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PREGNANCY AND CHILDREN'S DEVELOPMENT (PRECEDE): HOW MATERNAL INFLAMMATION IN PREGNANCY AFFECTS CHILD OUTCOMES

THE UNIVERSITY *of* EDINBURGH

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Contributions

During my PhD studies, I have contributed to the following relevant publications:

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Abstract

The main research question of this thesis is to examine how maternal inflammatory processes during pregnancy possibly affect a child's development in domains of cognition, behaviour, and general school readiness. It starts with providing relevant background and basis of Barker's hypothesis on the developmental origins of health and disease (DoHAD), which postulates effects on fetal and child development if the intrauterine environment is disrupted or compromised during pregnancy. It aims to narrow the gap between animal models and limited human studies through associating maternal inflammation in pregnancy with child outcomes. The predominant focus is using cohorts to examine how gestational biology processes such as infections or maternal metabolic markers are associated with child standardised developmental, cognitive, or socioemotional measures. This thesis also adopts different approaches towards how mother-child outcomes can possibly be affected by other factors, such as analysis of cord blood mediators to further understand mother-child associations during the perinatal period, or synthesis of high-quality evidence on how analgesic drug use during pregnancy affects child neurodevelopment. Overall conclusions will be drawn from quantitative models, seeking to provide careful evaluation and a translational review of previous and current empirical studies.

The first empirical chapter, Chapter 2 uses the Avon Longitudinal Study of Parents and Children (ALSPAC) United Kingdom cohort (N= 7,410 mother-child pairs with condition of infections present during pregnancy) to examine associations between maternal prenatal

infections occurring in specific pregnancy trimesters and a child's cognitive outcomes at three timepoints (18 months, 4 years, 8 years) using developmental and intelligence quotient scores. Regression analyses were run, adjusting for maternal and socioeconomic covariates. Results suggest associations between infections occurring at the third pregnancy trimester with verbal IQ at 4 years old, and verbal and performance IQ at 8 years old, however the magnitude of effect appears to be small.

Chapter 3 uses the Avon Longitudinal Study of Parents and Children (ALSPAC) United Kingdom cohort (N=15,133 mother-child pairs) to examine associations between maternal metabolic markers and child socio-emotional outcomes over time (4 to 16 years old; 7 timepoints). Growth curve models were fit, adjusting for maternal, child, and environmental covariates. Results showed specific maternal metabolic markers of fasting glucose, HDL, BMI, and triglycerides having differential effects on developmental trajectories of conduct and hyperactivity problems from 4 to 16 years old. Adjusted models also suggest maternal metabolic markers possibly having trimester-specific effects on child development.

Chapter 4 uses the Born in Bradford (BiB) United Kingdom cohort (N=10,600 mother-child pairs) to examine associations between maternal metabolic syndrome classification and child development outcomes at age 5, using child cord blood markers as potential mediators. Maternal markers in pregnancy were classified into metabolic syndrome risk, while child cord blood markers were individually measured. Child development outcomes were taken from a national development framework that assesses domains of school readiness. Mediation

models were adjusted for maternal, child, and socioeconomic covariates. Mediation results showed no significant effects when looking at individual cord blood markers, however, they suggested significant combined effects of cord blood markers mediating the association between maternal cardiometabolic health and some child outcomes.

Chapter 5 consists of a protocol paper and an umbrella review to synthesise evidence on how maternal drug use during pregnancy is linked with child development outcomes. The review examined high-quality evidence on analgesic drug exposure and attention-deficit hyperactivity disorder (ADHD) risk in children. Findings showed significant associations between maternal prenatal acetaminophen (paracetamol) use and ADHD outcomes, with a potential dose-dependent relationship. This review method provides a different perspective on exploring how interventions that are applied to seek to improve a mother's health may subsequently affect a child's neurodevelopment.

Overall, this thesis uses several different methodologies to combine current literature with empirical data analyses to examine how maternal health affects child outcomes. The discussion chapter of this thesis expands on limitations and future directions, with emphasis on translating results into implications for clinical and educational providers.

Lay Summary

Research based on Barker's hypothesis on development origins of health and disease (DoHAD) has found evidence for the intrauterine environment affecting quality of the fetal development process, which in turn affects child health outcomes over time. Literature has since expanded from animal models to human studies, with the purpose of examining maternal inflammation during pregnancy and associations with child development outcomes. This thesis explores maternal inflammation during pregnancy, characterised as either infections or increased maternal metabolic risk, with some emphasis on trimester-based effects. Child outcomes include standardised measures of cognition, socioemotional behaviour, and developmental milestones assessed by a United Kingdom (UK) national framework. Datasets used in this study included the Avon Longitudinal Study of Parents and Children (ALSPAC) and the Born in Bradford (BiB) cohorts. Using different modelling approaches, findings maternal inflammatory processes during pregnancy affecting children's cognitive and socioemotional development. Results provide strong support for further examination of maternal inflammatory mechanisms as predictive risk markers to better inform clinicians, parents, and educators for future targeted interventions.

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Chapter 1: Introduction

Synopsis

This chapter provides a narrative review of the literature on how maternal inflammatory biomarkers are associated with children's developmental outcomes. The introduction will examine maternal gestational biology processes and risk mechanisms in both preclinical (animal) models and human studies, with acknowledgement of limitations in current research and interpretation. Lastly, this chapter will introduce the thesis's aims and hypotheses, followed by an outline of the subsequent chapters.

Developmental origins of health and disease (DOHaD)

Emerging evidence is suggesting that disruptions to the intrauterine environment during pregnancy are associated with fetal programming, a crucial period of development which can translate into future pathology. In line with the fetal origins' hypothesis (Barker, 1995), changes in pregnancy mechanisms have been found to affect patterns of embryonic and fetal growth. This can manifest as future clinical disorders such as physical and mental illness in offspring, depending on maternal lifestyle and environmental factors (Capra et al., 2013). Psychological science has been further fuelled by this model and researchers are currently examining biopsychosocial processes from a multilevel perspective. There is strong evidence pointing to adverse developmental consequences of prenatal processes such as maternal stress during pregnancy, defined through neuroendocrine, immune, or behaviour processes (Dunkel Schetter, 2011).

Neurodevelopmental disorders and psychopathology tend to manifest as vulnerability during infancy (Luby et al., 2019). However, unlike established medical risk calculators, existing psychiatric diagnostic interviews are recognised to be inadequate in prognosis and are often lacking in external validity (Bernardini et al., 2017). This leads to a potential oversight of impaired development across life stages and impediment of clinical resources for when psychopathology emerges. With the above identified, current research now seeks to explore mechanisms relating to vulnerability while also accounting for developmental heterogeneity (Gumusoglu & Stevens, 2019) through both qualitative and quantitative assessments

(Wakschlag et al., 2005). This allows for early prognostication of risk and more tailored early intervention which results in stronger effects and higher cost-effectiveness in clinical decision-making. One identified example is environmental modification and increased maternal parenting knowledge being seen to moderate associations between prenatal risk and history of maternal childhood trauma on child socio-emotional behaviour outcomes (Ahmad et al., 2022).

While Barker's hypothesis initially focused on maternal undernutrition during gestation and fetal cardiovascular outcomes, subsequent studies have shown inconsistent results of poor nutrition affecting fetal development, possibly displaying the influence of other pre- or post-natal factors (Gillman, 1995) with dynamic contact-dependent physiological interactions (Wadhwa, 2005). Lowered birth outcomes were seen as possible determinants of adult health even after accounting for environmental confounds such as socioeconomic influences. As part of the shift towards preventive medicine, it is necessary to use cost-effective methods which can rapidly identify potential early predictive risk markers to quickly change outcome trajectories for children. One potential way to do so is potentially using clinical biomarker measures taken during pregnancy as prognosis markers. Examples of possible biomarker panels include lipid (cholesterol), endocrine (blood glucose), or inflammatory panels such as maternal infection data. In addition to understanding the quality of maternal-to-fetal development processes, it is also pertinent to examine if effects of biological disruption remain in pregnancy or influence future developmental risk during childhood and adolescence.

All the above points have urgent and serious implications on both clinical and educational providers, as early and personalised intervention has been evidenced to positively affect life-course outcomes (Salum et al., 2010). Therefore, it is necessary to use a life-course perspective with available data to examine factors that potentially mediate or attenuate risk over time (Fox et al., 2015). Based on the considerable literature of earlier studies linking maternal gestational biology and a disrupted intrauterine environment with fetal and child development outcomes (Gillman et al., 2007; Gluckman et al., 2016), this thesis aims to expand on the multiple fetal programming hypotheses through using maternal biomarker measures to examine how maternal inflammation affects child development.

Inflammatory risk markers and development

Research examining risk markers for mother-offspring outcomes for both animal and human studies has been evolving rapidly. The prenatal environment has been a targeted area of research for preclinical (animal) models, and converging evidence has shown that the maternal-fetal immune environment has great translational potential to understand underlying mechanisms that can separate at-risk pregnancies from healthy ones (Bauman & Van de Water, 2020). It is important to note that biological processes do not tend to occur in isolation, which makes it difficult to draw strong conclusions from examining one type of risk marker in relation to child outcomes. Risk markers can draw on each other to affect both mother and child. For example, maternal inflammatory markers have been associated with

maternal depressive symptoms, while maternal depression has been associated with internalising and externalising symptoms in their children (Swales et al., 2022) and also a three-fold risk for development of ADHD, behavioural, and emotional problems (Capra et al., 2013).

Through drawing from multidisciplinary scientific areas, this thesis seeks to provide explanations for how maternal inflammatory biomarkers can affect fetal development and eventually influence childhood and adolescence outcomes. This will be done through introduction of some relevant biomarkers as a topic focus of potential associations with child development.

Immune markers

During pregnancy, both pro-inflammatory and anti-inflammatory processes occur as a physiological regulation of adapting to fetal growth (Challis et al., 2009). These processes are dependent on regulation of cytokine production, which results in protective factors surrounding the maternal-fetal relationship in a normal pregnancy. Inflammation that disrupts this homeostasis leads to an increased cytokine production cascade, also termed as maternal immune activation.

The maternal immune activation (MIA) model is broadly defined as excessive immune response or dysregulation in pregnancy, triggered by external factors such as stress, infection,

diet, or pollution. MIA research follows molecular downstream pathways studying the impact of cytokine cascades causing a dysregulated in utero environment and affecting fetal development. Maternal immune dysregulation has been postulated as a disease primer (Estes & McAllister, 2016; Gumusoglu & Stevens, 2019) with observations showing the release of pro-inflammatory cytokines in the mother's bloodstream altering peripheral immunity and fetal neurodevelopment (Han et al., 2021; S. E. P. Smith et al., 2007).

Generally, immune dysregulation linked with inflammation has been pathologically associated with increased cardiovascular risk due to circulatory immune cells (Blackburn et al., 2015). For maternal-fetal physiological outcomes, maternal antibodies passed through the placenta has found associations with a fetus' developing immune system (Albrecht & Arck, 2020). A mother's immune dysregulation stemming from the presence of pro-inflammatory cytokines during pregnancy has been associated not only with impaired immunity, but also with an increased risk of cardiovascular and metabolic disorders such as diabetes in later life (Christian, 2012; Lawlor et al., 2012). Similar associations were found for maternal hypothalamic-pituitary-adrenal (HPA) axis and fetal HPA axis, where fetal glucocorticoid overexposure was associated with future cardiometabolic disease and neurodevelopment (Duthie & Reynolds, 2013), showing implications for not only child health outcomes, but also potential neurocognitive and psychological domains.

Maternal immune response to occurrence of infections during early pregnancy have been found to affect early brain cell proliferation and differentiation with implications for future

brain functioning (Meyer et al., 2007) and neurocognitive development in childhood (Ghassabian et al., 2018). Associations between maternal infection during pregnancy and child socio-behavioural outcomes such as externalising and internalising behavioural symptoms (Patel et al, 2021) have been suggested, but literature has been mixed after adjustments for potential maternal and environment confounds (Hall et al., 2021a).

Some studies have sought to examine immune responses more closely through using specific biomarkers. Using a large Norwegian birth cohort, the presence of immune markers signifying altered cytokine profiles during gestation and in cord blood was associated with increased risk of autism spectrum disorder (ASD), showing carryover immune activation affects through the placenta (Che et al., 2022). Elevated IL-6 concentration during pregnancy, a marker of systemic inflammation, shows altered fetal brain development in areas involved in social deficits and emotional regulation, with emerging behaviour phenotypes for emotional and behavioural problems during childhood (Graham et al., 2018) and even implications for ASD or schizophrenia etiology (Meyer et al., 2011) or comorbid disorders such as ASD and Intellectual Disability (ID) (Volk et al., 2020). Another a pro-inflammatory immune biomarker of interest is C-reactive protein (CRP). Maternal CRP has not only been associated with poorer neurobehavioral function at 6 days of age (Osborne et al., 2020) but also infant non-verbal cognitive development at 12 weeks old (Nazzari et al., 2020). Elevated maternal CRP levels were also found to be associated with a child's cognitive flexibility at 4-6 years old, implying longer-term effects of inflammation occurring during pregnancy (Volk et al., 2020).

Endocrine markers

In addition to the immune system as previously discussed, the maternal endocrine system also plays several crucial roles in fetal development. These roles include energy balance, metabolism, and hormone secretion (Murphy et al., 2006; Stern et al., 2021). Using proxies of studying endocrine-disrupting compounds or processes on early development, it has been suggested that dysregulation of this system over time can lead to adverse consequences for early life programming (Basak et al., 2020; Lewis et al., 2014).

One studied example of an endocrine regulator is the maternal thyroid hormone. Cohort studies from the UK, Spain, and The Netherlands have found that maternal thyroid function is associated with childhood IQ (Korevaar et al., 2018; Levie et al., 2018). While other studies using the ALSPAC UK cohort found no associations between the maternal thyroid hormone (FT4 and TPO-Ab) and child emotional and behavioural problems (Fetene et al., 2020), the Norweigan Mother, Father and Child Cohort Study (MoBa) presenting findings of children whose mothers had hypothyroidism and who were prenatally exposed to thyroid hormone replacement therapy (THRT) having more positive developmental outcomes in motor, communication, and behaviour at preschool age (van den Broek et al., 2021).

While endocrine regulation can be artificially induced as shown above, endocrine disruptions can also be elicited through a variety of ways. An extensively studied way of human endocrine disruption is through higher exposure of concentration to exogenous compounds or

substances such as phthalates, perfluorinated compounds (PFCs) or bisphenol (BPA), with evidence for pregnancy complications like gestational diabetes mellitus. Around twenty years ago, Danish researchers observed that mild analgesic drugs shared similar chemical characteristics with these environmental compounds, which lead to the hypothesis that analgesic drugs could also be potential endocrine disruptors during pregnancy (Skakkebæk et al., 2001). Subsequent research using UK, Danish, and Finnish cohorts have led to mixed adverse health outcomes with some gender-specific effects (Ernst et al., 2019; Fisher et al., 2016; Jensen et al., 2010; Kristensen et al., 2011), displaying an unclear safety profile of these drugs on fetal outcomes when taken during pregnancy. A more recent study using a Swedish cohort has found that the analgesic drug paracetamol when taken during pregnancy, increased risk for language delay at 30 months old, with dose-specific effects for females (Bornehag et al., 2018). As shown by a recent consensus statement from multiple scientific experts (Bauer et al., 2021) this is an area that is suggested for clinical intervention. Therefore, more research should be done to understand how endocrine-disrupting mechanisms from common and accessible medication can affect neurodevelopment outcomes.

Metabolic markers

A growing area of interest is how maternal metabolic markers influence fetal programming. Compared to other animals that exhibit lower capacity for transfer of long-chain fatty acids during pregnancy, it is suggested that in humans, fatty acid transfer plays an essential role for brain development both during prenatal and postnatal stages (Devarshi et al., 2019;

Kabaran & Besler, 2015). Epidemiological research based on the DOHaD hypothesis have uncovered molecular mechanisms that link a poor metabolic environment during pregnancy to impaired fetal development, with implications for long-term health outcomes (Hoffman et al., 2021).

