 16-20 weeks of pregnancy was categorized into 0 = none, 1 = 1-5 daily, 2 = 6-10 daily, 3 = 11-15 daily, 4 = 16-20 daily and 5 = 21 or more daily, and treated as a continuous variable. Data on alcohol consumption during pregnancy were also self-reported as the number of drinks per week during the first three months of pregnancy. Paternal psychiatric history was assessed using the mother’s response to the question “dad ever been treated for an emotional or mental health problem?” (0 = never, 1 = ever). Socioeconomic status was self-reported by women at study enrolment and included the number of years of school completed successfully to date, her age, her current marital status (0=married or common-law, 1=single) and household income. Income was dichotomized (below <\$24000 versus above the poverty line; 0 = above, 1 = below).

Given that maternal obesity increases the risk of diabetes mellitus (DM) in pregnancy and since the presence of DM during pregnancy is associated with neurodevelopmental problems in offspring,²⁰ it was also included as a confounder. This variable was defined as the presence of either pre-existing DM or DM that developed during pregnancy (0 = no DM, 1 = any form of DM). Maternal life stress during pregnancy was quantified as the total number of life stress events that occurred during pregnancy using 10 items from the Tennant and Andrews life stress inventory.²¹ Child sex was also included (0 = female, 1 = male) as a control variable.

Statistical Analysis

Associations between maternal pre-pregnancy BMI and Toddler Temperament Scale categories were examined using multinomial logistic regression analyses. This type of regression was used because this outcome is comprised of five unordered categories. In particular, while the easy, intermediate and difficult categories can be seen as ordered, it is uncertain where the slow-to-warm-up category sits on this continuum. For the purposes of this study, the easy temperament category was chosen as the reference. Multinomial logistic regression generates separate odds ratios for the association between a predictor (e.g., maternal pre-pregnancy BMI) and outcome for each categorical dependent variable except for the reference category (in this case, easy temperament). The association between maternal pre-pregnancy BMI and CBCL internalizing and externalizing scales was examined using ordinary least squares linear regression.

For each outcome, two statistical models were created. The first contained the predictor and outcome only (unadjusted) and the second (fully adjusted) consisted of the

variables in the first model plus our confounders (i.e., maternal and paternal psychiatric history, household income, maternal education, age and marital status, DM, child sex, and pregnancy stress, smoking and alcohol intake). Statistical analyses were conducted using SPSS 20 (IBM, Armonk, NY) and all statistical tests were 2-tailed, with significance levels set at $\alpha = 0.05$.

Missing Values. Missing data for all variables were imputed using the fully conditional specification multiple imputation in SPSS 20.0. This approach utilized the values of all of the other variables in the fully adjusted model of interest, separately for each outcome. Ten imputation data sets were generated and the results of these imputations were integrated into one final inference which provided the basis for the results generated by the regression analyses.

RESULTS

Table 1 contains a summary of the characteristics of the sample. Just over half of the offspring (50.9%) were male and the remainder female. Mean pre-pregnancy BMI was 22.41 (SD=4.29) and mean maternal age at the time of enrolment was 28.10 years (SD=5.94). Just over 85% of eligible study participants provided temperament ratings at 1 year of age (N=2310) and 71.4% of the offspring of women with a BMI>16 prior to pregnancy (N=1990) submitted CBCL ratings at age 2. Additional descriptive outcomes for the TTS and CBCL can be found in Table 2.

Table 1: Characteristics of the Raine Cohort Eligible for This Study (N=2785)

	Number (%)
Total Number of Participants	2785 (100%)
Offspring Sex	Female: 1368 (49.1%) Male: 1417 (50.9%)
Single Mothers	464 (16.7%)
Income Below Poverty Line	1147 (41.2%)
Mother Ever Treated for Emotional Problems	815 (29.3%)
Father Ever Treated for Emotional Problems	437 (15.7%)
Number of Cigarettes Smoked Per Day in Pregnancy	None: 1165 (41.8%) 1-5 daily: 335(12.0%) 6-10 daily: 332(11.9%) 11-15 daily: 332 (11.9%) 16-20 daily: 366 (13.1%) ≥21 daily: 255 (9.2%)
Maternal Diabetes Mellitus Present	109 (3.9%)
	Mean (SD)
Maternal Pre-Pregnancy Body Mass Index	22.41 (4.29)
Mother's Age at Study Enrolment	28.10 (5.94)
Maternal Number of Years of Education	12.21 (1.31)
Maternal Pregnancy Stress Score (# of events)	1.98 (1.91)
Number of Alcoholic Beverages Consumed per week in First Four Months of Pregnancy	1.37 (3.12)

Table 2: Toddler Temperament and Child Behavior Checklist Scores at 1 and 2 Years

Toddler Temperament Scale Category	Number (%)	
Easy	1060 (38.1%)	
Intermediate-Low	683 (24.5%)	
Intermediate-High	277 (9.9%)	
Difficult	193 (6.9%)	
Slow-To-Warm-Up	97 (3.5%)	
Missing	475 (17.1%)	
Child Behavior Checklist for Ages 2-3	Mean (SD)	
	Internalizing Scale 5.88 (4.66)	Externalizing Scale 20.20 (11.60)

Analyses of associations between maternal pre-pregnancy BMI and the odds of being in a particular TTS category can be found in Table 3. They show that increasing maternal BMI did not predict an increased risk of intermediate-low, intermediate-high, slow-to-warm-up or difficult temperament in either unadjusted or adjusted analyses.

Table 3: Associations between Maternal Pre-Pregnancy BMI and TTS Scores

Temperament Category	Model 1 (Unadjusted) (Odds Ratio, 95% CI)	Model 2 (Fully Adjusted) (Odds Ratio, 95% CI)
Easy	1.00 (Reference)	1.00 (Reference)
Intermediate-Low	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.03)
Intermediate-High	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.03)
Difficult	1.03 (1.00 to 1.05)	1.02 (0.99 to 1.05)
Slow-To-Warm-Up	0.97 (0.92 to 1.03)	0.97 (0.92 to 1.01)

Finally, no association was observed between pre-pregnancy BMI and internalizing problems in offspring at 2 years of age (Table 4), though maternal BMI did predict increased externalizing scores in both adjusted and unadjusted analyses.

Table 4: Associations between Maternal Pre-Pregnancy BMI and CBCL Scores

	Model 1 (Unadjusted) (Unstandardized β , 95% CI)	Model 2 (Fully Adjusted) (Unstandardized β , 95% CI)
Internalizing Scale	0.032, -0.013 to 0.077	0.022, -0.023 to 0.067
Externalizing Scale	0.161, 0.039 to 0.282*	0.131, 0.013 to 0.249*

* $p < 0.05$

DISCUSSION

Offspring exposure to increased maternal BMI during gestation was not associated with increased levels of temperamental difficulty at age 1 or internalizing problems at age 2. However, an association emerged at age 2 between maternal BMI and elevated scores on the externalizing problems scale of the CBCL. This association persisted despite adjustment for confounders, suggesting that exposure to the intrauterine milieu associated with maternal overweight and obesity during pregnancy could be involved in this link. To our knowledge, no study has specifically examined the role maternal pre-pregnancy BMI plays in the etiology of temperament or behavioral problems in offspring less than 3 years of age. Brion and colleagues⁷ reported elevated levels of externalizing problems in the 3-year-old offspring of overweight and obese women in the Dutch Generation R cohort and Rodriguez and colleagues noted higher rates of teacher-rated ADHD symptoms in school-aged children born to overweight and obese women in four

Scandinavian pregnancy cohorts.^{12,22} Interestingly, Brion and colleagues did not note increased levels of behavioral problems in the 4 and 8 year old offspring born to overweight and obese women in the ALSPAC. Whether discrepancies between our study results and those of the ALSPAC are due to socioeconomic differences in the cohorts examined, the use of disparate measures, or simply reflect differences in the ages or developmental stages of the children studied is not clear.

