THE IMPACT OF PRENATAL MATERNAL MEDICATION AND DIETARY HABITS AND PARENTAL ALCOHOL CONSUMPTION ON CHILDHOOD OBESITY AND OVERWEIGHT RISK IN AUSTRALIA

A Thesis submitted by

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ABSTRACT

In Australia, approximately a quarter of children are overweight or obese. Childhood obesity and overweight is a risk factor for poor academic performance, diabetes, cardiovascular disease, and certain cancers, among other issues. The objective of this study is to identify new parental risk factors for the condition, along with mediating factors involved in these relationships, and protective factors that impact upon these relationships. The risk factors examined were parental alcohol consumption and Prenatal Maternal (PM) medication use and dietary exclusion.

The Longitudinal Study of Australian Children (LSAC) was used to test for the relationship between these risk factors and childhood obesity and overweight risk. Each wave was individually fitted with a linear model (outcome variable: child body mass index z-score) and a multinomial logistic model (outcome variable: weight status) and known and hypothesized risk factors were treated as independent variables. Generalized estimating equations were also fitted to all waves collectively with similar outcome variables and independent variables. Moderation effects were tested for using the Hayes PROCESS macro and the Iacobucci technique of mediation analysis was used for testing for mediation effects.

Heavy parental drinking seemed to be associated with an increased risk of obesity and overweight at certain stages of childhood. Parental warmth appeared to moderate these effects at times. Exclusion of fish and eggs from the PM diet was associated with a higher risk of child obesity and overweight at times. PM dietary supplements did seem to protect against these effects. PM antibiotics, prescription antiemetics, prescription heartburn medicines, over-the-counter (OTC) analgesics and other OTC medicines not listed in LSAC seemed largely neutral in their effects on childhood obesity and overweight risk. Other medications were associated with higher risks of obesity and overweight at certain stages of childhood. PM dietary supplement use did not seem to protect against these effects.

These results show that the prenatal maternal diet and medication use, along with parental alcohol consumption are important predictors of childhood obesity and overweight. The results relating to prenatal maternal factors should be used to inform the healthy pregnancy campaign of the Australian Government as for the parental alcohol consumption risk factor it should inform existing public health campaigns aimed at curbing problem alcohol consumption in adults.

CERTIFICATION OF THESIS

I Brenton Horne declare that the Master of Research Thesis entitled *The impact of prenatal maternal medication and dietary habits and parental alcohol consumption on childhood obesity and overweight risk* is not more than 40,000 words in length including quotes and exclusive of tables, figures, appendices, bibliography, references, and footnotes.

This Thesis is the work of Brenton Horne except where otherwise acknowledged, with the majority of the contribution to the papers presented as a Thesis by Publication undertaken by the student. The work is original and has not previously been submitted for any other award, except where acknowledged.

Date: 10 October 2023.

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Student and supervisors' signatures of endorsement are held at the University.

STATEMENT OF CONTRIBUTION

Paper 1:

Horne, B., Kabir, E., & Alam, K. (2023). The impact of parental alcohol consumption on childhood obesity and overweight risk. Submitted to *The Journal of Obesity and Metabolic Syndrome*, under review.

Student contributed 70% to this paper. The coauthors collectively contributed the remaining 30% to it.

Paper 2:

Horne, B., Kabir, E., & Alam, K. (2023). The impact of prenatal maternal dietary exclusion on childhood obesity and overweight risk. Submitted to *PLoS One*, under review.

Student contributed 80% to this paper. The coauthors collectively contributed the remaining 20% to it.

Paper 3:

Horne, B., Kabir, E., & Alam, K. (2023). The effect of prenatal maternal medication on childhood obesity and overweight. Submitted to *The Journal of Obesity and Metabolic Syndrome*, under review.

80% of this paper was contributed by the student; the remainder was contributed by the coauthors.

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DEDICATION

I dedicate this thesis to my parents (Keith and Felicity Horne), for their love and kindness throughout my life, and my friends, for their support and encouragement.

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ABBREVIATIONS

ADPs	Antidepressants
AEDs	Antiepileptic Drugs
BMI	Body Mass Index
BMIz	BMI z-score
DOHaD	Developmental Origins of Health and Disease
FOAD	Fetal Origins of Adult Disease
GEEs	Generalized Estimating Equations
LBW	Low Birthweight
LMs	Linear Models
LSAC	Longitudinal Study of Australian Children
MCAR	Missing Completely At Random
MLMs	Multinomial Logistic Models
OTC	Over The Counter
SSRIs	Selective Serotonin Reuptake Inhibitors
T2DM	Type 2 diabetes mellitus

CHAPTER 1: INTRODUCTION

1.1 Introduction

Childhood obesity and overweight are a global pandemic with cases particularly prevalent in the developed world (Jebeile et al., 2022). In 2016, it was estimated that globally 340 million children and adolescents were overweight or obese (World Health Organization, 2022). Between 2017 and 2018, approximately a quarter of Australian children and adolescents were overweight or obese (Australian Bureau of Statistics, 2018). Childhood obesity and overweight predisposes children to carrying this status into adulthood (Di Cesare et al., 2019), along with numerous medical ailments such as cardiovascular disease, Type 2 Diabetes Mellitus (T2DM), asthma, musculoskeletal disorders, depression and certain cancers (Di Cesare et al., 2019), and other issues like school absenteeism (An et al., 2017), less academic attainment (Ryabov, 2018) and poor academic performance (Segal et al., 2019). In line with these facts, the modelling of Queensland Health and Wellbeing suggests that children born in the decade starting 2023 will be the first generation in recorded Queensland history to live shorter lives than their parents (Antonia O'Flaherty, 2022).

The aetiology of childhood obesity and overweight has been studied in an effort to reduce the incidence rate. It is known that childhood obesity and overweight is fundamentally an energy imbalance with children taking in more energy than they are expelling (Apperley et al., 2022). Despite this, interventions targeting this imbalance have often produced insignificant or underwhelming results (Pereira & Oliveira, 2021; Smith et al., 2020). This is due, in part, to the difficulty of altering the dietary and physical activity habits of children in a lasting and meaningful way. The number of cases must be reduced by identifying as many potentially modifiable risk factors as feasible such as skipping breakfast (Antonogeorgos et al., 2012; Mihrshahi et al., 2017). It is also important to understand the

mechanisms and protective factors involved in the effect of any identified risk factors, as these can be used to reduce the number of cases when the risk factors themselves are not targetable.

This chapter focuses on summarizing the theoretical framework, conceptual framework, research objectives, hypotheses, and questions and research problem.

1.2 Theoretical framework

1.2.1 Fetal Origins of Adult Disease

Fetal Origins of Adult Disease (FOAD) was first popularized by epidemiologist and physician David Barker (Calkins & Devaskar, 2011; Pincock, 2013). It is hypothesized that abnormalities, such as in nutrition, during fetal development have a considerable impact upon one's risk for adult disease. Low birthweight (LBW) – a marker for poor fetal nutrition – is now recognized as a major risk factor for numerous adult diseases including, but not limited to, cardiovascular disease, T2DM and obesity (Calkins & Devaskar, 2011). The basic idea behind the FOAD hypothesis is that a person's genome does not, by itself, determine the person's characteristics, that several environmental factors also affect it, and the influence of these environmental factors begins *in-utero* (Calkins & Devaskar, 2011). The influence of these factors is greatest at certain stages in the person's development and by adulthood this "plasticity", or ability to be moulded by one's environment, is largely lost (Calkins & Devaskar, 2011). This adaptability serves the purpose of achieving the best fit between people and their environment, although as the adaptability does not persist throughout life and many adaptations are permanent, it can lead to adults adapted to an environment that's since changed being maladapted to their current environment and developing disease as a result (Calkins & Devaskar, 2011). This plasticity is believed to be mediated by epigenetics, that is the factors beyond the genes themselves that affect gene expression (Calkins & Devaskar, 2011).

Alterations to one-carbon metabolism – which can be caused by deficiencies in nutrients involved in it such as choline, folate, and cobalamin – could be involved in these epigenetic change (Fall & Kumaran, 2019).

Antidepressant (ADP) exposure *in-utero* is known to be associated with an increased risk of LBW in humans (Xing et al., 2020), which is a known risk factor for childhood obesity and overweight (Andriani, 2021). Despite this, Grzeskowiak et al., 2012 found no association between maternal prenatal use of Selective Serotonin Reuptake Inhibitor (SSRI) ADPs during pregnancy and childhood obesity and overweight risk at age 4-5 years. Grzeskowiak et al., 2013 found an association between prenatal SSRI use and childhood overweight and obesity risk in boys at age 7, but not for girls. These studies, however, only examined the effect of the exposure on the children's weight status at particular ages, not over their entire childhood. These studies also did not examine possible mediating and moderating effects. They also limited their focus to SSRI ADPs and did not consider the effect of other antidepressants such as serotonin-noradrenaline reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and other antidepressants. These all represent research gaps that this study addressed.

Identifying mediating and moderating factors in these relationships is essential for a multitude of reasons. One reason is just for the sake of understanding the mechanisms involved in childhood obesity and overweight better, which is useful to guide further research. An additional reason is that these mechanisms and protective factors provide additional ways to target these risk factors when they cannot be targeted directly. For instance, if dietary supplements protected against childhood obesity caused by excluding eggs from the diet, then dietary supplements could be recommended to pregnant women that abstain from egg for any reason to reduce the risk of their children become obese or overweight.

Glucocorticoids are used in asthma treatment and elevated serum concentrations of cortisol, an endogenous glucocorticoid, in mothers prenatally is known to be associated with an increased risk of childhood obesity in the offspring (Entringer et al., 2017), hence making it reasonable to hypothesize that *in-utero* exposure to certain asthma medications may predispose children to obesity and overweight.

Several Antiepileptic Drugs (AEDs) (e.g., valproate, lamotrigine, carbamazepine, barbiturates and phenytoin) are known to inhibit either the absorption or metabolism of folic acid (Ornoy, 2009), as is the antibiotic agent trimethoprim (Wróbel et al., 2020), the antiprotozoal agent pyrimethamine (Gangjee et al., 2007) and the antidiabetic agent metformin (Owen et al., 2021) and low serum folate has been found associated with an increased risk of childhood obesity or overweight (Wang et al., 2016). In fact, Wang et al., 2016 found that low serum folate may be a mediating factor by which prenatal maternal obesity and overweight predisposes the child to childhood obesity or overweight. This could be through alterations to one-carbon metabolism leading to epigenetic changes which alters the programming of the fetus' organs. It is also important to note that folic acid supplementation has already been found to mitigate some of the harmful effects of prenatal exposure to AEDs, namely the reduced intelligence quotient and increased rate of congenital malformations associated with this class of drugs (Kjaer et al., 2008; Meador et al., 2013). Valproate is also known to inhibit histone deacetylases — a class of enzymes that play a crucial role in gene expression — and this could potentially also play a role in its developmental effects (Ornoy et al., 2022). Additionally, cobalamin deficiency is a well-known adverse effect of long-term metformin (Infante et al., 2021), histamine H_2 receptor antagonist and proton-pump inhibitor treatment (J. W. Miller, 2018) and some (but not all) studies have found an association between low cobalamin concentration during pregnancy

and LBW of the offspring (Rogne et al., 2017). Due to the role these nutrients play in one-carbon metabolism, there is also good theoretical basis for suspecting prenatal maternal deficiencies in these nutrients may predispose children to obesity or overweight. It may hence be reasonably hypothesized that cobalamin and folate supplements may mitigate the obesogenic effect prenatal maternal use of metformin appears to have on the offspring. In line with Owen et al., 2021, this study hypothesizes that such supplementation may prevent the metformin-induced childhood obesity. While this hypothesis is not new, to the best of the author's knowledge it has never been tested in a formal study.

Given that LBW is a marker of prenatal under-nutrition, it is not surprising that it has been found associated with certain vitamin deficiencies, such as of folate and cobalamin (Rogne et al., 2017; Sukla et al., 2013). It may hence be hypothesized that maternal exclusion of certain foods from their diet during pregnancy and the resulting nutritional deficiencies may be a risk factor for childhood obesity and overweight in the offspring. Although, as exclusion of particular food items from the diet is not necessarily the result of personal choice or preference alone and can be the result of medical advice (for instance, mothers with coeliac disease may exclude wheat and other gluten-containing food items from their diet due to gluten exclusion being the only known effective treatment for coeliac disease (Itzlinger et al., 2018)), this study attempted to control for the possible confounding effect of medical conditions. Other known risk factors for childhood obesity like socioeconomic status (which also influences which foods people can have in their diet) were also controlled for where possible.

It is also reasonable to hypothesize that dietary supplements containing essential micronutrients could potentially protect against the effect of maternal food exclusion on the newborn. This seems especially likely given folate supplementation has been found to reduce LBW risk in at

least one study (Charles et al., 2005), iron supplementation has been associated with a similar effect on LBW (Keats et al., 2021) and so have multiple micronutrient supplements (defined as supplements containing at least 3 micronutrients; this is as compared to iron with or without folic acid supplements) (Keats et al., 2021).

1.2.2 Developmental Origins of Health and Disease

Developmental Origins of Health and Disease (DOHaD) is an extension of the FOAD hypothesis to cover the entire developmental period of a person from gametogenesis of the gametes that conceived them to their adolescence (Suzuki, 2018). DOHaD is also used to explain disease risk in childhood based on early life development and hence is relevant to explaining childhood obesity and overweight risk (Bianco-Miotto et al., 2017). Numerous factors have been studied as potentially altering the developmental process and leading to changes in health and disease, including prenatal nutrition, maternal prenatal stress (Entringer et al., 2010; Khambadkone et al., 2020), exposures to drugs and pollutants, birth size, maternal prenatal obesity, and alterations to the microbiome (Hoffman et al., 2021; Suzuki, 2018).

The mechanisms by which parental alcohol consumption could lead to childhood obesity and overweight include the fact that it could encourage children to begin drinking at an early age and that some studies that suggest an association between drinking during adolescence and the risk of childhood overweight/obesity (Lee & Um, 2021; Roditis et al., 2009). Additionally, there is a well-established link between alcohol consumption and domestic violence (Mayshak et al., 2022; Muluneh et al., 2021; Semahegn & Mengistie, 2015) and the chronic stress this could result in for children could, through the metabolic effects of the stress hormone cortisol, predispose children to obesity (A. L. Miller & Lumeng, 2018; Russell & Lightman, 2019). This is further substantiated by A. L. Miller & Lumeng (2018) which found that early life stress (before age 5) was

associated with an increased risk of childhood and adult obesity. This hypothesis that alcohol-induced domestic violence could increase a child's risk of being obese or overweight is also further substantiated by (Wiss & Brewerton, 2020), who conducted a meta-analysis on the effect of adverse childhood experiences on the risk of adult obesity, and as childhood obesity is a well-established risk factor for adult obesity this link may be due to an increased risk of childhood obesity (Simmonds et al., 2016).

It is known that childhood obesity and overweight is fundamentally an energy imbalance wherein the child is consuming more food energy than they are burning (Thomas-Eapen, 2021). This is why for all postnatal risk factors under study are hypothesized to mediate their effects potentially via changes in child dietary habits and child physical activity.

It is unknown whether parental alcohol consumption impacts upon childhood obesity and overweight and if so, how, and what protective factors may influence this effect. Understanding this will help inform public health policy with regards to alcohol consumption in adults. A large proportion of Australian adults regularly consume alcohol. In the LSAC sample itself, about 36% of fathers drank at least weekly when the children were aged 0 or 1 years. Data from 2020 to 2021 show that 25.8% of Australians exceeded the national alcohol consumption guideline (Australian Bureau Of Statistics, 2022). Consequently, if parental alcohol consumption is a risk factor for childhood obesity and overweight, it would be quite a prevalent and potentially influential one.

1.3 Research problem

The first research problem this thesis addresses is the gaps in the literature related to parental alcohol consumption and its impact on childhood obesity and overweight, including the mechanisms and moderating factors involved in this relationship. Secondly, this thesis

addresses the research gaps related to prenatal maternal dietary exclusion and its effects on childhood obesity and overweight and the mechanisms and moderating factors involved in this relationship. Finally, this thesis addresses the research gaps related to prenatal maternal medication consumption and its effects on childhood obesity and overweight, including the mechanisms and moderating factors involved in this relationship.

1.4 Research objectives, hypotheses, and research questions

The objective of this research is to identify additional risk and protective factors for/against childhood obesity and overweight that pertain to the behaviours and characteristics of parents. The following are the specific objectives of this study:

1. To determine the impact of parental alcohol consumption on childhood obesity and overweight risk and the potential mediating effects of various child physical activity, child dietary habits, parenting style variables and child sleep characteristics variables and the potential protective effects of parental warmth.

2. To determine the impact of maternal prenatal dietary habits on childhood obesity and overweight risk and the mediating and moderating effects of birthweight and dietary supplements, respectively.

3. To determine the impact of maternal prenatal medication on childhood obesity and overweight risk and the mediating and moderating effects of birthweight and dietary supplements, respectively.

Based on these objectives, the following research questions (RQs) and hypotheses (H) were formulated:

Research question 1, 1a and 1b served as the motivation for research paper 1. Research question 2, 2a and 2b served as the motivation for research paper 2. Research question 3, 3a and 3b served as the motivation for research paper 3.

RQ1: Does parental alcohol consumption impact upon child body mass index z-score (BMIz) or childhood obesity and overweight risk?

H1: Parental alcohol consumption will be associated with an increased risk of obesity and overweight in children and higher BMIz.

RQ1a: Does child physical activity, child dietary habits, child sleep characteristics and parenting style variables mediate the effect of parental alcohol consumption on a child's risk of developing overweight or obesity?

H1a: Child physical activity, child dietary habits, child sleep characteristics and parenting style variables will mediate the effect of parental alcohol consumption on childhood obesity and overweight risk.

RQ1b: Does parental warmth moderate the effect of parental alcohol consumption on childhood obesity and overweight?
H1b: Parental warmth protects against the effect of parental alcohol consumption on childhood obesity and overweight through moderating this relationship.

RQ2: Does prenatal maternal dietary exclusion impact upon child BMIz and childhood obesity and overweight risk?

H2: Prenatal maternal dietary exclusion will increase child BMIz and childhood obesity and overweight risk.

RQ2a: Does child birthweight mediate the effect of prenatal maternal dietary exclusion on childhood obesity and overweight and child BMIz?

H2a: Child birthweight will mediate the effect of prenatal maternal dietary exclusion on childhood obesity and overweight risk and child BMIz.

RQ2b: Do dietary supplements protect against the effect of prenatal maternal dietary exclusion on childhood obesity and overweight risk and child BMIz?

H2b: Dietary supplements will protect against the effect of prenatal maternal dietary exclusion on child BMIz and childhood obesity and overweight risk.

RQ3: Does prenatal maternal medication impact upon child BMIz and childhood obesity and overweight risk?

H3: Prenatal maternal medication will increase child BMIz and childhood obesity and overweight risk.

RQ3a: Does child birthweight mediate the effect of prenatal maternal medication on child BMIz and childhood obesity and overweight?

H3a: Child birthweight will mediate the effect of prenatal maternal medication on child BMIz and childhood obesity and overweight risk.

RQ3b: Do dietary supplements protect against the effect of prenatal maternal medication on child BMIz and childhood obesity and overweight risk?

H3b: Dietary supplements will protect against the effect of prenatal maternal medication on child BMIz and childhood obesity and overweight risk.

1.5 Conceptual framework

The conceptual framework is contained within Figure 1. Figure 1 shows the hypothesized relationships between the variables that the three research papers in this thesis investigated. The risk factor variables are prenatal maternal factors such as dietary exclusion and medication consumption. The outcome variables are child BMIz and weight status. Protective factors are expected to act as moderators; this is to say that they are expected to modify the relationship between the risk factors and outcome variables through introducing an interaction term to the statistical models used to model the outcome variables. Mediating factors are expected to serve as intermediaries between the risk factors and the outcome variables as shown in Figure 1.

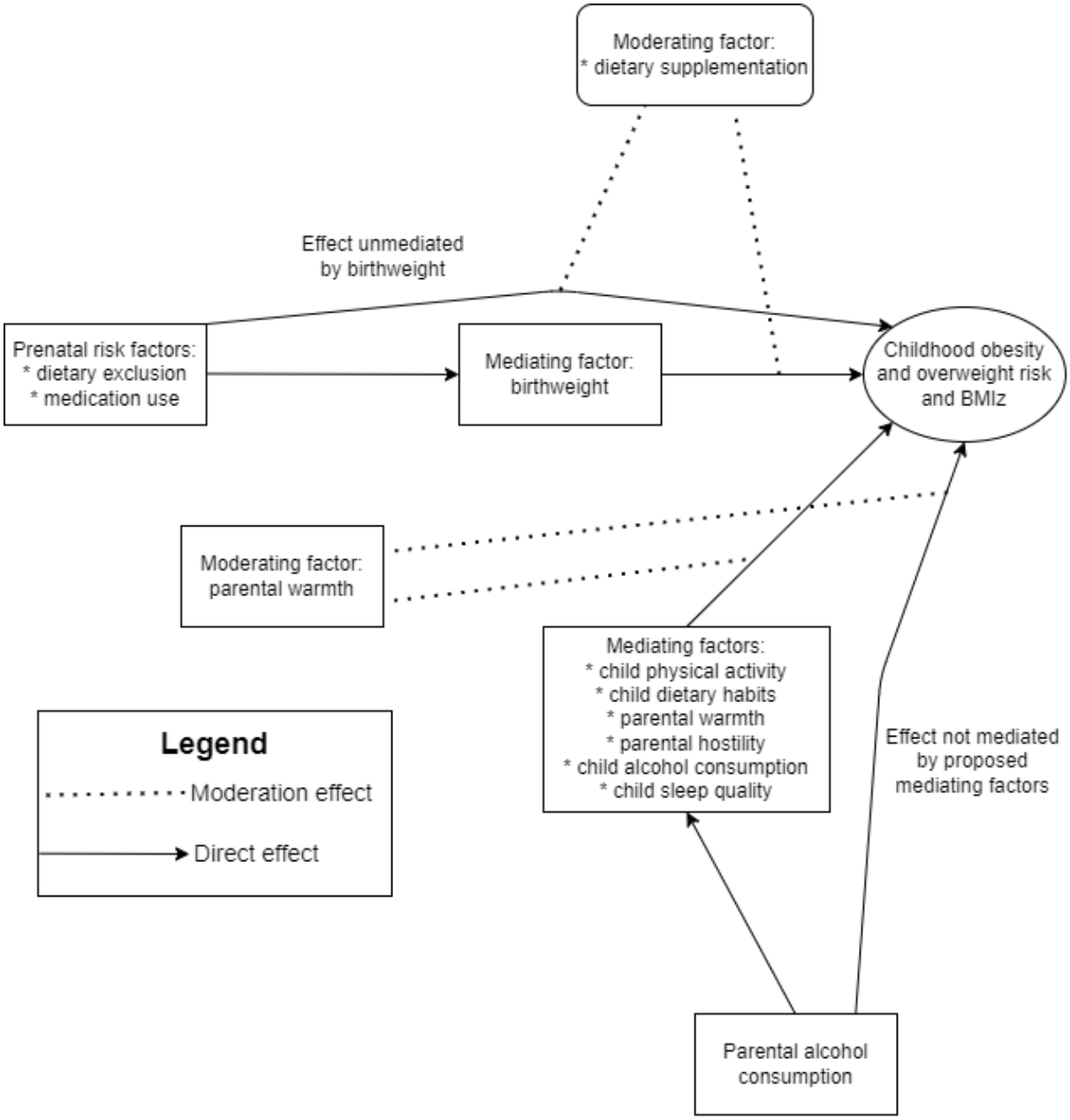

Figure 1: Conceptual framework for the research.