Maternal lipid abnormalities such as hypercholesterolemia, elevated triglyceride levels, gestational diabetes, or higher body mass index (BMI) have been associated with adverse pregnancy outcomes (Gootjes et al., 2022; Grimes & Wild, 2000). Maternal obesity, sometimes classified as low-grade systematic inflammation, is seen to target fetal brain cells, specifically microglia maturation and migration (Ozaki et al., 2020), leading to long-lasting inflammatory signatures and negative neurodevelopmental trajectories in both preclinical models and human studies (Cirulli et al., 2022; Rubini et al., 2022; J. Zhang et al., 2019). Studies examining maternal obesity and neurodevelopmental outcomes have found associations with increased ADHD risk in both children and adolescents (Jenabi et al., 2019; L. Li et al., 2020). Maternal chronic hypertension during pregnancy was seen to increase risk for ADHD (HR: 1.22) and developmental delay (HR:1.29), which was further increased through occurrence of maternal diabetes, preterm deliveries, or fetal growth restriction (Chen et al., 2021). Maternal lipid levels in pregnancy have been associated with corresponding child lipid levels at 6 and 10 years old (Adank et al., 2022). In addition, low serum levels of LDL cholesterol measured at 9 years old was associated with higher impulsivity later in adulthood for males (Tomson-Johanson et al., 2020). While is sufficient evidence on maternal-child associations in this domain, research on how child lipid levels are associated with future psychological outcomes has been very

limited. Given that lipid markers tend to co-occur as together, it is pertinent to examine patterns of metabolic health risk during pregnancy to understand their effects on the fetus, and subsequently during childhood.

Converging research looking at immune and endocrine markers as modulators of neurodevelopment have found that long-term effects of stress-related immune dysregulation in pregnancy is associated to maternal metabolic syndrome, which then increases risk for altered endocrine function and a high-risk lipid profile in a young adult (Entringer, 2013). Recent research found that some pregnancy patterns of inflammation involving multiple markers (e.g. maternal adiponectin and leptin) were subsequently associated with binding protein patterns in children at 9 years old, implying that maternal biomarkers acting together exert a greater influence on child development as compared to single biomarker effects (Entringer et al., 2015).

The above review of inflammatory biomarkers seems show a potential biological-to-psychological cascade caused by dysregulated maternal biological processes, which subsequently influence neural infrastructure development, fetal cardiovascular health risk, and child psychological outcomes. However, research examining effects of multiple maternal inflammatory biomarkers on child development outcomes is still relatively unexplored and therefore will be one of the focal points of this thesis.

Developmental outcomes

Research has placed much emphasis on maternal psychological stress and a child's psychosocial outcomes (Christian, 2015; Graham et al., 2022; Monk et al., 2019). Examination of literature shows an emerging research direction of developmental psychoneuroimmunology that points towards disrupted gestational biology mechanisms influencing the oxidative stress cascade and fetal brain development (Beijers et al., 2014). Our understanding of these mechanisms as strong mediators of neuropsychiatric risk is still limited despite similar effects shown on a child's cognitive, emotional, and behavioural outcomes (Hantsoo et al., 2019; O'Connor et al., 2014).

Longitudinal studies have established that early-life developmental risks are strong predictors of adverse lifetime outcomes (Walker et al., 2011), ranging from atypical brain development (Graham et al., 2018), neurodevelopment and behavioural disruption (Smith & Pollak, 2020), educational attainment (Ragnarsdottir et al., 2017), health disease risk (Tamburini et al., 2016), or mental health disorders (Salum et al., 2010). This results in greater healthcare utilisation and burden over time (Kalmakis & Chandler, 2015). It is also important to recognise that psychological outcomes can potentially influence each other. For example, self-regulation during preschool have been found to be predictors of mathematics, literacy, and socioemotional skills (Korucu et al., 2022). This implies a need to examine these factors together with potential mediating, confounding, or covarying factors such as time-sensitive effects or environmental variables.

Trimester effects

Despite driving mechanisms of risk being recognised as complex and multifactorial, one underexplored area are time-based effects, or trimester-effects during pregnancy. While immunological manipulations in mice studies have established that chronic inflammation in early pregnancy influenced brain and behavioural pathology (Meyer et al., 2008), other preclinical studies have found that late exposures of inflammation were associated with pathological brain aging (Giovanoli et al., 2015), commonly linked with increased risk of disorders of suspected neurodevelopmental origins such as ASD or schizophrenia (Arrode-Brusés & Brusés, 2012). These preclinical mice models on perinatal inflammation and adult psychopathology (Depino, 2018) give strong impetus for exploring trimester effects of disrupted human maternal biology during pregnancy and child outcomes.

In human studies, specific gestational trimesters have been more strongly associated with specific brain functional connectivity that can be seen in the infant after birth, displaying strong fetal-brain to infant-behaviour connections. For example, second trimester neural development has been associated with increased connectivity between female infant motor networks, resulting in more mature motor functions during infanthood (Thomason et al., 2018). Current research is starting to investigate trimester-based processes for further understanding of maternal or fetal complications to potentially take preventive actions for better outcomes (Arabin & Baschat, 2017; Lassi et al., 2014; Tu et al., 2021).

As shown above for immune biomarkers, cohort studies have examined maternal pro-inflammatory cytokines in relation to the fetal development process. Other studies looking at potential time-sensitive windows showed maternal viral infections in the first trimester and bacterial infections in the second trimester was associated with ASD diagnosis (HR: 2.98), implying that earlier prenatal infection possibly increases risk of ASD (Atladóttir et al., 2010). Another studied perspective using prenatal infections as measured through cortisol levels during the second trimester have been associated with higher depression scores in adolescence, suggesting greater risk of psychopathology when there are elevated glucocorticoids in presence of maternal immune activation (Lipner et al., 2022). Maternal third trimester inflammatory cytokines were associated with also poorer infant cognitive outcomes (Nazzari et al., 2020) and ADHD symptoms at 4 to 6 years old (Gustafsson et al., 2020). The above shows that elevated pro-inflammatory cytokines levels during different trimesters of pregnancy seems to affect the fetus differently.

Lipid metabolism seems to be a potential area for study as it is a complex process with fluctuations seen over the pregnancy period (Pusukuru et al., 2016). Poorer lipid profiles involving variables such as body fat, cholesterol, and triglycerides in the second and third trimester are associated with DNA damage and oxidative stress in the mother (Loy et al., 2013), where heightened levels of oxidative stress have pathological links with gestational diabetes (Lappas et al., 2011; Turek et al., 2015). A cohort study found maternal lipids of triglycerides and remnant cholesterol levels in early pregnancy being associated with large-for-gestational (LGA) infants, but not for SGA (Adank et al., 2020). However, a more recent

study looking at both second and third trimester lipid predictors of triglycerides and high-density lipoprotein levels found associations with LGA infants and macrosomia (Xi et al., 2021). Another study examining higher triglyceride levels and cholesterol concentrations in early trimester found that these were associated with increased embryonic size only when women were overweight (Gootjes et al., 2022). High glycaemic load during mid-pregnancy was also associated with LGA, but effects for child BMI were weakened over time (Maslova et al., 2019a).

The presented outcomes above display a clear association between maternal and fetal lipid transfer during pregnancy through effects on fetal cell growth and signalling, as supported by literature of maternal-fetal fatty acid transport and metabolism. However, literature on how this translates to development or psychiatric outcomes is still very limited, and so this thesis explored this through Chapters 3 and 4.

Pregnancy trimester-based research shows a possible temporal dependence of maternal inflammation occurring during pregnancy and risk of disrupted neurodevelopment in the offspring. As evidenced, the literature on maternal trimester effects on neurodevelopmental or psychological outcomes is lacking, likely due to the process of progressing pregnancy being both complex and dynamic in nature. To add to the limited literature, this thesis has included two chapters (Chapters 2 and 4) that accounted for maternal trimester-based effects on studied child outcomes.

Potential Confounders and Covariates

As with any examination of longitudinal processes, differentiation of confounders and covariates can be challenging, yet it is important to adjust for relevant variables to achieve unbiased estimates of prenatal effects on child outcomes. Confounders and covariates in this thesis were differentiated through the basis on traditional representation of exposure and outcomes (Shrier & Platt, 2008). When exploring causal relationships, confounders were classified as a factor for cause of both exposure and outcome, while covariates were classified as a factor that potentially influenced both exposure and outcome. As pregnancy is a long and complicated process, it is sometimes not clear what should be treated as a confounder, covariate, or moderator. This subsection presents literature on a few variables of interest that that were classified as a potential confounders or covariates within this thesis.

This thesis also attempted to account for this potential risk of bias through different models fits, such as running multiple regression models in a hierarchical manner with increasingly adjusted models to further understand associations through a stepwise addition of variables. Each thesis chapter further explains how variables were sorted into confounders and covariates.

Socioeconomic status

Socioeconomic status has been shown to be a stable and strong factor that influences neurodevelopment throughout and after the pregnancy period. A systematic review and meta-analysis across five continents examining general socioeconomic disadvantage as

defined through parental income, education, occupation, SES indices, and marital status, found links with increased prevalence of ADHD during childhood (Russell et al., 2016). From a biological perspective, presence of elevated gestational immune markers with socioeconomic disadvantage during pregnancy has been associated with fetal neurological abnormalities such as motor skills and response to stimuli either at 4 months or 1 year old (Gilman et al., 2017). Socioeconomic risk during pregnancy has also been associated with child socioemotional-behavioural problems at age one (Ahmad et al., 2022). More effects were found for financial difficulties on structural brain development, particularly those areas associated with school readiness skills. Children from low-income households were seen to have differences in frontal and temporal lobes and scored 4 to 7 points lower on standardised tests (Hair et al., 2015), as well as lowered functional connectivity and lowered IQ scores at 48 months (Xie et al., 2019).

Maternal lifestyle choices

Maternal smoking

Maternal prenatal smoking has been associated with both birth, health, and developmental outcomes (Römer et al., 2020). Shortened deoxyribonucleic acid (DNA) telomere length has been found in infants whose mothers smoked during pregnancy, which in turn lead to a higher risk for ADHD (Howell et al., 2022). Mothers who were heavy smokers had a slightly increased risk of ADHD in children (OR: 1.75) as compared to light smokers (OR: 1.54). A meta-analysis examining population-based cohorts found that prenatal exposure to maternal

smoking during pregnancy was associated with childhood ADHD after controlling for parental socioeconomic status and psychiatric history (Dong et al., 2018).

Maternal alcohol

Generally, cohort studies show around 50% of pregnant women drinking alcohol during pregnancy, despite well-established research on maternal alcohol intake being associated with birth and developmental outcomes such as fetal alcohol syndrome and gross motor deficits (Lucas et al., 2014). Prenatal alcohol exposure has also been associated with sensation-avoiding behaviour at 2 years old and cognition, though effects of the latter was attenuated after adjustments for social deprivation factors (Halliday et al., 2017). Beyond child outcomes, retrospective cohort study examining youths participants found that prenatal alcohol exposure was associated with greater attention deficit, impulsiveness, and psychopathology during adolescent stage (Lees et al., 2020). Meta-analysis results from other cohorts also found small negative associations for alcohol exposure and child cognition (Flak et al., 2014). Structural neuroimaging studies have found prenatal alcohol exposure being associated with lowered volume in the anterior cingulate cortex in children and adolescents (Andre et al., 2020), with adverse effects on both behaviour and cognition (Aghamohammadi-Sereshki et al., 2022; Migliorini et al., 2015).

Maternal psychiatric history

Maternal psychopathology, usually considered a pervasive trait, has been associated with child development outcomes. During the prenatal stage, family history of psychopathology

and maternal ADHD phenotype were associated with child's hyperactive-impulsive and combined symptoms within the ADHD diagnosis (Roigé-Castellví et al., 2021). Maternal history of major depressive disorder has been found to not only increase risk for child psychopathology (S. H. Goodman et al., 2011), but also disrupt mother-child interactions through reduced positive affect (Kudinova et al., 2019) or less expressed emotional availability as compared to healthy controls (Kluczniok et al., 2016). Another meta-analysis using 191 studies that investigated maternal antenatal depression and anxiety found higher risk for socioemotional, cognitive, motor, and adaptive behaviour from infancy into adolescence stage (Rogers et al., 2020).

Maternal education

Maternal education is seen as an important indirect factor that possibly mediates negative child outcomes. Higher maternal education has been found to attenuate negative associations between suboptimal maternal pre-pregnancy BMI and child cognitive outcomes (West et al., 2022). Maternal education, when controlled for SES, was associated with better math, reading, and working memory skills at the kindergarten entry stage (Muñez et al., 2022). A study examining 3- to 5-year-old children across 39 countries found that maternal education was associated with higher education level completion (Jeong et al., 2018). Another study examining the same age group of children in 51 countries identified maternal education as one of the significant contributing factors to the human development index (HDI). Higher HDI was associated with higher child development scores in learning, literacy and numeracy, socioemotional health, and physical health (Bornstein et al., 2021).

Low birthweight and early gestational age

Birth factors included in this thesis were low birthweight and early gestational age (prematurity), possible moderators of outcomes. A multilevel analysis review study found that the combination of maternal depressive symptoms and lower socioeconomic status was associated with reduced infant birth weight (Dunkel Schetter & Lobel, 2012), showing that the combination of these two risk factors possibly restricts child intrauterine growth. In addition, maternal depressive symptoms combined with prematurity, or lower gestational age, were seen to be indicators of emerging internalising disorders such as anxiety and depression in children at age 2 (Weiss & Leung, 2021). Compromised birth factors show long-term effects across development domains. A review examining low birth weight with decreased gestational age have been associated with increased prevalence of motor and cognitive delays from 18 months to 6 years old (Pascal et al., 2018). Gestational age was also found to be a mediator for links between maternal immune activation and total brain volume at 10 years old, with possible sex-specific effects (Suleri et al., 2022). Overall, it should be noted that prematurity has shown effects on neurodevelopment and that preterm infants have generally been associated with poorer developmental outcomes through both intrauterine and extrauterine growth restriction. However, the incidence of this in the selected cohorts have been low and this was only considered a potential secondary factor in child outcomes.

Child sex

Through observation of longitudinal brain and behaviour associations, it has been suggested that the female fetal brain is less susceptible to early environmental programming (Thomason et al., 2018). However, when examining adolescence-to-adult outcomes, it seems that females are more at greater risk for affective disorders upon peripubertal adversity, showing how pubertal hormones possibly plays an important role for female adult psychopathology when comparing sex differences (T. L. Bale & Epperson, 2015). Conversely, in the presence of exposure to perinatal stress, males frequently exhibit more maladaptive outcomes, particularly in relation to the mother's emotional climate, which may contribute to overall greater vulnerability in life. This can be seen through generally higher risk for disorders such as ADHD, ASD, and schizophrenia for when maternal stress is present during pregnancy (Beversdorf et al., 2005; Khashan et al., 2008; van Os & Selten, 1998).

Overarching findings

Epidemiological studies have found mixed outcomes when exploring the associations between maternal-to-fetal processes and child development, especially with presence of confounders and covariates. The above literature has generally shown that socioeconomic risk, maternal lifestyle choices, maternal stress from adversity or psychiatric history, and some birth factors are factors involved in associations between maternal inflammation and child development outcomes. As shown through developmental studies of risk (Black et al., 2017), certain factors show significant effects on lifespan outcomes, so they were considered and adjusted for within the empirical studies in this thesis.

Thesis Aims and Objectives

Table 1-1. Current research gaps

Current literature	Research gaps
Intrauterine processes already established in preclinical (animal) models for offspring outcomes	Limited human studies on how intrauterine processes affect child outcomes
Maternal inflammatory markers such as immune (CRP, IL-6) and endocrine (FT4 - thyroid) markers have been examined in relation to child health outcomes	Other maternal inflammatory markers such as metabolic markers (BMI, cholesterol, or lipid metabolism) have been underexamined in relation to child developmental outcomes
General understanding of disrupted gestational biology influencing child outcomes	Limited understanding of trimester-specific effects of gestational dysregulation or disruption on child outcomes
Found that endocrine regulators such as thyroid hormones taken during pregnancy can potentially affect fetal development	Limited understanding of how potential endocrine disruptors such as medication taken during pregnancy can affect subsequent child neurodevelopment

As displayed in the table above, there are specific gaps in the current literature. Firstly, despite having established that the intrauterine environment is important in preclinical studies (animal models), research on translating these to human studies to understand how maternal health affect child development outcomes is still lacking. Research has shown that maternal immune activation response and endocrine disruption likely corresponds with child health

and some development outcomes. However, maternal metabolic markers such as lipid metabolism dysregulation have been very underexplored when looking at child development outcomes. In addition, while it has been established that disrupted gestational biology influences fetal and child outcomes, research is still needed to explore how trimester-specific effects of any potential disruption affects child outcomes, while taking also into account that pregnancy is a complex and dynamic process. Lastly, while the effects of endocrine regulation during pregnancy have shown positive effects on fetal development, the long-term effects of potential endocrine disruptors such as medication exposure are still yet to be understood on child neurodevelopment.

Based on the above identified gaps, this thesis seeks to address the following questions:

1. Does maternal metabolic health risk during pregnancy affect childhood and adolescent outcomes?
2. Do child cord blood markers of metabolic risk mediate the effects of maternal metabolic health risk during pregnancy on child development?
3. Are there trimester-based effects of maternal inflammation during pregnancy on children's development?
4. Do effects of maternal metabolic health risk during pregnancy on childhood and adolescent outcomes hold after controlling for a range of external factors?
5. How does prenatal medication exposure affect a child's neurodevelopmental outcomes?