It should be noted that the externalizing measure generated by the version of the CBCL used in this study contained aggressive and destructive but not inattention scales. Using additional data from the Raine Cohort, we have observed a statistically significant, positive association between maternal pre-pregnancy BMI and CBCL externalizing scale raw scores from 5 to 17 years of age (R. J. Van Lieshout, MD, unpublished data, January 2012). These findings showed that the greater the maternal BMI, the higher the level of externalizing difficulties manifested throughout childhood and adolescence. In this study, stronger associations were noted between maternal pre-pregnancy BMI and aggression than for inattention or delinquent behaviour.

In the present study, evidence of a link with child difficulties emerged at 2 years but was not present in temperamental ratings at age 1. This may be due to the fact that exposure to increased maternal BMI during gestation simply does not affect temperament. It could also reflect limitations in the temperament outcomes chosen, the measure of temperament used in this study,²³ or the fact that temperament imperfectly predicts later emotional and behavioral problems.²⁴ The stage of development at which assessments were completed may also have played a role. Previous research suggests that while

aggressive behaviors such as hitting and kicking may emerge as early as 1 year of age, they do not peak until later in the second and third years of life.^{25,26,27}

Work in animal models has shown that the offspring of mothers who are obese during pregnancy manifest decreased central serotonergic²⁸ and dopaminergic signaling²⁹ in the brain, changes that have been implicated in the development of externalizing behavior in humans.³⁰ In one study, the offspring of high fat fed obese rat dams manifested hypomethylation of a promoter of the dopamine reuptake transporter gene,²⁹ an alteration that can lead to a hypodopaminergic state. Hypomethylation is an example of an epigenetic change, a functional modification of DNA that does not involve an alteration in DNA sequence. Such epigenetic changes could be one mechanism by which exposure to elevated maternal BMI during pregnancy could increase levels of externalizing behavior in offspring.

The current study has a number of strengths including the inclusion of validated measures of temperament and behavior at 1 and 2 years of age in a large, prospective pregnancy cohort. In addition, we made use of multiple imputation techniques to reduce the impact of missing data on our results. Further, the variables collected in the context of the Raine Study allowed us to control for both familial socioeconomic and mental health confounders so that we could attempt to isolate the effect of increased maternal BMI in pregnancy on the risk of temperament and behavior problems in offspring.

However, follow-up data was unavailable for approximately 30% of the cohort at 2 years of age, study outcomes are based solely on maternal reports, and the cohort utilized was relatively socioeconomically disadvantaged. Despite the fact that we were

able to adjust for a number of covariates, we did not have formal measures of parental temperament or personality, nor did we have extensive information on maternal or paternal psychopathology. Given that specific genetic variants (e.g., dopamine receptor D2) have been associated with externalizing problems, as well as with obesity,^{31,32} genetic inheritance provides an alternative explanation for our observations. Until such factors are assessed and adjusted for, it will remain unclear if links between increased maternal pre-pregnancy BMI and child behavior problems are due to intrauterine exposures, genetic inheritance, and/or postnatal environmental factors.

Finally, given the preliminary nature of these findings, in light of the known risks associated with maternal underweight,³³ we do not recommend that women attempt to reach as low a BMI as possible in order to reduce the risk of neurodevelopmental problems in their children.

CONCLUSIONS

A positive association between maternal pre-pregnancy body mass index and externalizing behavior appears to emerge as early as 2 years of age and may be due to intrauterine exposures. However, further research is required to replicate these findings and determine whether primary and/or secondary preventive interventions targeting overweight and obese women prior to pregnancy are likely to positively impact offspring behavior. Given increasing rates of maternal obesity around the world, attempts should be made to determine if these links are causal.

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CHAPTER SIX

STUDY 5

TITLE: Maternal Pre-Pregnancy Body Mass Index and Internalizing and Externalizing Problems in Offspring

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CONTEXT AND IMPLICATIONS OF THIS STUDY: This fifth and final study of the thesis builds on Studies 3 and 4 by examining links between maternal pre-pregnancy BMI and internalizing and externalizing problems in offspring throughout childhood and adolescence. While Study 4 provides evidence that an association with aggression may emerge as early as 2 years of age, it is unclear if this association persists or merely occurs then because this is a stage at which aggressive behaviour is common.

Study 5 builds on prior studies in this area that have examined youth psychopathology only at a single point in time and is the first to show that increased maternal pre-pregnancy BMI is associated with elevated levels of internalizing and externalizing psychopathology throughout childhood and adolescence. Its findings suggest that this association is likely due to the intrauterine environment associated with maternal BMI rather than pre and postnatal confounding variables. It further implies that previously observed links between macrosomia and externalizing behaviour may be due to pre-pregnancy overweight and obesity.

The findings of this work further contribute to a growing body of evidence that suggests that prenatal exposure to increased maternal BMI may prenatally program later psychopathology.

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Abstract

Objective: To examine associations between maternal pre-pregnancy body mass index (BMI) and trajectories of internalizing and externalizing problems in offspring from 5 to 17 years of age.

Method: The 2868 women enrolled in the Western Australian Pregnancy Cohort rated their children's behaviour at 5, 8, 10, 14 and 17 years of age using the Child Behavior Checklist. Growth curves were generated to examine links between maternal pre-pregnancy BMI and offspring internalizing and externalizing psychopathology over time.

Results: Increased maternal BMI was associated with stably elevated levels of externalizing problems and youth born to mothers with a higher pre-pregnancy BMI had more rapid increases in internalizing scores as they got older. Significant associations between increasing pre-pregnancy BMI and elevated levels of internalizing problems emerged at 8 years and increased through age 17. All findings persisted despite adjustment for confounders.

Conclusions: Exposure to elevated maternal BMI during gestation is associated with increased levels of internalizing and externalizing problems throughout childhood and adolescence. While more work is required to establish if these associations are causal, if elevated maternal pre-pregnancy BMI is causally linked to offspring psychopathology, it could provide a useful target for the prevention of mental health problems in youth.

Keywords: Body mass index, pregnancy, mental disorders, child, adolescent

Introduction

Maternal obesity in pregnancy poses significant risks to the health of women and their offspring. Infants born to women who were obese during pregnancy have higher rates of congenital malformations (1) and an increased risk of obesity (2) and asthma (3) later in life. Despite these findings and the fact that up to 40% of pregnant women are obese (4), its prevalence continues to rise (5).