Specifically, it is proposed that parental alcohol consumption impacts upon childhood obesity and overweight risk and BMIz directly and indirectly through the mediating factors of child physical activity, child dietary habits, parental hostility, parental warmth, child alcohol consumption and child sleep quality. It is also proposed that parental warmth serves as a moderating factor in this relationship. It is also proposed that prenatal maternal dietary exclusion and medication use impact upon childhood obesity and overweight risk and BMIz both directly and indirectly through the intermediary of child birthweight. It is also

proposed that dietary supplement use plays a moderating role in this relationship.

1.6 Study design and description of secondary data

The Longitudinal Study of Australian Children (LSAC) is an ongoing biennial study conducted by the Australian Institute of Family Studies and the Australian Government Department of Social Services that includes two cohorts: cohort B (for "baby") and cohort K (for "kindergarten"). Both cohorts were sampled using a two-stage clustering method to achieve a nationally representative sample of Australian children. Cohort B started with 5,107 infants aged 0 or 1 years old in 2004. Cohort K started with 4,983 kindergarteners aged 4 or 5 years old in 2004.

Cohort B was the focus of this thesis, partly because it was the only cohort with the required prenatal maternal details for two of the studies conducted, and in part because it was not feasible to fit the analysis of both cohorts into a single paper for the one study that did not involve prenatal maternal risk factors. Additionally, cohort B had more waves with child BMIz and BMI percentile (which was used to determine weight status) recorded, which allowed for effects on obesity or overweight to be analysed.

Before analysis was conducted, the data was cleaned to remove children with missing or nonsensical values for variables that would be used in the analysis. This and all the analysis were conducted in R version 4.2.2 to 4.3.1.

The effect of the proposed risk factors was tested by fitting linear and multinomial logistic models (MLMs) to each wave that recorded child BMIz and BMI percentile (BMI percentile was necessary for determining the child's weight status). In these models, the regressors were factors

known to influence childhood obesity and overweight risk that were recorded in LSAC, and the proposed risk factors and the outcome variable was child BMIz (for the linear model) and weight status (for the multinomial logistic model). These factors known to influence childhood obesity and overweight were determined via a scoping literature review. The MLMs were all nominal in how they treated their outcome variables and when incorporating all known risk factors into them caused singular matrix errors, the less significant factors (as found from the linear models fitted) were removed until the singular matrix errors ceased to be a problem. If a factor known to influence childhood obesity or overweight risk was going to be investigated as a possible mediator in the precise study (e.g., child birthweight in papers 2 and 3), it would be omitted from these initial linear and multinomial logistic models as a regressor.

These models were used because they can establish correlation between variables, and they are designed to work with the type of variables studied. Specifically, linear models are well-suited to analyses in which the outcome variable can take on any real value. Child BMIz satisfies this criterion as it can, in theory, take on any real value. Linear models are also best suited to normally distributed outcome variables and the fact that child BMIz is a z-score shows the common assumption in medicine that it will follow a standard normal distribution. Multinomial logistic models were fitted to weight status as they are the standard model used when working with an outcome variable that is multicategorical like weight status is.

When the risk factor was postnatal and recorded across all the waves analysed (which is the case for parental alcohol consumption), generalized estimating equations (GEEs) were fitted to all the waves as part of a pooled wave analysis. The regressors used in this analysis were known risk factors that were recorded across all analysed waves, along with the proposed risk factors. The outcome variables for this analysis

were also child BMIz (when a linear predictor GEE was fitted) and weight status (when a nominal logistic GEE was fitted).

GEEs were fitted for this pooled wave analysis as they account for the correlation between observations on the same child at different times, which is necessary when analysing data from multiple waves at once. It is necessary as this correlation violates the independence assumption of fixed effects models like linear models and generalized linear models, but GEEs relax this assumption to allow the analysis of such correlated data.

Mediation analysis was conducted using the Iacobucci (2012) method. In this method, appropriate (for the type of data) generalized linear models (GLMs) are fitted for the proposed mediator variables (where the mediator variable is the outcome variable) and outcome variables (where the outcome variables were the outcome variables in the model). Two sets of GLMs are fitted for the outcome variables: one with the mediator variables included as regressors and another without them. Known risk factors were incorporated into the outcome variable GLMs as regressors. These mediator and outcome GLMs are used to estimate the direct and indirect effects of the risk factors on the outcome variables, along with the significance of any mediation effect. Multinomial logistic models were fitted to multicategorical variables, binomial logistic models were fitted to dichotomous variables and linear models were fitted to quantitative variables. The Iacobucci (2012) method was used because it had the required flexibility to carry out the analysis. Some mediation and outcome variables in the analyses conducted were multicategorical and this limited the author's options for how to conduct the analysis. The Andrew F. Hayes PROCESS R macro could perform the analysis if the mediator and outcome variables were all quantitative or dichotomous, for instance, but it could not with either of these variables being multicategorical (which weight status, child dietary habits, child physical activity and a few other mediator variables were).

Moderation analysis was conducted using the Andrew F. Hayes PROCESS R macro version 4.3. Covariates included in the analysis were other possible risk factors under investigation along with the known risk factors included in the linear models and multinomial logistic models fitted. The PROCESS R macro was used for this analysis as it is simple, but appropriate for the data and hypotheses tested.

The variables used in the analysis depend on the study in question, but include covariates that relate to possible confounders like parental BMI (Lecorguillé et al., 2023) and socioeconomic status (Williams et al., 2018), along with the postulated risk factor of interest (parental alcohol consumption, prenatal maternal dietary exclusion or prenatal maternal medication) and the outcome variables of child BMIz and weight status.

1.7 Structure and content of thesis

This thesis is divided into six chapters, including three studies on novel posited risk factors for childhood obesity. The structure of each chapter is detailed below.

Chapter one is an introductory chapter; it summarizes the rationale and motivation for the research. It discusses the theoretical and conceptual framework for the research, the research objectives, hypotheses, and questions that direct the research and the research problems that this research addresses.

Chapter two is a literature review that summarizes the current state of knowledge in the field and identifies the relevant research gaps in the literature and thus further solidifies the foundation for the research.

Chapter three contains research paper 1, which is on parental alcohol consumption's effect on childhood obesity and overweight. An additional

introduction section was included in this chapter, as was a links and implications section.

Chapter four contains research paper 2, which is on prenatal maternal dietary exclusion's effect on childhood obesity and overweight. Like chapter three, there are additional introduction and links and impactions sections in this chapter.

Chapter five contains research paper 3, which is on prenatal maternal medication consumption's effect on childhood obesity and overweight. Introduction and links and implications sections were included in this chapter too.

Chapter six concludes the thesis by summarizing the findings of the preceding chapters and discusses their implications for public health policy. It also mentions the limitations of this research and the avenues for further research.

Each of the research papers focus on possible risk factors for childhood obesity and overweight that pertain to the behaviours and characteristics of the parents. The second and third papers pertain specifically to prenatal maternal risk factors, and it is hypothesized that both investigated risk factors would mediate their effects through effects on fetal nutritional adequacy.

1.8 Conclusions

In conclusion, this research is aimed at improving knowledge on the risk factors of childhood obesity and overweight by investigating three previously unstudied or understudied possible risk factors and the mechanisms and protective factors involved in these relationships. These relationships were investigated in three separate research papers that come after the literature review contained within the next chapter. Then

this thesis will be concluded by a discussion and summary of the preceding chapters, their implications, and limitations.

CHAPTER 2: LITERATURE REVIEW

2.1 Introduction

Childhood obesity and overweight rates are on the rise worldwide and in Australia, and seriously threaten the gains in life expectancy made by medical science in the last century. As a result, it is essential that modifiable risk factors for childhood obesity and overweight are identified and so are protective factors against these risk factors (to help in situations wherein the risk factor is unavoidable), to inform public policy about the allocation of scarce resources. Determining the mechanism by which risk factors lead to increased risks of childhood obesity and overweight is also important as it can lead to ideas for how the risk can be offset, and these ideas can be tested in future studies. In the following sections, research gaps surrounding potential risk factors, potential mediating factors involved in the effect of these risk factors and potential protective factors to counter these risk factors will be identified.

2.2 Search method

Scopus, PubMed, and Google Scholar were used for the literature review. The risk factor of interest was one of the search terms along with childhood obesity and overweight and all synonyms or alternative spellings (such as "pediatric obesity", "paediatric obesity", "paediatric overweight", etc.). To be included in the review, the studies had to be original investigations of the risk factor in question and its effect on childhood obesity. This review was a systematic review.

2.3 Parental alcohol consumption

No studies have been identified in preliminary database searches that investigated the effect of parental alcohol consumption on childhood obesity and overweight risk and mean BMIz. Adolescent alcohol consumption has been studied as a risk factor for their own obesity and overweight (Lee & Um, 2021; Roditis et al., 2009), but never has parental alcohol consumption been studied in this context. Parental alcohol

consumption is a potentially modifiable risk factor for childhood obesity, although due to addiction and other issues it is not completely modifiable and hence it is important to identify potential protective factors and mediating factors.

If a harmful effect of alcohol consumption on childhood obesity and overweight risk and BMIz were found, it could lead to interventional studies designed to determine whether the link is causal, as analyses based on observational studies like LSAC usually cannot prove causality (Gianicolo et al., 2020). And these studies would in turn inform public policy decisions, including potentially advertisement campaigns designed to inform parents of the risk if the link is found to be causal, and could contribute to a reduction in the rate of childhood obesity and overweight. If the factors do not lend themselves to study in interventional studies (such as due to ethical constraints), this study's results may help inform public policy either on their own (in which case it will be particularly helpful in informing Australian public policy as it was conducted within the Australian context), or along with subsequent observational studies.

2.4 Prenatal maternal food exclusion and childhood overweight/obesity

Several studies have investigated the effect of maternal prenatal malnutrition on childhood obesity and overweight risk, although the focus of these studies have largely been on the effect of famines (Calkins & Devaskar, 2011), dietary interventions (such as assignment to a low glycaemic diet, dietary counselling, or to an antihypertensive diet, without sodium restriction) (Dalrymple et al., 2018), dietary quality (Chen et al., 2021; Fortin-Miller et al., 2022) dietary inflammatory potential (Chen et al., 2021; Fortin-Miller et al., 2022), dietary glycaemic index (Dalrymple et al., 2018), excessive gestational weight gain and maternal obesity/overweight (Deal et al., 2020), not the effect of the exclusion of particular food items from the diet.

No study was found in preliminary database searches that studied whether exclusion of particular food items from a mother's diet during pregnancy impacts upon the child's risk of developing obesity and overweight during childhood. Consequently, there is a gap in the literature that research paper 2 fills. It is also the first paper to do this within the Australian context; as such it is of particular importance to guiding Australian public health policy. In filling this gap, it may inform future expectant mothers about what foods should be in their diet whilst pregnant and which they can manage without. As it will examine the effect of dietary supplements on any effect of prenatal maternal food exclusion on childhood overweight or obesity risk, it may also help inform decisions about ways of mitigating the harm that unavoidable prenatal maternal food exclusion does to children.

2.5 Prenatal maternal use of prescription and OTC medication and childhood overweight/obesity

Some studies have investigated the effect of antibiotic, antifungal, antidiabetic and antidepressant exposure *in-utero* on childhood obesity and overweight risk (Cassidy-Bushrow et al., 2018; Grzeskowiak et al., 2012, 2013; Mor et al., 2015; Rowan et al., 2018) but several other categories of prescription and OTC medications are unstudied in their effect on childhood obesity/overweight risk. Asthma medications, thyroid medications, antihypertensives, nausea and sickness medications, analgesics, heartburn medications, herbal preparations and anti-allergy medications have, to the best of this researcher's knowledge, never been studied in this context in humans. As such there is a research gap research paper 3 helped to fill. This study will not only be the first ever conducted in this field to the best of this researcher's knowledge, but also the first conducted in the Australian context, and consequently will be of particular relevance to Australian public health policy.

Whilst prenatal exposure to antibiotic, antifungal, antidiabetic and AE medication has been studied as a potential risk factor for childhood obesity/overweight (with positive evidence to support an effect for all but antifungal medications) (Cassidy-Bushrow et al., 2018; Galappatthy et al., 2018; Mor et al., 2015; Rowan et al., 2018; Wen et al., 2017), what has not been studied is possible mitigating factors, such as prenatal use of vitamins such as folic acid and cobalamin. This is despite the fact that there is theoretical basis to support a protective effect of these nutrients. Some prenatal medication use is unavoidable due to the medical needs of the mother, hence research into protective factors to offset harms from this unavoidable reality is essential.

Some dietary supplements have been studied in this context, with prenatal ω-3 fatty acid supplements found to be ineffective at reducing childhood obesity and overweight risk (Vahdaninia et al., 2019), prenatal high protein supplements were found harmful (as it increased the risk of SGA births, a risk factor for childhood obesity and overweight) (Grobler et al., 2019) and prenatal balanced energy/protein supplements were found effective at reducing the risk of childhood obesity and overweight (Grobler et al., 2019). The researcher has also conducted searches for antiepileptics, antibiotics, antimicrobials and antidiabetics and the effect dietary supplements has on the risk of childhood obesity and overweight in children exposed to them *in-utero*, which returned no relevant results. Consequently, there are definite research gaps in this field and this study's aim is to fill those gaps and hopefully encourage further study in this area. As this is an Australian study its results are of particular relevance to Australian public health policy.

2.6 Conclusion

Filling the identified research gaps has potential applications both in guiding Australian public health policy and in shaping public health policy in other developed nations. While the data analysed only pertains to the

Australian context, childhood obesity and overweight is a global epidemic, and it seems likely that similar relationships between these variables will also exist in other countries. Although naturally, follow-up studies will be required to confirm this.

In Australia, information on prenatal maternal risk factors could help inform the Australian Government's healthy pregnancy campaign (Australian Government Department of Health and Aged Care, 2023). Specifically, the chapter 4 could help inform the nutritional advice given to expectant mothers as part of this campaign and similar campaigns in other developed nations. Additionally, chapter 5 could help inform which medications are prescribed to expectant mothers. Chapter 3 could help inform public health policy related to alcohol use by adding in an extra reason to discourage alcohol consumption in adults, namely, to protect their children from harm.

CHAPTER 3: PAPER 1: THE IMPACT OF PARENTAL ALCOHOL CONSUMPTION ON CHILDHOOD OBESITY AND OVERWEIGHT RISK

3.1 Introduction

Parental alcohol consumption has never been studied as a risk factor for childhood obesity and overweight to the best of this researcher's knowledge. Despite this, there are reasons to suspect the two could be related. Specifically, alcohol use has a well-studied relationship to domestic violence (Mayshak et al., 2022) and traumatic events, such as witnessing or being the victim of domestic violence, during childhood have been found in some studies to be associated with an increased risk of subsequent obesity (Schroeder et al., 2021). Additionally, it is conceivable that parents that consume alcohol to excess may be less attentive to the dietary and physical activity habits of their children, potentially allowing them to develop bad habits that predispose them to obesity and overweight. In this paper, parental alcohol consumption is examined as a possible risk factor for childhood obesity and overweight.

3.2 Submitted paper

The impact of parental alcohol consumption on childhood obesity and overweight risk

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Abstract and keywords

Background

Despite a well-established link between drinking and domestic violence and between traumatic events in childhood and obesity and overweight, the relationship between parental alcohol consumption and childhood obesity has not been studied.

Methods

Longitudinal population-based study was based on a nationally representative cohort of Australian children; waves analyzed were conducted between 2004 and 2019. Participants were aged 0-15 years. BMIz and weight status were the outcome variables; risk factors under study were drinking frequency and weekly quantities for both parents. 5,107 participants participated in the first wave.

Results

The effect of parental alcohol consumption on body mass index z-score and unhealthy weight status was moderated by parental warmth at certain ages and with respect to certain alcohol consumption characteristics. For instance, paternal warmth moderated the effect of fathers drinking twice to thrice a month to reduce child BMIz by 0.6551 (95% confidence interval (CI): 0.0604 to 1.2499). Paternal drinking frequency of greater than annual was associated with lower child BMIz across childhood. The precise effect of this varied by frequency but varied between a 0.2478 (95% CI: 0.03064 to 0.4650) reduction in child BMIz to a 0.4319 (95% CI: 0.1393 to 0.7245) reduction in child BMIz relative to children whose fathers did not drink. Severe obesity was 0.2799-fold (95% CI: 0.0830 to 0.9436) less likely in children whose fathers drank twice monthly to thrice weekly, relative to children whose fathers did not drink. Mild-to-moderate obesity was 2.19-fold (95% CI: 1.0466 to 4.5824) more likely in children whose fathers drank four times a week or more relative to children whose fathers did not drink. Moderate frequency of parental drinking was associated with a lower rate of unhealthy weight status during some

stages of childhood and with regards to certain specific weight statuses, whereas the effects of high parental drinking frequency were more mixed. For instance, maternal drinking frequency of greater than thrice a week was associated with a 0.1035-fold (95% CI: 0.0102 to 0.9716) reduction in underweight risk in wave 2 and a 5.22-fold (95% CI: 1.094 to 24.91) increase in mild-to-moderate obesity risk in wave 7 relative to the reference category of mothers drinking less than twice a month.

Conclusions

Moderate drinking frequency is likely not associated with any harmful effect on child weight status, although higher frequencies and quantities are associated with a higher risk of certain unhealthy weight statuses at certain stages of childhood. Parental warmth moderated this effect at times.

Keywords

Ethanol, risk factor, pediatric obesity, longitudinal study.

Introduction

In recent decades, there has been a global surge in the prevalence of childhood obesity and overweight (for the purposes of this study, childhood is between the ages of 2 and 17 years). In Australia, almost one in four children were overweight or obese between 2017 and 2018.[1] Obesity and overweight predisposes children to cardiovascular disease, certain cancers and type 2 diabetes, among other problems.[2] This makes it imperative to identify as many risk factors for childhood obesity and overweight as possible, along with the mechanisms by which these risk factors contribute to childhood obesity and overweight and anything that may protect against these risk factors.

Alcohol use and domestic violence have a well-established relationship.[3] Traumatic events, like witnessing or being the victim of domestic violence, predispose children to develop obesity or overweight.[4] Children of parents with excessive alcohol consumption (AC) are also more likely to experience chronic stress,[5] and chronic stress could lead to higher serum cortisol concentrations, which are known to affect adiposity.[6] Given that alcohol is an intoxicant, it is also possible that parents who consume alcohol may be less attentive to their children's activities, potentially allowing them to skip breakfast, eat unhealthy food, adopt sedentary lifestyles and watch television while eating dinner, which are known risk factors for childhood obesity and overweight.[7–10] Due to the heritability of alcohol use disorder[11] and parental influence there could be a correlation between parental alcohol consumption (PAC) and child AC and drinking in some parts of childhood have been associated with an increased risk of childhood obesity and overweight.[12] Despite these reasons to suspect a possible link between PAC and childhood obesity and overweight, to the best of the authors' knowledge, the impact of PAC on children obesity or overweight risk has never been investigated.

The intention of this study was to investigate the effect of PAC on childhood obesity and overweight risk and body mass index z-score (BMIz) and potential mechanisms by which such an effect could be mediated. Additionally, it was intended to determine whether parental warmth

had a protective effect against this. It was hypothesized that parental warmth could help reduce child cortisol[13] and hence mitigate the effect of stress on child weight status and BMIz as a protective factor. Hypothesized mediating factors included: child physical activity and child diet (both proposed due to obesity being an energy imbalance), child AC, whether the child skipped breakfast[7] and how often the television is on during meal times.[10] Additionally, it was hypothesized that disruption in sleep habits due to stress could be a mechanism by which PAC could lead to childhood obesity or overweight, so additional mediators of whether child has a sleep problem (as a correlation between poor sleep and childhood obesity[14] and an association between insomnia and stress in children[15] have been identified), child sleep quality and child sleep length adequacy were investigated. It was also proposed that parents who drink excessively may be more hostile towards their children, which may contribute to child stress, and hence childhood obesity and overweight, so parental hostility was also studied as a possible mediator. In a similar vein, it was proposed that parental warmth may also be a mediator as parents who drink excessively may be less affectionate, which may cause their children to experience greater stress.