The corresponding research hypotheses are as follows:

1. Maternal metabolic health risk during pregnancy affects developmental outcomes in childhood and adolescence.
2. Cord blood markers displaying metabolic risk will have mediating effects on maternal metabolic risk during pregnancy and child development outcomes.
3. Maternal inflammation occurring at later pregnancy trimesters will have negative effects on children's developmental outcomes.
4. Negative effects of maternal metabolic health risk during pregnancy will still hold for childhood and adolescent outcomes even after controlling for other external factors.
5. Prenatal medication exposure of analgesic drugs will negatively affect children's neurodevelopmental outcomes.

The Barker hypothesis has provided strong theoretical underpinnings for more maternal-fetal neurodevelopmental research. The above literature has elucidated a combination of endogenous (genetics) and exogenous stress (environment) variables interacting with impacted immunity over time (inflammatory cytokines), thereby possibly resulting in disrupted fetal and child programming. Added considerations also include possible critical windows such as pregnancy trimesters effects and other confounding or covarying factors. This thesis focuses on data from prospective cohort studies. Data from such studies provide several advantages: a) it provides us with an ethical avenue to examine disrupted maternal exposures during pregnancy on developmental outcomes, b) it includes temporal ordering of exposures and outcomes and allows for studying change of outcomes over time, c) given

the richness of the data available, it allows for modelling multiple exposures with multiple outcomes while adjusting for other factors in large sample sizes (Wang & Kattan, 2020).

This thesis will draw from multidisciplinary research with primary focus on establishing proof of concept that specific intrauterine or maternal processes caused by inflammation are associated with adverse child cognitive or psychological outcomes. For obvious reasons, interpretations from immunological manipulation or invasive experiments on humans are not ethically possible, so most human research is limited to analysis of at-risk pregnancies. Conditions of interest in this thesis include effects of maternal infections in pregnancy, maternal metabolic health risk in pregnancy, and prenatal exposure to medications, of which this thesis explores a range of outcomes including behaviour, cognition, potential developmental delays during childhood, and persistence of potential effects from childhood to adolescence.

This thesis has 3 empirical chapters and 1 review chapter. Chapter 2 examines associations between maternal prenatal infections in specific pregnancy trimesters and child developmental and cognitive outcomes at three time points (18 months, 4 years, 8 years). Chapter 3 examines associations between maternal metabolic markers during pregnancy in each trimester and child socio-emotional outcomes over time (4 to 16 years old). Chapter 4 examines associations between maternal metabolic syndrome classification and child outcomes at 5 years old, using child cord blood markers as potential mediators. Thes empirical chapters used United Kingdom cohort studies from either the Avon Longitudinal

Study of Parents and Children or the Born in Bradford cohort. Chapter 5 presents an umbrella review that synthesises evidence on how maternal analgesic drug use during pregnancy affects child neurodevelopmental outcomes of autism spectrum disorder (ASD) or attention-deficit hyperactivity disorder (ADHD). Chapter 6 provides an overall discussion of literature and thesis chapters, with conclusions and suggestion for further research.

Chapter 2: Maternal Infections and Child Cognitive Development

Synopsis

This chapter uses the Avon Longitudinal Study of Parents and Children (ALSPAC) United Kingdom cohort sample to examine how self-reported maternal infection occurrence during individual pregnancy trimesters is associated with child cognitive outcomes at 18 months, 4 years, and 8 years. Regression analyses were run using developmental and intelligence quotient measures, adjusting for maternal and socioeconomic covariates. Results suggest that maternal infection occurrence during the third pregnancy trimester was associated with decreased verbal IQ at 4 years old, and decreased verbal, performance, and total IQ at 8 years old. The magnitude of effect appears to be small.

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Authors' contributions

I conceptualised and designed the study, conducted analysis, interpretated the data, drafted and revised the manuscript drafts and revisions, and published the paper. Dr H. A. Hall contributed to study coding, and manuscript revisions. Dr A. L. Murray provided feedback throughout all stages of the process; study design, data analysis and write-up, manuscript revision, and the journal submission process. Dr B Auyeung contributed to data acquisition, funding, and journal submission. Dr M. V. Lombardo contributed to manuscript review.

The manuscript has been slightly modified for the purpose of this thesis.

Maternal infections during pregnancy and child cognitive outcomes

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List of Study Abbreviations

ALSPAC: Avon Longitudinal Study of Parents and Children

DQ: Development Quotient

IQ: Intelligence Quotient

GMDS: Griffiths Mental Development Scales

WPPSI-RUK: Wechsler Preschool and Primary Scale of Intelligence – Revised UK edition

WISC-III: Wechsler Intelligence Scale for Children, 3rd edition

Abstract

Background: Maternal prenatal infections have been linked to children's neurodevelopment and cognitive outcomes. It remains unclear, however, whether infections occurring during specific vulnerable gestational periods can affect children's cognitive outcomes. The study aimed to examine maternal infections in each trimester of pregnancy and associations with children's developmental and intelligence quotients. The ALSPAC birth cohort was used to investigate associations between maternal infections in pregnancy and child cognitive outcomes.

Methods: Infection data from mothers and cognition data from children were included with the final study sample size comprising 7,410 mother-child participants. Regression analysis was used to examine links between maternal infections occurring at each trimester of pregnancy and children's cognition at 18 months, 4 years, and 8 years.

Results: Infections in the third trimester were significantly associated with decreased verbal IQ at age 4 ($p < .05$, adjusted $R^2 = 0.004$); decreased verbal IQ ($p < .01$, adjusted $R^2 = 0.001$), performance IQ ($p < .01$, adjusted $R^2 = 0.0008$), and total IQ at age 8 ($p < .01$, adjusted $R^2 = 0.001$).

Conclusion: Results suggest that maternal infections in the third trimester could have a latent effect on cognitive development, only emerging when cognitive load increases over time, though magnitude of effect appears to be small. Performance IQ may be more vulnerable to trimester-specific exposure to maternal infection as compared to verbal IQ. Future research could include examining potential mediating mechanisms on childhood cognition, such as possible moderating effects of early childhood environmental factors, and if effects persist in future cognitive outcomes.

Keywords: pregnancy, infections, cognition, child development, ALSPAC

Background

Research has suggested links between a mother's immune system during pregnancy and fetal growth and brain development. (Alvarado & Schwartz, 2017; J. F. Bale, 2009) Central nervous system infections in pregnancy, such as herpes simplex virus and rubella, have been associated with intrauterine growth restriction, prematurity, and long-term neurodevelopmental deficits or disability (Curcio et al., 2020). Maternal prenatal bacterial infections have been linked with lower mean IQ scores at age 7 (Carter et al., 2003), and viral infections have shown associations with decreased IQ scores at age 7 (strong effect sizes) (Y. H. Lee et al., 2020) and learning disabilities (Racicot & Mor, 2017). In addition to reported effects on children's cognition (Parboosing et al., 2013) and socioemotional difficulties (Hall et al., 2021b), maternal infections have also been linked to a variety of psychiatric conditions such as bipolar disorder and schizophrenia(Brown et al., 2005; Cordeiro et al., 2015). These studies demonstrate associations between maternal infections and general difficulties in cognition, behaviour, and psychopathology.

The occurrence of viral maternal infection is proposed to influence the pathogenesis of infant central nervous system abnormalities via placental transfer-mediated vertical transmission (Silasi et al., 2015). This transmission may further disrupt the fetus' organ and brain tissue development, negatively affecting the infant's immune system, resulting in further pathology of a compromised immune system and increased risk of childhood inflammation (J. F. Bale, 2009). Childhood low-grade inflammation then activates a systemic immune response associated with negative effects on brain development and function, with research showing

small to moderate effect sizes on general intelligence (Mackinnon et al., 2018). These processes reflect multiple potential mechanisms of harm acting upon the child when maternal infection is present during pregnancy.

Even though trimester-specific associations have been reported for maternal infections and fetal neurodevelopment (Y. H. Lee et al., 2020), evidence is still lacking on whether cognitive outcomes depend on the specific timing of maternal infection exposure during gestation. The idea of fetal neurodevelopment being stage-dependent is based on the fact that brain myelination only begins during the second trimester of pregnancy with further growth reinforcements in the third trimester, followed by postnatal growth (Cordeiro et al., 2015; Yarnykh et al., 2018). Therefore, inflammation such as infections during specific gestation periods may differentially affect the fetal growth process. However, only a limited number of studies have found that maternal inflammation during later gestational periods negatively affects a child's cognitive-developmental infrastructure (Meyer et al., 2006) and functional connections such as working memory (Rosenberg, 2018).

Current research shows converging evidence between animal and human studies, with a review of large cohort studies suggesting a causal relationship between prenatal maternal inflammation and child outcomes (Hantsoo et al., 2019), particularly with effects on the fetal brain development (Lautarescu et al., 2020). Examining the links between prenatal infection at different stages of gestation and cognitive outcomes is, however, subject to significant methodological challenges. In particular, it is not possible to conduct randomized

experiments in humans for obvious ethical reasons. This makes it difficult to attribute causality to a factor such as prenatal infection. On the other hand, animal studies in which experimental manipulations are possible have been criticized for potential problems with generalization to humans (Harvey & Boksa, 2012). As such, the field must rely on triangulation across these different evidence sources with complementary strengths and weaknesses (Banik et al., 2017; Morales-Suárez-Varela et al., 2010; Mulkey et al., 2019).

Despite human studies generally having to rely on observational evidence, they can provide valuable predictive information about which children may be most at risk of poorer cognitive outcomes. For example, identifying an association between prenatal infection at a particular stage of pregnancy and poorer cognitive ability can help identify children who may benefit from a higher level of monitoring and intervention early in life, such as screening for learning difficulties or prioritization for early-life preventive interventions. This study seeks to utilize observed evidence to provide predictive evidence of mother-fetal associations, despite limitations in examining specific underlying processes or mechanisms.

The aim of this study is to use a cohort sample to investigate whether the occurrence of maternal infections in each trimester of pregnancy is associated with children's verbal, performance, and total IQ scores.

Methods

Setting

Data for this project were from the Avon Longitudinal Study of Parents and Children (ALSPAC), a population-based cohort study based in Avon, United Kingdom (UK), focusing on pregnant women with expected dates of delivery 1st April 1991 to 31st December 1992 (Boyd et al., 2013; Rosenberg, 2018). Regular follow-up clinic assessments were conducted over the years to track development over time. The ALSPAC dataset is a large, nationally representative sample of parents and children from the UK. Detailed medical information were gathered from pregnant women and their children from 8 weeks of gestation up to 22 years of age. Participants in ALSPAC have a slightly higher sociodemographic profile on average as compared to the general population in Avon and Great Britain (Fraser et al., 2013). For example, ALSPAC mothers are more likely to be married, live in owner-occupied accommodation, have a car in their household, and less likely to be non-White.

Participants

The final sample of data collected and used in this study was for when the children were eight years old was *n*=15,645. For the purposes of this study, participants with missing infection data across all trimesters (*n*=2,125) were excluded from the sample, as well as those who had missing outcome data across all cognitive domains (*n* = 6,110). The final sample size comprised *n* = 7,410 mother-child participants.

Outcome measures

Prenatal infections

Data on prenatal infections from the first, second and third trimesters were gathered in weeks 18 and 32 of gestation, and 8 weeks postpartum (Fraser et al., 2013). Retrospective assessment was completed at 8 weeks after birth for infections occurring in the third trimester of pregnancy. Women were asked whether they experienced any of the following infections: urinary tract infection, influenza, rubella, thrush, genital herpes, or other infections.

Response options provided at 18 weeks were: 'Yes, in 1st to 3 months', 'Yes, 4 months to now', 'Yes for both time periods' and 'Not at all'. Response options at week 32 and 8 weeks postpartum were: 'Yes', 'No', and 'Don't Know'. Response options for infections reported occurring during the first, second, or third trimester of pregnancy were coded and termed as 'any trimester'. Infection data were coded into dichotomous variables, where any incidence of infection was coded as a 'yes', and no incidence was coded as a 'no'. Infections were further coded according to trimesters, with any occurrence of infection coded as present (e.g., rubella or urinary tract infection at 18 weeks = infection present in the first trimester).

Childhood IQ scores

Developmental and cognitive measures included the Griffiths Mental Development Scales (GMDS), administered at 18 months, the Wechsler Preschool and Primary Scale of Intelligence – Revised UK edition (WPPSI-RUK), administered at 4 years, and the Wechsler Intelligence Scale for Children, 3rd edition (WISC-III), administered at 8 years. The GMDS evaluates early

development and consists of five subscales (locomotion, personal/social skills, hearing and speech, hand-eye coordination, and performance) (R. Griffiths, 1984). The hearing and speech scale (language, response, speech development) (Rosner & Simon, 1971) and the performance scale (skill development and manipulation), comprising 86 items each, were selected for use in the current study. Standardised developmental quotients were calculated through this formula: Developmental Quotient (DQ) = (Mental age x 100) / Chronological age. A new average GMDS development score variable was then calculated using the mean scores across all 5 scales by the ALSPAC team. All variables were age-adjusted by the ALSPAC research team. The study further included two measures of cognitive functioning: WPPSI-RUK for children aged 3–7 years (Rosner & Simon, 1971) and a short-form version of the WISC-III for children aged 6–17 years (Wechsler, 1974). Both tests comprise two scales: verbal and performance (non- verbal ability and executive function), with each scale containing five subtests. Scores on both the WPPSI-RUK and the WISC-III range from 40 to 160. All IQ scores were used as continuous variables. Descriptive statistics for verbal IQ, performance IQ, and fullscale IQ scores are provided in Appendix A, Table A1.

Confounders and covariates

Data on other perinatal and social factors which may be associated with prenatal infections and/or children's cognitive outcomes were gathered from assessments from mothers and children. Child factors included child sex (male/female), gestational age (weeks) and birthweight (grams). Standard cut-offs for prematurity were applied to gestational age (≥37 weeks/<37 weeks) and birthweight (≥2500 g/<2500 g) as per clinical standards of falling

within the 10th percentile of pregnancies, with increased infant mortality risk (Eskes et al., 2019; Hughes et al., 2017). Maternal and socioeconomic factors included maternal age at birth, maternal education, maternal history of smoking, maternal psychiatric history, and deprivation indices. Maternal education was assessed at 32 weeks of gestation through interviews and categorized as A-levels or lower. Maternal smoking was coded as 'yes' or 'no' and assessed through questionnaires for every trimester of pregnancy (18 weeks, 32 weeks, 8 weeks postpartum for the third trimester). Maternal psychiatric history was assessed in the first trimester, where women were asked if they had any psychiatric conditions (anorexia, bulimia, severe depression, schizophrenia, other psychiatric issues), and coded as yes if they indicated having any psychiatric illness. Deprivation indices were sorted into quintile ranks and measured by the official Indices of Multiple Deprivation, an area-level deprivation index measured in England accounting for several domains of deprivation: income, employment, health, education, housing, and living environment (Noble et al., 2006).

Previous literature has identified these factors to be associated with children's cognitive development (Mackes et al., 2020; Sania et al., 2019; Sommerfelt et al., 2000). These factors were classified into potential confounders and covariates for the regression models in this study, with confounders being selected based on whether previous literature showed associations between infection exposure and cognitive outcomes (such as deprivation), and covariates (such as child's sex) selected based on their potential association with children's cognitive outcomes. Adjusting for the latter was of interest to determine the unique contribution of infection exposure over and above other established influences.

Statistical Analysis

All statistical analyses were conducted using R (version 3.4.1)(R programme, 2021). Data was inspected for and met parametric statistical assumptions. Linear regression models were used to examine the relations between infections occurring at each trimester and children's cognitive scores at ages 18 months, 4 years, and 8 years. Three types of models were fit: an unadjusted model, a model adjusted for potential confounders, and a model adjusted for potential confounders and additional covariates as introduced in Chapter 1. These models were run in a hierarchical manner, with increasingly adjusted models specified by adding predictors to models from previous steps. The fully adjusted model included possible confounders of maternal and socioeconomic factors, and the additional covariates of child sex, gestational age, birthweight, maternal psychiatric history, and maternal smoking (Appendix A, Table A2). As the models were trimester-specific, regression analyses for infections in each trimester were also adjusted for infections in the other two trimesters.

In the primary analysis, missing data were handled with full information maximum likelihood estimator, and an alpha level of 0.05 indicated statistical significance ($p<.05$). Sensitivity analysis included multiple imputation models using the MICE package in R, with 25 imputations applied in order to avoid Monte Carlo error (Buuren, 2018; Royston, 2004). Models were fit from the multiple imputed data sets, with estimates pooled into a single set of estimate and standard errors, which was then used for the analysis.