The process by which persistent physiological alterations in offspring result from exposure to intrauterine conditions is referred to as prenatal programming. Such changes are thought to be made by the fetus in response to environmental signals present during gestation (e.g. nutrients, hormones) in an attempt to anticipate their postnatal environment and optimize survival. If these alterations fail to accurately predict postnatal conditions, an increased risk of disease can result (6). Identifying modifiable risk factors that are present during pregnancy and causally related to an outcome in offspring can lead to the development of primary preventive interventions and provide valuable insights into the pathogenesis of disease outcomes. The elucidation of non-causal associations is also of value as they can help to identify individuals at increased risk early on and result in the application of secondary preventive interventions.

There is reason to believe that fetal exposure to maternal overweight and obesity could lead to early emotional and behavioural problems in offspring. The intrauterine environment associated with overweight and obesity in pregnancy is characterized by a number of perinatal factors that have been linked to psychopathology in offspring including increased levels of maternal stress (7-9), diabetes mellitus (10, 11), and pro-

inflammatory cytokines (12, 13). Moreover, a recent systematic review (14) reported that six of the eight studies that had examined associations between maternal pre-pregnancy and pregnancy obesity and mental health problems in offspring provided support for a link. This included three studies of schizophrenia (15-17), one of eating disorders (18) and both reports of attention-deficit/hyperactivity disorder (ADHD; 19, 20). One subsequently published study (21) examined associations between pre-pregnancy overweight and obesity and offspring behavioural problems at 3, 4 and 8 years. While they noted statistically significant associations in the Dutch Generation R cohort, these were not present in the Avon Longitudinal Study of Parents and Children (ALSPAC).

It is still unclear if the links between maternal pre-pregnancy obesity and offspring psychopathology are due to a direct prenatal programming effect or confounding variables. Because maternal psychopathology (22) and socioeconomic disadvantage (23) are risk factors for obesity as well as for the development of externalizing and internalizing problems in youth (24), they must be taken into account when attempting to isolate the role maternal obesity *in pregnancy* plays in the development of emotional and behavioural difficulties in offspring. It is notable that just five of the nine studies completed to date (15-17, 20, 25) have attempted to adjust for a familial or genetic risk for psychopathology, and only five others (15, 18, 26, 20, 21) have controlled for socioeconomic disadvantage. Attempts to control for both types of confounders were present in just two studies (15, 20). While both of these studies reported that associations persisted after adjustment, the scarcity of research that controls for all relevant confounders limits our understanding of the risks that should be attributed to pregnancy

obesity (i.e., prenatal programming). Finally, only four studies (18-21) have examined emotional and behavioural problems in children and adolescents and three of these (18-20) assessed outcomes at a single point in time. As a result, our understanding of the developmental trajectories these youth take over time is limited.

Aims of the Study

In this study, we set out to determine if: a) maternal pre-pregnancy body mass index is associated with increased levels of internalizing and externalizing problems in the offspring of a pregnancy cohort assessed on five occasions between 5 and 17 years of age, and b) if these links persist after adjusting for the confounders of these associations. The present study makes a unique contribution to the literature by: 1) taking into account pre-existing risk arising from parental mental health and socioeconomic status, and 2) modelling trajectories of emotional and behavioural problems among offspring over multiple assessment occasions throughout childhood and adolescence.

Methods

Sample

Data for this work come from the Western Australian Pregnancy Cohort (Raine) Study, a sample of 2900 women recruited at 16-20 weeks gestation from the public antenatal clinics at the King Edward Memorial Hospital (KEMH) in Perth and nearby private clinics between May 1989 and November 1991. Women were required to speak English and plan to reside in Western Australia after delivery. Ninety percent of women approached agreed to participate (27). The 2900 women recruited had 2868 live born children who provided postnatal data. Mothers enrolled in the cohort were more likely to

be teenagers and to never be married than women in Western Australia's general population (28).

Predictors (Maternal Pre-Pregnancy Body Mass Index)

At enrolment, women were asked to estimate their pre-pregnancy weight. If they were unable to provide this, their measured weight at enrolment was substituted for their pre-pregnancy weight. Heights were measured by study staff at enrolment. Body mass index was calculated by dividing their weight in kilograms by their height in metres squared. Women with a BMI < 16 (i.e., extremely thin; n=83) were excluded as values in this range were believed to be erroneous since it is unlikely that these women would be able to conceive.

Outcomes (Internalizing and Externalizing Subscales of the Child Behavior Checklist)

Parents provided ratings of symptoms of child emotional and behavioural problems on the 4-18 year-old version of the Child Behavior Checklist (CBCL; 29) when children were aged 5, 8, 10, 14 and 17 years. The CBCL includes 118 items rated on a 3-point scale coded as 0 = not true, 1 = somewhat or sometimes true, 2 = very true or often true. The internalizing scale is comprised of summed scores from the withdrawn, anxious/depressed and somatic complaints subscales and the externalizing scale from scores on the aggressive behavior and delinquent behavior subscales. Raw scale scores were utilized in all analyses.

Confounding Variables

The presence of maternal psychopathology was defined by an answer in the affirmative to the question: "have you ever been treated for an emotional or mental health

problem?” (0 = never, 1 = ever) at any time in the study (8 through 17 year old sweeps). This definition was supplemented by the inclusion of variables assessing smoking and alcohol intake by mothers. The number of cigarettes smoked per day during the first 16-20 weeks of pregnancy was categorized into 0 = none, 1 = 1-5 daily, 2 = 6-10 daily, 3 = 11-15 daily, 4 = 16-20 daily and 5 = 21 or more daily, and treated as a continuous variable. Data on alcohol consumption during pregnancy was also self-reported as the number of drinks per week during the first three months of pregnancy. Paternal psychiatric history was assessed using the mother’s response to the question “dad ever been treated for an emotional or mental health problem?” Socioeconomic status was self-reported by women at study enrolment and included the number of years of school she had completed to date, her current age, marital status (0 = married or common-law, 1 = single) and her household income. Income was dichotomized (below the poverty line <\$24000 vs. above it; 0 = above, 1 = below). Given that maternal obesity increases the risk of diabetes mellitus (DM) in pregnancy and since DM at this time is associated with neurodevelopmental problems in offspring (30), maternal diabetes mellitus was also included as a confounder. It was defined as the presence of either pre-existing DM or DM that developed during pregnancy (0 = no DM, 1 = any form of DM). Maternal life stress during pregnancy was assessed using via the total number of stress events occurring during pregnancy using Tennant and Andrews’ life stress inventory (31). Child sex was also included as a confounding variable (0 = female, 1 = male).

Statistical Analyses

We used multilevel growth curve analysis and the software MLwiN 2.20 (32) to quantify the association between maternal pre-pregnancy BMI and parent ratings of problem behavior in their offspring from age 5-17 years. Growth curve analysis is a form of regression in which repeated measures (outcomes) are regressed on the timing of these assessments to estimate rates of change for individuals. In growth curve analysis, there are two important parameters; a) ‘fixed effects’ – a starting point or baseline and, b) a change per unit of time or (i.e., slope). These parameters address two questions: a) does BMI influence ratings at the first occasion of measurement (age 5), and b) does BMI influence changes in ratings over time (i.e., from age 5 to 17)? Growth curve models easily accommodate other variables which can be time invariant or time varying; the former adjusts for overall differences in the baseline or slope; the latter adjusts for individual changes from one assessment occasion to the next. These models do not require equally spaced observations among respondents and adjust for the correlated responses associated with repeated measures.