Method

This study, which consisted entirely of secondary analysis of data from the Longitudinal Study of Australian Children (LSAC), received ethics approval from the University of Southern Queensland Human Research Ethics Committee with the ID ETH2023-0175.

Original study

Data from the LSAC was used. LSAC's design has been described elsewhere,[16] but in short LSAC is a biennial prospective cohort study that began in 2004 and includes two cohorts: cohort B (for "baby") and K (for "kindergarten"). Cohort B comprises children for whom the first wave recorded began from age <2 years and this study analyzes this cohort. Cohort K consisted of children who were followed beginning when they were 4 or 5 years old. LSAC recruited its sample using two-stage cluster sampling. Postcodes were sampled after they were stratified by

state and rural vs urban status in the first stage. Children on the Australian Medicare database within each postcode were randomly sampled in the second stage. Written parental consent was obtained for all children that participated in the study and the study was approved by the Australian Institute of Family Studies Ethics Committee.

Most data were collected by trained interviewers using in-person interviews with the primary caregiver in the family home. Child weight was measured to the nearest 50 grams using glass bathroom scales with the child wearing light clothing and height to the nearest 0.1 centimeters using a portable rigid stadiometer. This was used to calculate the child's body mass index (BMI).

Variables

The outcome variables of interest were BMIz and a weight status variable. PAC variables, which were studied as risk factor variables, were recorded for waves 1–8. The outcome variables were only recorded for waves 2–8 and consequently only these waves were analyzed, although some variables with a known effect on the risk of childhood obesity or overweight were recorded in wave 1 (such as child birthweight),[17] so data from this wave was also included in the analysis. Information on all the variables used in the analysis, including how they were calculated and collected, is presented in Table 1.

Bias

The sample was obtained randomly, so the main source of potential bias was likely to be that only participants with sufficiently complete data were included in the analysis. How this was addressed is mentioned in the data cleaning section.

Data cleaning

Cases with missing values or nonsensical negative values that were not explained in the data dictionary for any of the analyzed variables were excluded from the final analysis. Multiple imputation was attempted using the mice R package, but singular matrix errors (SMEs) prevented it from being used. Little's missing completely at random test[35] from the misty R

package yielded no results due to SMEs and missing variance errors.

Study size

The study size was the number of participants whose data was collected in enough detail for their data to be analyzed. The study sizes are specified in Table 2.

Statistical methods

R versions 4.2.2, 4.2.3 and 4.3.0 were used to perform the analysis. $p < 0.05$ was used as the threshold for statistical significance. Significance tests were all two-sided. All regression models fitted were univariate but multivariable. No attempt to address loss to follow-up was made; participants lost to follow-up were simply ignored in the analysis.

Linear and logistic regression were used to test the effect of parental alcohol consumption on child BMIz and childhood obesity and overweight risk. To each wave for which the outcome variables and the independent variables of interest were recorded linear models (LMs) and multinomial logistic models (MLMs; for which the reference category was healthy weight) were fitted for which the outcome variables were BMIz and weight status, respectively. MLMs were fitted using the VGAM library. These models were fitted with the intention of determining whether PAC variables were correlated with childhood obesity, overweight or BMIz at any time during childhood.

The LMs included the PAC variables previously mentioned, along with the covariates listed in Table 1. Additional covariates were initially tried in the LMs but later abandoned, they are listed as "Abandoned covariates" in Table 1. None of them were significantly correlated with the outcome variables and their inclusion occasionally caused SMEs when fitting the models, consequently they were omitted from the final models.

The MLMs fitted to weight status included the PAC variables (with recoded drinking frequency variables per Table 1), current parental BMI, maternal BMI at wave 1 and the child's birthweight. Fewer regressors were included in these models and the drinking frequency variables were recoded because including all the regressors in the LMs without recoding led to

singular data matrix errors, and these regressors had the strongest correlation with BMIz in the LMs.

Moderation analysis

The moderating effect of parental warmth on the relationship between PAC variables and BMIz and binary weight status was investigated. The univariate technique of moderation analysis developed by Andrew F. Hayes was used to answer queries regarding protective factors,[36] specifically with BMIz and binary weight status as the outcome variable (as it cannot handle a multicategorical response variable like weight status). The covariates used in the BMIz moderation models were all other PAC variables that were not included as an independent variable, along with all the covariates included in the LM for BMIz, except parental occupation because its inclusion caused errors. The binary weight status moderation models had the other PAC variables along with the covariates included in the MLM for weight status included as covariates. Version 4.3 of the Hayes PROCESS R macro was used to perform the analysis.

Mediation analysis

The mediator variables studied are listed in Table 1. The technique for mediation analysis that was used is outlined in Iacobucci (2012).[37] Specifically, MLMs were fitted to multicategorical mediator variables and the weight status outcome variable, binomial logistic models (BLMs) were fitted to dichotomous mediator variables, and LMs were fitted to quantitative mediator variables and the BMIz outcome variable. The coefficient estimates and standard errors for the mediator models and the outcome variables (with mediators included as regressors) were used to calculate a z-score for mediation using the formulas in Iacobucci (2012).[37] A p-value for mediation was then calculated based on this z-score. Iacobucci (2012)[37] did not provide a means of calculating a confidence interval for mediation effects, hence, this is not reported in this paper.

The models with the mediator variables as the outcome variable only included the PAC variables as regressors. The BMIz LM had the covariates included in the other BMIz LM fitted

for each wave and PAC variables included in it as regressors, along with all the mediator variables under study. The weight status MLM included all the covariates mentioned earlier for the other MLM fitted for each wave, along with all the mediator variables under study.

Generalized estimating equations (GEE) analysis

Waves 2–8 were analyzed using GEE to determine whether PAC influenced childhood underweight, overweight or obese risk or BMIz across all the analyzed stages of childhood. The regressors included in the linear GEE were PAC variables, current parental BMI, highest qualification completed by parents, highest schooling completed by parents, child age, child sex and usual parental weekly income. Other regressors were not included due to limitations in the number of children who participated in all waves and had all these variables correctly recorded. For the multinomial GEE, the following regressors were included: current parental BMI and PAC variables (with the frequency variables recoded to only have three categories). The geepack R package was used to fit the linear GEE with the AR(1) correlation structure[38] and the multgee R package was used to fit the multinomial GEE with the time exchangeability local odds ratio structure.[39] For both models, robust variance estimators were used.

Results

Descriptive data

Table 2 provides an overview of the demographics of participants in the B cohort of LSAC. As shown in the table, the cohort is almost evenly split between the sexes. It consists almost exclusively of Australia-born children. A higher proportion of children have parents who were born in other countries. Total follow-up time was approximately 14 years total. Average follow-up time between waves was about 2 years. Table 3 indicates the number of cases with missing values for each independent and dependent variable.

PAC effect on BMIz

No PAC variables had a significant effect on BMIz. Coefficients with p-values between 0.05

and 0.1 were obtained, but none reached the threshold for statistical significance used in this study ($p < 0.05$).

PAC effect on weight status

Table 4 shows the effect of PAC variables on child weight status by wave. The result in row 1, column 3 (corresponding to wave 4, "Average maternal drinks/week") indicates that the odds ratio of being overweight was multiplied by 1.399 for each additional drink the mother had per week. As can be seen drinking quantity was significantly associated with increases in the prevalence of unhealthy child weight statuses. Moderate drinking frequencies were significantly associated with lower rates of unhealthy child weight statuses compared to low drinking frequencies. Higher drinking frequencies were associated with both higher and lower rates of unhealthy child weight statuses, depending on wave and specific weight status of interest relative to low drinking frequencies. Paternal drinking frequency greater than triweekly was associated with both the highest and lowest odds ratios, relative to the reference category of the father drinking monthly or less, found in the analysis.

Mediation analysis

There was no significant mediation effect for any risk factor or mediator variable on either BMIz or weight status. Some p-values between 0.05 and 0.10 were obtained, but none reached the threshold for statistical significance used in this study.

Moderation analysis

Table 5 summarizes the results of the moderation analysis. The effects on BMIz are just what the moderation effect adds to BMIz as the warmth variable is increased. For instance, the effect in column 2, row 2 (wave 3, MQ×pwarm→BMIz) indicates that if maternal drinking average weekly quantity is held constant at one, a one unit increase in paternal warmth would, through the moderation effect, be associated with an increase in BMIz. Consequently, the moderating effect of paternal warmth on maternal drinking average weekly quantity appears to result in a higher BMIz at age 4/5 years but a lower BMIz at age 12/13 years, with no effect at different

ages. Maternal warmth had no moderating effect at any age. As can be seen, moderation effects are almost evenly split between reducing and increasing BMIz. Most moderation effects that reduce BMIz are associated with wave 7, although one occurs in wave 4.

The effects on binary weight status are the odds ratio that multiplies the odds of overweight/obesity as the warmth variable is increased. As can be seen the moderation effect of parental warmth, when it exists, is usually associated with a lower risk of overweight/obesity. This was exclusively the case for ages 10 to 13 years. For ages 4 or 5 years, the moderation effect of paternal warmth on parental drinking average weekly quantity was associated with higher risk of childhood obesity/overweight. Although maternal warmth had a moderation effect on maternal drinking frequency for certain frequencies that was associated with a lower risk of overweight or obesity. At age 14 or 15 years the only moderation effect observed lead to increased risk of overweight or obesity and involved maternal warmth and the highest category of paternal drinking frequency studied.

GEE analysis

Table 6 shows the result of the GEE BMIz analysis. Evidently, paternal drinking frequency of monthly or greater is associated with a reduced child BMIz. Moderate paternal drinking frequency (less than monthly to triweekly) was associated with a reduced risk of child severe obesity. However, for paternal drinking frequency of greater than four times per week, a higher incidence of childhood mild-to-moderate obesity was observed.

Discussion

Greater than annual paternal AC was associated with reduced child BMIz. Typically, this seemed to be associated with, if anything, a lower rate of unhealthy weight status, although in wave 2, it was associated with a significantly higher rate of child underweight if the father drank more than triweekly. Moderation effects involving parental warmth seemed to be largely associated with children having a higher BMIz, although there were exceptions where it appeared to be associated with a lower child BMIz. Additionally, the moderation effect of

parental warmth also seemed to usually be associated with a lower risk of overweight or obesity, although exceptions at ages 4, 5, 14 and 15 years existed.

To the best of the authors' knowledge, no other studies have investigated the effect of PAC on childhood obesity and overweight risk, therefore, there are no comparable studies with which to compare the results. Despite this, at least one of the proposed mechanisms by which PAC could lead to childhood obesity and overweight could also cause children to consume fewer calories, which could help explain some of the results. For instance, parents that are frequently intoxicated may struggle to maintain employment and, hence, may struggle to feed their children. These parents may also have difficulty preparing nutritious meals for their children or acquiring nutritious food for them to consume. Therefore, it is proposed that future studies investigate the moderating effect of socioeconomic status.

No mediation effect involving the outcome variable BMIz was found to be significant, which was unsurprising given that no PAC variables were found to be significantly correlated with BMIz in the individual wave analysis. A possible explanation for why the mediation analysis with the weight status outcome variable failed to produce any significant results is that the proposed mediation mechanisms were simply incorrect, and that PAC produces its effects on weight status through other mechanisms. Another explanation is that the variables used to represent the proposed mechanisms did not include enough information. For instance, the dietary variables that were tested as possible mediators only pertained to what the child consumed in the day prior to the interview, which may not necessarily be representative of the child's typical diet. Additionally, these dietary variables only included the frequency with which the child consumed the various food categories, not the precise quantity.

The results of this study are likely not generalizable beyond the Australian context as the sample this study was based on was entirely composed of Australian children. These findings suggest that moderate parental drinking frequency is not associated with child obesity, overweight or underweight. In fact, it may be associated with a lower risk of these unhealthy

weight statuses. The effect of high frequency and quantity of parental drinking is more variable, depending on the parent, child's age and the specific weight status of interest. Additionally, parental warmth seems to impact upon the effect of PAC on child BMIz and weight status, usually leading to higher child BMIz, and lower odds of unhealthy weight status.

Limitations

This study had several limitations, including the need to assume that the missing data from the data set was absent at random when Table 2 suggests that ethnic minorities may be underrepresented in the data set after cleaning. A further limitation of the study was its observational design; consequently, no causal inferences can be made. Additionally, some regressors corresponding to possible confounders that were recorded in the data set had to be omitted from the MLMs due to convergence issues. The data set also did not record all known risk factors for childhood obesity like gestational weight gain.[27,40] Additionally, many of the variables that were controlled for and used as mediators were less than ideally recorded, which was previously mentioned. The variables were also just a single snapshot taken at each wave, or sometimes between waves, and hence if these variables vary significantly between the interview dates these variables may not be truly representative of what they are taken to measure. Additionally, SMEs prevented some of the mediation and moderation analysis from being conducted.

Interpretation

This study has found that paternal drinking frequency is correlated with reduced BMIz in children and that moderate PAC is generally associated with higher weight status in children, although higher levels of PAC are associated with a mixture of lower rates and higher rates of unhealthy weight statuses in children. Additionally, parental warmth usually seemed to moderate the effect of PAC by being associated with a lower likelihood of unhealthy child weight statuses and usually higher child BMIz, but with some exceptions. Due to the complexity of the results of this study, it is suggested that further studies be undertaken that help illuminate

the cause of these contradictions.

Generalizability

This study was based entirely on data from an Australian study, so its results could not be generalized to other populations. Its results also pertained to children who were born in 2003 or 2004, so its results may not be generalizable to later generations of children.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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Author contributions

Brenton Horne wrote the original draft of this paper, came up with the conceptualization and design of the study, conducted the original analysis and accessed the original data set. Enamul Kabir and Khorshed Alam supervised the research and provided feedback on draft of the paper.

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Tables

Table 1: Variables used in the study.

Variable	Waves	Type	Description and/or justification
Abandoned covariates			
Child Indigenous status	1	MC[a]	1 means not Indigenous; 2 means Aboriginal; 3 means Torres Strait Islander; and 4 means both Aboriginal and Torres Strait Islander. Considered due to ethnic disparities in the prevalence of childhood obesity/overweight.[18]
Child country of birth	1	MC	Standard Australian Classification of Countries (SACC) code of the country. Part of the child's ethnic status.
Parental[b] country of birth			
Hours worked by parents	1–8	Q[c]	Average weekly hours. Some studies have shown a correlation with childhood obesity/overweight.[19]
Covariates			
Parental BMI	1–8	Q	High parental BMI is a known risk factor for childhood obesity.[20]
Child sex	1	DC[d]	Controlled for due to sex disparities in obesity/overweight rate.[21]
Child age	1–8	Q	Controlled for due to some evidence for a correlation between age and childhood obesity risk.[22]
Parental weekly income			Part of socioeconomic status (SES).[23]
Parental highest qualifications		MC	Part of SES. 1 for postgraduate degree; 2 for graduate diploma or certificate; 3 for bachelor's degree; 4 for advanced diploma/diploma; 5 for certificate; and 6 for others.
Parental highest schooling			Part of SES. 1 for year 12 or equivalent; 2 for year 11 or equivalent; 3 for year 10 or equivalent; 4 for year 9 or equivalent; 5 for year 8 or

			below; 6 for never attended school; and 7 for still at school.
Parental occupation			4-digit Australia and New Zealand Standard Classification of Occupations code was used. Part of SES.
Parental smoking frequency	1–3, 5–8		Parental smoking is a known risk factor for childhood obesity, at least in earlier childhood.[23,24] 1 means do not smoke at all; 2 means less than once a day; and 3 means at least once a day.
Breastfeeding cessation age	1–3	Q	Was set to child current age if still breastfeeding. Breastfeeding is a protective factor against childhood obesity.[25,26]
PM[e] DM[f]	1	DC	Coded as 1 for Yes and 2 for No. Was controlled for as it is a known risk factor for childhood obesity.[27]
PM hypertension			Coded similarly to DM. Known risk factor for childhood obesity.[27]
Maternal age at child's birth		Q	Calculated from mother and child's dates of birth. In some studies it has been found correlated with child BMIz or weight status.[28]
Child birthweight			There is evidence that child birthweight, particularly low birthweight, is a risk factor for childhood obesity.[29]
Maternal BMI from 1st wave			Closest variable to the mother's pre-pregnancy BMI, which is associated with childhood obesity/overweight risk.[27]
PM antibiotic use		DC	Coded as 1 for yes and 2 for no. Controlled for as a proxy for prenatal maternal infection.[30]
PM depression/anxiety/stress			Coded as 1 for yes and 2 for no. Maternal stress during pregnancy has been implicated as a childhood obesity and overweight risk factor in some studies.[31]
Cigarettes mom smoked/day during each pregnancy trimester		MC	Has categories of: 0 for none; 1 for 1-10; 2 for 11-20; 3 for 21-30; 4 for 31-40; 5 for 41-50; 6 for ≥51; and 9 for occasional, not every day. PM smoking has been identified as a risk factor for child obesity and overweight.[32]
Independent variables			
Parental drinking frequency	1–8	MC	Coded for LM analysis as: 0 for never; 1 for not in the last year; 2 for ≤ 1/month; 3 for 2–3/month; 4 for 1/week; 5 for 2–3/week; 6 for 4–6/week; and 7 for every day. Recoding to the following categories was done before fitting MLMs due to singular matrix errors: 1 for ≤ 1/month;

			2 for 2/month–3/week; and 3 for ≥ 4/week.
Parental drinking quantity	1–8	Q	Average weekly quantity.
Mediator variables			
Child ate breakfast	2–8	DC	Pertains to the day of the interview. Coded as 0 for yes and 1 for no. The primary caregiver was asked this question for waves 2–5; for waves 6–8, the child themselves was asked.
Child has sleep issues	1–8		Whether the child has any sleep problems. Obtained from the primary caregiver. Coded as 0 for yes and 1 for no.
Child ate fresh fruit	2–8	MC	It pertains to the 24 hours prior to interview and is about the number of times they ate the food item. 0 means none; 1 means once; 2 means twice; 3 means thrice or more. For wave 2, a slightly different variable is recorded only, and it is coded almost the same except without a level of 3 and the level of 2 means more than once.
Child drank fresh juice			
Child ate cooked vegetables			
Child ate raw vegetables			
Child ate processed meat			
Child ate hot chips			
Child ate snack food			
Child ate sugary food			
Child ate full milk products			
Child ate skim milk products			
Child drank water			
Child drank SSBs[#]			

Parental hostility version 3	2–3	Q	It was an average of (each relating to the last six months, and each rated on a scale from 1 to 10, with 1 being never and 10 being all the time): the parent has been angry with the child; the parent shouted at the child; and the parent lost their temper with the child.
Parental warmth	1–8		Was an average of the following six variables (all relating to the last six months and all scored from 1 for never/almost never to 5 for always/almost always), how often the parent: has hugged/held the child for no particular reason; has told the child how happy they make them; has warm, close times with the child; has enjoyed listening and doing things with the child; has felt close to the child when the child was happy or upset; and the parent physically expressed affection for the child.
How often the TV is on during meals	2.5, 3.5, 5–8	MC	2.5 and 3.5 refers to data collected by between wave questionnaires. When recorded between waves it took on values from 1 for always to 5 for never. For waves 5–8, a scale from 1 to 5 was also used but 5 meant always and 1 meant never. Between wave variables were used in the analysis of the wave that came immediately afterwards.
How child spends spare time	2–7		If: 1, chooses inactive pastimes; 3, chooses active pastimes; and 2, equally likely to choose active/inactive pastimes.
Child enjoys physical activity	3–5		Rated from 1 to 5, in increasing order of enjoyment of physical activity.
Child sleep duration adequacy	6–8		Over last month as reported by child. 1 meant plenty; 2 meant just enough; 3 meant not quite enough; and 4 meant not really enough.
How well the child slept			1 means very well; 2 means well; 3 means bad; and 4 means very bad. Pertains to last month and was reported by the child.
Days/week ≥ 30 mins exercise	7–8	Q	Only moderate to vigorous physical activity is included. Pertains to the child and the child provided this information.
Days/week ≥ 60 mins exercise			
Child alcohol consumption			Number of drinks the child has drunk in the last 7 days. As reported by the child.
Moderator variable			
Parental warmth, covered under mediator variables			

Outcome variables and related variables			
BMI[h] z-score (BMIz)	2–8	Q	Calculated based on US Centers for Disease Control and Prevention (CDC) and UK 1990 growth reference data.[33]
BMI percentile (BMIpct)			Based on CDC growth reference data.
Weight status		MC	BMIpct<5 was classed as underweight and coded as 0. 5 ≤ BMIpct < 85 was classed as healthy weight and coded as 1. 85 ≤ BMIpct < 95 was classed as overweight and coded as 2. 95 ≤ BMIpct < 99 was classed as mild to moderate obesity and coded as 3. 99 ≤ BMIpct was classed as severe obesity and coded as 4.[34]
Binary weight status		DC	Calculated based on weight status. 0 corresponds to healthy weight; 1 corresponds to overweight or obesity. Underweight children were excluded from analyses involving binary weight status.

a. MC: multicategorical. These variables are categorical and have more than two categories.

b. Variables listed as pertaining to the parents were recorded for both parents separately.

c. Q: quantitative. These variables are also continuous.

d. DC: dichotomous. These variables are categorical and have two categories.

e. PM: Prenatal maternal.

f. DM: diabetes mellitus.

g. SSB: sugar-sweetened beverages.

h. BMI: body mass index.

Table 2: Characteristics of participants. The first value is when cases with missing data are omitted and the second (after the forward slash) is when such cases are not omitted.