Table 2-1. Regression models on infections in pregnancy and cognitive outcomes

(n = 7,410)			Any trimester	1st trimester	2nd trimester	3rd trimester
			B values (*SE*)			
Model 1[a]	**GMDS**	Hearing & Speech (verbal)	-1.55 (*.985*)	-.429 (*1.20*)	-1.32 (*1.15*)	-.940 (*1.31*)
		Performance	-.099 (*.778*)	.029 (*.943*)	-.191 (*.901*)	-.177 (*1.03*)
		Average	-.854 (*.543*)	-.647 (*.655*)	-.623 (*.626*)	-.297 (*.717*)
	WPPSI-RUK	Verbal	-1.45 (*.887*)	-.547 (*1.07*)	-.051 (*1.02*)	-2.51 (*1.16*) *
		Performance	-.438 (*.951*)	.647 (*1.15*)	.430 (*1.10*)	-.810 (*1.25*)
		Fullscale	-1.07 (*.923*)	.037 (*1.11*)	-.061 (*1.07*)	-1.95 (*1.21*)
	WISC-III	Verbal	-.287 (*.418*)	.945 (*.509*)	-.120 (*.482*)	-1.48 (*.562*) **
		Performance	-.378 (*.427*)	.449 (*.517*)	-.062 (*.491*)	-1.49 (*.571*) **
		Total	-.368 (*.412*)	.796 (*.501*)	-.116 (*.475*)	-1.64 (*.553*) **
Model 2[b]	**GMDS**	Hearing & Speech (verbal)	-.150 (*.148*)	-1.09 (*1.38*)	-1.54 (*1.33*)	-.915 (*1.55*)
		Performance	-.228 (*.885*)	-.169 (*1.06*)	.078 (*1.02*)	-.606 (*1.19*)
		Average	-.637 (*.605*)	-.913 (*.729*)	-.313 (*.706*)	-.530 (*.820*)
	WPPSI-RUK	Verbal	-1.37 (*.960*)	-1.14 (*1.15*)	-1.42 (*1.10*)	-1.75 (*1.26*)
		Performance	-.508 (*1.04*)	.163 (*1.25*)	-.116 (*1.20*)	-.490 (*1.38*)
		Fullscale	-1.04 (*.993*)	-.614 (*1.19*)	-.871 (*1.14*)	-1.30 (*1.31*)
	WISC-III	Verbal	-.063 (*.431*)	.317 (*.523*)	-.262 (*.498*)	-.859 (*.584*)
		Performance	-.192 (*.457*)	.151 (*.552*)	.228 (*.524*)	-1.65 (*.615*) **
		Total	-.139 (*.425*)	.289 (*.515*)	-.070 (*.489*)	-1.34 (*.574*) *
Model 3[c]	**GMDS**	Hearing & Speech (verbal)	-1.71 (*1.22*)	-1.21 (*1.44*)	-.349 (*1.39*)	-1.61 (*1.64*)
		Performance	-.132 (*.952*)	-.077 (*1.11*)	.396 (*1.08*)	-.315 (*1.27*)
		Average	-.612 (*.642*)	-.791 (*.756*)	.286 (*.734*)	-.565 (*.862*)
	WPPSI-RUK	Verbal	-1.08 (*1.05*)	.852 (*1.22*)	-.983 (*1.17*)	-1.64 (*1.36*)
		Performance	-.167 (*1.13*)	.682 (*1.32*)	-.028 (*1.27*)	-.448 (*1.47*)
		Fullscale	-.692 (*1.08*)	-.150 (*1.26*)	-.540 (*1.21*)	-1.24 (*1.40*)
	WISC-III	Verbal	.304 (*.467*)	.415 (*.557*)	-.036 (*.531*)	-.603 (*.623*)
		Performance	.172 (*.493*)	.259 (*.587*)	.496 (*.559*)	-1.41 (*.655*) *
		Total	.255 (*.459*)	.412 (*.548*)	.188 (*.522*)	-1.34 (*.574*)

Note: linear regression analyses and beta coefficients for trimester-based infections in pregnancy and cognitive outcomes.

[a] *Unadjusted models*

[b] *Adjusted for potential confounds of maternal education, maternal age, deprivation, infections in other trimesters*

[c] *Adjusted for confounds, and additional covariates of maternal smoking, maternal psychiatric history, gestation, birth weight, and child sex*

**p<.05, **p<.01, ***p<.001*

Results

Descriptive statistics showed that the occurrence of maternal prenatal infections at any time during pregnancy was 54.6%, with most infections occurring during the 2nd trimester (34.9%). Mean developmental quotient and intelligence quotient scores were similar to the general population (GMDS=108, WPPSI-RUK=104, WISC-III=104). More descriptive statistics for maternal and child variables can be found in Appendix A, Tables A1 and A2.

Unadjusted models identified no links between infections occurring in the first or second trimesters and children's outcomes. Significant associations were found between third trimester infections and WPPSI-RUK verbal scores (β= − 0.076, p = .031) at age 4, and WISC-III verbal IQ scores (β= −0.036, p=.008), performance IQ scores (β= − 0.036, p = .009), and total IQ scores (β= −0.040, p=.003) at age 8. These results showed that an infection during the third tri- mester of pregnancy was associated with a 2.5 IQ point decrease for WPPSI-RUK verbal scores at age 4, 1.5 IQ point decrease in WISC-III verbal scores, 1.5 IQ point decrease for WISC-III performance scores, and 1.6 IQ point decrease for WISC-III total scores at age 8. No significant associations were found between prenatal infections in all three trimesters and any of the children's cognitive outcomes (Table 2-1).

Significant associations were attenuated after the first adjustment for confounders maternal age, maternal education, deprivation, and infections in the other two trimesters (Table 2-1, Model 2). Associations were no longer found for WPPSI-RUK verbal IQ scores (β= −0.053, p=.166) at 4 years and WISC-III verbal IQ scores (β= −0.021, p=.141) at 8 years. Significant associations remained between third-trimester infections and WISC-III performance IQ scores (β= −0.039, p=.007) and WISC-III total IQ scores (β= −0.033, p=.020) at 8 years (Table 2-1, Model 3). These results showed that an infection during the third trimester of pregnancy was associated with a 1.7 IQ point decrease in WISC-III performance scores, 1.3 IQ point decrease for WISC-III total scores at age 8.

Fully adjusted models (Table 2-1, Model 3) with confounders (maternal age, maternal education, deprivation indices, other two trimesters) and additional covariates (maternal smoking, maternal psychiatric history, gestation, birth weight, and child sex) showed that infections in the third trimester were associated with lower WISC-III performance scores at 8 years (β= −0.033, p=.032) (Table 2-1, Model 3). These results represent a 1.4 IQ point decrease in WISC- III performance IQ scores.

Sensitivity analysis

A sensitivity analysis of the study models found consistent associations between infections occurring at the third trimester and outcomes for WISC-III verbal IQ scores (β= -1.33, *p*=.022), performance IQ scores (β= -1.19, *p*=.028), and total IQ scores (β= -

1.39, p=.009) at age 8 in the unadjusted model. While no significant associations were shown between occurrence of infections at any trimester and cognitive outcome scores for the partially and fully adjusted models, lower maternal education (p<.05) and highest deprivation (p<.05) were generally seen to have associations with lowered cognitive scores across all trimesters.

Discussion

A prospective birth cohort was used to examine associations between maternal infections occurring at each trimester of pregnancy and children's developmental and intelligence scores at 18 months, 4 years, and age 8. Results from unadjusted models provided evidence for maternal infections during the third trimester being associated with verbal IQ scores at age 4, and verbal, performance, and total IQ scores at age 8. The associations between third-trimester infections and cognitive outcomes were seen to be attenuated after adjustment for confounders, with significant associations seen only for performance and total IQ scores at age 8 after the first adjustment. Further adjustment with additional covariates left only significant associations for performance IQ scores at age 8. A similar prevalence of maternal infections during pregnancy was shown in this study as compared to other cohort samples (Curcio et al., 2020; Harvey & Boksa, 2012).

Findings suggest that children's cognitive outcomes may depend on critical periods in gestation, with evidence pointing to effects of infection limited to later gestation. Animal models have provided evidence on potential mechanisms, showing that inflammatory cytokines produced in response to infection may be linked to fetal brain development changes. Mice treated with analogues of bacterial or viral infections at different gestational periods showed different neurodevelopmental profiles of hippocampal reelin and GAD67 cell number expression in the hippocampal dorsal or ventral stratum oriens of offspring (Harvey & Boksa, 2012). Studies investigating

infection-associated immunological events on the fetus showed early maternal inflammation to be linked with negative effects on the development of a fetus' dopaminergic system at multiple levels such as cell distribution and connectivity (Meyer et al., 2007). In contrast, later brain insults during pregnancy have been linked to deficits in cell organization and maturation of synapses which occur over an extended period, affecting cognitive function (Meyer et al., 2006).

While animal models provide a possible explanation as to how brain neurochemistry and structure can potentially be affected by different times of infection exposure, evidence from human studies, especially looking at specific trimester effects and cognitive outcomes, is lacking. Further, while some genetic patterns have been found in maternal intellectual ability and child IQ scores (Lean et al., 2018), no firm conclusions can be drawn that suggests genetics fully accounts for children's cognitive abilities. Instead, there is current growing emphasis on using the gene-environment interaction to examine the role of maternal inflammation and biological pathways that lead to fetal brain development and cognition (Dozmorov et al., 2018; L. Rasmussen et al., 2018).

Literature on human studies has been mixed, showing varying results on vulnerability to inflammation occurring in different gestational periods, especially on a child's cognitive development (Cordeiro et al., 2015; Rosenberg, 2018; Yarnykh et al., 2018). The significant associations between third trimester infection and cognitive outcomes

at age 8 identified in this study suggest a possible latent effect of maternal systemic inflammation which may possibly influence cognitive development. This could be due to an interaction with unaccounted environmental factors after birth, such as lowered socioeconomic status, which could confound child development as it is also considered an inflammatory process during childhood(Schmeer & Yoon, 2016). The link with maternal infections during later gestation shows that despite having fetal brain infrastructure in place, environmental factors such as deprivation could still affect brain structure or functional connections after birth.

This suggests that infections in late pregnancy may influence the postnatal processes of cognitive development. With differences shown in results using the developmental (GMDS) and intelligence quotients (WPPSI-RUK, WISC-III), it could be possible that effects of prenatal maternal infection are not evident in early development, with no identification of potential developmental delay as reflected in GMDS. However, results from formal IQ assessments such as the WPPSI-RUK and WISC-III could possibly be showing effects that emerge only under increased cognitive load, with cognitive IQ assessments created to assess advanced skills such as abstract reasoning or working memory.

While this study could not directly infer causality, study results are still consistent with previous research on maternal-fetal associations, where clinical evidence shows how presence of maternal inflammation during pregnancy using elevated cytokine profiles

contribute to prenatal risk programming (Andersson et al., 2016; R. J. Wright et al., 2010). Other studies using these same maternal cytokines found negative influences on prenatal central nervous system development (Zaretsky et al., 2004), with animal models showing further evidence for negative neurobehavioral outcomes (Bronson & Bale, 2014). In sum, research supports how prenatal programming consists of multiple variables such as occurrence and regulation of inflammation, genetic susceptibility, and environmental stressors; all of which interact in a complex manner that is still not yet fully understood in humans (Hantsoo et al., 2019), which could explain why study results were mixed. Nevertheless, this study contributes further evidence through the specific scope of how maternal infections during different trimesters of pregnancy could possibly affect childhood developmental and intelligence quotient outcomes.

Strengths and limitations

Main study strengths were the use of a large high-quality longitudinal design and a well-characterized sample. While cohort studies such as the ALSPAC tend to have considerable attrition due to reasons such as loss to follow-up related to socioeconomic status, it has been shown that differences in estimates when comparing full or restricted cohorts tended to be small (Howe et al., 2013). Similar infection rates during pregnancy and study attrition allowed for comparability with other cohort studies also looking at mother-child associations. Study limitations include a reliance on mother self-reported infection data; that the records of infections were not classified by severity; and that causes of infections (e.g. bacterial/viral/fungal) were not

recorded and could not be stratified by pathogen type for analysis. In addition, while the study has included a list of confounders and covariates, not all factors such as parental attitudes, styles or other variables related to the quality of care of the child, or genetic factors could be accounted for in this study. In addition, this version of GMDS was created to identify developmental delays and therefore should be interpreted with caution as to whether it is a true assessment of cognition at 18 months. Despite not being able to account for these above factors, study results still showed predictive associations for the cognitive measures assessing IQ, which was consistent with research from both animal and human studies focusing on maternal-fetal interactions. Finally, assessments from the dataset were only measured up to age 8, so lasting effects of cognitive development could not be analysed beyond those years.

Conclusion

Our study highlighted possible third-trimester specific effects of maternal infection on children's cognitive abilities. However, effect sizes were small, suggesting a weak link between maternal infections during the third trimester of pregnancy and childhood cognitive outcomes. One potential direction of future research could include examining mechanisms which mediate these effects of prenatal infections on childhood cognition such as fetal brain gene expression after maternal immune activation (Lombardo et al., 2018). Other research could also explore temporal dependency and specificity to performance IQ scores from 4 years onwards, whether the effect of infection is moderated by specific early childhood environmental factors, and if its effect persists in future cognitive outcomes.

Chapter 3: Maternal Metabolic Markers and Child-to-Adolescence Socioemotional Trajectories

Synopsis

As an expansion from the previous study, it is acknowledged that using retrospective self-report variables which may be prone to bias. Therefore, this empirical chapter focused on objective predictor variables derived from biological blood samples or clinical panels to complement the findings based on self-report. This chapter uses the Avon Longitudinal Study of Parents and Children (ALSPAC) United Kingdom cohort to examine associations between maternal cardiometabolic markers (fasting glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and body mass index (BMI)) and child socio-emotional outcomes over seven time points (4, 7, 8, 9, 11, 13, 16 years old). Growth curve models showed results of maternal fasting glucose, BMI, and triglycerides generally showing more problems for conduct and hyperactivity problems over time. Maternal markers of LDL and HDL markers also showed differences across trimesters for conduct and hyperactivity problems. Study implications reveal a potential critical period of vulnerability during earlier gestation on conduct and hyperactivity problems persisting from childhood to adolescence stage.

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Authors' contributions

I conceptualised and designed the study, conducted analysis, interpretated the data, drafted and revised the manuscript drafts and revisions, and submitted the paper for publication. Dr L. G. Speyer and Ms D. P. Khanolainen contributed to study coding, data analysis and interpretation, and manuscript revisions. Ms M. Torppa and Dr B. Auyeung contributed to data interpretation and manuscript reviews. Dr A. L. Murray provided feedback throughout all stages of the process; study design, data analysis and write-up, manuscript revision, and the journal submission process.

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Examining maternal cardiometabolic markers in pregnancy on child emotional and behaviour trajectories: using growth curve models on a cohort study

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List of Study Abbreviations

ALSPAC: Avon Longitudinal Study of Parents and Children

BMI: Body Mass Index

HDL: High-density lipoprotein cholesterol

LDL: Low-density lipoprotein cholesterol

SDQ: Strengths and Difficulties Questionnaire

TRI: Triglycerides

Abstract

Background: Poor maternal cardiometabolic health in pregnancy is associated with negative effects on child health outcomes, but there is limited literature on child and adolescent socio-emotional outcomes. The study aims to investigate associations between maternal cardiometabolic markers during pregnancy with child and adolescence socio-emotional trajectories.

Methods: Participants consisted of mother-child pairs (n=15,133) from the Avon Longitudinal Study of Parents and Children (United Kingdom) cohort. Growth curve models were run to examine how maternal cardiometabolic markers in pregnancy affected child socio-emotional trajectories from age 4 to 16. Models were adjusted for predictors in all pregnancy trimesters, maternal, child, and socioeconomic covariates. Maternal predictors of fasting glucose, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and body mass index (BMI) were taken from each pregnancy trimester (T1: assessed at week 12, T2: assessed at week 18-27, T3: 37-39). Child outcomes included emotional problems, conduct problems, and hyperactivity problems from the Strengths and Difficulties Questionnaire (SDQ).

Results: Fully adjusted models showed significant associations between elevated T1 fasting glucose and increased conduct problems, higher T1 BMI and increased hyperactivity problems, lowered T1 HDL and decreased hyperactivity problems, and elevated T2 triglycerides and increased hyperactivity problems. Statistical significance was set at $p<.05$.

Conclusion: Maternal cardiometabolic risk is associated with conduct and hyperactivity outcomes from age 4 to 16. This study suggests that maternal markers of fasting glucose, LDL, HDL, and triglycerides during pregnancy could be added as supplemental clinical measures of risk when predicting child and adolescent's socio-emotional trajectories.