Our data structure is a two-level hierarchy with individual ratings at each occasion (level 1) nested in individual offspring (level 2). We first specified the correct model for individual change – linear in this instance – and then quantified associations between BMI and internalizing and externalizing problem scores, taken separately, through two statistical models. Model 1 (unadjusted) contained BMI (to test for its association with the baseline score on the internalizing or externalizing scale) and the interaction between BMI and age (to test for its association with the slope). Model 2 introduced confounders

(maternal and paternal psychiatric history, household income, maternal education, age and marital status, DM, child sex, and pregnancy stress, smoking and alcohol intake).

Multiple imputation based on all of the variables in Model 2 was used to estimate values for missing responses. Ten imputation data sets were created using REALCOM-IMPUTE (33) and used in MLwiN to generate the final parameter estimates. Informed consent was obtained at enrolment and at every follow-up visit. The study protocol was approved by the Human Ethics Committee at KEMH and/or Princess Margaret Hospital in Perth.

Results

Table 1 contains a summary of the characteristics of the sample. Just over half of the cohort offspring (50.9%) were male and the remainder female. Mean levels of internalizing and externalizing problems gradually decreased over time in the cohort. Given that our predictors and confounders were assessed at baseline, the amount of missing data in these variables was limited. However, the percentage of participants that had valid CBCL outcome data at 5, 8, 10, 14 and 17 years of age was 75.7%, 72.7%, 70.6%, 62.2% and 48.3% respectively.

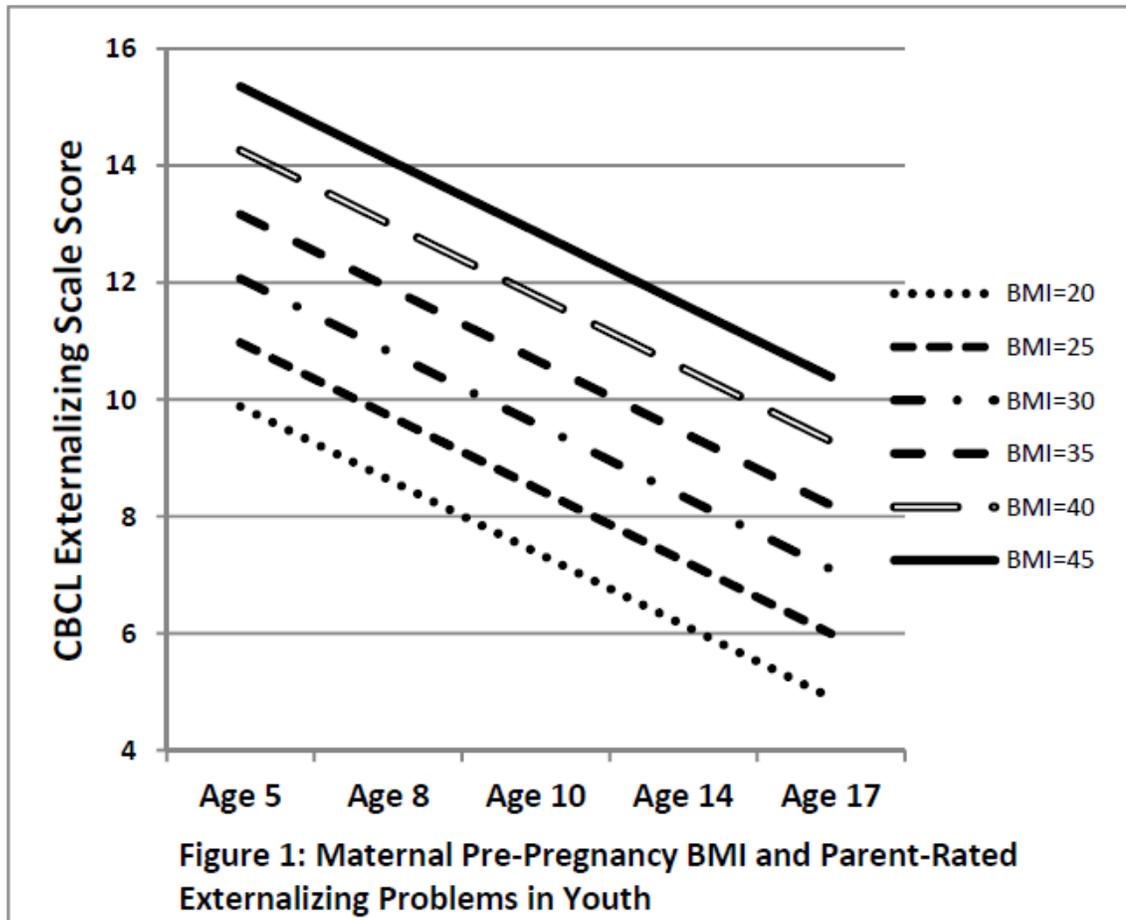
Table 1: Characteristics of the Eligible Raine Study Participants (N=2785)

	Number of Participants (% of study sample)	% with Complete Data
Eligible Participants	2785 (97%)	N/A
Offspring Sex	Female: 1368 (49.1%) Male: 1417 (50.9%)	100%
Maternal Pre-Pregnancy BMI	Mean=22.41, SD=4.29	100%
Underweight	299 (10.7%)	
Normal Weight	1979 (69.2%)	
Overweight	323 (11.6%)	
Obese	184 (6.6%)	
Mother's Age at Study Enrolment	Mean=28.10, SD=5.94	100%
Number of Years of Maternal Education	Mean 12.21 years, SD=1.31	99.6%
Single Mothers	464 (16.7%)	100%
Income Below Poverty Line	1147 (41.2%)	100%
Mother Ever Treated For Emotional Problems	815(29.3%)	100%
Father Ever Treated For Emotional Problems	437(15.7%)	100%

Maternal Pregnancy Stress Score (Number of events)	Mean=1.98, SD=1.91	90.8%	
Maternal Diabetes Mellitus Present	109 (3.9%)	100%	
Number of Cigarettes Smoked Per Day in Pregnancy	None: 1165 (41.8%) 1-5 daily: 335(12.0%) 6-10 daily: 332(11.9%) 11-15 daily: 332 (11.9%) 16-20 daily: 366 (13.1%) 21 or more daily: 255 (9.2%)	100%	
Number of Alcoholic Beverages Consumed per week in 1 st 4 Months of Pregnancy	Mean=1.37, SD=3.12	100%	
CBCL Mean Raw Scores(SD)	Internalizing Scale	Externalizing Scale	
Age 5	6.09 (5.59)	10.54 (7.80)	75.7%
Age 8	6.37 (6.00)	9.32 (8.02)	72.7%
Age 10	5.76 (5.82)	7.70 (7.47)	70.6%
Age 14	5.41 (6.00)	6.99 (7.79)	62.2%
Age 17	4.36 (5.43)	5.18 (6.78)	48.3%

SD: Standard Deviation

The parameter estimates for associations between maternal BMI and internalizing and externalizing problem scores for our two models appear in Table 2. As can be seen in Figure 1 (externalizing), for externalizing problems there is a statistically significant positive association between BMI and increased baseline scores at age 5 but no evidence that BMI influences the trajectories of externalizing problems over time (i.e., the slopes). In other words, the higher one's mother's pre-pregnancy BMI, the higher the levels of symptoms of aggression and rule-breaking problems children will exhibit at age 5 and carry through to adolescence.