Characteristic\Analysis	Wave 2	Wave 3	Wave 4	Wave 5	Wave 6	Wave 7	Wave 8	GEE
Number	1,001 / 4,606	915 / 4,386	874 / 4,242	1,146 / 4,085	1,073 / 3,764	791 / 3,381	862 / 3,127	381 / 2,722
Male sex, number (%)	508 (50.75) / 2,349 (51.00)	465 (50.82) / 2,251 (51.32)	454 (52.43) / 2,187 (51.56)	559 (48.78) / 2,096 (51.31)	534 (49.77) / 1,929 (51.25)	398 (50.32) / 1,734 (51.29)	441 (51.16) / 1,606 (51.36)	190 (49.87) / 1,405 (51.62)
Age in years, median (IQR)	2.8419 (0.3149) / 2.8528 (0.3258)	4.8296 (0.2847) /4.8350 (0.3251)	6.8405 (0.3963)/6.8446 (0.4162)	8.8980 (0.3970)/8.9172 (0.4216)	10.9377 (0.4983)/ 10.9213 (0.4846)	12.9090 (0.4709) / 12.9665 (0.5175)	14.8227 (0.4463) / 14.8446 (0.4559)	NA[a]
Indigenous Australian, number (%)	5 (0.4995) / 180 (3.9079)	7 (0.7650) / 149 (3.397)	11 (1.259) / 145 (3.418)	12 (1.047) / 139 (3.403)	10 (0.9320) / 106 (2.816)	5 (0.6321) / 87 (2.573)	6 (0.6961) / 79 (2.526)	2 (0.5249) / 58 (2.131)
Child born in Australia, number (%)	998 (99.70) / 4,589 (99.63)	912 (99.67) / 4,370 (99.64)	870 (99.58) / 4,227 (99.65)	1,141 (99.56) / 4,070 (99.63)	1,071 (99.81) / 3,749 (99.60)	789 (99.75) / 3,371 (99.70)	859 (99.65) / 3,117 (99.68)	380 (99.74) / 2,713 (99.67)
Mother born in Australia, number (%)	811 (81.02) / 3,632 (78.85)	747 (81.64) / 3,494 (79.66)	722 (80.91) / 3,388 (79.87)	936 (81.68) / 3,262 (79.85)	862 (80.34) / 3,010 (79.97)	632 (79.90) / 2,724 (80.57)	697 (80.86) / 2,514 (80.40)	315 (82.68) / 2,200 (80.82)
Father born in Australia, number (%)	777 (77.62) / 3,260 (70.78)	728 (79.56) / 3,156 (71.96)	711 (81.35) / 3,070 (72.37)	888 (77.49) / 2,971 (72.73)	831 (77.45) / 2,765 (73.46)	624 (78.89) / 2,514 (74.36)	669 (77.61) / 2,316 (74.06)	297 (77.95) / 2,072 (76.12)
Father drinks alcohol, number (%)	951 (95.00) /	871 (95.19) /	850 (97.25) /	1,082 (94.42) /	1,013 (94.41) /	741 (93.68) /	801 (92.92) /	2,566[c] (96.21) /

	2,871 (62.33)[b]	2,562 (58.41)	2,524 (59.50)	2,286 (55.96)	2,185 (58.05)	1,890 (55.90)	1,765 (56.44)	12,488 (65.54)
Mother drinks alcohol, number (%)	889 (88.81) / 2,933 (63.68)	820 (89.62) / 3,633 (82.83)	874 (100) / 3,582 (84.44)	1,047 (91.36) / 3,423 (83.79)	979 (91.24) / 3,140 (83.42)	716 (90.52) / 2,817 (83.32)	785 (91.07) / 2,634 (84.23)	2,591 (97.15) / 16,046 (84.21)
Underweight, number (%)	30 (2.997) / 124 (2.692)	30 (3.283) / 144 (3.279)	28 (3.204) / 126 (2.970)	27 (2.356) / 96 (2.350)	34 (3.169) / 117 (3.108)	24 (3.034) / 105 (3.106)	18 (2.088) / 85 (2.718)	74 (2.775) / 566 (2.971)
Overweight, number (%)	184 (18.38) / 828 (17.98)	188 (20.55) / 826 (18.83)	112 (12.81) / 607 (14.31)	151 (13.18) / 580 (14.20)	152 (14.17) / 539 (14.32)	101 (12.77) / 510 (15.08)	127 (14.73) / 494 (15.80)	344 (12.90) / 3,034 (15.92)
Mild-to-moderate obesity, number (%)	78 (7.792) / 456 (9.900)	71 (7.760) / 414 (9.439)	45 (5.149) / 309 (7.284)	77 (6.719) / 348 (8.519)	70 (6.524) / 322 (8.555)	51 (6.448) / 267 (7.897)	50 (5.800) / 251 (8.027)	141 (5.287) / 1,538 (8.072)
Severe obesity, number (%)	32 (3.197) / 178 (3.864)	27 (2.951) / 166 (3.785)	10 (1.144) / 83 (1.957)	9 (0.7853) / 50 (1.224)	5 (0.4660) / 30 (0.7970)	4 (0.5057) / 32 (0.9465)	8 (0.9281) / 45 (1.439)	30 (1.125) / 339 (1.779)

a. Not applicable as the GEE analysis is of children over all seven waves with the outcome variable recorded.

b. Parental drinking variables do have missing values for some children. This is partly why the percentage differs so markedly between the cleaned and uncleaned data sets.

c. The weight status and alcohol drinking numbers for the GEE column pertains to the total number of cases of the weight status or alcohol drinking over all the waves.

Table 3: Number of subjects with missing values for independent and dependent variables.

Variable \ Wave	2	3	4	5	6	7	8
Maternal drinking frequency	1,102	35	93	144	156	164	114
Paternal drinking frequency	1,487	1,610	1,520	1,607	1,408	1,332	1,214
Maternal drinking average weekly quantity	1,127	35	654	145	157	166	121
Paternal drinking average weekly quantity	1,500	1,627	1,547	1,611	1,423	1,359	1,287
BMIz and BMI percentile	84	62	50	87	192	212	200

Table 4: Effect of parental alcohol consumption on childhood weight status across seven waves of a longitudinal study. Odds ratios (95% confidence interval in brackets), relative to healthy weight, are shown.

Variable\Wave	2	3	4	5	6	7	8
Average maternal drinks/week	SO:[a] 2.451[b] (1.037, 5.795)[c]	NS[d]	OW:[a] 1.399 (1.018, 1.922)	NS	NS	NS	NS
Average paternal drinks/week	NS	NS	NS	NS	OW:[f] 1.229 (1.017, 1.485)	NS	NS
Mother drinking 2/month–3/week (inclusive).[g]	UW: 0.3724 (0.1406, 0.9866)	NS	NS	NS	NS	NS	NS
Mother drinking >3/week.	UW: 0.1035 (0.0102, 0.9716)	NS	NS	NS	NS	MTMO:[h] 5.220 (1.094, 24.91)	NS
Father drinking 2/month–3/week (inclusive).	NS	SO: 0.2900 (0.09851, 0.8537)	UW: 0.2468 (0.08751, 0.6958) MTMO: 6.103 (1.181, 31.54)	NS	NS	NS	MTMO: 0.2551 (0.1133, 0.5744)
Father drinking >3/week.	UW: 18.88 (3.483, 102.3).	SO: 0.1285 (0.01971, 0.8382)	NS	NS	OW: 0.4552 (0.2089, 0.9917)	NS	MTMO: 0.07714 (0.01532, 0.3884)

a. SO: severe obesity.

b. This is the odds ratio for each one unit increase in the variable, keeping in mind that the drinking frequency variables are all binary.

c. In brackets is the 95% confidence interval.

d. NS: not significant.

e. UW: underweight.

f. OW: overweight.

g. All drinking frequency odds ratios are relative to the reference category of the parent drinking monthly or less.

h. MTMO: mild-to-moderate obesity.

Table 5: Moderation effects on Body Mass Index z-score (BMIz) and binary weight status (95% confidence interval in brackets) of parental warmth with respect to PAC variables.

Variable\Wave	2	3	4	5	6	7	8
MQ[a]×mwarm[b]→BMIz	NS[c]						
MQ×pwarm[d] →BMIz	NS	0.2413 (0.0104, 0.4721)[e]	NS			-0.1373 (-0.2633, -0.0113)	NS

PQ[f] ×mwarm→BMIz	NS					
PQ× pwarm→BMIz						
PF1[g] ×mwarm→BMIz						
PF1×pwarm→BMIz	NS	1.5421 (0.0336, 3.0506)	NS			
PF2[h]×mwarm→BMIz	NS	0.8697 (0.0986, 1.6407)				
PF2×pwarm→BMIz	NS					
PF3[i]×mwarm→BMIz						
PF3×pwarm→BMIz	NS		-0.6551 (-1.2499, -0.0604)	NS		
PF4–6[j]×mwarm→BMIz	NS					
PF4–6×pwarm→BMIz						
PF7[k]×mwarm→BMIz	NS					0.5249 (0.0534, 0.9964)
PF7×pwarm→BMIz	NS					
MF1[l]×mwarm→BMIz						
MF1×pwarm→BMIz	0.7415 (0.0062, 1.4769)	NS				
MF2[m]×mwarm→BMIz	NS	-0.7910 (-1.2957, -0.2863)	NS			
MF2×pwarm→BMIz	NS					
MF3[n]×mwarm→BMIz	NS				-0.5083 (-0.9329, -0.0837)	NS
MF3×pwarm→BMIz	NS					

MF4[o]×mwarm→BMIz	NS		0.8412 (0.1333, 1.5492)	NS		
MF4×pwarm→BMIz	NS					
MF5[p]×mwarm→BMIz	NS	-0.5631 (-1.0843, -0.0418)	NS			
MF5×pwarm→BMIz	NS					
MF6[q]×mwarm→BMIz						
MF6×pwarm→BMIz	NS				-0.5237 (-0.8886, -0.1587)	NS
MF7[r]×mwarm→BMIz	NS					
MF7×pwarm→BMIz						
MQ×mwarm→BWS[s]	NS	NS	NS	NS		
MQ×pwarm→BWS				NS	0.5935 (0.3857, 0.9130)[t]	NS
PQ×mwarm→BWS				NS	0.7256 (0.5693, 0.9249)	
PQ×pwarm→BWS		1.4159 (1.0970, 1.8276)		NS		
PF1×mwarm→BWS		SME[u]	NS	NS	NS	
PF1×pwarm→BWS						
PF2×mwarm→BWS						
PF2×pwarm→BWS					NS	
PF3×mwarm→BWS					NS	
PF3×pwarm→BWS						

PF4×mwarm→BWS							
PF4×pwarm→BWS				NS	0.1874 (0.0482, 0.7282)		
PF5×mwarm→BWS				NS			
PF5×pwarm→BWS							
PF6×mwarm→BWS							
PF6×pwarm→BWS				NS	0.1883 (0.0567, 0.6254)	NS	
PF7×mwarm→BWS				NS			NS
PF7×pwarm→BWS							
MF1×mwarm→BWS		NS					
MF1×pwarm→BWS							
MF2×mwarm→BWS		0.1263 (0.0331, 0.4819)					
MF2×pwarm→BWS							
MF3×mwarm→BWS							
MF3×pwarm→BWS		NS		NS	0.1808 (0.0521, 0.6276)	NS	
MF4×mwarm→BWS				NS			
MF4×pwarm→BWS							
MF5×mwarm→BWS		0.1560 (0.0403, 0.6046)					
MF5×pwarm→BWS		NS					

MF6×mwarm→BWS				NS	0.2034 (0.0496, 0.8336)	NS
MF6×pwarm→BWS					0.1041 (0.0290, 0.3732)	
MF7×mwarm→BWS				NS		
MF7×pwarm→BWS						

a. MQ: maternal drinking average weekly quantity.

b. mwarm: maternal warmth.

c. NS: not significant.

d. pwarm: paternal warmth.

e. The results with the BMIz outcome variable should be interpreted as how much the moderation effect would increase (or decrease if the sign is negative) BMIz for every unit increase in the parental warmth variable mentioned (assuming the drinking variable in question is held constant at one).

f. PQ: paternal drinking average weekly quantity.

g. PF1: paternal drinking frequency (PDF) of <1/year, but not never.

h. PF2: PDF of 1/year – 1/month.

i. PF3: PDF of 2–3/month.

j. PF4–6: PDF of between 1–6/week.

k. PF7: PDF of daily.

l. MF1: maternal drinking frequency (MDF) of <1/year, but not never.

m. MF2: MDF of monthly or monthly or less, but sometime in the last year.

n. MF3: MDF of 2—3/month.

o. MF4: MDF of weekly.

p. MF5: MDF of 2—3/week.

q. MF6: MDF of 4—6/week.

r. MF7: MDF of daily.

s. BWS: binary weight status.

t. BWS outcome variable results are odds ratios of overweight/obesity relative to healthy weight/underweight. They are what the odds of being overweight/obesity will be multiplied by, assuming the drinking variable in question is held constant at one, for every one unit increase in the respective parental warmth.

u. SME: singular matrix error.

Table 6:Effect of paternal drinking frequency on Body Mass Index z-score (BMIz) and weight status across all waves (95% confidence intervals in brackets).

Risk factor\Outcome variable	BMIz[a]	Weight status[b]
PDF,[c] not in the last year	Not significant	Part of reference category, along with abstinence.
PDF, monthly or less	-0.2991 (-0.5261, -0.07214)[d]	
PDF, 2–3/month	-0.3041 (-0.5320, -0.07616)	Severe obesity: 0.2799 (0.0830, 0.9436)
PDF, weekly	-0.3276 (-0.5589, -0.09632)	
PDF, 2–3/week	-0.2478 (-0.4650, -0.03064)	
PDF, 4–6/week	-0.4120 (-0.6525, -0.1715)	Mild-to-moderate obesity: 2.1900 (1.0466, 4.5824)
PDF, daily	-0.4319 (-0.7245, -0.1393)	

a. In the BMIz column the entries refer to how much BMIz differs between the reference category of paternal abstinence from alcohol and the parental drinking frequency category the cell is in.

b. Odds ratios are reported for weight status and are all relative to healthy weight.

c. PDF: paternal drinking frequency.

d. In brackets are confidence intervals. For the BMIz analysis the reference category is paternal abstinence from alcohol.

3.3 Implications

This paper further substantiates that childhood obesity and overweight can be predicted by childhood factors and thereby substantiates the DOHaD hypothesis. It shows that while moderate parental alcohol consumption is probably not a major risk factor for childhood obesity and overweight, excessive alcohol consumption appears to predispose children to developing obesity and overweight. In papers 2 and 3, the focus will be on prenatal risk factors for childhood obesity and overweight and therefore rely on the FOAD hypothesis.

CHAPTER 4: PAPER 2: THE IMPACT OF PRENATAL MATERNAL DIETARY EXCLUSION ON CHILDHOOD OBESITY AND OVERWEIGHT RISK

4.1 Introduction

To the best of this researcher's knowledge, the effect of excluding certain food items from the mother's prenatal diet has never been studied as a risk factor for childhood obesity and overweight in humans. This is despite reason to suspect a link, including that one-carbon metabolism is known to play a key role in regulating childhood susceptibility to obesity and overweight and many nutrients that are involved in one-carbon metabolism (such as cobalamin, folate and choline) are more common in certain categories of foods (for example, cobalamin is predominantly found in fortified foods and animal products) (Fall & Kumaran, 2019). Additionally, birthweight is a known marker for fetal nutrition and has been found to be associated with childhood obesity and overweight risk in many studies (Andriani, 2021; Matthews et al., 2017; Qiao et al., 2020). Hence prenatal maternal dietary changes could, through an effect on birthweight, affect children's risk of childhood obesity and overweight. In the following paper, the effect of prenatal maternal dietary exclusion on child BMIz and childhood obesity and overweight risk will be investigated.

4.2 Submitted paper

Impact of prenatal maternal dietary exclusion on childhood obesity and overweight risk

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Abstract and keywords

Background

Child birthweight is a measure of fetal nutrition that is primarily determined by prenatal maternal (PM) diet. Child birthweight and child obesity/overweight risk are well established to be linked. Nevertheless, no studies have investigated the impact of PM dietary exclusion on child obesity/overweight risk or body mass index z-score (BMIz).

Objectives

The study aimed to determine whether PM dietary exclusion affected the child's BMIz, obesity/overweight risk, whether child birthweight serves as a mediator of this, and whether PM use of dietary supplements can protect against this.

Methods

Waves within the years 2004–2019 from the Longitudinal Study of Australian Children, a population-based cohort study, were analyzed. The participants were aged 0 to 15 years during these waves of the study. Analysis was conducted using logistic and linear models. A total of 5,107 participants were involved in the first wave of the study.

Results

The PM exclusion of fish was associated with a 4.154-fold (95% confidence interval (CI): 1.121 to 15.39) higher risk of being underweight at age 14 or 15 years and a 3.424-fold (95% CI: 1.338 to 8.764) higher risk of mild-to-moderate obesity at age 6 or 7 years, both respective to the

reference category of healthy weight. The PM exclusion of egg was associated with a 5.320-fold (95% CI: 2.023 to 13.99) higher risk of being overweight at age 14 or 15 years, relative to the reference category of healthy weight. The exclusion of dairy was associated with more mixed effects. Mediation effects did not reach statistical significance. Moderation effects involving PM dietary supplement use, when they did occur, were associated with higher child BMIz and usually a higher risk of obesity/overweight.

Conclusions

Fish and eggs are likely important parts of PM diets for preventing childhood obesity and overweight. Further studies will be needed to determine reasons for this and the apparent adverse effects of dietary supplements on overweight/obesity risk.

Keywords: Longitudinal Studies, Maternal Exposure, Diet, Pediatric Obesity.

55 # Introduction

56 Childhood obesity and overweight are a major global health crisis in the 21st Century. The
57 conditions contribute to numerous causes of morbidity and mortality, including cardiovascular
58 disease, type 2 diabetes mellitus, and certain cancers [1]. It is particularly prevalent in Australia,
59 where 24% of children were overweight or obese between 2017 and 2018 [2]. Thus, attempting
60 to combat these forms of malnutrition is essential for the wellbeing of society. An important part
61 of such attempts is identifying modifiable risk factors for the condition, such as the dietary habits
62 of mothers during pregnancy. The mechanisms by which these risk factors achieve their effects
63 also need to be identified because these mechanisms can pave additional research avenues for
64 reducing the risk of childhood obesity and overweight. Protective factors have been investigated
65 for this same reason.

66 A well-established relationship exists between fetal malnutrition and obesity and overweight risk
67 later in life [3,4]. For instance, young men exposed to famine during the first half of their
68 mothers' pregnancy, as during the Dutch famine of 1944–1945, were found to have a higher
69 obesity risk [5]. However, the opposite effect was observed when these men were exposed to
70 starvation during the last half of pregnancy or infancy [5]. Child birthweight appears to mediate
71 the effect of fetal malnutrition on subsequent obesity and overweight risk [3,4]. According to the
72 Developmental Origins of Health and Disease (DOHaD) hypothesis, this is explained by prenatal
73 malnutrition adapting the child's metabolism to cope with a similar postnatal environment [6]. A
74 mismatch between the prenatal and postnatal environment can lead to conditions such as
75 childhood obesity and overweight [6]. Studies on animals have found evidence of an effect of
76 prenatal maternal (PM) diet on postnatal metabolic outcomes in offspring [7]. There have been

77 studies that have investigated the effects of PM use of dietary supplements on child obesity and
78 overweight [8]. For instance, one study in Nepal has shown that folate, iron, and zinc
79 supplementation during pregnancy is associated with reduced skinfold thickness (a measure of
80 adiposity) in children aged 6-8 years [9]. This finding suggests that taking these supplements
81 during pregnancy may have a protective effect against childhood obesity.

82 Meat and fish are rich sources of iron and zinc [10,11], so the aforementioned Nepalese study
83 provides a rationale for suspecting that the exclusion of these foods may be associated with an
84 increased risk of childhood obesity and overweight. Dairy, meat, fish, and eggs are all sources of
85 vitamin B12 [12]. Dairy, eggs, and liver are also rich sources of choline [13]. The one-carbon
86 cycle, which provides methyl groups for deoxyribonucleic acid (DNA) methylation, involves
87 vitamin B12 and choline, among other nutrients (such as folate), and has been implicated in the
88 mechanisms of DOHaD. Alterations in this cycle can lead to epigenetic changes that
89 permanently program the fetus' organs to be ready for a postnatal environment of nutritional
90 deprivation [14].Nevertheless, to the best of the authors' knowledge, no previous study on
91 humans has specifically examined the effect of PM dietary exclusion (PMDE) on childhood
92 obesity and overweight risk or body mass index z-score (BMIz). Accordingly, the present study
93 aimed to address this notable research gap. The data used were obtained from a longitudinal
94 study conducted in Australia, where children under the age of two years were followed since
95 2004. The primary caregivers (usually the mother) were interviewed to collect various
96 information regarding the mother's pregnancy, specifically during wave 1 in 2004.

97 This study investigated the effect of excluding certain food items from the mother's diet during
98 pregnancy on the risk of children later developing childhood obesity and overweight and on their

BMIz. Child birthweight was investigated as a possible mediating factor in this relationship. PM dietary supplement use was examined as a possible protective factor against the effects of excluding food items from the mother's prenatal diet on childhood obesity and overweight risk.

Materials and Methods

Ethics approval

This study (consisting entirely of secondary data analysis) received ethics approval from the University of Southern Queensland's Human Research Ethics Committee with the project ID ETH2023-0175.

Data

Data were obtained from the Longitudinal Study of Australian Children (LSAC). The design of the LSAC is described elsewhere [15]. Briefly, LSAC started in 2004 and is an ongoing two-yearly prospective cohort study. It had two cohorts, namely, B (for "baby") and K (for "kindergarten"). Cohort B focused on children aged <2 years in 2004.Cohort K focused on children aged 4 or 5 years in 2004. Only cohort B was analyzed in this study because it had the required PM details. In 2004, the first wave of LSAC was conducted. The second wave was conducted in 2006, the third wave in 2008, and so forth. Two-stage cluster sampling was used to obtain the sample that LSAC used. LSAC received ethics approval from the Australian Institute of Family Studies Ethics Committee and written parental consent was obtained for all participants.