Keywords: Pregnancy, Biomarkers, Child Development, Metabolic, ALSPAC

Background

Prenatal metabolic markers have been identified in research as modifiable factors predictive of child development outcomes. Maternal adipokines have been linked with placental dysfunction, leading to increased cytokine activity which contributes to oxidative stress and a toxic environment to the growing fetus (Saben et al., 2014). Elevated measures of high-density lipoprotein (HDL) and triglycerides from umbilical cord blood at birth are linked with lowered emotion regulation, self-awareness, and interpersonal functioning at age 5 (Manczak & Gotlib, 2019). More specifically, in utero exposure to maternal elevated triglycerides and lowered (HDL) have been associated with outcomes of cortisol reactivity in 3 to 5-year-olds, an indicator of stress programming (Mina et al., 2017). However, there are still literature gaps shown for metabolic adaptations in pregnancy, where disruption of essential biomolecule processes on fetal development is not yet fully understood (Zeng et al., 2017). This study looks to examine how maternal cardiometabolic risk during pregnancy can affect a child's behavioural and emotional developmental trajectories from childhood to adolescence.

It is suggested that maternal-fetal programming stretches beyond birth outcomes and has an enduring effect on child development. On a clinical scale, maternal obesity and gestational diabetes mellitus have been linked to lowered cognitive skills and psychiatric disorders in offspring (Pugh et al., 2015; Rivera et al., 2015; Van Lieshout et al., 2011). Maternal pre-pregnancy obesity and metabolic complications have been

linked to inattention symptoms in children aged 5 years (Rodriguez, 2010). This is important as early emotional and behavioural symptoms affect around 20% of children (Rijlaarsdam et al., 2015; von Klitzing et al., 2015), presenting further risk factors for lower educational attainment (Trout et al., 2003; Wagner et al., 2005) and development of psychopathology in adulthood (Caspi et al., 1996; Hofstra et al., 2002).

There is also limited evidence on how risk present in different pregnancy trimesters can potentially affect child development differently. Cohort studies (Edlow, 2017) that measured maternal obesity as a risk factor for childhood developmental outcomes looked at either pre-pregnancy BMI (Getz et al., 2016; M. Li et al., 2016; Rodriguez, 2010; Van Lieshout et al., 2013) or specific trimesters of pregnancy (Gardner et al., 2015). Prenatal inflammatory biological pathways have been shown in third trimester maternal plasma presenting with risk for later development of autism spectrum disorder (ASD)(Schmidt et al., 2021). As the pregnancy process consists of anti-inflammatory immunological shifts contributing to fetal development (Bränn et al., 2019), current research is moving in the direction of examining if there are critically vulnerable periods of risk during pregnancy that can potentially lead to future negative childhood outcomes. The study aims to examine associations between maternal cardiometabolic risk markers present in all pregnancy trimesters and their effect on childhood emotional and behavioural trajectories from ages 4 to 16 years old.

This study's hypotheses are a) that presence of maternal cardiometabolic risk is associated with a more negative trajectory of emotional and behavioural development from 4 to 16 years old, and b) maternal cardiometabolic risk applied in mid-to-late trimesters affects emotional and behavioural trajectories more than in the earlier trimesters.

Methods

Participants

The present study drew on the same dataset from Chapter 2, from the Avon Longitudinal Study of Parents and Children (ALSPAC) (Golding et al., 2001). All pregnant women who were resident in Avon (in the United Kingdom) and expecting a delivery between 1st of April 1991 and 31st of December 1992 were eligible for participation and were recruited through maternity clinics, community centres and advertisements. Ethical approval for the study was received from the ALSPAC Law and Ethics Committee and the Local Research Ethics Committees. The final sample used in this study included n=15,133 mother-child pairs. Maternal cardiometabolic markers were sampled three times over pregnancy and children's socioemotional and behavioural outcomes were reported on at least one time point. Missing data was accounted for in the study analysis.

Cardiometabolic markers during pregnancy

Maternal cardiometabolic markers were measured at first (12 weeks), second (18-27 weeks), and third (32-39 weeks) trimesters of pregnancy. Information was extracted from maternal clinical obstetric records documented by medical staff. These markers include fasting glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and body mass index (BMI). All cholesterol markers were converted to mmol/L for comparison in the analysis. Glucose was added as it is the predominant

source of energy for the placenta and fetus, as most of fetal glucose is derived from the mother (Hay, 1991).

Social-emotional and behavioural outcomes

Mother reports of her child from the Strengths and Difficulties Questionnaire (R. Goodman, 1997) were taken as study outcomes. The SDQ was designed to measure childhood socio-emotional and behavioural problems, showing high internal consistency and high test-retest reliability across countries. The measure consists of 25 items divided into five subscales: emotional problems, hyperactivity, conduct problems, peer relationship problems, and pro-social behaviour. This study used subscales of emotional problems, hyperactivity, and conduct problems. Higher scores on these subscales correspond to poorer socio-emotional and behavioural outcomes, with ranges from 0 to 10. Sum scores were calculated for each subscale. SDQ outcomes for ages 4, 7, 8, 9, 11, 13, and 16 were used in this study.

Confounders and covariates

Study confounders included deprivation indices, maternal smoking in the first, second, or third trimester, maternal alcohol intake in the first or third trimester, maternal psychiatric history (bulimia, schizophrenia, anorexia, depression, other recorded psychiatry history). Child covariates included gestation age and birth weight.

Statistical analysis

Data was managed in R statistical software (R programme, 2021) and analysed using Mplus statistical software (version 8.7) (Muthen & Muthen, 1998). Predictor variables, deprivation, and BMI were mean-centred on, and categorical variables in confounders and covariates were coded so that higher scores represented more risk. Loadings were fixed for models. Higher SDQ scores represented presence of more behavioural problems. Structural equation modelling was used to examine how maternal cardiometabolic markers affected child SDQ trajectories over 7 timepoints (4, 7, 8, 9, 11, 13, 16 years old). Analysis was split into a 3-stage process. First, a latent growth curve model was fit for SDQ outcomes. Models were constructed where intercept factors (i) represented the baseline for each individual, slope factors (s) represented the linear slope of change trajectory, and quadratic factors (q) represented the quadratic slope of change trajectory. All loadings for intercept predictor variables started from zero and were fixed to reflect time spacing for the six selected ages in this study. Once latent growth curve models were estimated, the second step was to extend the model to include individual maternal cardiometabolic variables as predictors of latent growth curve components. Nine models were fit, one for each pregnancy trimester per SDQ domain. Last, further analysis was conducted for three fully adjusted models where all trimesters were analysed simultaneously in the same model per SDQ domain. Models were adjusted for confounders and covariates as stated above. Models were fit using a robust maximum likelihood estimator and evaluated using comparative fit index (CFI), and Tucker-Lewis index (TLI), root mean square error of

approximation (RMSEA), standardized root mean square residual (SRMR). Cut-offs for good fit were set at <.06 for RMSEA and SRMR, and ≥.90 for CFI and TLI (Hu & Bentler, 1999). Missing data was handled using full information maximum likelihood estimation.

Table 3-1. R2 estimates, Intercept, Slope, Quadratic (adjusted for covariates)

	R^2 Estimates (SE)			Unstandardised Intercepts (SE)			Standardised Intercepts (SE)		
	I	**S**	**Q**	**I**	**S**	**Q**	**I**	**S**	**Q**
Trimester 1									
Conduct	.052 (.007)***	.017 (.007)*	.017 (.007)*	1.005 (.158)*	-.875 (.609)	-.042 (.565)	.754 (.265)**	-.463 (.369)	.075 (.376)
Hyperactivity	.040 (.006)***	.015 (.006)*	.018 (.007)	3.478 (.259)*	-1.282 (.975)	-.717 (.897)	1.96 (.250)***	-.812* (.358)	.229 (.379)
Emotional	.017 (.004)***	.018 (.007)**	.015 (.007)*	1.062 (.181)*	1.077 (.792)	-1.703 (.783)	1.18 (.277)***	.238 (.360)	-.627 (.402)
Trimester 2									
Conduct	.057 (.008)***	.015 (.008)*	.017 (.008)*	1.008 (.161)*	-1.007 (.620)	.077 (.575)	.829 (.320)*	-.051 (.438)	-.245 (.454)
Hyperactivity	.038 (.006)***	.015 (.007)*	.019 (.008)*	3.377 (.261)	-1.203 (.984)	-.811 (.902)	1.72 (.321)***	-.395 (.428)	-.037 (.439)
Emotional	.017 (.005)***	.018 (.007)*	.015 (.007)*	1.034 (.183)	1.244 (.804)	-1.848 (.795)	1.40 (.335)***	.101 (.434)	-.383 (.481)
Trimester 3									
Conduct	.058 (.008)***	.027 (.010)**	.024 (.010)*	.969 (.162)	-1.072 (.628)	.178 (.583)	.561 (.297)	.320 (.398)	-.655 (.403)
Hyperactivity	.039 (.006)***	.010 (.005)*	.015 (.006)*	3.403 (.267)	-1.454 (.996)	-.584 (.913)	1.48 (.289)***	-.255 (.418)	-.142 (.434)
Emotional	.014 (.004)***	.017 (.007)*	.020 (.009)*	1.069 (.186)	1.058 (.821)	-1.753 (.812)	1.05 (.307)**	.320 (.398)	-.591 (.442)
All Trimesters									
Conduct	.062 (.008)***	.035 (.010)**	.030 (.010)**	.519 (.620)***	-2.596 (-2.209)	-1.415 (-1.055)	.859 (.151)***	-.340 (.220)	.035 (.229)
Hyperactivity	.047 (.007)***	.032 (.011)**	.033 (.011)**	3.451 (.266)***	-1.577 (.998)	-.433 (.917)	1.856 (.146)***	-.357 (.227)	-.113 (.238)
Emotional	.024 (.006)***	.023 (.008)**	.024 (.010)*	1.051 (.187)***	1.015 (.816)	-1.639 (.811)*	.915 (.164)***	.277 (.223)	-.515 (.255)*

I: Intercept, S: Slope, Q: Quadratic
p<.05, p<.01**, p<.001****

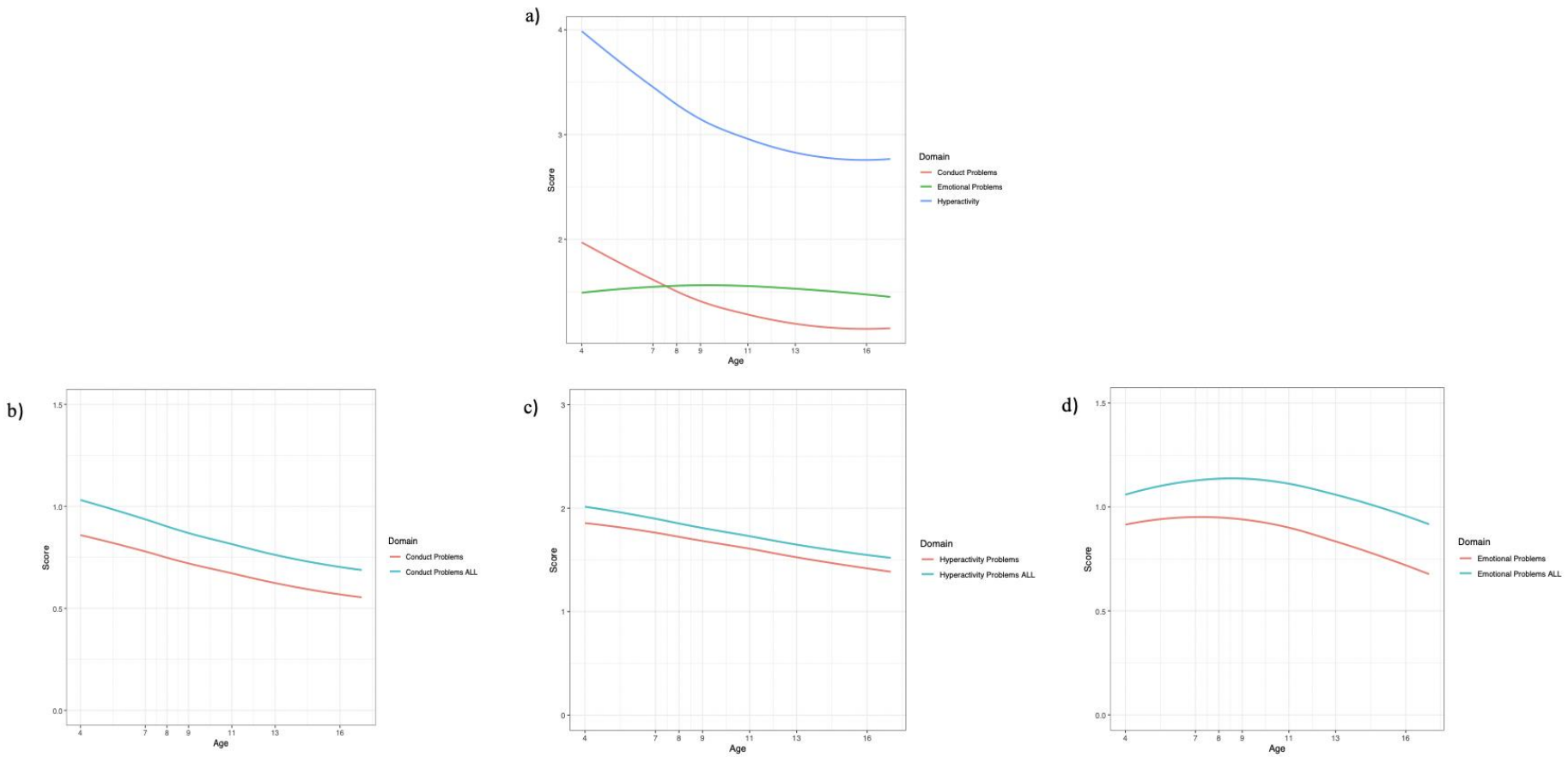

Figure 3-1. SDQ trajectories (a) Raw plot for SDQ trajectories without adjusting for maternal metabolic risk or covariates[1]. Overall growth curves showing trajectories of SDQ profiles consisting of (b) conduct, (c) hyperactivity, (d) and emotional problems from 4 to 16 years old. Graphs were adjusted for all trimesters. Red curves in b), c), and d) show the SDQ profile of an individual child whose mother had average levels of metabolic markers and average covariates. Blue curves in b), c), and d) show the SDQ profiles of an individual child with whose mother had levels of metabolic markers 2 standard deviations above the mean, to illustrate how developmental trajectories may look like for children of individuals with elevated levels of metabolic markers across all trimesters of pregnancy. Metabolic markers included fasting glucose, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and body mass index (BMI).

[1] SDQ profile of an individual whose mother had average metabolic health, average socioeconomic status, who did not smoke or drink during pregnancy, and had a baby with gestation ≥37 weeks and birthweight of >2500g resulted in similar child SDQ profiles when compared the general population. The raw plot was generated as a comparison model without adjusting for maternal cardiometabolic variables, confounders, or covariates.

Results

Descriptive statistics showed about 1/4 of mothers smoked and about 1/2 of mothers consumed alcohol in the first trimester. This percentage decreased slightly by the third trimester, where 1/5 of mothers smoked and 1/2 of mothers consuming alcohol. Mothers with psychiatric history made up 13.6% of the sample. Deprivation data was missing for 1/2 of the cohort, and 14% fell in the lowest (0-20% quintile) categories. Less than 10% of children had gestational age of < 37 weeks (premature) and < 2500g (low birthweight). Total sample size was 15,133 mother-child participants. More information can be found in Appendix B, Tables B1 and B2.

Model fits were adequate according to fit indices. For fully adjusted models, fit indices for conduct problems showed CFI =.978, TLI =.964, RMSEA =.016, SRMR =.008. Fit indices for hyperactivity problems showed CFI =.937, TLI =.956, RMSEA =.021, SRMR =.009. Fit indices for emotional problems showed CFI =.971, TLI =.952, RMSEA =.016, SRMR =.009. More information can be found in Appendix B, Table B3.

Primary results are first split into individual pregnancy trimesters, with standardised (Bi) regression coefficients reported to show per unit change of SDQ outcomes for when maternal cardiometabolic risk is present. Each model contained one SDQ domain per pregnancy trimester. Unstandardised values and 95% confidence intervals can be

found online in OSF (https://osf.io/6tpuz/, titled "Unadjusted models") The slope (Bs) and quadratic (Bq) coefficients are reported to display growth curve trajectories.

The fully adjusted models including all three trimesters showed some significant effects of metabolic markers of glucose, HDL, BMI, and triglycerides associated with child outcomes. Higher T1 glucose was associated with a steeper increase in conduct problems (Bs= .145) and a slower flattening out (Bq= -.143) in the curve over time. Higher T1 HDL was associated with fewer hyperactivity problems (Bi=-.088) at age 4. Higher T1 BMI was associated with a steeper increase in hyperactivity problems (Bs= .208) and slower flattening out (Bq= -.207) in the curve over time. Higher T2 triglycerides were associated with a steeper increase in hyperactivity problems (Bs= .147) and slower flattening out (Bq= -.167) in the curve over time. No individual metabolic markers were associated with the emotional problems domain. More results on individual trimesters can be found in Table 3-1 and more information on all models can be found online in OSF (https://osf.io/6tpuz/).