This association remains little changed and statistically significant despite statistical adjustment for all confounders (Table 2). *Post hoc* analyses indicated the presence of significant associations between increasing maternal pre-pregnancy BMI and aggressive (0.16 (SE 0.03)) and delinquent behaviours (0.04 (0.01)), as well as attention problems (0.05 (SE 0.02)), even after adjustment for confounders (Model 2).

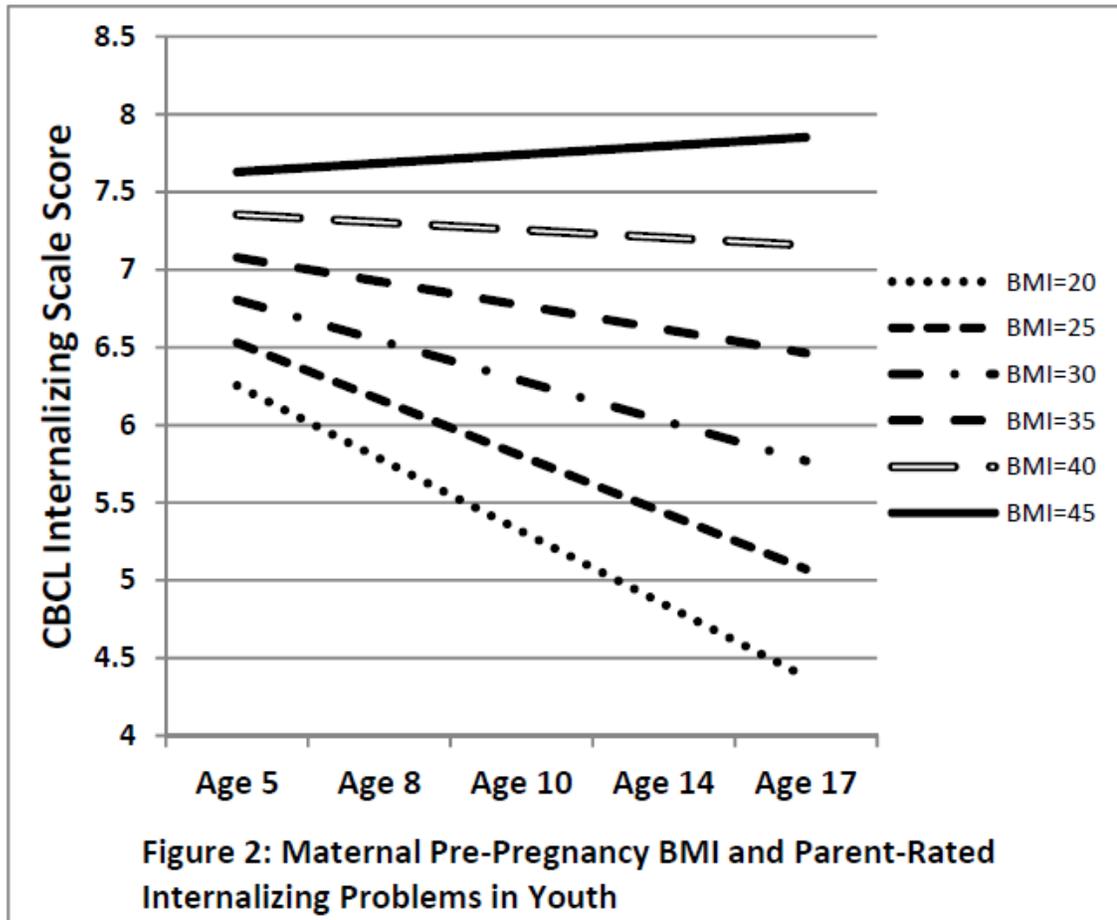
Table 2: Fixed Effects Regression Coefficients for Associations Between Maternal Pre-Pregnancy BMI and Internalizing and Externalizing Problem Raw Scores Across Childhood and Adolescence

	Model 1 (Unadjusted)		Model 2 (Adjusted for Confounders)	
	Internalizing	Externalizing	Internalizing	Externalizing
Maternal BMI	0.03 (0.034)	0.22 (0.06)*	0.01 (0.04)	0.19 (0.06)*
BMI x Occasion Interaction	0.02 (0.01)*	0.00 (0.02)	0.02 (0.01)*	0.00 (0.02)
Child Sex			-0.51 (0.19)*	1.83 (0.23)*
Maternal Psychiatric History			2.11 (0.19)*	2.29 (0.25)*
Paternal Psychiatric History			0.00 (0.23)	0.51 (0.30)
Maternal Life Stress Events			0.44 (0.05)*	0.51 (0.07)*
# Years of Maternal			-0.18 (0.07)*	-0.27 (0.10)*

Education		
Maternal Age		0.01 (0.02) -0.07 (0.03)*
Maternal Marital Status		0.27 (0.27) 0.48 (0.37)
Income Below Poverty Line		0.44 (0.21)* 0.87 (0.29)*
Maternal Smoking		-0.04 (0.05) 0.08 (0.07)
Maternal Alcohol Use		-0.05 (0.03) -0.02 (0.04)
Maternal Diabetes in Pregnancy		0.30 (0.46) -0.38 (0.65)

Results are presented as Fixed Effects Regression Coefficient (Standard Error) *p<0.05

For internalizing problems, there is a statistically significant interaction between maternal BMI and time, indicating that children and adolescents born to mothers with higher maternal pre-pregnancy BMIs had more rapid increases in internalizing scores (Table 2). Although there was no statistically significant association between BMI and internalizing scores at age 5, significant positive associations emerged at age 8 and grew larger through age 17, even after adjustment for confounders (Figure 2). *Post hoc* analyses of the CBCL subscales comprising the internalizing problems scale indicated that in fully adjusted models, increasing pre-pregnancy BMI was associated with a statistically significant less rapid decrease in symptoms on the anxious/depressed (Interaction=0.015 (SE 0.005)) and withdrawn subscales (Interaction=0.08 (SE 0.003)) but not the somatic complaints.



Associations between maternal BMI and internalizing and externalizing problems in offspring did not differ whether BMI was assessed prior to pregnancy, at 16-20 weeks or at 34 weeks gestation. Moreover, the increase in mothers' BMIs between pre-pregnancy and 34 weeks of gestation was not associated with increased levels of internalizing or externalizing symptoms nor was weight gain greater than that recommended by Institute of Medicine's Guidelines (34).

Discussion

In this cohort of 2785 mother-offspring pairs, increasing maternal pre-pregnancy BMI was associated with stably elevated levels of externalizing problems from 5 to 17 years of age. In contrast, BMI was associated with differences in trajectories of internalizing psychopathology: significant differences emerged at age 8 and grew larger through to age 17, even after statistical adjustment for confounders.