The majority of the data analyzed in this study were collected by trained interviewers through in-

person interviews with the child's primary caregiver. The child's weight was measured to the nearest 50 g using glass bathroom scales, and the child was wearing light clothing. In waves 2 and 3, the scales used were Salter Australia glass bathroom scales (150 kg × 50 g) and HoMedics digital body mass index (BMI) bathroom scales (180 kg × 100 g) [16 p8]. For waves 4 to 8, Tanita body fat scales were used [16 p8]. The child's height was measured to the nearest 0.1 cm by using a portable rigid stadiometer. In waves 2 and 3, an Invicta stadiometer from Modern Teaching Aids was used to find the child's height [16 p8]. In waves 4 to 8, a laser stadiometer was used to measure the child's height [16 p8]. Two height measurements were taken, and if they differed by 0.5 cm or more, a third measurement was taken. The two closest measurements were then averaged and included in the dataset as the child's height [16 p8]. These measurements were used to calculate the child's BMI.

Data contained within the LSAC restricted data set were accessed from the Australian Data Archives on 21 March 2023 [17]. The data set accessed was de-identified by its owner, the Australian Government Department of Social Services. However, the data contained sufficient information to potentially re-identify participants.

Variables

BMIz and weight status served as outcome variables. Dietary exclusion variables were treated as risk factor variables. Dietary supplement variables were treated as moderator variables, and child birthweight was treated as a mediator variable. These risk factors, mediator, and moderator variables were all recorded in wave 1 only. The outcome variables were recorded through waves 2–8. Information on variables used in the analysis, including covariates, is provided in Table 1.

140 **Table 1: Variables used in study.**

Variable	Wave(s)	Type	Description and/or justification
Covariates			
Child sex	1	DC[a]	Controlled due to sex differences in childhood obesity/overweight risk [18].
PM[b] DM[c]			1 meant yes; 2 meant no. Gestational diabetes is a known risk factor for childhood obesity [19].
PM hypertension			Same coding as PM DM. PM hypertension is a known risk factor for childhood obesity [19,20].
PM depression/anxiety/stress			Same coding as PM DM. PM stress is a known risk factor for childhood obesity [21].
PM antibiotic use			Same coding as PM DM. Controlled for as a proxy for PM infection [22].
Child ate breakfast	2-8[d]		Only pertains to the day of interview. 0 means yes and 1 means no. The primary caregiver gave the answer for waves 1-5; for waves 6-8 the child provided this information. Controlled for due to evidence that skipping breakfast is associated with higher childhood obesity and overweight risk [23].
Child has sleep issues	1-8		0 for yes and 1 for no. Controlled for due to evidence for the role of sleep in childhood obesity and overweight risk [24].
Maternal age at child's birth	1	Q[e]	Calculated from date of birth of mother and child. Was correlated with BMIz in some studies [25].
Maternal BMI at wave 1			Closest recorded variable to pre-pregnancy BMI, which is known to be correlated with childhood obesity and overweight risk [25].
Breastfeeding cessation age	1-3		In units of days. If the child is still breastfeeding, their current age is used. Controlled for as breastfeeding is protective against childhood obesity and overweight [26].

Parental hostility version 3	2-3		Average of the parent has (each pertaining to the last 6 months and rated from 1 to 10 in ascending order of frequency): been angry with the child; lost their temper with the child; and shouted at the child. Controlled for due to the role of parenting in childhood obesity/overweight risk [27].
Days/week ≥30 mins exercise	7-8		Pertains to the child; information provided by child. Only physical activity of at least moderate intensity is included in this. Controlled for due to obesity/overweight being fundamentally an energy imbalance issue.
Days/week ≥60 mins exercise			
Child alcohol consumption			Number of drinks the child has had in the last week as reported by the child. Controlled for due to some evidence of a correlation with child obesity/overweight risk [28].
Parental warmth	1-8		Average of how often the parent has (each pertaining to the last 6 months and rated from 1 to 5 in ascending order of frequency): told the child how happy they make them; held/hugged the child for no specific reason; had close moments with the child; enjoyed listening/doing things with the child; expressed physical affection for the child; and felt close to the child when the child was upset. Some studies have found an effect of parenting style on child BMI [27].
Child age			Age disparities in childhood obesity/overweight risk [29].
Parental weekly income			Part of socioeconomic status (SES), which is known to be associated with childhood obesity/overweight [30].
Parental highest qualification		MC[f]	Part of SES. Coded as: 1 for postgraduate degree; 2 for graduate diploma/certificate; 3 for bachelor's degree; 4 for (advanced) diploma; 5 for trade certificate; and 6 for others.
Parental highest schooling			Part of SES. Coded as: 1 for year 12 or equivalent; 2 for year 11 or equivalent; 3 for year 10 or equivalent; 4 for year 9 or equivalent; 5 for year ≤8; 6 for never attended school; and 7 for still at school.

Parental occupation			4-digit Australia and New Zealand Standard Classification of Occupations (ANZSCO) code. Part of SES.
Cigarettes mom smoked/day during each pregnancy trimester	1		Coded as: 0 for never; 1 for ≤10; 2 for 11-20; 3 for 21-30; 4 for 31-40; 5 for 41-50; 6 ≥51; and 9 for occasional, not every day. PM smoking is a risk factor for childhood obesity/overweight [31].
Parental smoking frequency	1-3, 5-8		Coded as: 1 for does not smoke at all; 2 for <1/day; and 3 for ≥1/day. Parental smoking has been associated with an increased risk of childhood obesity and overweight in some studies [32].
Child ate fresh fruit	2-8		Only pertains to 24 hours before the interview and is the number of times they have consumed the food/drink in question. Controlled for due to the role of diet in childhood obesity and overweight. 0 means none; 1 means once; 2 means twice; and 3 means thrice or more. These last two categories are merged into a single category coded as 2 for wave 2. Controlled for as obesity and overweight is known to be fundamentally an energy imbalance [33].
Child drank fresh juice			
Child ate raw vegetables			
Child ate cooked vegetables			
Child ate processed meat			
Child ate hot chips			
Child ate snack food			
Child ate sugary food			
Child ate full milk products			
Child ate skim milk products			
Child drank water			
Child drank SSBs[5]			
How child spends spare time	2-7		Categorized as: 1 for inactive pastimes; 2 for inactive/active pastimes equally likely; and 3 for active pastimes. Obesity and overweight is fundamentally an energy imbalance, hence why this is controlled for

			[33].
Child enjoys physical activity	3-5		Rated from 1 to 5; higher the value the more the child enjoys physical activity.
How often TV is on during meals	2.5, 3.5, 5-8		2.5/3.5 refers to data from between wave questionnaires that were sent out to parents. For these waves the variables recorded took on values of 1 (for always) to 5 (for never). A similar scale was used for the remaining waves, except with the order reversed. Between wave variables were used in the analysis of the wave that came immediately after. Known risk factor for childhood obesity and overweight [34].
Child sleep duration adequacy	6-8		Pertains to the last month and was reported by child. Coded from 1 to 5 in descending order of adequacy. Controlled for due to some studies that showed a relationship between sleep parameters and child obesity and overweight [35].
Child sleep quality			Same as for duration adequacy, except ranked in descending order of quality.
Independent variables			
PM dietary exclusion of meat	1	DC	Each of these variables are individually coded as: 0 for no; 1 for yes.
PM dietary exclusion of fish			
PM dietary exclusion of dairy			
PM dietary exclusion of eggs			
PM dietary exclusion of other foods			
Mediator variable			
Child birthweight	1	Q	Controlled for due to evidence of a correlation with child obesity risk [36–38].

Moderator variables			
PM Rx[h] iron supplement use PM OTC[i] iron supplement use PM OTC folate supplement use PM other dietary supplement use	1	DC	Each of these variables are individually coded as: 0 for no; 1 for yes. For instance, if prescription iron supplements were used the PM Rx iron supplement use variable will be recorded as 1.
Outcome and related variables			
BMI[j] z-score (BMIz)	2-8	Q	Based on US Centers for Disease Control and Prevention (CDC) and UK 1990 growth reference data [39].
BMI percentile (BMIpct)			CDC growth reference data were used to calculate these percentiles.
Weight status		MC	BMIpct<5 was classed as underweight and coded as 0; 5 ≤ BMIpct < 85 was classed as healthy weight and coded as 1; 85 ≤ BMIpct < 95 was classed as overweight and coded as 2; 95 ≤ BMIpct < 99 was classed as mild-to-moderate obesity and coded as 3; 99 ≤ BMIpct was classed as severe obesity and coded as 4 [33].
Binary weight status		DC	Calculated based on weight status. 0 corresponds to healthy weight and 1 corresponds to overweight or obesity. Underweight (defined as those with a BMI percentile of less than 5) children were excluded from the analyses involving binary weight status.

a. DC: dichotomous. These variables are categorical with two categories.

b. PM: prenatal maternal.

c. DM: diabetes mellitus.

d. This refers to waves 2 to 8. In other words, the child ate breakfast variable was recorded for waves 2, 3, 4, 5, 6, 7 and 8.

e. Q: quantitative. These variables are also continuous.

f. MC: multicategorical. These variables are categorical and have more than two categories.

g. SSBs: sugar-sweetened beverages.

h. Rx: prescription.

i. OTC: over the counter.

j. BMI: body mass index.

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Figure 1 is a flowchart describing the examined relationship between the variables. The independent variables pertaining to the PMDE were hypothesized to affect the outcome variables of weight status and BMIz, at least partially, through the mediator variable child birthweight. The moderator variables pertaining to PM dietary supplement use were hypothesized to reduce the effect of the independent variables on the outcome variables. The covariates were expected, based on previous research, to potentially affect the outcome variables too, so they must be controlled for.

Figure 1: Proposed relationship between variables.

Data cleaning

Children with missing data in the variables analyzed were excluded from the analysis. Children that had these variables recorded with nonsensical negative values that were not explained in the data dictionary were also excluded from the analysis. Multiple imputation was attempted using the mice R package as a means of filling in the missing data, but singular matrix errors prevented its use. The misty R package was used to conduct Little's Missing Completely at Random test [40]; however, the results were inconclusive due to singular matrix errors.

Statistical analysis

A p-value of < 0.05 served as the cutoff for statistical significance. Two-sided significance testing was used throughout the analysis. Regression models fitted were all fixed effects, univariate and multivariable. R version 4.3.0 and 4.3.1 were used to perform all the analyses.

Linear and logistic regression were used to test the effect of prenatal maternal dietary exclusion

on child BMIz and childhood obesity and overweight risk, respectively. To each wave for which the outcome variables were recorded, linear models (LMs) were fitted to test whether the hypothesized risk factors were correlated with child BMIz. Similarly, to each wave, multinomial logistic models (MLMs) were fitted to test whether the hypothesized risk factors were associated with weight status. The VGAM library was used to fit the MLMs. These models were used to determine whether any PMDE variables were correlated with child BMIz or overweight or obesity risk.

The LMs included as regressors the PMDE variables and all the covariates listed in Table 1. The MLMs included as regressors the PMDE variables, current parental BMI, wave 1 maternal BMI, and child age.

Univariate moderation analysis was conducted using version 4.3 of the PROCESS R macro developed by Andrew F. Hayes [41] with the outcome variables of BMIz and binary weight status. When binary weight status was the outcome variable, underweight children were excluded from the analysis because this allowed the two categories used in the analysis to be overweight/obese and healthy weight. Univariate mediation analysis was conducted using the method described in Iacobucci (2012) [42] with outcome variables of BMIz and weight status.

Results

Participant demographics

Table 2 summarizes the demographics of the participants before and after cases with missing data removed. Indigenous Australian children were found to be under-represented in the sample across all waves after excluding cases with missing data, suggesting that the data were likely not

183 missing completely at random. Table 3 summarizes the missing values for variables of interest.

184 **Table 2: Demographics of participants included in analysis before/after excluding subjects with missing data.**

Characteristic \ Wave	1	2	3	4	5	6	7	8
Number	5,107 / 3,887	4,606 / 1,008	4,386 / 918	4,242 / 953	4,085 / 1,145	3,764 / 1,073	3,381 / 798	3,127 / 891
Age in years, median (IQR)	0.769 (0.296) / 0.769 (0.290)	2.85 (0.326) / 2.84 (0.315)	4.84 (0.325) / 4.83 (0.285)	6.84 (0.416) / 6.84 (0.389)	8.92 (0.422) / 8.90 (0.397)	10.9 (0.485) / 10.9 (0.498)	13.0 (0.518) / 12.9 (0.470)	14.8 (0.456) / 14.8 (0.444)
Indigenous children, no (%)	230 (4.50) / 126 (3.24)	180 (3.90) / 5 (0.496)	149 (3.40) / 6 (0.654)	145 (3.42) / 10 (1.05)	139 (3.40) / 12 (1.05)	106 (2.82) / 9 (0.839)	87 (2.57) / 5 (0.627)	79 (2.53) / 8 (0.898)
Male sex, no (%)	2,608 (51.1) / 2,010 (51.7)	2,349 (51.0) / 512 (50.79)	2,251 (51.3) / 463 (50.4)	2,187 (51.6) / 499 (52.4)	2,096 (51.3) / 558 (48.7)	1,929 (51.2) / 531 (49.5)	1,734 (51.3) / 401 (50.3)	1,606 (51.4) / 452 (50.7)
Child born in Australia, no (%)	5,088 (99.6) / 3,874 (99.7)	4,589 (99.6) / 1,005 (99.7)	4,370 (99.6) / 915 (99.7)	4,227 (99.6) / 949 (99.6)	4,070 (99.6) / 1,140 (99.6)	3,749 (99.6) / 1,071 (99.8)	3,371 (99.7) / 796 (99.7)	3,117 (99.7) / 888 (99.7)
Mom born in Australia, no (%)	3,989 (78.1) / 3,084 (79.3)	3,632 (78.9) / 819 (81.3)	3,494 (79.7) / 749 (81.6)	3,388 (79.9) / 771 (80.9)	3,262 (79.9) / 934 (81.6)	3,010 (80.0) / 859 (80.1)	2,724 (80.6) / 639 (80.1)	2,514 (80.4) / 718 (80.6)
Dad born in Australia, no (%)	3,526 (69.0) / 2,798 (72.0)	3,260 (70.8) / 785 (77.9)	3,156 (72.0) / 728 (79.3)	3,070 (72.4) / 767 (80.5)	2,971 (72.7) / 885 (77.3)	2,765 (73.5) / 827 (77.1)	2,514 (74.4) / 630 (78.9)	2,316 (74.1) / 689 (77.3)
Underweight, no (%)	NA[a]	124 (2.69) / 29 (2.88)	144 (3.28) / 30 (3.27)	126 (2.97) / 29 (3.04)	96 (2.35) / 28 (2.45)	117 (3.11) / 33 (3.08)	105 (3.11) / 23 (2.88)	85 (2.72) / 19 (2.13)
Overweight, no (%)		828 (18.0) /	826 (18.8) /	607 (14.3) /	580 (14.2) /	539 (14.3) /	510 (15.1) /	494 (15.8) /

		185 (18.4)	188 (20.5)	121 (12.7)	151 (13.2)	151 (14.1)	101 (12.7)	130 (14.6)
Mild-to-moderate obesity, no (%)		456 (9.90) / 78 (7.74)	414 (9.44) / 71 (7.73)	309 (7.28) / 52 (5.46)	348 (8.52) / 77 (6.72)	322 (8.55) / 69 (6.43)	267 (7.90) / 50 (6.27)	251 (8.03) / 51 (5.72)
Severe obesity, no (%)		178 (3.86) / 32 (3.17)	166 (3.78) / 26 (2.83)	83 (1.96) / 10 (1.05)	50 (1.22) / 9 (0.786)	30 (0.797) / 5 (0.466)	32 (0.946) / 4 (0.501)	45 (1.44) / 8 (0.898)
a. NA: not applicable. It is not applicable as the definition of these unhealthy weight statuses used in this study cannot be used for wave 1, as in wave 1 BMI percentile was not recorded.								

185 **Table 3: Number of cases with missing values for independent and dependent variables.**

Variable \ Wave	1	2	3	4	5	6	7	8 186
BMIz and BMI percentile	NA	84	62	50	87	192	212	200
PME[a] of meat	45	NA						
PME of fish								
PME of dairy								
PME of eggs								
PME of other foods								
a. PME: prenatal maternal exclusion (from diet).								

187

188 ## Effect of PMDE on BMIz

189 None of the effects of PMDE variables on child BMIz were statistically significant.

190 ## Effect of PMDE on weight status

191 Table 4 shows that the PM exclusion (PME) of other foods from the diet, when associated with a
192 different odds ratios of unhealthy weight status, was universally associated with a lower rate of
193 unhealthy weight statuses. The PME of meat was not significantly associated with child weight
194 status. The PME of dairy was associated with a higher rate of underweight in wave 5 and a lower
195 rate of overweight in wave 8. The PME of fish was associated with a higher rate of underweight
196 in wave 8 and mild-to-moderate obesity in wave 4. The PME of egg was associated with a higher
197 risk of overweight during wave 8. Finally, the PME of other foods was associated with a lower
198 risk of overweight in wave 3, mild-to-moderate obesity in wave 5, and underweight, and mild-to-
199 moderate obesity in wave 7.

200 **Table 4: Effect of PMDE on weight status odds ratio (95% confidence interval are indicated in parentheses).**

Variable\Wave	2	3	4	5	6	7	8
Sample size	1,008	918	953	1,145	1,073	798	891
PME[a] of meat	NS[b]	NS	NS	NS	NS	NS	NS
PME of fish	NS	NS	MTMO:[c] 3.424 (1.338, 8.764)	NS	NS	NS	UW:[d] 4.154 (1.121, 15.39)
PME of dairy	NS	NS	NS	UW:[e] 5.560 (1.813, 17.05)	NS	NS	OW:[e] 0.3530 (0.1253, 0.9947)
PME of egg	NS	NS	NS	NS	NS	NS	OW: 5.320 (2.023, 13.99)
PME of other foods	NS	OW: 0.6010 (0.4209, 0.8584)	NS	MTMO: 0.5681 (0.3264, 0.9887)	NS	UW: 0.3527 (0.1246, 0.9988) MTMO: 0.4363 (0.2078, 0.9163)	NS

a. PME: prenatal maternal exclusion.

b. NS: nonsignificant.

c. MTMO: mild-to-moderate obesity.

d. OW: overweight.

e. UW: underweight.

201

Mediation analysis

None of the mediation effects were statistically significant.

Moderation analysis

As shown in Table 5, all significant moderation effects on BMIz involved folate supplementation and meat or fish exclusion and lead to higher BMIz. Specifically, the moderation effect of folate supplementation on the effect of PM meat exclusion was associated with increased BMIz in wave 4. The moderation effect of folate supplementation on the effect of PM fish exclusion was associated with increased BMIz in waves 2 and 6.

Over-the-counter (OTC) iron supplementation had a moderation effect on PM meat exclusion that was associated with an increased risk of overweight or obesity in wave 6. OTC iron supplementation also had a moderation effect on the PME of fish that was associated with an increased risk of overweight or obesity in wave 6. OTC iron supplementation also had a moderation effect on the PME of egg that was associated with a reduced risk of overweight or obesity in wave 2 and an increased risk in wave 4. The moderation effect of folate supplementation on the PME of fish was associated with an increased risk of overweight and obesity in waves 4 to 6. Folate supplementation had a moderation effect on the PME of egg that was associated with an increased risk of overweight and obesity in wave 4. Folate supplementation also had a moderation effect on the PME of other foods that was associated with an increased risk of overweight and obesity in wave 5. Finally, dietary supplementation had a moderation effect on the PME of meat that was associated with a lower risk of overweight and obesity in wave 7.