Discussion

The purpose of this study was to examine if maternal cardiometabolic risk during pregnancy was associated with a child's emotional and behavioural trajectories over time. Study findings supported the first hypothesis and provided a detailed picture of how elevated maternal cardiometabolic risk across pregnancy was associated with negative change in trajectories for the conduct and hyperactivity domains when compared against an average maternal cardiometabolic profile in pregnancy. Maternal elevated fasting glucose, higher BMI, elevated triglycerides, and lowered HDL showed effects of more problems and slower decrease of problems over time. No associations were found for emotional problems after adjustments. Study findings also suggested trimester-based effects of maternal metabolic risk, with associations found between trimester one of pregnancy and negative trajectories of children's conduct and hyperactivity problems. This suggests a window period of vulnerability for when maternal metabolic risk is present in early pregnancy as compared to later pregnancy, not supporting the study's second hypothesis. Individual markers associated with child development trajectory changes showed some differences across each trimester, particularly in LDL and HDL markers. Mixed results were found for individual biomarkers across each trimester while accounting for covariates, displaying the importance of identifying any critical window of vulnerability during pregnancy for child outcomes.

Study findings further emphasise that pathogenic mechanisms underlying maternal metabolic pathways that influence early life programming are still poorly understood (Domínguez-Perles et al., 2019). Metabolic conditions can include factors such as nutrition and dietary quality, stress, and inflammation (J. M. Rasmussen et al., 2022). Nonhuman primate studies on maternal inflammation linked obesity with reduction of serotonin synthesis, suggesting that the same mechanisms are likely responsible for increased risk for behavioural abnormalities or psychological disorders(Sullivan et al., 2015). Similarly, maternal inflammation has been found to affect dopaminergic systems and cause increased risk of offspring with ASD, ADHD, anxiety, and depression) (Hamilton et al., 2015; L.-T. Lee et al., 2015; Y. Liu et al., 2018; Tong et al., 2015; Voineagu et al., 2011, p. 1) . To date, literature is still lacking in a complete understanding of how maternal chronic low-grade inflammation such as metabolic risk not only disrupts the intrauterine environment (Parisi et al., 2021) but actual significant effects on fetal programming and future health.

Fetal programming is highly dependent on nutritional availability, coordination and regulation of biological processes that support pregnancy. Cohort studies on maternal nutrition quality and child emotional and behavioural outcomes showed that more proinflammatory maternal nutritional profile is linked with childhood outcomes such as increased risk for child emotional problems (Miyake et al., 2018), aggressive behaviour symptoms and even attention deficit hyperactivity symptoms (Ji et al., 2017; Polanska et al., 2021). While we did not examine direct markers of exposure such as

maternal diet, the study included biomarkers of health such as fasting glucose and cholesterol levels, drawing further support for associations with neurodevelopmental outcomes (Ji et al., 2017). Findings corroborate with research on metabolic flexibility, where more proinflammatory lipid profiles were linked with subsequent childhood health outcomes (Houttu et al., 2018; Moran-Ramos et al., 2017; Tinius et al., 2020).

A review of evidence has suggested that pregnancy test panels should be expanded to include biomarkers that potentially contribute to inflammation (Czamara, 2020). This can not only help to identify disease risk and create targets for intervention during pregnancy (Girchenko et al., 2020), but also provide further understanding in fetal and child development. While varying metabolic demands across pregnancy are seen contribute to fluctuating maternal inflammatory profiles, which affect support for fetal brain development, there are still gaps in understanding for how metabolic adaptations in pregnancy or disruption of essential biomolecule processes affects fetal development (Zeng et al., 2017). Impaired cholesterol homeostasis has been linked with negative embryonic development (Zeng et al., 2017). Maternal hyperlipidaemia has been being linked with adverse birth outcomes like preterm birth (Bartels & O'Donoghue, 2011), while maternal dyslipidaemia in early pregnancy being linked with lowered communication and gross motor skills at 12 months old (Motoki et al., 2022). Despite growing evidence on maternal lipid markers being associated with child outcomes, cholesterol is still commonly not a routine clinical measurement in obstetric practice. Study findings provide further justification for these biomarkers to be

included in pregnancy testing panels due to potential long-term effects on child socio-emotional development.

Findings demonstrate how maternal cardiometabolic health risk is linked with the growth trajectories of conduct problems and hyperactivity problems across all trimesters, potentially with earlier risk exposure leading to more significant negative outcomes. This study adds to current literature on lowered maternal cardiometabolic health being associated with fetal programming. Findings expand on this by looking beyond physical health and at child emotional and behavioural outcomes from 4 to 16 years old, providing insight in developmental trajectories. Findings also suggest presence of trimester-based effects when looking at specific markers such as maternal LDL and HDL, showing need to also explore specific metabolic profiles such as lipid panels during pregnancy.

Strengths and Limitations

Study strengths include using a large high-quality cohort where metabolic markers were taken from clinical data collected throughout pregnancy trimesters. Self-reports were filled in by parents throughout the ages 4 to 16 years old, allowing for more consistent assessment. This study had several limitations. Due to lack of data availability across all trimesters, insulin was not included as a predictive biomarker despite literature showing it to be a potential predictor of metabolic and endocrine disruptions in offspring. The study attempted to supplement this through adding

fasting glucose instead, another potential indicator of metabolic and endocrine disruption. Pubertal growth could have had effects on development due to hormonal changes, which was not accounted for in the study. In addition, this study did not run a full metabolomic analysis panel or examine if any interventions applied to improve cardiometabolic health during pregnancy affected results.

Conclusion

Maternal cardiometabolic risk during pregnancy is associated with conduct and hyperactivity problems from the childhood to adolescence stages of development. Findings also suggest risk exposure earlier on during pregnancy being associated with more conduct and hyperactivity problems. Findings held after adjusting for variables in all pregnancy trimesters, maternal, child, and deprivation factors. These findings provide new insight in differential effects of maternal cardiometabolic risk on child and adolescent development, providing justification for more clinical monitoring using these markers. Further research can include expanding clinical services to include metabolic or lipid panels to establish associations between more these biomarkers and future child developmental trajectories.

Chapter 4: Child Cord Blood Biomarkers as Mediators of Maternal Metabolic Health on Child Development Outcomes

Synopsis

This chapter uses the Born in Bradford (BiB) United Kingdom cohort to examine associations between maternal metabolic syndrome classification and child development outcomes at age 5, with child cord blood markers as potential mediators. Maternal metabolic syndrome classification was constructed using metabolic measures of body mass index (BMI), triglycerides, high-density lipoprotein (HDL), blood pressure, fasting glucose, and previously diagnosed diabetes. Child cord blood markers included low-density lipoprotein (LDL), high-density lipoprotein (HDL), adiponectin, leptin, and triglycerides. Child outcomes included starting school measures and a national framework for school readiness. After adjustment for maternal, child, and socioeconomic covariates, results showed maternal metabolic syndrome classification being directly and indirectly (through changes in child cord blood markers) associated with children's literacy domain at 5 years old. Findings showed that the combined effects of child cord blood markers mediated the association between maternal metabolic syndrome and children's communication and language, and personal, social, and emotional domains via changes in child cord blood markers at 5 years old.

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Authors' contributions

I conceptualised and designed the study, conducted analysis, interpretated the data, drafted and revised the manuscript drafts and revisions, and submitted the paper for publication. Dr L. G. Speyer and Ms G. Soursou contributed to study coding, data analysis and interpretation, and manuscript revisions., Dr K. Fanti, and Dr B. Auyeung

contributed to data interpretation and manuscript reviews. Dr A. L. Murray provided feedback throughout all stages of the process; study design, data analysis and write-up, manuscript revision, and the journal submission process.

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Maternal metabolic syndrome in pregnancy and child development at age 5: exploring mediating mechanisms using cord blood markers

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List of Study Abbreviations

BiB: Born in Bradford

ADI: Adiponectin

BMI: Body Mass Index

LEP: Leptin

HDL: High-density lipoprotein cholesterol

LDL: Low-density lipoprotein cholesterol

SDQ: Strengths and Difficulties Questionnaire

TRI: Triglycerides

BPVS: British Picture Vocabulary Scale

LID: Letter Identification Domain

EYFS: Early Years Foundation Stage

COM: Communication and language

LIT: Literacy

MAT: Mathematics

PHY: Physical development

PSE: Personal, social and emotional

Abstract

Background: There is limited evidence on how classification of maternal metabolic syndrome during pregnancy and possible birth mediators affects children's developmental outcomes. This study uses a cohort sample of 12,644 to 13,832 mother-child pairs from the UK Born in Bradford Study to examine associations between maternal metabolic syndrome classification (MetS) and child development outcomes at age 5, using cord blood markers as candidate mediators.

Methods: Maternal cardiometabolic markers included diabetes, obesity, triglycerides, high-density lipoprotein cholesterol, blood pressure, hypertension, and fasting glucose during pregnancy. Cord blood markers of high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, leptin, and adiponectin were used as child mediators. Child outcomes included two starting school variables: British Picture Vocabulary Scale (BPVS) and the Letter Identification assessment (LID), and five developmental milestone domains from a national UK framework: 1) Communication and Language, (COM) 2) Personal, Social and Emotional (PSE), 3) Physical Development (PHY), 4) Literacy (LIT), 5) Mathematics (MAT). Mediation models were used to examine associations between classification of maternal metabolic syndrome and child developmental milestones. Models were adjusted for potential maternal, socioeconomic (deprivation), and child confounders such as maternal education, deprivation, and gestational age at birth.

Results: In mediation models, significant total effects were found for MetS associations with children's development the LIT domain at age 5. MetS predicted individual cord blood mediators of lower HDL and increased leptin levels in both adjusted and unadjusted models. Total indirect effects (effects of all mediators combined) for MetS on a child's COM and PSE domain were significant, through all child cord blood mediators of LDL, HDL, triglycerides, adiponectin, and leptin for adjusted models.

Conclusion: Results support the hypothesis that maternal metabolic syndrome classification during pregnancy was associated with some child developmental outcomes at age 5. After adjusting for maternal, child, and environmental covariates, maternal metabolic syndrome classification during pregnancy was associated with children's LIT domain through direct effects of maternal metabolic health and indirect effects of cord blood markers (total effects), and COM and PSE domains via changes only in a child's cord blood markers (total indirect effects).

Keywords: Metabolic, Prenatal, Pregnancy, Biomarkers, Child Development, Born in Bradford, Cord Blood, Mediation Analysis

Background

There is limited evidence from human studies on how maternal cardiometabolic health during pregnancy affects a child's cognitive and behavioural development. During pregnancy, high energy demands are placed on both mother and fetus through a series of crucial immunological and metabolic adaptations to support the developing fetus (Parrettini et al., 2020; Zeng et al., 2017). Fetal growth is vulnerable to disruption of these processes, particularly due to metabolic disruption from external sources such as air pollution (Friedman et al., 2022), or other forms of oxidative stress (Hantsoo et al., 2019). While it has been established that a mother's metabolic state during gestation plays an essential role in fetal early-life programming, little is known about subsequent effects of this programming on a child's development beyond immediate birth outcomes (Manokhina et al., 2017). Emerging evidence on maternal cardiometabolic factors such as BMI, glucose, cholesterol levels (Bartels & O'Donoghue, 2011), and blood pressure (Hakala et al., 2021) have shown to possibly alter key signalling pathways for brain development through energy metabolization and fetal cell-growth modulation. Further, dysfunction in fetal programming is linked with higher susceptibility for immune function and cardiovascular disease from childhood and even into adolescence (Palinski, 2014). This in turn affects not only birth and health outcomes (Perak et al., 2021; Staley et al., 2015), but is also suspected to affect a child's neurodevelopment (Buss et al., 2012). Presence of maternal cardiometabolic risk has been found to be associated with executive functioning, impulse control behaviour (J. R. Thompson et al., 2018), language skills (Torres-

Espinola et al., 2015), psychomotor development (Camprubi Robles et al., 2015), communication (Krakowiak et al., 2012), and mental health (Scott & Manczak, 2022) in children.

Cholesterol levels in pregnancy have been linked to adverse health outcomes in the fetus and child (Q. Chen et al., 2020; Perak et al., 2021). High cholesterol levels generally contribute to the excess deposition of lipoproteins, particularly low-density lipoproteins (LDL). This is linked to increases in oxidative stress and induction of chronic inflammation, leading to higher health risk in mother and fetus, though the effects of elevated cholesterol levels during pregnancy are still not yet fully understood (Bartels & O'Donoghue, 2011). Conversely, decreased levels of high-density lipoproteins (HDL) affect production of nitric oxide, leading to endothelium dysfunction and disruptions in liver metabolization during pregnancy. The combination of increased LDL and decreased HDL is linked with cardiovascular conditions such as atherosclerosis risk in the mother, which then further increases risk for cardiovascular risk in the child (Palinski, 2014). Effects of childhood cardiovascular risk were shown in a cohort study examining elevated systolic blood pressure and total cholesterol during childhood. Associations were found for lowered cognitive performance in learning and memory from childhood to 40 years old, and visual processing and sustained attention at 40 years old (Hakala et al., 2021).

Associations have also been found between maternal obesity and childhood cardiometabolic outcomes through intrauterine mechanisms (Gaillard et al., 2016), with these processes causing stress on the developing fetus and subsequently affecting fetal growth. For example, a U.S. cohort consisting of 30,212 pregnancies found that pre-pregnancy obesity and excessive weight gain during pregnancy was linked with lower Intelligence Quotient (IQ) scores of up to 6.5 points (Huang et al., 2014).

Dysregulated glucose levels contribute to chronic inflammation and dysregulated metabolism during pregnancy, which are further associated with disruptions in fetal development (Fitzgerald et al., 2020). Excess maternal insulin resistance affects placenta transfer and concentrations, taxing the fetus' pancreas and causing extra insulin production as compensation (Arshad et al., 2014). Cohort studies in Sweden and the United Kingdom found that presence of maternal diabetes in pregnancy was associated with lower male offspring cognitive ability at age 16 and lower educational attainment (Fraser et al., 2012, 2014). However, a meta-analysis of 12 studies found mixed results for associations between maternal diabetes and lower scores on mental and psychomotor development in 1-2 year old infants compared to controls (Camprubi Robles et al., 2015). Certain adipokines such as leptin and adiponectin have also been identified as important circulatory markers in pregnancy and contribute to fetal-maternal metabolism and communication (Santos et al., 2015). A recent study has shown leptin to be associated with more prosocial behaviour at 3 years old, and

adiponectin to be associated with decreased milestone development in the emotional domain at 5 years old (Scott & Manczak, 2022).

Some studies have attempted to draw associations using risk factors with high inflammatory potential, linking maternal diet quality, dietary glycaemic index, or glycaemic load during pregnancy to adverse birth outcomes such as smaller birth size or small-for-gestational age (L.-W. Chen et al., 2021; Maslova et al., 2019b). However, cardiometabolic risk factors often occur in a cluster rather than independently (Adamo et al., 2012) due to multifactorial interactions (Adamo et al., 2012). Biologically, co-occurrence of these factors present as more intrauterine stress and subsequent inflammatory downstream responses (Ansar & Ghosh, 2016). Persistently high levels of biological inflammation such as presence of maternal obesity was associated with increased risk for child neurodevelopmental delay, of which child outcomes were mediated by infant regulatory behaviour problems (Girchenko et al., 2018).

Maternal metabolic syndrome in pregnancy, also classified as cardiometabolic risk, is associated with more adverse pregnancy and birth complications (Grieger et al., 2019). Metabolic syndrome is a constellation of risk factors for developing cardiovascular disease, diabetes, and obesity. Raised glucose levels, high cholesterol, high blood pressure and increased Body Mass Index (BMI) are classified as measures of metabolic syndrome. Components such as hyperglycaemia and related changes in blood lipids (increase in triglycerides and decrease in HDL) further increase a person's risk of having

metabolic syndrome. The World Health Organization (World Health Organization, 2016), the European Group for the Study of Insulin Resistance (EGIR), and the National Cholesterol Education Program – Third Adult Treatment Panel presented several core components of the metabolic syndrome: obesity, insulin resistance, dyslipidaemia and hypertension (Carr et al., 2004; Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

Recent evidence has also found maternal metabolic syndrome during pregnancy to be associated with shortened telomere length in offspring, showing cell tissue damage which increases future disease risk (McAninch et al., 2020). While shortened telomere length as result of oxidative stress has also been associated with predisposition to future mood disorders (Squassina et al., 2019), there is still much unknown on the mechanistic effects of metabolic syndrome on offspring neurodevelopment (Peleg-Raibstein, 2021), showing the need to understand these associations as early on as possible.