These results support the findings of a recent systematic review that suggested that levels of psychopathology are elevated in individuals born to women with higher pregnancy and pre-pregnancy BMIs (14). Rodriguez and colleagues' (19) and Rodriguez (20) also noted statistically significant links between increased maternal BMI in gestation and symptoms of ADHD in offspring based on teacher-reports. While their latter study did not report a statistically significant link between pre-pregnancy BMI and parent-reported inattention, the direction of their results for overweight women are congruent with our observation of a link between increased maternal BMI and the CBCL inattention scale.

Brion and colleagues (21) reported that the three year old offspring of overweight and obese women in the Generation R cohort had an increased risk of externalizing problems and total behaviour problems that persisted even after adjustment for confounders. However, increased levels of emotional and behavioural problems were not noted in the ALSPAC at age 4 or 8. Whether discrepancies between the findings of the ALSPAC cohort and the current study are due to the use of different samples, disparate measurement scales, or their use of categorical predictors is unclear.

Given the multitude of biochemical abnormalities seen in obese individuals, the potential mechanisms of the association between increasing maternal BMI emotional and behavioural problems in offspring could be myriad. These have not been examined in humans to date, though data from high fat fed pregnant animal models do exist. The findings of these studies mirror our results as increases in anxiety (35, 36) and aggression (35) are seen in the offspring of obese mothers. These offspring also appear to manifest suppressed central serotonergic signalling, decreased brain-derived neurotrophic factor expression, increased lipid peroxidation (37), and increased pro-inflammatory cytokine expression (36). Vucetic and colleagues (38) have also observed upregulation of the dopamine reuptake transporter (DAT) in the ventral tegmental area, nucleus accumbens and prefrontal cortices - changes that may result in a hypodopaminergic state and be due to hypomethylation of the promoter regions of the DAT gene. Hypodopaminergic states have been linked to increased attempts to access rewarding stimuli in order to produce homeostasis in reward circuitry (39) and may underlie the pathogenesis of some externalizing disorders in humans (40,41). As a result, epigenetic alterations including hypomethylation may be one mechanism by which maternal obesity in pregnancy affects emotional and behavioral problems in offspring. As such changes may be modifiable, they may represent a potential point for preventive intervention.

While it may be tempting to conclude that the intrauterine conditions accompanying pregnancy obesity are causally related to emotional and behavioural problems in offspring, these associations may be due to unmeasured genetic confounders. For example, serotonergic and dopaminergic neurotransmitter systems may be

dysregulated in obese individuals (42) raising the possibility that such alterations are inherited together by offspring from their obese mothers. Some obese individuals' tendency to manifest maladaptive personality characteristics such as low conscientiousness (43) may also predispose them to obesity and cause them to struggle with consistency in parenting which could also contribute to the development of internalizing and/or externalizing problems in offspring.

There are a number of health reasons for expectant mothers to avoid being overweight and obese and some evidence to indicate that these conditions may increase health risks among offspring. However, this does not imply that maternal under-weight is a desirable objective, and we advise against women attempting to reach as low a BMI as possible in order to reduce the risk posed to their offspring as maternal underweight is associated with increased risks of infertility, preterm birth and intrauterine growth restriction (44).

The current study has a number of strengths including the use of a validated measure of child and adolescent psychopathology, the use of growth curve analysis to model emotional and behavioural problems assessed on five occasions - throughout childhood and adolescence; and the use of multiple imputation techniques to reduce the impact of missing data on the validity of our results. The richness of the data collected in the context of the Raine Cohort study has also allowed us to control for both familial socioeconomic and mental health confounders so that we can attempt to isolate the effect of maternal obesity in pregnancy on the risk of mental health problems in offspring.

This study also has limitations. For example, we depended exclusively on the use of maternal reports to assess offspring psychopathology and are unable to comment on the extent to which maternal BMI is associated with DSM-IV-TR psychiatric disorders. Given the existence of associations between maternal and offspring adiposity and childhood obesity's link to mental health problems, it is possible that this covariate could account for observed associations (45). In addition, just over half of the sample was lost by the 17 year follow-up, though we attempted to minimize the impact of this sample loss by the use of growth curves created and multiple imputation. Finally, the current findings are based on a relatively socioeconomically disadvantaged sample of individuals born in Western Australia.

More research is required to better understand the nature of the link between maternal overweight and obesity during pregnancy and psychiatric and cognitive problems in offspring. Future studies examining this link should use validated measures of clinical outcomes as well as putative confounders and mediators. They should also attempt to examine potential biochemical mediators or causes of the association including maternal diet, nutrient levels, hormones and genetic variants involved in risk pathways. While such observational data will be helpful in further establishing this link, a clear demonstration of causal effects requires the use of experimental approaches. Experimental studies done in humans and aimed at examining strategies to reduce pre-pregnancy obesity could be used to assess the cognitive, emotional and behavioural outcomes of the offspring of these gestations and compare them to control groups.

However, it is vital that these studies be adequately powered to examine outcomes in offspring if they are to advance our knowledge.

Given continuing increases in rates of maternal obesity around the world, the demonstration of causal associations between maternal pregnancy obesity and psychopathology in offspring is an important goal and could provide realizable targets for the primary prevention of emotional and behavioural problems across the lifespan. However, more data are needed before obesity treatments can be touted as beneficial to the neurodevelopment of offspring.

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CHAPTER SEVEN

CONCLUSIONS

Mental health problems are among the most pervasive and costly illnesses of our time. The identification of prenatal factors that are causally related to later psychopathology and that are amenable to intervention is key to unlocking the potential of developmental plasticity to improve mental health across the lifespan. The elucidation of such exposures could potentially lead to the development of primary preventive interventions and provide valuable insights into the pathogenesis of adverse mental health outcomes. Properly conducted observational studies that control for confounding can provide a convincing case for examining causality in animal models and in human experimental studies. However, the elucidation of non-causal associations is also of value as they can help to identify individuals at increased risk early on and result in the application of secondary preventive interventions. This thesis identified two perinatal factors which have the potential to be shown in future studies to be causally linked to psychopathology and favourably affected by intervention.

Study 1 of this thesis reviewed research on the association between macrosomia and psychopathology and drew attention to the small number of studies available, as well as their methodological shortcomings – factors that severely limit our inferences about the nature of these links. When these limitations are addressed however (i.e., in Study 2), it appears as if youth macrosomic have higher levels of externalizing symptomatology, an association that persists despite adjustments for the known confounders of this link. However, the size of this effect was small and because the cohort upon which this work

was based lacked data on pre-pregnancy BMI and gestational diabetes mellitus, it is possible that this association is due to a risk factor for macrosomia rather than macrosomia itself. As a result, macrosomia may be better classified as a marker of later psychopathology rather than a cause.

The last three studies of the thesis showed that a positive association exists between maternal pre-pregnancy body mass index and psychopathology in child and adolescent offspring. Study 3 reviewed the literature on this association and indicated that conclusions regarding causality were limited by methodological weaknesses present in available studies. Studies 4 and 5 addressed many of these shortcomings, with the former demonstrating that an association first emerges between maternal pre-pregnancy BMI and externalizing behaviours at 2 years of age, and that this persists despite adjustment for known confounders. Study 5 showed that this association continues throughout childhood and adolescence. It also demonstrated that a link with internalizing problems emerges at 8 years of age and gradually grows stronger over time. That these associations persist despite adjustment for confounders, suggests that the intrauterine environment provided by women with elevated BMI during pregnancy may be causally linked to emotional and behavioural problems in offspring.