223 **Table 5: Moderation effects of prenatal maternal dietary supplement use on prenatal maternal dietary exclusion (95%**

224 **confidence intervals are indicated in parentheses).**

Moderation effect\Wave	2	3	4	5	6	7	8
Sample size for BMIz analysis	1,008	918	953	1,145	1,073	798	891
PMEM[a]×OTCFe[b]→BMIz	NS[c]	NS	NS	NS	NS	NS	NS
PMEM×Folate[d]→BMIz	NS	NS	0.4710 (0.0080, 0.9341)*	NS	NS	NS	NS
PMEM×DietS[f]→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEM×RxFe[g]→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEF[h]×OTCFe→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEF×Folate→BMIz	0.5104 (0.0389, 0.9819)	NS	NS	NS	0.5550 (0.0678, 1.042)	NS	NS
PMEF×DietS→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEF×RxFe→BMIz	NS	NS	NS	NS	NS	NS	NS
PMED×OTCFe→BMIz	NS	NS	NS	NS	NS	NS	NS
PMED×Folate→BMIz	NS	NS	NS	NS	NS	NS	NS
PMED×DietS→BMIz	NS	NS	NS	NS	NS	NS	NS

PMED×RxFe→BMIz	NS	NS	NS	SME[j]	SME	SME	SME
PMEE[i]×OTCFe→BMIz	SME	NS	NS	NS	NS	NS	NS
PMEE×Folate→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEE×DietS→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEE×RxFe→BMIz	NS	NS	NS	SME	NS	SME	SME
PMEO[k]×OTCFe→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEO×Folate→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEO×DietS→BMIz	NS	NS	NS	NS	NS	NS	NS
PMEO×RxFe→BMIz	NS	NS	NS	NS	NS	NS	NS
Sample size for BMIz analysis	979	888	924	1,117	1,040	775	872
PMEM×OTCFe→BWS[l]	NS	SME	NS	NS	4.892 (1.092, 21.91)	NS	SME
PMEM×Folate→BWS	NS	SME	NS	NS	NS	NS	SME
PMEM×DietS→BWS	NS	SME	NS	NS	NS	0.0899 (0.0085, 0.9486)	SME
PMEM×RxFe→BWS	NS	SME	NS	SME	SME	NS	SME
PMEF×OTCFe→BWS	NS	SME	NS	NS	5.509 (1.437, 21.11)	NS	SME

PMEF×Folate→BWS	NS	SME	5.828 (1.201, 28.28)	5.198 (1.291, 20.93)	3.976 (1.004, 15.76)	NS	SME
PMEF×DietS→BWS	NS	SME	NS	NS	NS	NS	SME
PMEF×RxFe→BWS	NS	SME	NS	NS	SME	NS	SME
PMED×OTCFe→BWS	NS	SME	NS	NS	NS	NS	SME
PMED×Folate→BWS	NS	SME	NS	NS	NS	NS	SME
PMED×DietS→BWS	NS	SME	NS	NS	NS	NS	SME
PMED×RxFe→BWS	SME	SME	SME	SME	SME	SME	SME
PMEE×OTCFe→BWS	0.0790 (0.0067, 0.9374)	SME	17.96 (1.685, 191.5)	NS	SME	NS	SME
PMEE×Folate→BWS	NS	SME	17.78 (1.172, 269.8)	NS	SME	SME	SME
PMEE×DietS→BWS	NS	SME	NS	NS	NS	NS	SME
PMEE×RxFe→BWS	SME	SME	SME	SME	SME	SME	SME
PMEO×OTCFe→BWS	NS	SME	NS	NS	NS	NS	SME
PMEO×Folate→BWS	NS	SME	NS	2.716 (1.109, 6.651)	NS	NS	SME
PMEO×DietS→BWS	NS	SME	NS	NS	NS	NS	SME
PMEO×RxFe→BWS	NS	SME	SME	NS	NS	NS	SME

a) PMEM: prenatal maternal (PM) exclusion of meat from diet.

b) OTCFe: PM over the counter (OTC) iron supplement use.

c) NS: nonsignificant.

d) Folate: OTC folate supplement use.

e) Moderation effects involving BMIz should be interpreted as how much the BMIz changes with each one unit increase in the moderator (which appears after the multiplication sign) when the independent variable is held constant at 1.

f) DietS: OTC use of other dietary supplements.

g) RxFe: prescription use of iron supplements.

h) PMEF: PM exclusion of fish from diet.

i) PMEE: PM exclusion of egg from diet.

j) SME: singular matrix errors.

k) PMEO: PM exclusion of other foods from diet.

l) BWS: binary weight status. Moderation effects with BWS as the outcome variable are all given as odds ratios of overweight/obesity relative to the reference category of healthy weight.

225

Discussion

Key results

No association was found between PMDE and child BMIz, except with regard to other foods in wave 6.

The PME of meat was not associated with any change in the risk of unhealthy weight statuses such as overweight and obesity at any stage of childhood. When the PME of fish and eggs was associated with a different odds of unhealthy weight statuses, it was associated with higher odds. When PME of other foods was associated with a different risk of unhealthy weight statuses, it was associated with lower odds. The effects of the PME of dairy were more mixed.

No mediation effect on BMIz and weight status was observed. This finding suggested that child birthweight did not play a significant role in mediating the effects of PMDE on child BMIz and overweight/obesity risk. Moderation effects involving PM dietary supplementation were associated with higher BMIz and usually were associated with a higher risk for overweight/obesity, although exceptions exist. Most significant moderation effects involved folate or iron supplementation, although one involving other dietary supplements was observed.

Limitations

This study had numerous limitations. Among them, data had to be assumed to be missing completely at random, which was apparently false (Table 2). Some ethnic minorities were apparently under-represented in the cleaned data set, and the possibility that dietary exclusion was for medical reasons cannot be controlled for. The effect of dietary exclusion also cannot be

controlled at different stages of pregnancy, despite the known differences in the effect of fetal malnutrition at different stages of pregnancy. This finding was based on an observational study, so causal inferences cannot be made according to these results.

Interpretation

The PME of meat likely has no effect on childhood obesity or overweight risk. The PME of fish may be associated with an increased risk of mild-to-moderate obesity at ages 6 or 7 years and underweight at ages 14 or 15 years. The PME of egg may be associated with an increased risk of overweight at ages 14 or 15 years. The PME of dairy appears to be associated with a more mixed effect on child unhealthy weight status risk, with a higher risk of underweight at age 8 or 9 years and a lower risk of overweight at age 14 or 15 years. The PME of other foods appears to be associated with a lower risk of unhealthy weight status, specifically with a lower risk of overweight at age 4 or 5 years, mild-to-moderate obesity at age 8 or 9 years, and underweight and mild-to-moderate obesity at age 12 or 13 years. PM dietary supplement use had a mixed effect on this relationship and was sometimes associated with higher risks of child unhealthy weight status.

Keeping in mind the data came from an observational study, these results generally indicated that fish and egg were probably food items that were beneficial for expectant mothers to consume. Perhaps this finding was due to eggs and fish having nutrients unique to them that are important for preventing the development of childhood obesity. These nutrients are likely not vitamin B12, choline, iron, or zinc, because other animal products also contain these nutrients. Further studies are needed to identify these nutrients. The exclusion of food items besides dairy, egg, meat, and fish from the mother's prenatal diet was likely beneficial to the child. Further studies are needed

268 to clarify exactly which food items, when excluded from the mother's diet during pregnancy,
269 have a beneficial effect on the child's risk of becoming overweight or obese. There is the
270 possibility that these food items are highly processed and calorically dense, however, it is
271 important to note that this assertion remains speculative until further research is conducted.
272 Dietary supplements did not appear to reduce the risk of unhealthy weight status associated with
273 dietary exclusion. However, this data set recorded only whether these supplements were used
274 during pregnancy, not when, their quantity, frequency of use, nor any underlying conditions they
275 were taken to treat. These observations supported the hypothesis that iron may be an important
276 micronutrient during pregnancy when deciding the child's later weight status. The observed
277 effect may be due to an underlying deficiency of iron that these supplements were meant to treat.

278 The human studies most closely identified with this one are those involving dietary supplements
279 or adherence to a Mediterranean diet and their effect on childhood obesity or overweight risk
280 [14,43]. Adherence to a Mediterranean diet is not correlated with BMIz or childhood obesity or
281 overweight risk but is associated with lower waist circumference, another measure of child
282 adiposity. The Mediterranean diet is rich in fish, olive oil, fruits, vegetables, and unprocessed
283 cereals and is moderate in lean meat and dairy [44]. The current work corroborated the
284 importance of the fish component of the Mediterranean diet. Dietary supplements were found to
285 have no impact on childhood obesity and overweight risk. Thus, the effect of dietary
286 supplements may depend on the mother's diet. More studies should ideally investigate whether
287 the mother's nutritional status impacts this effect.

288 These findings can, if corroborated by further studies that can be better control for possible
289 confounders, lead to changes to the Australian Government's campaign for the healthy

pregnancy that explicitly recommend pregnant women not to abstain from egg and fish during pregnancy. Hopefully, future studies will ascertain exactly what components of these foods are essential for preventing childhood obesity and overweight in the offspring. This information can be used to ensure that women who abstain from these foods for ethical, health, or other reasons still be able to provide their babies with the nutrition they need for the best possible start in life.

Generalizability

This study was solely conducted within the Australian context. Hence, the results probably cannot be generalized to other populations.

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440

4.3 Implications

This paper illustrates the importance of fetal nutrition to the later development of childhood obesity and overweight. It also illustrates the complexity of fetal nutrition as dietary supplements did not clearly reduce the risk of childhood obesity and overweight. The importance of fetal nutrition in contributing to childhood obesity and overweight risk clearly substantiates the FOAD hypothesis given that childhood obesity and overweight is a risk factor for adult obesity and overweight (Di Cesare et al., 2019). Many medications are known to interfere with nutrient absorption or utilization, and hence, finding an effect for dietary exclusion lends credence to the notion that prenatal maternal medication consumption may contribute to childhood obesity and overweight.

CHAPTER 5: PAPER 3: THE EFFECT OF PRENATAL MATERNAL MEDICATION ON CHILDHOOD OBESITY AND OVERWEIGHT

5.1 Introduction

Prenatal maternal exposure to some medications and medication classes have been examined as possible risk factors for childhood obesity and overweight. Among those medications and medication classes are metformin (Fornes et al., 2022), antifungals (Cassidy-Bushrow et al., 2018), and antibiotics (Cassidy-Bushrow et al., 2018). Although there are other classes of medications that have not been studied in this context, despite reason to suspect they may have an effect, including that many medications are known to inhibit the absorption and utilization of certain nutrients, including nutrients involved in one-carbon metabolism, which is known to programme susceptibility to obesity and overweight (Fall & Kumaran, 2019). Whether birthweight plays a mediating role and whether dietary supplements play a moderating role in these relationships has not been studied. In the following study, these effects were investigated using data from the LSAC.

5.2 Submitted paper

The effect of prenatal maternal medication on childhood obesity and overweight

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Abstract and keywords

Background

The effects of fetal exposure to certain medications on childhood overweight or obesity risk have been studied, but the effects of several other classes have remained understudied. Mechanisms for these effects remain understudied. Whether dietary supplements can protect against these effects is unstudied.

Methods

The Longitudinal Study of Australian Children (LSAC) dataset was used. LSAC had 5,107 participants. Linear models and multinomial logistic models were used to examine the effect of prenatal maternal medication use on child body mass index z-score (BMIz) and weight status, respectively. Moderation analysis was conducted to investigate moderating effects of dietary supplements. Mediation analysis was used to determine whether child birthweight mediated the effect of medication use on BMIz or weight status.

Results

Prenatal maternal medication use was only ever associated with a lower child BMIz. For instance, prescription heartburn medications were associated with a 1.083 (95% confidence interval (CI): 0.421 to 1.745) reduction in child BMIz in wave 3. Aside from antibiotics, for which the effect was more mixed, other medications were only ever associated with higher risks of unhealthy weight status. For instance, over-the-counter cold and flu medicines were associated with a 5.703-fold (95% CI: 1.088 to 29.9) increase in underweight risk in wave 2. Dietary supplements did not protect against the effect of prenatal maternal medication use.

Conclusions

Aside from antibiotics, prescription antiemetics, prescription heartburn medicines, over-the-

counter analgesics, and other over-the-counter (OTC) medicines not listed in LSAC, medications should be avoided by pregnant mothers to minimize the risk of obese, overweight, or underweight children. OTC dietary supplement use is likely unhelpful when medication use during pregnancy cannot be avoided. Better designed and controlled studies should ideally be conducted to confirm that the effects observed were causal and not the result of uncontrolled confounders.

Keywords: Prenatal Exposure Delayed Effects, risk factors, Longitudinal Studies.

Introduction

The prevalence of childhood obesity and overweight has been on the rise across the world in recent decades, and contributing to cardiovascular disease, certain cancers, type 2 diabetes,[1] school absenteeism[2] and poor academic performance.[3] In Australia in particular almost a quarter of children were overweight or obese between 2017 and 2018.[4] Consequently, identifying childhood obesity and overweight risk factors, their underlying mechanisms and protective factors is imperative, in order to effectively combat this public health crisis.

The effect of prenatal maternal use of certain medications including antibiotics,[5] antifungals[6] and metformin[7] on childhood obesity and overweight risk or body mass index z-score (BMIz) has been examined in some studies. Although whether prenatal maternal use of dietary supplements impacts upon the effects of these medications has not been examined, nor has whether prenatal maternal use of thyroid medications, antiemetics, asthma medications, antihypertensives and antidepressants impacts upon childhood obesity or overweight risk. Possible mechanisms by which medications could conceivably predispose children exposed *in utero* to them to obesity and overweight include through altering lipid and glucose metabolism (especially in the case of the glucocorticoids occasionally used to treat asthma)[8,9] and inhibiting the absorption and utilization of essential nutrients such as

folate and cobalamin[10–12] leading to fetal malnutrition. This malnutrition could program the fetus to be best adapted to a postnatal environment where food is scarce under the developmental origins of health and disease (DOHaD) hypothesis. A study on Wistar rats also supports the hypothesis that fetal exposure to fluoxetine may be associated with an increased risk of obesity.[9] Consequently, there is a research gap that this study investigated. Data form the Longitudinal Study of Australian Children (LSAC) was used to address this gap. In this Australia-wide study, measurements on children were collected biennially from the age of less than two years beginning in 2004. The primary caregiver – usually the mother – provided many other pieces of information about the child as part of interviews conducted during the study.

The purpose of this study was to investigate whether prenatal maternal use of certain categories of medication impacted upon the child's risk of developing obesity or overweight as well as their BMIz. The possible mediating effect of child birthweight – a measure of fetal nutritional adequacy – was also examined in the context of these effects. The possible moderating effect of prenatal maternal use of dietary supplements was examined, due to the hypothesis that the effects of medications on childhood obesity and overweight risk may be mediated by alterations in the absorption and utilization of nutrients.

Methods

This study received the approval of the University of Southern Queensland (UniSQ) Human Research Ethics Committee with the project ID ETH2023-0175. UniSQ has no institutional review board (IRB).

Data source

Data from LSAC was used in this study. LSAC's design has been detailed in other sources,[13] but briefly, it started in 2004 and is a biennial cohort study. It consists of two cohorts: B

cohort (for "baby") and K cohort (for "kindergarten"). Cohort B was used for this study as it was the only cohort with the required prenatal maternal details. Both cohorts had their sample obtained using two-stage cluster sampling. The B cohort started with 5,107 participants; however, some were lost to follow up in subsequent waves. LSAC received its ethics approval from the Australian Institute of Family Studies Ethics Committee. Written consent was obtained from the parents of all the children who participated in the study.

Many of the variables used in the analysis were obtained by interviews of the child's primary caregiver conducted by trained interviewers. A portable rigid stadiometer was used to measure the child's height to the nearest 0.1 centimetres. Glass bathroom scales were used to measure the child's mass to the nearest 50 grams when the child was wearing light clothing. These measurements were used to calculate the child's body mass index (BMI).

Variables

The outcome variables used in this study were child BMIz and weight status in different waves. Prenatal maternal medication use variables were used as the independent variables. Variables pertaining to dietary supplement use were used as moderator variables. Child birthweight was used as a mediator variable. The independent variables, moderator variables and mediator variable were all recorded in wave 1 only. The outcome variables were only recorded for waves 2-8. The variables used in the analysis are explained in Table 1.

It is expected that prenatal maternal medication use will be correlated with the outcome variables and produce at least some of this effect through its impact on child birthweight. It is also believed that prenatal maternal dietary supplement use will act as a moderating factor in this relationship. The covariates listed in Table 1 are also expected to be correlated with the outcome variables.

Data cleaning

Participants who had missing data or nonsensical (and unexplained) negative values in the variables analyzed were excluded from the analysis. An attempt to fill in missing values using multiple imputation with the mice R package was made but failed due to singular matrix errors. To check whether missing values were missing completely at random (MCAR), Little's MCAR test[35] was conducted using the misty R package but yielded inconclusive results due to singular matrix errors.

Statistical analysis

The analysis was conducted in R version 4.3.0 and 4.3.1. Hypothesis tests used a threshold of $p<0.05$ and were two-sided. Regression models were univariate, fixed-effects and multivariable.

Linear and logistic regression were used to test the effect of prenatal maternal medication on child BMIz and childhood obesity and overweight risk, respectively. Linear models (LMs) were used when the outcome variable was BMIz, and multinomial logistic models (MLMs) fitted with the VGAM R library were used when the outcome variable was the multicategorical version of weight status. LMs and MLMs were fitted to each wave individually to test the relationship between the independent and outcome variables. In other words, the LMs and MLMs were used to test whether prenatal maternal medication impacts upon child BMIz and childhood overweight and obesity risk, respectively.

Version 4.3. of Andrew F. Hayes' PROCESS macro[36] was used to conduct the univariate moderation analysis with BMIz and binary weight status as outcome variables. When binary weight status was the outcome variable underweight children were excluded from the dataset prior to analysis was conducted. This was done so that the reference category could be healthy weight and the other category could represent overweight or obesity. The

technique outlined in Iacobucci (2012)[37] was used to conduct univariate moderation analysis with BMIz and weight status as outcome variables.

Results

Participant demographics

Table 2 summarizes the demographics of participants before and after cases with missing data were removed. It does appear that Indigenous Australian children are underrepresented in the sample after data cleaning, suggesting that data is not missing completely at random. Table 3 shows the number of participants with missing values for the variables of interest.

Effect of prenatal maternal medication use on child BMIz

Table 4 summarizes the effect of prenatal medication use on child BMIz. As can be seen, no medication has an effect across more than one wave of childhood. All correlations were with lower child BMIz. Prescription heartburn medication appeared to be correlated with child BMIz at age 4 or 5 years (wave 3), thyroid medication and over-the-counter asthma medication appeared to be correlated with child BMIz at age 6 or 7 years (wave 4) and other prescription-only medication was correlated with child BMIz at age 14 or 15 years (wave 8).

Effect of prenatal maternal medication use on weight status

As can be seen in Table 4, the correlation between prenatal maternal antibiotic use and weight status seems mixed. At age 4 or 5 years (wave 3) it is associated with both a lower risk of overweight and a higher risk of severe obesity, while at age 10 or 11 years (wave 6) it is associated with a lower risk of mild-to-moderate obesity and at age 14 or 15 years (wave 8) it is associated with an increased risk of overweight. Diabetes and hypertension medication use were associated with an increased risk of underweight at age 12 or 13 years (wave 7) and age 14 or 15 years (wave 8), respectively. Prescription asthma medication use was associated

with an increased risk of being overweight at age 6 or 7 years (wave 4) and mild-to-moderate obesity at age 10 or 11 years (wave 6). Prescription antidepressant use was associated with an increased risk of underweight at age 4 or 5 years (wave 3) and at age 12 or 13 years (wave 7) and an increased risk of mild-to-moderate obesity at ages 12 to 15 years (waves 7 and 8). Thyroid medication use was associated with an increased risk of underweight at age 12 or 13 years (wave 7) and overweight at age 14 or 15 years (wave 8). Other prescription medicines were associated with an increased risk of severe obesity at age 6 or 7 years (wave 4) and underweight at age 10 to 13 years (waves 6 and 7). Over-the-counter herbal remedies and asthma medications were associated with an increased risk of underweight at age 12 or 13 years (wave 7) and 2 or 3 years (wave 2), respectively. Over-the-counter cold and flu remedies were associated with an increased risk of being underweight at age 2 or 3 years (wave 2) and overweight at age 6 or 7 years (wave 4). Prescription heartburn and antiemetic medications and over-the-counter analgesic and anti-allergy medications, along with over-the-counter medications not otherwise classified (i.e., those placed in the other over-the-counter medicines category) were not significantly associated with weight status.

Mediation analysis

There were no significant mediation effects detected. Although singular matrix errors prevented some of the required models from being fitted for wave 4.

Moderation analysis

As can be seen in Table 5, all significant moderation effects involving the outcome variable of weight status involved iron and folate supplementation and all but one involved over-the-counter medicines. This exception was at age 12 or 13 years (wave 7) and involved the effect of an iron prescription on other prescription-only medicines, which appeared to be correlated with a higher risk of unhealthy weight status (underweight, overweight, or obese).

Prescription use of iron supplements were also involved in two other significant moderation effects with binary weight status as the outcome variable, both were at age 2 or 3 years (wave 2). One was associated with a lower risk of unhealthy weight status and involved over-the-counter analgesics, while the other was associated with an increased risk of unhealthy weight status and involved over-the-counter heartburn medicines. There was also an over-the-counter iron supplement effect on the effect of herbal preparations on binary weight status that was associated with a lower risk of unhealthy weight status. Folate supplementation, when it was associated with a moderation effect on binary weight status (at age 2 or 3 years with respect to other over-the-counter medicines and at age 6 or 7 years with respect to anti-allergy medicines), was associated with a lower risk of unhealthy weight status.

All categories of dietary supplements were involved in moderation effects with BMIz as the outcome variable. When prescription iron was associated with a moderation effect with BMIz as the outcome variable, it was generally associated with lower child BMIz, however, at age 10 or 11 years (wave 6), it was associated with an increased BMIz in children born to mothers taking over-the-counter heartburn medicines during pregnancy. Over-the-counter iron supplementation was associated with higher child BMIz when it was associated with a significant moderation effect on child BMIz. Folate supplementation, when associated with a moderation effect involving the outcome variable of child BMIz, was usually associated with higher child BMIz, although at age 12 or 13 years (wave 7) with respect to other prescription medicines it was associated with lower child BMIz. The use of other over-the-counter dietary supplements was usually associated with lower child BMIz when an association involving a moderation effect reached statistical significance, except at ages 12 to 15 years (waves 7 and 8) and with respect to cold/flu remedies and anti-allergy remedies, respectively, when it was associated with higher child BMIz.

Discussion

Key results

All associations between prenatal maternal medication use and child BMIz involved lower child BMIz and involved prescription heartburn medication and thyroid medication, as well as other prescription medicines and over-the-counter asthma medications.

Associations between prenatal maternal medication use and weight status were more complicated. Most involved higher risks of unhealthy weight statuses, although when it came to antibiotics an association with a lower risk of being overweight at age 4 or 5 years (wave 3) and mild-to-moderate obesity at age 10 or 11 years (wave 6) was observed. The following associations were only observed at certain ages, the specifics are omitted as they were detailed in the results section. Diabetes medications, antihypertensives, herbal preparations and over-the-counter asthma medications were all associated with an increased risk of being underweight but had no effect on overweight or obesity risk. Prescription asthma medication use, and over-the-counter heartburn medication use were associated with increased overweight or obesity risk only. Antidepressant use, thyroid medication use, other prescription medication use and cold or flu medication use were all associated with an increased risk of both underweight and overweight/obesity. In fact, fetal exposure to antidepressants at age 12 or 13 years (wave 7) was associated with both increased underweight and mild-to-moderate obesity risk.