Maternal cardiometabolic profiles and child mediators

Despite evidence for links between maternal metabolic health profiles and child outcomes, there is a gap in understanding the biological pathway for association. An under-explored area in human studies is the maternal-newborn biological interface. Using cord blood markers as proxies of a child's cardiometabolic health status, temporal associations can then potentially be drawn where the newborn has not yet

been directly exposed to other environmental influences, such as education or peer relationships. This is crucial for separating gestational biology and environmental influences, and can potentially be a biomarker for a child's eventual neurodevelopmental trajectory (Czamara, 2020), leading to important clinical implications such as medical interventions during pregnancy or early monitoring at the start of formal education for the child.

Standardised developmental assessments are important for closer examination of a child's development when examining practical outcomes. The British Picture Vocabulary Scale (BPVS), Letter Identification Domain (LID), and domains within Early Years Foundation Stage (EYFS) statutory framework are examples of such developmental milestones expected of a child. They are assessed by early year school providers in England through classroom observations at the end of the school year by the time a child turns 5 years old (Department for Education, 2021). Fulfilling the EYFS framework is a standard set by the government for early year providers to assess how children learn and develop well, and possess the skills required to start school, which can be a precursor for future cognitive development and educational attainment (Department for Education, 2021) and therefore relevant to this study.

This study aims to examine associations between maternal metabolic syndrome and child development outcomes at 5 years old, and whether child metabolic health at birth using cord blood markers mediates the association between maternal metabolic

health and child development outcomes, while also accounting for potential environmental influences. This study's hypotheses are a) maternal metabolic syndrome classification during pregnancy is associated with lowered scores in children's developmental domains at 5 years old, and b) child cord blood markers mediate the association between maternal metabolic syndrome and a children's developmental scores at 5 years old.

Methods

Study Participants

The Born in Bradford (BiB) study is a longitudinal multi-ethnic birth cohort study aiming to examine the impact of environmental, psychological and genetic factors on maternal and child health and wellbeing (J. Wright et al., 2013). Bradford is a city in the North of England with high levels of socio-economic deprivation and ethnic diversity. Women were recruited at the Bradford Royal Infirmary at 26-28 weeks of gestation. For those consenting, a baseline questionnaire was completed. The full BiB cohort recruited 12,453 women and 3,353 of their partners across 13,776 pregnancies and 13,858 children between 2007 and 2010. The cohort is broadly characteristic of the city's maternal population. Ethical approval for the data collection was granted by Bradford Research Ethics Committee (Ref 07/H1302/112). Full details on recruitment, attrition and assessment procedures in BiB can be found on the study website (https://borninbradford.nhs.uk/). Of the total sample, singleton births made up n=13,455, while twins and triplets made up n=354 and n=9. As proportion of multiple births was not substantial, this study's mediation models did not consider these effects.

Measures

Cardiometabolic Measures

Data on cardiometabolic measures were taken from the mother baseline questionnaire, pregnancy blood biomarkers, and pregnancy data from electronic

records. Continuous variables taken from the mother's baseline questionnaire dataset included mother's Body Mass Index (BMI) (12.9-57.0) and triglycerides (mmol/L; 0.6-17.8). Continuous variables taken from the pregnancy data from electronic records, backfilled notes, or pregnancy blood biomarkers included systolic blood pressure at 28 weeks (mmHg; 52-188), diastolic blood pressure at 28 weeks (mmHg; 35-114), fasting glucose (mmol/L; 3.0-13.3), and HDL (mmol/L; 0.6-4.1). Categorical variables included existing hypertension (Yes or No) and diabetes prior to pregnancy (Yes or No). Descriptive information for all maternal cardiometabolic markers is available in Table S1. More information can be found in the Supplement Index (Table S5) and at the BIB cohort profile paper (J. Wright et al., 2013).

Maternal Metabolic Syndrome Classification

In this study, maternal metabolic syndrome is classified according to the International Diabetes Federation definition: maternal BMI of >30kg/m^2, together with two of the following factors: raised triglycerides (≥1.7mmol/L), reduced HDL cholesterol (<1.29mmol/L), raised blood pressure (systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or treatment of previously diagnosed hypertension), raised fasting plasma glucose (≥ 5.6 mmol/L), or previously diagnosed type 2 diabetes (Alberti et al., 2006).

Child Cardiometabolic Mediators

Cord blood markers is commonly used as a clinical evaluation of newborn health and were selected to be candidate child mediators for this study. In addition to previously

selected lipid markers to match maternal metabolic markers, hormones of adiponectin and leptin were selected due to emerging literature on effects on infants' cognition between 6 to 24 months , IQ levels and working memory between ages 3 to 8 years old (N. Li et al., 2019). All child cardiometabolic markers were continuous variables. Child markers in this study included low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, adiponectin, and leptin levels as taken from blood assays at birth. Descriptive information for all child cardiometabolic markers is available in Table S2.

Development Outcomes

Starting School Variables

Starting school measures included the British Picture Vocabulary Scale (BPVS)(Atkinson, 1991), and the Letter Identification Domain (LID) by the Born in Bradford team. The BPVS is a one-to-one test assessment of a child's receptive vocabulary. It is used to assess language development in non-readers or students with communication difficulties or expressive language impairments. The LID is a school-based assessment used by teachers to test for the core skill of identifying letters and sounds at a school age.

Early Years Foundation Stage framework

The Early Years Foundation Stage (EYFS) statutory framework was included to assess developmental milestone outcomes. Each EYFS domain was categorized as '1=emerging', '2=expected', '3=exceeding', and '4=absent for long periods or recently arrived' per measure. In this study, '4=absent for long periods or recently arrived' was coded as missing. The number of children that fell in this category was n=9 and only 1-3 was analysed for the scale to show developmental ability. Providers are to indicate on the EYFS profile whether children are meeting the expected levels of development, are exceeding expected levels, or have not yet reached expected levels ('emerging'). This study included five domains from this developmental framework to cover a range of essential developmental skills for a child at 5 years of age.

- COM: Communication and language development (listening and attention, understanding, and speaking)
- PSE: Personal, social and emotional development (self-confidence and self-awareness, management of feelings and behaviour, making relationships)
- PHY: Physical development (moving and handling, and health and self-care)
- LIT: Literacy (reading and writing)
- MAT: Mathematics (numbers, and shapes, space, and measures)

For all child outcomes, mother-child pairs participant samples were n=12,644 to n=13,364 for the unadjusted models and n=13,812 to 13,832 for the adjusted models based on the availability of data, with no children excluded from analysis. Descriptive

information for the starting school variables and developmental domains on childhood outcomes is available in Table S2.

Confounders and covariates

Possible confounders included maternal and socioeconomic factors as obtained by the research team. Previous studies have acknowledged important potential confounders such as parental education, maternal smoking during pregnancy, socioeconomic status, and gestational age when examining maternal cardiometabolic markers and childhood outcomes (Capra et al., 2013; Carr et al., 2004; Huang et al., 2014). Maternal age was coded as a continuous variable. Dichotomous variables included maternal education being coded into A' levels and higher or lower than A' levels, previous alcohol intake as Yes or No, and previous smoking as Yes or No. The deprivation index in this study was taken from the official United Kingdom Index of Multiple Deprivation, where area-level deprivation was measured which accounts for domains of deprivation (employment, income, health, education, housing, and living environment), and was already sorted into quintile ranks of 1-5, with 1 being the lowest deprivation and 5 being the highest deprivation exposure. Additional covariates included maternal ethnicity, child sex, gestational age, and birthweight. Maternal ethnicity was coded as 'White British', 'Pakistani', and 'Other'. Child sex was coded as Male or Female. Gestational age was used as a continuous variable in measurement of weeks, and birthweight was coded as a continuous variable in measurement of kilograms. The fully adjusted model included possible confounders of maternal education, maternal age,

maternal alcohol intake, maternal smoking, and deprivation indices, and the additional covariates of maternal ethnicity, child sex, gestational age, and birthweight. Descriptive information for all study confounders and covariates is available in Table S3.

Statistical Analysis

Age and child sex were raw standard scores. The other variables were standardised for analysis to facilitate estimation by putting variables on similar scales. A structural equation model was used to test the mediating role of child cardiometabolic markers of LDL, (HDL), triglycerides, adiponectin, and leptin in relationships between the maternal metabolic syndrome construct and child developmental outcomes (BPVS, LID, COM, PSE, PHY, LIT, MAT). Correlations were run for child cardiometabolic variables (HDL, LDL, triglycerides, adiponectin, leptin) and study covariates. A mediation model was specified using the maternal metabolic syndrome construct as the predictor (*X*), with child cardiometabolic markers as the mediators (*M*), and developmental assessments as the outcome (*Y*). This study defined direct effects as effects of X on *Y* after adjustment for indirect effects, indirect effects as effects of *X* on *Y* transmitted through *M,* and total effects of as the sum of all effects of *X* on *Y* (both indirect and direct), and total indirect effects as the sum of all indirect effects (Agler & De Boeck, 2017). Direct, indirect, total indirect, and total (direct + indirect) effects on child development outcomes were modelled, accounting for multiple mediators (VanderWeele & Vansteelandt, 2014).

Models were estimated using a robust estimator to account for non-normal distribution of the outcome. Missing data was handled using full information maximum likelihood estimation. To evaluate statistical significance of mediation effects using bootstrapped confidence intervals, we also ran bootstrapped models with standard maximum likelihood estimation. Models were fit using MPlus statistical software (version 8.7) (Muthen & Muthen, 1998) Model fits were evaluated according to fit indices of root mean square error of approximation (RMSEA), standardized root mean square residual (SRMR), comparative fit index (CFI), and Tucker–Lewis index (TLI). Cut-offs were set at <.06 for RMSEA and SRMR, and ≥.95 for CFI and TLI for judging good fit (Hu & Bentler, 1999). Structural equation models were selected due to their advantages for path mediation analysis. This method of analysis was chosen for its flexibility to understand mediating mechanisms, unlike multiple regressions which requires the running of multiple separate regression models to test for mediation and lower statistical power (Mallinckrodt et al., 20060710).

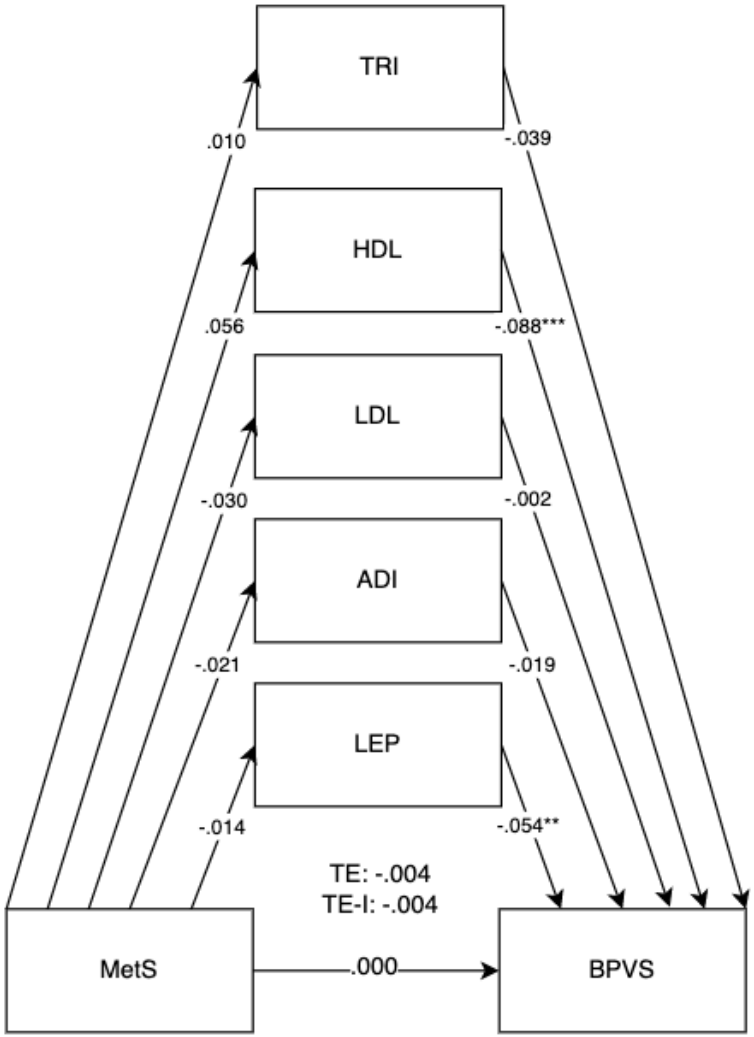

Figure 4-1. Mediation models for maternal metabolic syndrome on BPVS outcomes

Mediation model for British Picture and Vocabulary Scale (BPVS) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL). Adjusted for potential covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

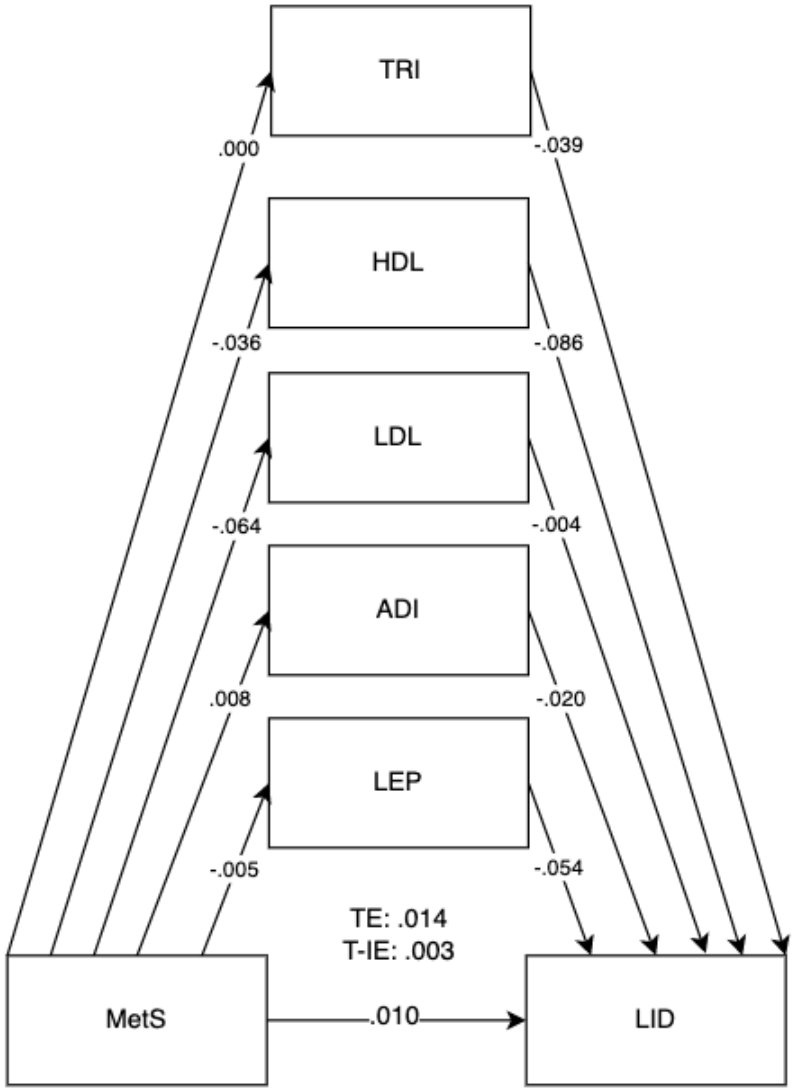

Figure 4-2. Mediation models for maternal metabolic syndrome on LID outcomes

Mediation model for Letter Identification (LID) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL). Adjusted for potential covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

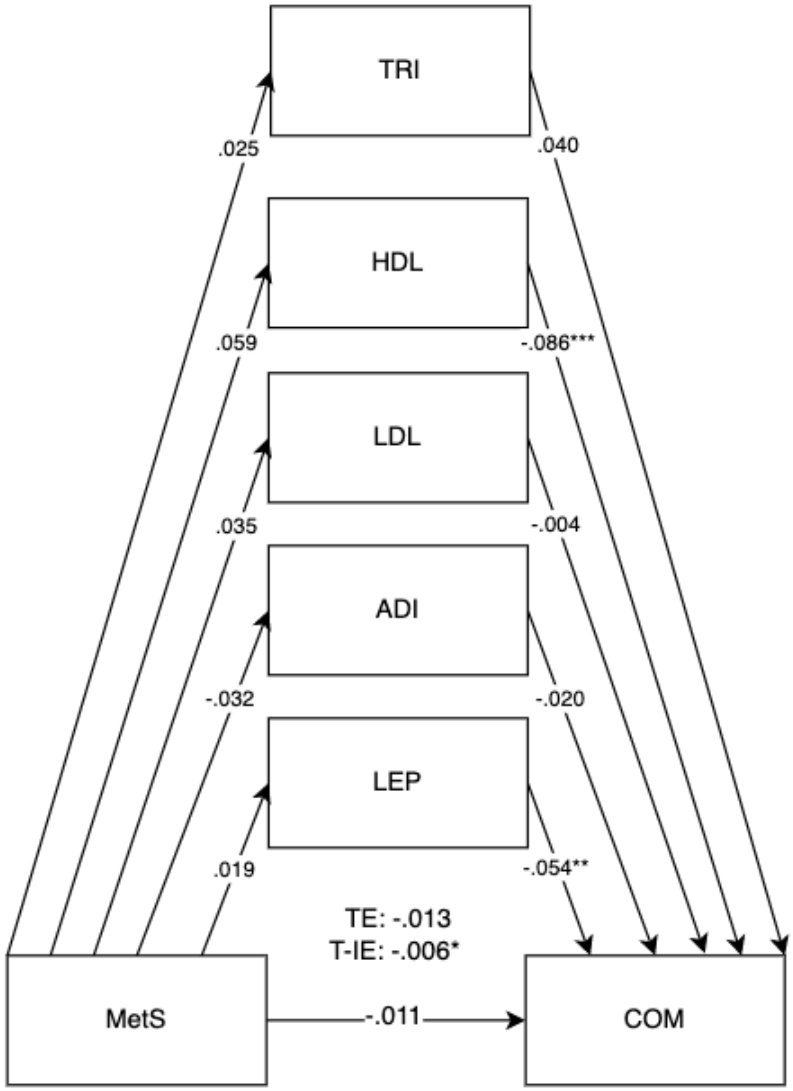

Figure 4-3. Mediation models for maternal metabolic syndrome on COM outcomes.