Implications

The findings of this thesis demonstrate that youth mental health may be affected by exposure to the intrauterine conditions accompanying high birth weight and may even be prenatally programmed. Given the long-term adverse health and vocational outcomes associated with youth mental health problems (e.g., Beitchman, Inglis, & Schacter, 1992;

Patterson, DeBaryshe, & Ramsey, 1989; Weissman, Wolk, Goldstein, Moreau, Adams, Greenwald, Klier, Ryan, Dahl, & Wickramarante, 1999; Leibson, Katusic, Barbaresi, Ransom, & O'Brien, 2001), this is a noteworthy finding.

That being born especially small or large are both associated with externalizing psychopathology suggests that their gestational antecedents or the maternal, fetal and placental responses made to represent a common final pathway to mental disorder. Whether these are related biochemically to the HPA, growth, thyroid or other hormonal axes, or are due to exposures associated with nutritional intake should be examined in future work. However, given the small effect size of the link between macrosomia and externalizing problems and the possibility that unmeasured confounders could have contributed to this association, it is premature to base clinical practice recommendations (i.e., increased monitoring of infants born macrosomic for the development of behavioural problems) on these findings. Further studies focusing on establishing the nature and magnitude of this association will help to determine if such early detection and intervention programs utilizing birth weight data are warranted.

The body of work contained in this thesis further suggests that an important factor involved in the association between macrosomia and psychopathology is increased maternal pre-pregnancy body mass index. Studies 3, 4, and 5 suggest that macrosomia may be an early marker of mental health problems rather than a cause and are the first to show that links with elevated levels of externalizing symptomatology emerge as early as the age of 2. The persistent association between maternal pre-pregnancy body mass index and externalizing behaviour throughout childhood and adolescence is also a novel

finding. Finally, its finding of a link between this predictor and internalizing problems that increases in strength over time has not previously been reported.

Perhaps as important as demonstrating the existence of these links is that they persist despite adjustment for both familial psychiatric and socioeconomic confounders. In addition to providing support for the prenatal programming hypothesis of psychopathology, this body of work helps to move the field closer to the practical goal of realizing a modifiable risk factor that is causally related to later mental health problems. Given that the number of children born to overweight and obese mothers is increasing, there is great potential in the application of this knowledge to promote public health, improve health and well-being, reduce costs for health care and social services and enhance the productivity and wealth of society. However, prior to the translational application of this knowledge further strengthening of its underlying evidence base is needed. In particular, more data are required on the effect sizes of this association, sensitive periods of exposure, and how effects vary according to individual characteristics (e.g., genetic predisposition or sex).

Underlying Mechanisms: Genetic Inheritance, Prenatal Programming, or Both?

Currently available evidence suggests that the links observed in this body of work could be genetically inherited or prenatally programmed. For example, research using the five factor model of personality shows that obese individuals manifest higher levels of neuroticism and decreased levels of conscientiousness (Terracciano, Sutin, McCrae, Deiana, Ferrucci, Schlessinger, Uda, & Costa, 2009). Interestingly, two of the personality characteristics that are core features of externalizing problems are elevated levels of

neuroticism and high rates of disinhibition (Krueger & South, 2009). As disinhibition is comprised of low levels of agreeableness and conscientiousness (Costa & Widgier, 2002), it may be that women who are obese during pregnancy directly pass the risk of externalizing problems to their offspring via the genetic inheritance of these personality traits. Data further supporting genetic inheritance as an explanation for the links observed in this thesis come from studies that have examined similarities between alcohol/drug addiction (both externalizing disorders themselves), and obesity. Observations from brain imaging studies suggest that obese individuals and those with alcohol and substance use disorders have similar abnormalities in the brain circuits mediating reward, compulsive behaviour, decision making and impulse control (Volkow, Wang, Fowler, Tomasi, & Baler, 2011). In particular, they all show decreases in dopamine receptor D2 density in the striatum, the orbitofrontal and dorsolateral prefrontal cortices, and the anterior cingulate cortex, brain regions involved in the regulation of these functions (Volkow et al., 2011). Moreover, data from the separate obesity and aggression literatures show that changes indicative of a hyposerotonergic state are present in both types of pathology (Miczek, de Almeida, Kravitz, Rissman, deBoer, & Raine, 2007; Halford, Boyland, Lawton, Blundell, & Harrold, 2011). The serotonergic neurotransmission system has also been strongly implicated in the development of internalizing disorders such as depression and anxiety (Lanfumeu, Mongeau, Cohen-Salmon, & Hamon, 2008). In other words, what may be passed from women who are overweight/obese prior to pregnancy, to their offspring, are a set of abnormalities in neurotransmitter systems and neural circuitry that

contribute both to maternal obesity and to internalizing and externalizing problems in their offspring.

However, while some data suggests that these alterations in dopaminergic and serotonergic neurotransmission in obese individuals is inherited, recent research in animal models has also indicated that these changes can be *induced* by exposure to maternal obesity during gestation. Such findings are consistent with the prenatal programming hypothesis. Indeed, two studies using animal models have shown that the offspring of obese rat dams fed a high fat diet during pregnancy have decreased dopamine type 2 receptors in the striatum and prefrontal cortices, findings that are similar to those in the brains of humans with substance problems and individuals who are obese (Vucetic, Kimmel, Totoki, Hollenbeck, & Reyes, 2011; Naef, Moquin, Dal Bo, Giros, Gratton, & Walker, 2011). In a separate study, the offspring of obese rat dams fed a high fat diet showed decreased central serotonergic tone and increases in levels of aggressive and anxious behaviour (Sullivan, Grayson, Takahashi, Robertson, Maier, Bethea, Smith, Coleman, & Grove, 2010), findings that parallel those noted of Study 5 of this thesis. Such data raises the possibility that instead of being genetically inherited, changes in neurotransmission in brain areas mediating functions relevant to internalizing and externalizing psychopathology may be caused by exposure to maternal obesity during pregnancy. Clearly, more data are required to determine if associations between maternal pre-pregnancy BMI and psychopathology in offspring are due to genetic factors, prenatal programming or are contributed to by a combination of the two.

Maternal Pre-Pregnancy BMI and Offspring Psychopathology: Implications for the Developmental Plasticity Theory of Prenatal Programming

Researchers who have examined the prenatal programming effects of maternal obesity prior to and during pregnancy have had a difficult time explaining their findings from a developmental plasticity perspective. It is also a challenge to explain how the fetal predictive adaptive responses arising from excess maternal adiposity during gestation might affect later mental health. However, there are at least two mechanisms by which this could occur.

First, paradoxically, overweight and obese individuals have elevated rates of vitamin, nutrient and dietary deficiencies. When pregnant, obese women also manifest increased levels of inflammatory (Ramsay, Ferrell, Crawford, Wallace, Greer, & Sattar, 2002) and oxidative stress (Zavalza-Gomez, 2011) markers. Such abnormalities could be interpreted by a fetus as a form of ‘stress’ that could lead to a lowering of the threshold of activation of their sympathoadrenal axes, inducing what are thought to be more optimal responses to stress in the future. However, regular activation of this axis could lead to externalizing problems in the short-term or internalizing with chronic activation over time.