No significant mediation effects were detected. Moderation effects were largely associated with a higher risk of overweight or obesity, except at age 2 or 3 years (wave 2) with respect to prescription iron and over-the-counter analgesics wherein the risk was reduced.

Limitations

One limitation of this study inherent to using data from an observational study was that causal inferences cannot be drawn from the results.

Another important limitation of this study is that many of the conditions for which these medications are used to treat could not be controlled for as possible causes of any effects observed. For instance, it cannot be determined with certainty whether the observed effect of prenatal maternal antibiotic use was caused by the antibiotics or by the infection the antibiotics were intended to treat. This is an important caveat, partly because other studies have suggested that any observed effect of prenatal maternal antibiotic use on childhood obesity or overweight risk is likely due to the underlying infection and not antibiotics themselves.[5]

Additionally, the stage of pregnancy during which the medications were used was not recorded, which is an important caveat given that the Dutch famine study found that undernutrition's effect on obesity risk in the offspring was affected by the stage of pregnancy the child was exposed to the undernutrition.[38] In addition, the duration and extent of the exposure, and the exact medication the children were exposed to *in utero* was not recorded, which muddied the results obtained and made it impossible to examine dose-response relationships.

Furthermore, some known risk factors, such as gestational weight gain, could not be controlled for and others had to be imperfectly controlled, such as maternal BMI during pregnancy, which had to be controlled for using the mother's BMI at wave 1 (child age 0 or 1 years), the closest variable in the data set.

For the analysis to be valid, it was necessary to presume that missing data had to be assumed to be missing completely at random (MCAR), despite some evidence suggesting this

assumption was violated.

Interpretation

Prescription heartburn medication can include proton-pump inhibitors, which are known to block the absorption of certain nutrients like vitamin B12.[39] The Dutch famine study revealed that malnutrition during late pregnancy was associated with a lower risk of obesity in the offspring,[38] hence providing a possible explanation for the association with lower BMIz at age 4 or 5 years (wave 3). Additionally, thyroid hormones regulate metabolism so an association with lower child BMIz at age 6 or 7 years (wave 4) is not completely unexpected. The effect of other prescription medicines on child BMIz is more difficult to explain given that the specific medications used were not recorded. One class of prescription medicines not included in the other categories was antiepileptics, some of which are known to interfere with the uptake and utilization of B group vitamins like folate (for example, lamotrigine[40]), which, if it occurred in later pregnancy, could explain the observed association with lower child BMIz at age 14 or 15 years (wave 8). The observed effect of over-the-counter asthma medications is less easy to explain, given that over-the-counter asthma medications are typically inhalers of short-acting β_2-adrenoceptor agonists.

The associations between other medications and unhealthy weight statuses can be challenging to explain without further data recorded on possible mechanisms. For example, the association between antibiotic use and unhealthy weight statuses could be result of the underlying infection, effects on the child's microbiome or due to effects on nutrient absorption and utilization. Overall, this data seems to suggest that medication use during pregnancy should largely be avoided – with the possible exceptions of antibiotics (due to the mixed effect on weight status), prescription antiemetics, over-the-counter analgesics, over-the-counter anti-allergy medication and over-the-counter medications that were not specifically categorized in this study.

Child birthweight does not appear to mediate the effect of any medication class on unhealthy weight status risk or BMIz. Dietary supplements appear to be largely associated with a higher risk of overweight or obesity, except for prescription iron supplements when taken by mothers using over-the-counter analgesics. All the specific medications with a mitigating effect were, surprisingly, over-the-counter medications. No protective effect was observed for prescription medications. Consequently, it does not appear prudent for dietary supplements to be used by pregnant women to prevent their children's overweight or obesity due to medication use.

Conflicts of interest

There are no conflicts of interests that the authors have to disclose.

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Author contributions

The first draft of this manuscript was prepared by Brenton Horne. Brenton Horne also came

up with the original idea for the study and its method and conducted the analysis. Enamul Kabir and Khorshed Alam provided supervision to Brenton Horne's research and revised his draft of this paper.

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Table 1: Variables used in study.

Variables	Waves	Type	Description and/or justification
Covariates			
PM[a] DM[b]	1	DC[c]	Gestational DM is a risk factor for childhood obesity/overweight.[14] Coded as: 1 for yes and 2 for no.
PM depression/anxiety/stress			Coded similarly to PM DM. Risk factor for childhood obesity/overweight.[15,16]
PM hypertension			Coded similarly to PM DM. Risk factor for childhood obesity/overweight.[14,17]
Child sex			Coded as 1 for male and 2 for female. Sex differences in childhood obesity/overweight risk.[18]
Child has sleep issues	1-8		Coded as: 0 for yes and 1 for no. Controlled due to the role sleep has in childhood obesity/overweight risk.[19,20]
Child ate breakfast	2-8		Pertains to the day of the interview. Coded similarly to "child has sleep issues". Answer given by primary caregiver for waves 1-5 and by child for waves 6-8. Skipping breakfast is associated with higher childhood obesity/overweight risk.[21,22]
Maternal age at child's birth	1	Q[d]	Correlated with child BMIz in some studies.[23]
Maternal BMI at wave 1			Controlled for as a proxy for pre-pregnancy maternal BMI, which is correlated with childhood obesity/overweight risk.[14,23]
Breastfeeding cessation age	1-3		The current age is used if the child is still breastfeeding. Breastfeeding is protective against childhood obesity/overweight.[24]
Parental warmth	1-8		Pertains to last 6 months. Average of the parent has (rated 1-5 in ascending order of frequency): held/hugged the child for no specific reason; had close moments with the child; enjoyed listening/doing things with the child; told the

			child how happy they make them; expressed physical affection for the child; and felt close to the child when the child was upset. Parenting style has been found to play a role in childhood obesity/overweight in some studies, hence why it is controlled for.[25]
Child age			Controlled due to age-related disparities in childhood obesity/overweight prevalence.[26]
Parental weekly income			Part of socioeconomic status (SES). SES has been associated with childhood obesity/overweight risk in some studies.[27]
Parental hostility version 3	2-3		Pertains to last 6 months. Average of the parent has (rated 1-10 in ascending order of frequency): lost their temper with the child; shouted at the child; and been angry with the child. Due to the role of parenting style in childhood obesity/overweight.[25]
Days/week ≥30 mins exercise	7-8		Information provided by and pertained to the child. Physical activity of at least moderate intensity is included in this. Obesity/overweight is fundamentally the result of an energy imbalance, hence why this is controlled for.
Days/week ≥60 mins exercise			
Child alcohol consumption			The number of drinks the child reports they drank in the last week. There is some evidence of a correlation with childhood obesity and overweight risk.[28]
Cigarettes mum smoked/day during each pregnancy trimester	1	MC*	Coded as: 0 for never, 1 for ≤10, 2 for 11-20, 3 for 21-30, 4 for 31-40, 5 for 41-50, 6 for ≥51 and 9 for occasional, not every day. PM smoking is linked to increased adiposity in offspring.[29]
Parental smoking frequency	1-3, 5-8		Coding of 1 means does not smoke at all, 2 means smoke less than once a day and 3 means smokes at least once per day. Childhood obesity/overweight has been found correlated with parental smoking in some studies.[30]
Parental occupation	1-8		Controlled as part of SES, consists of 4-digit Australia and New Zealand Standard Classification of Occupations code.

Parental highest schooling			Categorized as (with each year level being that year level or equivalent): 1 for year 12, 2 for year 11, 3 for year 10, 4 for year 9, 5 for year 8 or less, 6 for never attended school and 7 for still at school.
Parental highest qualification			Categorized as: 1 for postgraduate degree, 2 for graduate certificate or diploma, 3 for bachelor's degree, 4 for advanced diploma or diploma, 5 for trade certificate and 6 for other.
Child ate fresh fruit	2-8		Pertains to the 24 hours prior to the interview. Is just the number of times they have consumed the food/drink in question. Due to the well-established role diet plays in childhood obesity and overweight, it was controlled for. Coded as: 0 for none, 1 for once, 2 for twice and 3 for thrice or more. For wave 2, the last two categories were merged into one.
Child drank fresh juice			
Child ate raw vegetables			
Child ate cooked vegetables			
Child ate processed meat			
Child ate hot chips			
Child ate snack food			
Child ate sugary food			
Child ate full milk products			
Child ate skim milk products			
Child drank water			
Child drank SSBs[f]			
How child spends spare time	2-7		Coded as: 1 for inactive pastimes, 2 for inactive/active pastimes equally likely and 3 for active pastimes.
Child enjoys physical activity	3-5		Ranges from 1 to 5. Higher values correspond to greater enjoyment of physical activity.
How often TV is on during meals	2.5,		Decimal values refer to responses to questionnaires sent out between waves sent to parents. These were used in the

	3.5, 5-8		analysis of the wave that came immediately after the questionnaire was sent out. Takes on values of 1 (always) to 5 (never). Similar scale but opposite order was used for waves 5-8. Controlled for as watching TV during meals is a known risk factor for childhood obesity/overweight.[31]
Child sleep duration adequacy	6-8		Was reported by study child and relates to the last month. Coded in ascending order of adequacy from 1 to 5. Some studies have found a relationship between sleep parameters like sleep adequacy and quality and childhood obesity and overweight risk.[32]
Child sleep quality			Like above, although ranked in descending order of quality.
Independent variables			
PM antibiotic use	1	DC	Coded as: 0 for no and 1 for yes.
PM Rx[f] asthma medication use			
PM diabetes medication use			
PM Rx antiemetic use			
PM antihypertensive use			
PM Rx heartburn medicine use			
PM antidepressant use			
PM thyroid medication use			
PM other Rx medication use			
PM OTC[g] analgesic use			
PM OTC herbal preparation use			

PM OTC heartburn medicine use			
PM OTC cold/flu tablet use			
PM OTC anti-allergy tablet use			
PM OTC asthma medication use			
PM other OTC medication use			
Mediator variables			
Child birthweight	1	Q	Units of grams.
Moderator variables			
PM Rx iron tablet use	1	DC	Coded as: 0 for no and 1 for yes.
PM OTC iron tablet use			
PM OTC folate use			
PM OTC dietary supplement use			
Outcome variables			
BMI[h] z-score	2-8	Q	Calculated based on UK 1990 and US CDC[i] growth reference data.[33]
BMI percentile (BMIpct)			Calculated based on US CDC growth reference data.
Weight status		MC	Calculated based on BMIpct. A value of less than 5 was classed as underweight and coded as 0. A value between 5 (inclusive) and 85 (non-inclusive) was classed as healthy weight. A value between 85 (inclusive) and 95 (non-inclusive) was classed as overweight. A value between 95 (inclusive) and 99 (non-inclusive) was classed as mild-to-moderate obesity. A value of 99 or above was classed as severe obesity.[34]

Binary weight status		DC	Weight statuses of overweight, mild-to-moderate obesity and severe obesity are classed as overweight/obesity and coded as 1 and the weight status of healthy weight is coded as 0. Underweight children were excluded from analyses in which binary weight status was the outcome variable (which was the moderation analysis).

a. PM: Prenatal maternal.

b. DM: Diabetes mellitus.

c. DC: Dichotomous. This means the variable is categorical with two categories.

d. Q: Quantitative. These variables are also continuous.

e. MC: Multicategorical. These variables are categorical and have more than two categories.

f. Rx: Prescription-only.

g. OTC: Over-the-counter.

h. BMI: Body mass index.

i. CDC: Centers for Disease Control and Prevention.

Table 2: Characteristics of participants before / after data cleaning.

Characteristic\Wave	1	2	3	4	5	6	7	8
Number	5,107 / 3,911	4,606 / 1,015	4,386 / 923	4,242 / 957	4,085 / 1,149	3,764 / 1,081	3,381 / 803	3,127 / 897
Age in years, median (IQR)	0.769 (0.296) / 0.767 (0.287)	2.85 (0.326) / 2.84 (0.315)	4.84 (0.325) / 4.83 (0.285)	6.84 (0.416) / 6.84 (0.389)	8.92 (0.422) / 8.90 (0.397)	10.9 (0.485) / 10.9 (0.498)	13.0 (0.517) / 12.9 (0.467)	14.8 (0.456) / 14.8 (0.444)

Male sex, no (%)	2,608 (51.1) / 2,025 (51.8)	2,349 (51.0) / 517 (50.9)	2,251 (51.3) / 466 (50.5)	2,187 (51.6) / 502 (52.5)	2,096 (51.3) / 561 (48.8)	1,929 (51.2) / 536 (49.6)	1,734 (51.3) / 404 (50.3)	1,606 (51.4) / 457 (50.9)
Indigenous Australian, no (%)	230 (4.50) / 127 (3.25)	180 (3.91) / 5 (0.493)	149 (3.40) / 7 (0.758)	145 (3.42) / 11 (1.15)	139 (3.40) / 12 (1.04)	106 (2.82) / 10 (0.925)	87 (2.57) / 5 (0.623)	79 (2.53) / 8 (0.892)
Child born in Australia, no (%)	5,088 (99.6) / 3,898 (99.7)	4,589 (99.6) / 1,012 (99.7)	4,370 (99.6) / 920 (99.7)	4,227 (99.6) / 953 (99.6)	4,070 (99.6) / 1,144 (99.6)	3,749 (99.6) / 1,079 (99.8)	3,371 (99.7) / 801 (99.8)	3,117 (99.7) / 894 (99.7)
Mom born in Australia, no (%)	3,989 (78.1) / 3,099 (79.2)	3,623 (78.9) / 823 (81.1)	3,494 (79.7) / 753 (81.6)	3,388 (79.9) / 775 (81.0)	3,262 (79.9) / 938 (81.6)	3,010 (80.0) / 867 (80.2)	2,724 (80.6) / 643 (80.1)	2,514 (80.4) / 724 (80.7)
Dad born in Australia, no (%)	3,526 (69.0) / 2,815 (72.0)	3,260 (70.8) / 790 (77.8)	3,156 (72.0) / 733 (79.4)	3,070 (72.4) / 771 (80.6)	2,971 (72.7) / 889 (77.4)	2,765 (73.5) / 835 (77.2)	2,514 (74.4) / 634 (79.0)	2,316 (74.1) / 695 (77.5)
Underweight, no (%)	NA[a]	124 (2.69) / 30 (2.96)	144 (3.28) / 30 (3.25)	126 (2.97) / 29 (3.03)	96 (2.35) / 28 (2.44)	117 (3.11) / 34 (3.15)	105 (3.11) / 24 (2.99)	85 (2.72) / 20 (2.23)
Overweight, no (%)		828 (18.0) / 185 (18.2)	826 (18.8) / 189 (20.5)	607 (14.3) / 122 (12.7)	580 (14.2) / 152 (13.2)	539 (14.3) / 153 (14.2)	510 (15.1) / 102 (12.7)	494 (15.8) / 132 (14.7)
Mild-to-moderate obesity, no (%)		456 (9.90) / 79 (7.78)	414 (9.44) / 71 (7.69)	309 (7.28) / 52 (5.43)	348 (8.52) / 77 (6.70)	322 (8.55) / 70 (6.48)	267 (7.90) / 51 (6.35)	251 (8.03) / 51 (5.69)
Severe obesity, no (%)		178 (3.86) / 33 (3.25)	166 (3.78) / 27 (2.93)	83 (1.96) / 10 (1.04)	50 (1.22) / 9 (0.783)	30 (0.797) / 5 (0.463)	32 (0.946) / 4 (0.498)	45 (1.44) / 8 (0.892)

a. Not applicable as body mass index is not recorded in wave 1.

Table 3: Number of missing values for each independent and dependent variable.

Variable \ Wave	1	2	3	4	5	6	7	8
BMIz[a] / BMI[b] percentile	NA[c]	84	62	50	87	192	212	200
PM[d] antibiotic use	10	NA						
PM Rx[e] asthma medication use								
PM diabetes medication use								
PM Rx antiemetic use								
PM antihypertensive use								
PM Rx heartburn medication use								
PM antidepressant use								
PM thyroid medication use								
PM other Rx medication use								
PM OTC[f] analgesic use	5							
PM OTC herbal preparation use								
PM OTC heartburn medication use								
PM OTC cold/flu medication use								
PM OTC anti-allergy medication use								
PM OTC asthma medication use								
PM use of other OTC medications								

a. Body mass index z-score.

b. Body mass index.

c. Not applicable.

d. Prenatal maternal.

e. Prescription-only.

f. Over-the-counter.

Table 4: The effect of prenatal maternal medication on body mass index z-score (95% confidence interval in brackets) and weight status (odds ratios of unhealthy weight relative to healthy weight is given with 95% confidence intervals for these odds ratios in brackets).

Variable \ Wave	2	3	4	5	6	7	8
PM[a] antibiotic→BMIz[b]	NS[c]	NS	NS	NS			NS
PM Rx[d] asthma medication→BMIz							
PM diabetes medication→BMIz							
PM Rx antiemetic→BMIz							
PM antihypertensive→BMIz							
PM Rx heartburn medication→BMIz		-1.083 (-1.745, -0.421)[e]					
PM antidepressant→BMIz		NS					
PM thyroid medication→BMIz			-1.058 (-1.884, -				

			0.232)				
PM other Rx medication→BMIz							-0.4004 (-0.7761, -0.02467)
PM OTC[e] analgesic →BMIz							
PM OTC herbal preparation→BMIz			NS				
PM OTC heartburn medication→BMIz							
PM OTC cold/flu medication→BMIz							
PM OTC anti-allergy medication→BMIz							NS
PM OTC asthma medication→BMIz			-0.5453 (-0.9930, -0.0976)				
PM use of other OTC medications→BMIz							
PM antibiotic→WS[g]		OW:[h] 0.4482 (0.2246, 0.8943) SO:[i] 3.511 (1.158, 10.65)	NS	NS	MTMO:[j] 0.1701 (0.03429, 0.8436)	NS	OW: 1.913 (1.021, 3.584)
PM Rx[d] asthma medication→WS		NS	OW: 3.679 (1.074, 12.61)		MTMO: 4.846 (1.175, 19.98)		NS
PM diabetes medication→WS			NS		NS	UW: 19.78 (1.369, 285.7)	
PM Rx antiemetic→WS			NS			NS	
PM antihypertensive→WS							UW: 6.770

							(1.073, 42.72)
PM Rx heartburn medication→WS							NS
PM antidepressant→WS		UW:* 11.26 (1.769, 71.65)				UW: 15.15 (1.225, 187.4) MTMO: 8.605 (1.249, 59.29)	MTMO: 10.70 (1.839, 62.21)
PM thyroid medication→WS		NS				UW: 11.27 (1.772, 71.74)	OW: 3.791 (1.076, 13.36)
PM other Rx medication→WS			SO: 6.773 (1.372, 33.44)		UW: 4.122 (1.437, 11.82)	UW: 12.90 (3.964, 41.97)	NS
PM OTC* analgesic→WS			NS		NS	NS	
PM OTC herbal preparation→WS						UW: 4.922 (1.364, 17.76)	
PM OTC heartburn medication→WS			MTMO: 2.152 (1.120, 4.132)			NS	
PM OTC cold/flu medication→WS	UW: 5.703 (1.088, 29.90)		OW: 3.768 (1.159, 12.25)		NS		
PM OTC anti-allergy medication→WS	NS		NS				
PM OTC asthma medication→WS	UW:						

	4.071 (1.054, 15.72)						
PM use of other OTC medications→WS	NS						

a. Prenatal maternal.

b. Body mass index z-score.

c. Not significant.

d. Prescription-only.

e. Over-the-counter.

f. This is how much BMIz is changed by if the mother uses the medication in question.

g. Weight status (multicategorical).

h. Overweight.

i. Severe obesity.

j. Mild-to-moderate obesity.

k. Underweight.

Table 5: Moderation effects (95% confidence intervals in brackets) of prenatal maternal medication use on child BMIz and weight status (reported in terms of odds ratios of obesity/overweight relative to healthy weight/underweight).

Effect \ Wave	2	3	4	5	6	7	8
PM[a]Ab[b]×Rx[c]Fe[d]→BMIz[e]	NS[f]	NS	NS	-1.3699 (-2.0648, -0.6750)[g]	NS	NS	NS
PMAb×OTC[h]Fe→BMIz				NS			
PMAb×OTCFolate→BMIz							
PMAb×OTCDietS[i]→BMIz					-0.5040 (-0.9917, -0.0163)		
PMRxAs[j]×RxFe→BMIz					NS		
PMRxAs×OTCFe→BMIz							
PMRxAs×OTCFolate→BMIz							
PMRxAs×OTCDietS→BMIz							
PMDM[k]×RxFe→BMIz							
PMDM×OTCFe→BMIz					NS		
PMDM×OTCFolate→BMIz							
PMDM×OTCDietS→BMIz							
PMAE[l]×RxFe→BMIz							
PMAE×OTCFe→BMIz							
PMAE×OTCFolate→BMIz							0.6622 (0.0092, 1.3152)

PMAE×OTCDietS→BMIz				-0.6723 (-1.2070, -0.1376)			
PMAH^{m}×RxFe→BMIz				NS			
PMAH×OTCFe→BMIz							NS
PMAH×OTCFolate→BMIz							
PMAH×OTCDietS→BMIz							
PMRxHB^{a}×RxFe→BMIz							
PMRxHB×OTCFe→BMIz							1.3700 (0.4884, 2.2517)
PMRxHB×OTCFolate→BMIz							
PMRxHB×OTCDietS→BMIz							
PMAd^{e}×RxFe→BMIz						-1.8474 (-2.9438, -0.7510)	NS
PMAd×OTCFe→BMIz							
PMAd×OTCFolate→BMIz	1.334 (0.0702, 2.1966)		1.2370 (0.2655, 2.2086)			NS	
PMAd×OTCDietS→BMIz	NS	NSS	NS	NS	NS	NS	NS
PMTh^{p}×RxFe→BMIz		SME	SME				
PMTh×OTCFe→BMIz		NS	NS				

PMTh×OTCFolate→BMIz	1.1643 (0.0833, 2.2454)	1.4169 (0.2853, 2.5485)					
PMTh×OTCDietS→BMIz		NS					
PMORx×RxFe→BMIz							
PMORx×OTCFe→BMIz							
PMORx×OTCFolate→BMIz						-0.8083 (-1.4334, -0.1832)	
PMORx×OTCDietS→BMIz							
PMOTAn×RxFe→BMIz							
PMOTAn×OTCFe→BMIz							
PMOTAn×OTCFolate→BMIz	NS		NS				
PMOTAn×OTCDietS→BMIz		NS					
PMHP×RxFe→BMIz							
PMHP×OTCFe→BMIz						NS	
PMHP×OTCFolate→BMIz							
PMHP×OTCDietS→BMIz							
PMOTHB×RxFe→BMIz					0.4443 (0.1084, 0.7802)		
PMOTHB×OTCFe→BMIz					NS		

PMOTHB×OTCFolate→BMIz							
PMOTHB×OTCDietS→BMIz							
PMCFᵘ×RxFe→BMIz			-3.7191 (-5.5394, -1.8988)			-2.0623 (-3.9110, -0.2136)	
PMCF×OTCFe→BMIz			NS			1.0962 (0.1291, 2.0633)	
PMCF×OTCFolate→BMIz		1.6248 (0.0320, 3.2176)	1.4055 (0.2634, 2.5475)				
PMCF×OTCDietS→BMIz			-1.0732 (-2.0649, -0.0815)		1.5144 (0.4258, 2.6031)	NS	
PMAAᵛ×RxFe→BMIz				SME	SME		
PMAA×OTCFe→BMIz		NS					
PMAA×OTCFolate→BMIz			NS				
PMAA×OTCDietS→BMIz				NS	NS	0.8455 (0.0476, 1.6434)	
PMOTAsᵛ×RxFe→BMIz						NS	
PMOTAs×OTCFe→BMIz							
PMOTAs×OTCFolate→BMIz	NS	NS	NS	NS	NS	NS	NS
PMOTAs×OTCDietS→BMIz							

PMOOTC××RxFe→BMIz							
PMOOTC×OTCFe→BMIz							
PMOOTC×OTCFolate→BMIz							
PMOOTC×OTCDietS→BMIz							
PMAb×RxFe→BWS[y]					NS		
PMAb×OTCFe→BWS							
PMAb×OTCFolate→BWS							
PMAb×OTCDietS→BWS							
PMRxAs×RxFe→BWS			SME	SME			
PMRxAs×OTCFe→BWS							
PMRxAs×OTCFolate→BWS			NS				
PMRxAs×OTCDietS→BWS				NS	SME		SME
PMDM×RxFe→BWS							
PMDM×OTCFe→BWS	SME*						
PMDM×OTCFolate→BWS			SME			SME	
PMDM×OTCDietS→BWS				SME	NS		
PMAE×RxFe→BWS						NS	
PMAE×OTCFe→BWS	NS		NS	NS			
PMAE×OTCFolate→BWS							

PMAE×OTCDietS→BWS						SME	
PMAH×RxFe→BWS	SME		SME			NS	
PMAH×OTCFe→BWS			NS		SME		
PMAH×OTCFolate→BWS			SME			SME	
PMAH×OTCDietS→BWS	NS			SME	NS	NS	
PMRxHB×RxFe→BWS							
PMRxHB×OTCFe→BWS			NS	NS	NS		
PMRxHB×OTCFolate→BWS							
PMRxHB×OTCDietS→BWS							
PMAd×RxFe→BWS	SME		SME	SME	SME	NS	
PMAd×OTCFe→BWS	NS		NS		NS		
PMAd×OTCFolate→BWS			SME				
PMAd×OTCDietS→BWS	SME		NS		SME		
PMTh×RxFe→BWS	NS		SME	NS	NS		
PMTh×OTCFe→BWS							
PMTh×OTCFolate→BWS	SME						
PMTh×OTCDietS→BWS	NS	SME	SME	NS	NS	NS	SME
PMORx×RxFe→BWS			NS				
PMORx×OTCFe→BWS							

PMORx×OTCFolate→BWS							
PMORx×OTCDietS→BWS							
PMOTAn×RxFe→BWS	0.1217 (0.0200, 0.7385)						
PMOTAn×OTCFe→BWS	NS						
PMOTAn×OTCFolate→BWS							
PMOTAn×OTCDietS→BWS							
PMHP×RxFe→BWS				SME	SME		
PMHP×OTCFe→BWS	NS		SME	NS	NS		
PMHP×OTCFolate→BWS			NS				
PMHP×OTCDietS→BWS							
PMOTHB×RxFe→BWS	9.4037 (1.2492, 70.786)						
PMOTHB×OTCFe→BWS	NS						
PMOTHB×OTCFolate→BWS							
PMOTHB×OTCDietS→BWS							
PMCF×RxFe→BWS			SME	SME	SME		
PMCF×OTCFe→BWS			NS	NS		SME	
PMCF×OTCFolate→BWS	SME		SME	SME			

PMCF×OTCDietS→BWS				NS	NS		
PMAA×RxFe→BWS				SME	SME		
PMAA×OTCFe→BWS	NS					NS	
PMAA×OTCFolate→BWS				NS		SME	
PMAA×OTCDietS→BWS			NS				
PMOTAs×RxFe→BWS	SME			SME	NS		
PMOTAs×OTCFe→BWS						NS	
PMOTAs×OTCFolate→BWS	NS						
PMOTAs×OTCDietS→BWS							
PMOOTC×RxFe→BWS	SME		SME	NS	SME		
PMOOTC×OTCFe→BWS						8.2581 (1.0883, 62.665)	
PMOOTC×OTCFolate→BWS	NS		NS		NS	SME	
PMOOTC×OTCDietS→BWS						NS	

a. PM is prenatal maternal.

b. Ab is short for antibiotics.

c. Rx is short for prescription-only.

d. Fe is used to indicate an iron supplement.

e. BMIz is short for body mass index z-score.

f. NS stands for not significant.

g. This means that if the mother used antibiotics during pregnancy and took a prescription iron supplement this was correlated with a 1.3699 reduction in child BMIz. In brackets is the 95% confidence interval for this effect.

h. OTC stands for over-the-counter.

i. DietS stands for dietary supplements.

j. RxAs is abbreviated from prescription-only asthma medications.

k. DM stands for diabetes medications.

l. AE stands for antiemetics.

m. AH stands for antihypertensives.

n. RxHB stands for prescription-only heartburn medicines.

o. Ad stands for antidepressants.

p. Th stands for thyroid medications.

q. ORx stands for other prescription-only medications.

r. OTAn stands for OTC analgesic medications.

s. HP stands for herbal preparations.

t. OTHB stands for OTC heartburn medications.

u. CF stands for cold/flu medications.

v. AA stands for anti-allergy medications.

w. OTAs stands for OTC asthma medications.

x. OOT stands for other OTC medications.

y. BWS stands for binary weight status.

z. SME indicates that singular matrix errors prevented the calculation.

5.3 Implications

This paper shows that fetal exposure to certain classes of medications is a risk factor for childhood obesity and overweight. This further substantiates the importance of the prenatal environmental in guiding the development of children, including their susceptibility to medical conditions such as childhood obesity and overweight. It also shows that dietary supplements are not protective against these effects, unless the LSAC data set did not have the required level of detail (like of when dietary supplements were consumed during pregnancy and when the medications were consumed) to detect an effect.

CHAPTER 6: DISCUSSION AND CONCLUSION

6.1 Introduction

The purpose of this thesis was to determine the impact of the proposed risk factors on childhood obesity and overweight risk and BMIz as well as the mechanisms and protective factors involved in these relationships. This objective was achieved by chapters 3-5 of this thesis, namely:

- Chapter 3 investigated the effect of parental alcohol consumption as a proposed risk factor.
- Chapter 4 investigated the effect of prenatal maternal dietary exclusion as a proposed risk factor.
- Chapter 5 investigated the effect of prenatal maternal medication use as a proposed risk factor.

6.2 Discussion of key findings

To understand the impact of parental alcohol consumption and prenatal maternal medication use and dietary exclusion on childhood obesity and overweight risk and BMIz, each of these proposed risk factors were studied separately in each of the research papers included in this thesis.

6.2.1 The effect of parental alcohol consumption on childhood obesity and overweight

This study was necessary as parental alcohol consumption, while prevalent in the Australian context (Australian Bureau Of Statistics, 2022), has not been studied as a possible risk factor for childhood obesity and overweight despite a theoretical basis to suspect a linkage. Mediating factors and moderating factors in this relationship had also not been investigated, even though these factors could represent alternative targets for public health policy when targeting parental alcohol consumption is impractical. This study consisted of secondary data analysis of LSAC data to investigate these effects. Specifically, linear, and multinomial logistic models were fitted to each wave individually to test for an age-specific effect of parental alcohol consumption on child BMIz

and weight status, respectively. Generalized estimating equations were also fitted for a pooled wave analysis to test for these effects across child age 2 to 15 years. Mediation analysis was conducted using the Iacobucci (2012) method. Moderation analysis was conducted using the PROCESS R macro of Andrew F. Hayes.

Paternal alcohol consumption frequency of greater than once a year was negatively correlated with child BMIz in the pooled wave analysis. Individual wave analyses showed no significant effect of parental alcohol consumption on child BMIz. Typically, paternal alcohol consumption frequency was associated with lower risks of unhealthy weight statuses (like underweight, overweight and obesity) when it was associated with any effect, although greater than triweekly alcohol consumption was associated with a higher risk of child underweight in wave 2. Moderation effects involving parental warmth were usually associated with higher BMIz, although there were exceptions wherein the opposite effect was observed. None of the studied proposed mediating factors had a mediating effect.

These results suggest that while adult alcohol consumption is an important public health issue due to its prevalence and effects on the adults themselves (Australian Bureau Of Statistics, 2022; Hendriks, 2020), it is unlikely to have a significant adverse effect on their children in terms of childhood obesity and overweight risk. Although, there may be an effect of parental alcohol consumption contribution to child underweight, for which parental warmth may be a protective factor.

6.2.2 The effect of prenatal maternal dietary exclusion on childhood obesity and overweight

This study was important as some mothers, either due to personal preference or medical reasons, omit certain food items from their diet during pregnancy. It is known that certain nutritional deficiencies like of

folate (Wang et al., 2016), as well as famine (Ravelli et al., 1976), can impact upon the offspring's risk of developing obesity and overweight later in life. Despite this, no previous studies have been identified that investigated the effect of prenatal maternal dietary exclusion on childhood obesity and overweight risk. Whether birthweight mediates this effect or dietary supplements are protective against this effect also remain understudied, despite a theoretical basis to suspect a role for them. If dietary supplements were protective against the effect, it would suggest that dietary supplements could be used to mitigate the effect when dietary exclusion was unavoidable (such as when it was due to medical reasons). The analysis to determine whether prenatal maternal dietary exclusion impacted upon child BMIz, and childhood obesity and overweight risk was conducted using linear models and multinomial logistic models, respectively. Mediation analysis was conducted using the Iacobucci (2012) technique and moderation analysis was conducted using the PROCESS R macro.

Exclusion of fish and eggs from the prenatal maternal diet was associated with higher risks of unhealthy weight status, when it was associated with any effect on weight status. Exclusion of dairy was associated with a more mixed effect; sometimes it was associated with a higher risk of unhealthy weight status and sometimes with a lower risk. Exclusion of other foods was associated with lower risk of unhealthy weight statuses when it was associated with any effect on weight status. Child birthweight's mediation effect did not reach statistical significance. The moderation effect of dietary supplement use was associated with higher BMIz and usually a higher risk of obesity or overweight.

These findings suggest that the Australian Government's healthy pregnancy campaign should recommend specifically that mothers consume fish and eggs as part of their diet (Australian Government Department of Health and Aged Care, 2023). Dietary supplements should

not be recommended as a way of mitigating the effect of avoiding fish and eggs during pregnancy as they do not seem to be protective and may even have a detrimental effect.

6.2.3 The effect of prenatal maternal medication on childhood obesity and overweight

This study was important as some mothers consume medications during pregnancy due to medical necessity. Some previous studies have investigated the effect of certain classes of medication like antifungal and antibiotic medications, but there are several classes that had not been investigated until this study. Furthermore, the role of birthweight in mediating the effect of medications on childhood obesity and overweight risk had not been studied. This is even though many medications are known to inhibit the absorption or utilization of certain nutrients and child birthweight is a marker of fetal nutrition. Additionally, the effect of dietary supplements on the effect of medications on childhood obesity and overweight have been unstudied, even though many medications are known to inhibit the absorption or utilization of essential nutrients that dietary supplements can provide. This study consisted of secondary data analysis of LSAC data. Specifically, linear, and multinomial logistic models were fitted to test for an effect of prenatal maternal medication on child BMIz and childhood overweight and obesity risk, respectively. Mediation analysis was conducted using the Iacobucci (2012) method and moderation analysis using the PROCESS R macro.

Most classes of medication, except for antibiotics, were associated with higher risks of unhealthy weight status when they were associated with any effect on weight status. The effect of antibiotics on weight status was more mixed. When medication classes were associated with changes in BMIz, they were associated with lower BMIz and never had an effect across more than one wave. Child birthweight did not mediate any of these effects. Some moderation effects existed with regards to dietary

supplement use. Sometimes these moderation effects were associated with higher risks of childhood obesity/overweight and higher child BMIz and other times with lower risks and lower child BMIz.

These findings suggest that it is generally advisable for mothers to avoid medications during pregnancy, although antibiotics may be an exception. Although, it is important to note that these results could be due to an effect of the underlying condition the medications were intended to treat rather than of the medication itself. For instance, other studies have established that prenatal maternal antibiotics themselves do not increase obesity and overweight risk in children, but instead the underlying infection they were prescribed to treat does (Li et al., 2020).

6.3 Recommendations

Excessive alcohol consumption by parents should be discouraged. Moderate alcohol consumption does not appear to be associated with any negative effects on children in this study. Fish and egg consumption during pregnancy should be encouraged. Medication use during pregnancy should be discouraged, with prescription antiemetics and heartburn medications and OTC analgesics and anti-allergy medicines and other OTC medications being exceptions. Dietary supplements should not be encouraged as a strategy for protecting against the effects of medication use or dietary exclusion during pregnancy.

6.4 Contribution of the thesis

This thesis created new knowledge on risk factors for childhood obesity and overweight. In addition, new knowledge was generated regarding the mechanisms and moderating factors underlying the effects of the risk factors studied. This research also raised important questions that can help guide further research.

As far as the author is aware, Chapter 3 is the first study to investigate the effect of parental alcohol consumption on childhood obesity and overweight risk, and BMIz. As such, it has provided the first evidence in humans on this possible risk factor. This is also the first study to investigate the possible mediating effect of child dietary habits, child physical activity, child alcohol consumption, parental warmth, child sleep quality and parental hostility in this relationship. Additionally, no other study has investigated the possible moderating effect of parental warmth.

Filling these gaps in chapter 3 also helps to inform public health campaigns related to alcohol consumption in adults as it could provide a further reason to discourage excessive alcohol consumption in adults beyond their own health. Australian statistics show that over a quarter of Australian adults drink to an extent that has been associated with detrimental health effects in human studies (Australian Bureau Of Statistics, 2022) and hopefully having further data on the detrimental effects of alcohol can help motivate public health campaigns. Knowing the mechanisms of these effects and moderating factors in this relationship also provides ways of safeguarding the health of children whose parents are unable to reduce their alcohol consumption, such as because of addiction.

Prenatal maternal dietary exclusion also had never been investigated as a risk factor for childhood obesity and overweight, to the best of the author's knowledge and hence Chapter 4 fills this research gap. No previous study has investigated the mediating effect of child birthweight, nor the moderating effect of dietary supplement use, and these are other research gaps Chapter 4 fills. This also helps illuminate the importance of prenatal maternal diet and nutrition on child health, which has already been investigated but from different angles (like famine and vitamin deficiencies) (Devakumar et al., 2014; Ravelli et al., 1976).

Filling these gaps in chapter 4 will help inform public health campaigns related to diet in pregnancy, such as the Australian Government's healthy pregnancy campaign (Australian Government Department of Health and Aged Care, 2023). Whether dietary supplements impact upon this effect is also important to know as it can inform mothers that exclude certain foods from their diet due to health or other reasons a further way of safeguarding their child's health if excluding those foods seems to predispose children to overweight or obesity.

Chapter 5 is the first study on the effect of thyroid medication, antiemetics, asthma medications, antihypertensives and antidepressants on childhood obesity and overweight risk and BMIz that the author is aware of. No study has investigated the mediating effect of child birthweight, nor the moderating effect of dietary supplement use in these relationships either. Additionally, no previous study has investigated the mediating effect of child birthweight, nor the moderating effect of dietary supplement use in the effect of prenatal maternal antibiotics, antidiabetics and antifungals on childhood obesity and overweight risk and BMIz. Consequently, these are research gaps that Chapter 5 fills.

Filling these gaps in chapter 5 can help inform clinicians and pharmacists in the medication advice they give expectant mothers. It helps reinforce the evidence for the safety of some medications during pregnancy (such as antibiotics (Li et al., 2020)) and helps show the potential harm of some others and hence guide decisions made regarding medications during pregnancy. Knowing whether dietary supplements can moderate these effects is also important for informing such clinical decisions, as they could provide an alternative way of protecting children exposed to developing obesity.

Filling these research gaps also furthers the understanding of FOAD and DOHaD. Chapter 3 could help further the understanding of the role of

postnatal factors in the development of childhood obesity and overweight and hence advance the understanding of DOHaD. This is important as most DOHaD research has focused on prenatal development (Fleming et al., 2018). One proposed mechanism that could not be examined in this study was that child stress could have led to the effects of parental alcohol consumption on childhood obesity and given other proposed mechanisms were not substantiated by the mediation analysis, it seems probable that this mechanism is at least one mechanism by which parental alcohol consumption impacts upon childhood obesity and overweight. Especially since chronic stress leads to higher serum cortisol concentrations which affects adiposity (Russell & Lightman, 2019). Chapter 4 and 5 could further the understanding FOAD by adding to the evidence for the importance of fetal one-carbon metabolism (Steegers-Theunissen et al., 2013) in the development of childhood obesity and overweight. Additionally, they could illustrate the importance of other nutrients that do not appear to be related to one-carbon metabolism in the development of childhood obesity and overweight.

This research also raised an important methodological question. Namely, how does one account for all the potential complexities of variable relationships? It is conceivable that the reason the results obtained for each of these risk factors were at times rather underwhelming (with significant effects only found for some waves or some variables) is due to unaccounted for interactions between variables. It is possible, for instance, that parental alcohol consumption's effects are moderated by socioeconomic factors. Maybe the apparent link between high paternal drinking frequency and child underweight was due to the father being the primary source of income for the family and when the father is frequently intoxicated, they are less able to earn an income to feed their children. Likewise, it is possible that an interaction term between the exclusion of all animal-derived foods should have been included in the prenatal maternal dietary exclusion analysis as animal-derived foods are rich in

cobalamin, which is known to play a pivotal role in one-carbon metabolism. Machine learning may be better suited for checking for such complex relationships (Colmenarejo, 2020).

6.5 Limitations and avenues for further research

Most limitations of this study originate from the fact that it is based on LSAC data. As LSAC is an observational study that was not designed to detect causal relationships, causal inferences cannot be made based on its data. LSAC also did not record many known risk factors for childhood obesity, such as gestational weight gain and prenatal maternal BMI, which meant these known risk factors could not be controlled for or had to be controlled for using proxy variables.

Many LSAC variables also lacked important details, like in the case of prenatal maternal medication use the dataset did not record at what time in pregnancy the medication was taken. It is also not known whether dietary supplements, when they were taken, were taken at the same time or after dietary exclusion or medication use and hence the conclusions from Chapters 4 and 5 about the moderation effect of dietary supplements on the effect of prenatal maternal dietary exclusion and medication consumption on childhood obesity and overweight risk were based on flawed evidence.

Many details about the mother's health during pregnancy were also not recorded in the LSAC dataset and these details would be important to control for when studying prenatal maternal risk factors as they are possible confounders. Additionally, many cases had missing data across some of the variables, and this required that these cases had to be excluded from the analysis and since the missing data did not seem to be MCAR, the independence assumption of the hypothesis tests may be violated.

Consequently, it is recommended that further studies be conducted to investigate these associations. These follow-up studies should record all known risk factors for childhood obesity in the required detail and record the proposed risk factors studied in this thesis in greater detail. It is likely that future studies will have to be observational and not experimental, due to ethical considerations. Gianicolo et al., 2020 provides methods by which observational studies can be used to establish causality and it is recommended that future studies investigating these links follow their recommendations. Randomized controlled trials should be used to investigate possible interventions aimed at preventing childhood obesity and overweight based on these risk factors once they are established by observational studies designed to establish causality.

6.6 Concluding remarks

This thesis has shown that parental alcohol consumption, prenatal maternal dietary exclusion and medication consumption all have complicated relationships with childhood obesity and overweight risk and BMIz. This thesis is intended to inform Australian public health policy. It has identified multiple potentially modifiable risk factors for childhood obesity and overweight, such as excessive parental alcohol consumption, mothers abstaining from fish and eggs during pregnancy and mothers consuming prescription asthma medications, antidepressant medications, thyroid medications, other prescription medications and over-the-counter heartburn medicines during pregnancy. No mediating factors were identified, but parental warmth and dietary supplements were moderating factors with regards to parental alcohol consumption and the prenatal maternal risk factors.

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APPENDIX A

Below is Figure 1 (titled “Proposed relationship between variables”) from Research Paper 2. Per PLoS One guidelines it was submitted to the journal as a separate file from the manuscript.