As mentioned above, exposure to obesity in gestation resulting from maternal obesity/high fat diets in animal models can adversely affect the functioning of reward and saliency circuits later on. The disorders in humans that are associated with such alterations (e.g., obesity, externalizing problems) are marked by a decreased avoidance of negative consequences. Such changes, which are thought to be mediated by alterations in

the dopaminergic neurotransmission system, may represent changes made by the fetus in response to a relatively plentiful caloric supply in-utero. It is therefore plausible that fetus' who are exposed to environments where their energetic requirements are routinely met may make physiologic changes that predict a postnatal environment where their needs are also regularly addressed. This may include not devoting as many resources to the development of behavioural systems that are directed toward avoiding negative consequences because such outcomes are estimated to be less likely based on their prenatal experience. Such a resource-rich intrauterine experience may also lead them to become somewhat reward-dependent, owing to their expectation that resources will be readily available to meet their needs. As previously mentioned, decreased avoidance of negative stimuli and increased reward seeking are features of externalizing disorders that may represent responses that are in keeping with the theory of developmental plasticity. While it is less clear how this intrauterine environment might influence development in ways that increases the risk of internalizing problems, this could involve interactions between excessive reward dependence and repeated exposure to environments that fail to meet their needs.

Limitations

Despite the fact that this work advances our understanding of the prenatal programming of mental health in youth, its findings and implications should be viewed with the following limitations in mind. First, the publications contained in the review papers (i.e., Studies 1 and 3) examined heterogeneous outcomes and were not amenable to meta-analysis. As a result, conclusions can only be based on counts of studies. Second,

the Ontario Child Health Study did not contain data on maternal pre-pregnancy or pregnancy BMI or diabetes mellitus and so we cannot rule out the possibility that these risk factors are responsible for the link between macrosomia and externalizing symptoms. Furthermore, the sample upon which Studies 4 and 5 were based has its own limitations. These are outlined in chapters 5 and 6 of the thesis.

One potential criticism that could be leveled against studies 4 and 5 is their examination of pre-pregnancy maternal body mass index as a continuous predictor rather than dividing women into underweight, normal weight, overweight and obese categories. This was selected because there is no *a priori* biological reason to believe that the intrauterine environment provided by a woman with a BMI of 25 (overweight) is different than one with a BMI of 24.9 (i.e., a healthy BMI). In light of this and the knowledge that categorizing continuous data results in a diminution of statistical power (Ragland, 1992; Harrell, 2001; Taylor & Yu, 2002; Royston, Altman, & Sauerbrei, 2006), and may produce biased results (e.g., Filardo, Hamilton, Hamman, Ng, & Grayburn, 2007), the decision to examine BMI as a continuous measure is sound.

Some may also criticize the use of emotional and behavioural problem scales (continuous measures) to assess outcomes rather than diagnostic categories. While the clinical cutoffs of the CBCL have some utility in terms of predicting an increased likelihood of mental disorder, they do not correspond directly to DSM-IV-TR based diagnoses (e.g., Dingle, Clavarino, Williams, Bor, Najman, & Alati, 2011; Dingle, Alati, Williams, Najman, Bor, & Clavarino, 2010; Ferdinand, 2008). However, given the high rates of comorbidity seen in child and adolescent psychopathology, and recent taxometric

data that suggest that the majority of internalizing and externalizing problems in children and adolescents are best defined dimensionally rather than categorically (See Chapter 1), the decision to examine outcomes in this way is believed to be the best choice.

The major limitation of this body of work, as in most epidemiological studies of prenatal programming, is in its ability to determine whether causal associations exist between prenatal exposures and later psychopathology. Indeed, given the profound impact of postnatal environmental factors on the development of mental illness, along with the complex and multifactorial etiology of most mental disorders (Eaton, 2004), establishing causation may be even more challenging than in studies of non-mental health outcomes. As a result, the question of whether associations between pre-pregnancy BMI and psychopathology in offspring are causal may remain unresolved for some time.

Future Research

The presence of unmeasured or unknown confounders is the most significant barrier to establishing the causal importance of the associations observed in this thesis. Going forward, a number of study designs could be used in an attempt to address this shortcoming. The simplest would be a prospective cohort where continuous measures of the outcome to be assessed in the offspring are taken in one or both parents. However, the challenge of identifying and assessing constructs that can be measured in equivalent ways in both adult and their young offspring (e.g., impulsivity, aggression) leaves this approach vulnerable to alternative (i.e., non-causal) explanations.

Although fraught with practical challenges, one could also utilize ‘within family’ designs whereby psychopathology in offspring born before and after significant maternal

weight loss or gain are compared. However, such studies require lengthy follow-up and the identification and recruitment of such women would be a challenge.

Unfortunately, traditional approaches to isolate the effect of genes and environments such as twin and adoption studies are also unable to completely separate prenatal environments and inherited genetic effects. In light of these shortcomings, Thapar and colleagues (2009) have proposed a strategy aimed at disentangling environmental and genetic contributions of the prenatal environment to later disorder via the utilization of children born by assisted reproductive technologies. In these studies, one can theoretically examine pure intrauterine environmental effects by recruiting children who are born via in vitro fertilization (IVF) with embryo donation. While not able to isolate pure intrauterine effects as completely as the above, IVF with sperm donation and IVF with egg donation allow partial isolation of gestational environmental effects. Unfortunately, this promising new approach to studying prenatal programming in humans is limited by difficulties relating to recruitment and study power.

Whether the association between maternal pre-pregnancy BMI and offspring psychopathology is causal or not could also be examined via the ‘piggybacking’ of measures of psychopathological outcomes on to a randomized controlled trial of weight loss for women prior to conception. However, if such work is to be undertaken, special attention would need to be paid to the sample size so as to ensure the study is adequately powered to examine these outcomes in offspring.

Given that sub-optimal dietary intake can contribute to overweight and obesity, future observational work should also aim to examine the role these potential confounders

might play in observed links between maternal pre-pregnancy obesity and offspring psychopathology. Such diets can lead obese individuals to paradoxically manifest decrements in vitamin and nutrient levels that are vital to the neurodevelopment of offspring in-utero (Garcia, Long, & Rosado, 2009). Research in this area will also need to examine the role decreased maternal levels of iron, vitamin B12, vitamin D and folate play in mediating associations between maternal pre-pregnancy obesity and offspring psychopathology. Additional mediators that should be examined for their role in this link include maternal gestational diabetes mellitus, pro-inflammatory cytokines, and obstetric complications, as well as maternal hormone levels (e.g., cortisol, estrogen, progesterone) and breastfeeding given their alteration in overweight and obese women.

Conclusions

Mental health in childhood and adolescence may be influenced by the prenatal conditions leading to macrosomia, including increasing maternal pre-pregnancy body mass index. While these exposures may be causally related to mental health problems in youth, further research is required to establish if maternal pre-pregnancy BMI causes psychopathology so that its utility as a potential primary preventive intervention can be assessed.

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