Mediation model for MetS on child communication and language (COM) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglyceride (TRI)s, and high-density lipoprotein levels (HDL) levels. Adjusted for covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

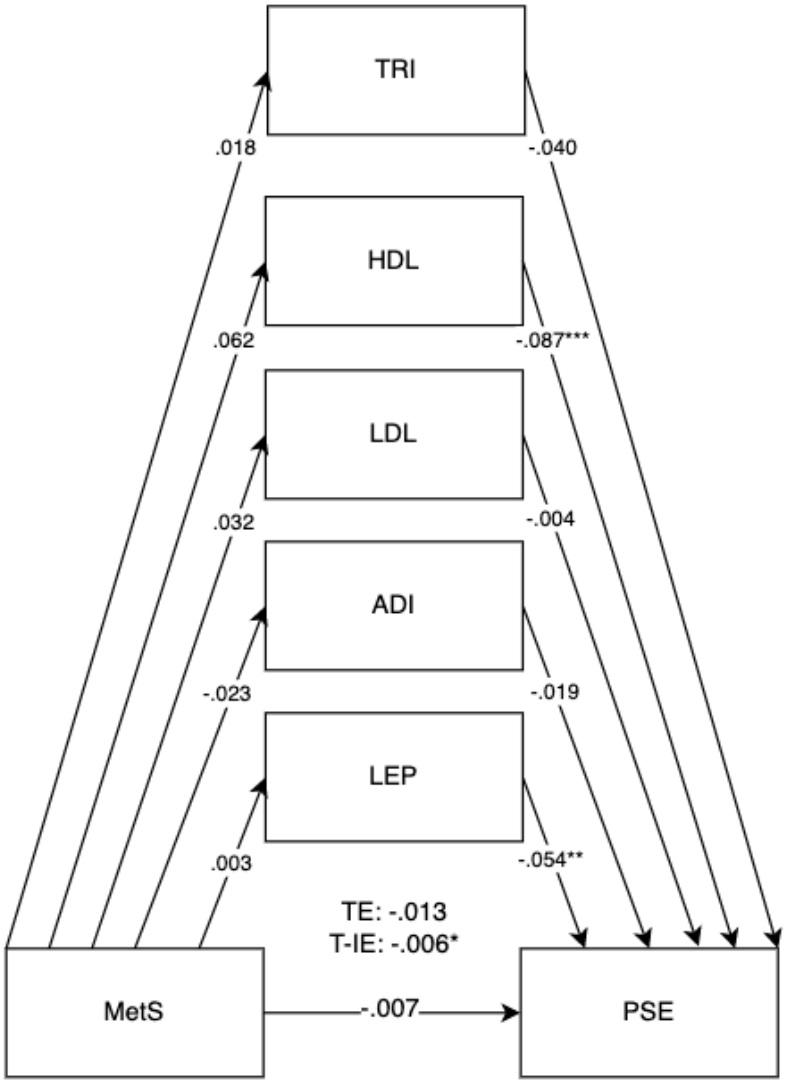

Figure 4-4. Mediation models for maternal metabolic syndrome on PSE outcomes.

Mediation model for MetS on child personal, social, and emotional (PSE) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL) levels. Adjusted for potential covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

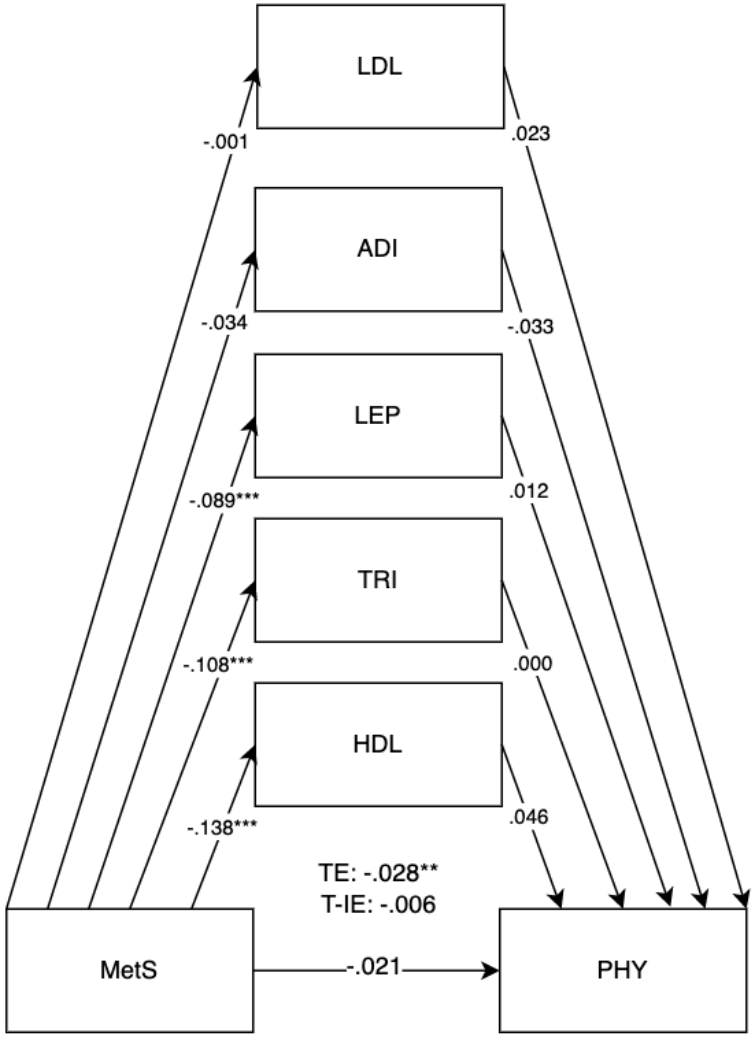

Figure 4-5. Mediation models for maternal metabolic syndrome on PHY outcomes.

Mediation model for MetS on child physical development (PHY) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL). Adjusted for potential covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

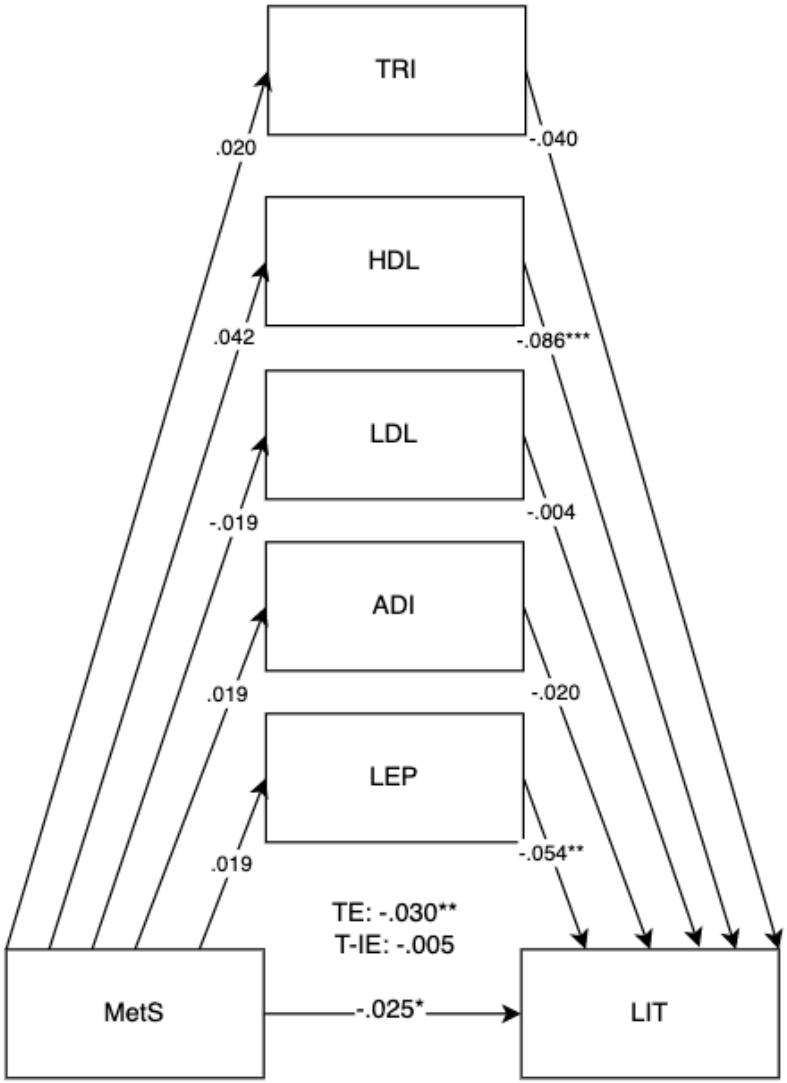

Figure 4-6. Mediation models for maternal metabolic syndrome on LIT outcomes.

Mediation model for MetS on child literacy (LIT) outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL) levels. Adjusted for covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

*p<.05, **p<.01, ***p<.001

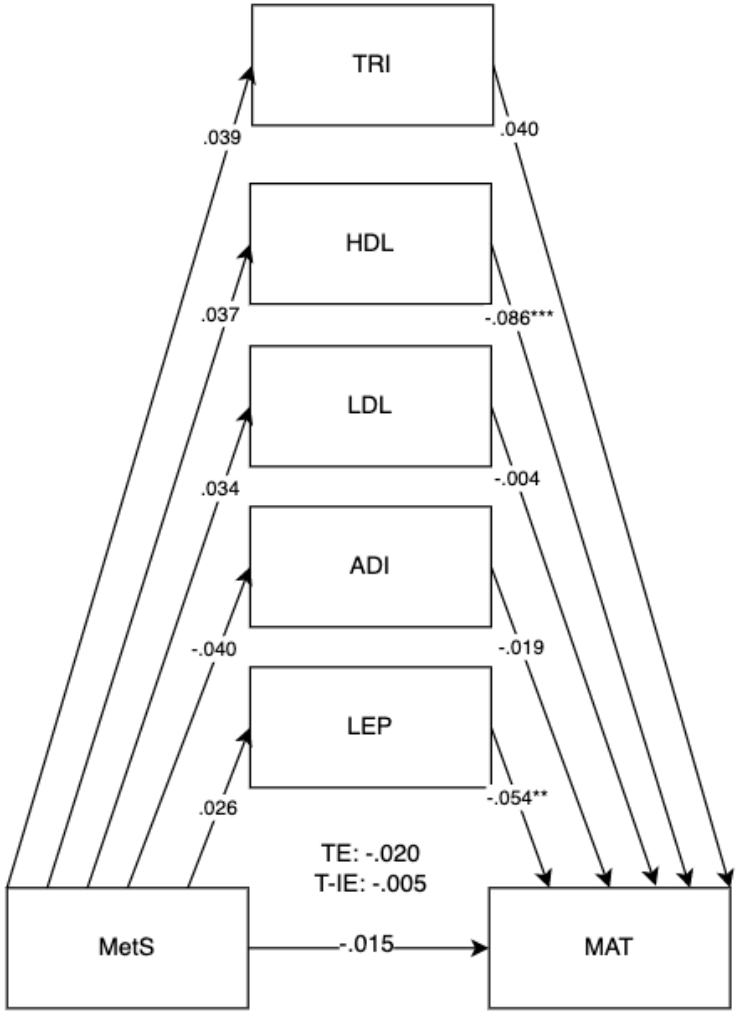

Figure 4-7. Mediation models for maternal metabolic syndrome on MAT outcomes.

Mediation model for MetS on child mathematics outcomes at 5 years old with cord blood mediators of low-density lipoprotein (LDL), adiponectin (ADI), leptin (LEP), triglycerides (TRI), and high-density lipoprotein levels (HDL) levels. Adjusted for covariates of maternal education, maternal age, maternal alcohol intake, maternal smoking, deprivation indices, child sex, ethnicity, gestational age, and birthweight.

TE: Total Effect (Direct Effect + Indirect Effect), T-IE: Total Indirect Effect

**p*<.05, ***p*<.01, ****p*<.001

Table 4-1. Descriptive statistics for predictors.

Categorical variables	N	%	
Metabolic Syndrome Classification			
Yes	537	4.9	
No	10495	95.1	
BMI			
≥30	2248	21.2	
<30	8379	78.8	
Triglycerides (mmol/L)			
> 1.7	6775	57.9	
≤ 1.7	4920	42.1	
HDL (mmol/L)			
≤ 1.6	1864	15.9	
> 1.6	9831	84.1	
Systolic BP (mmHg)			
≥ 140	180	1.5	
< 140	12162	98.5	
Diastolic BP (mmHg)			
≥ 90	62	0.5	
< 90	12281	99.5	
Fasting Glucose (mmol/L)			
> 5.6	387	3.0	
≤ 5.6	12016	96.9	
Hypertension (previously diagnosed)			
Yes	117	0.9	
No	12808	99.1	
Previously diagnosed diabetes			
Yes	350	3.0	
No	11235	97.0	
Continuous variables	**Mean (SD)**	**Median (IQR)**	**Range**
BMI (n=10627)	26.04 (5.7)	25.04 (21.93 – 29.10)	12.9 – 57
Triglycerides (mmol/L) (n=11695)	1.98 (0.74)	1.90 (1.50 – 2.30)	0.6 – 17.8
HDL (mmol/L) (n=11695)	1.97 (0.43)	1.90 (1.70 – 2.20)	0.6 – 4.1
Systolic BP (mmHg) (n=12342)	109.53 (11.51)	110.0 (100.0 – 120.0)	52 – 188
Diastolic BP (mmHg) (n=12343)	64.87 (8.34)	64.0 (60.0 – 70.0)	35 – 114
Fasting Glucose (mmol/L) (n=12403)	45.3 (0.55)	4.40 (4.20 – 4.70)	3 – 13.3

SD: Standard Deviation
IQR: Interquartile Range

Table 4-2. Descriptive statistics for child mediators and developmental outcomes.

Child Mediators	Mean (SD)	Median (IQR)	Range
HDL (mmol/L)	0.66 (0.22)	0.62 (0.50 – 0.78)	0.09 – 1.66
LDL (mmol/L)	0.80 (0.28)	076 (0.613 – 0.940)	0.02 – 3.21
Triglycerides (mmol/L)	0.53 (0.26)	0.46 (0.36 – 0.62)	0.18 – 2.64
Adiponectin (ng/ml)	31.68 (13.32)	29.8 (22.5 – 38.5)	2.6 – 98.1
Leptin (ng/ml)	10.53 (12.18)	7.11 (3.79 – 13.21)	0.15 – 430.87
Child Outcomes	**Mean (SD)**		**Range**
Age at assessment (months)	59.6 (1.00)	60.0 (56.0 – 63.0)	56 – 61
Starting School Variables			
British Picture Vocabulary Scale (n=3293)	100.75 (15.66)	100.0 (92.0 – 110.0)	39 – 161
Letter Identification (n=3259)	106.45 (12.60)	106.0 (97.0 – 117.0)	68 – 143
EYFS Childhood Outcomes (n=10,600)			
COM: Communication and Language	5.93 (1.77)	6.0 (5.5 – 6.0)	3 – 9
PSE: Personal, Social and Emotional	5.91 (1.54)	6.0 (6.0 – 6.0)	3 – 9
PHY: Physical Development	4.02 (1.00)	4.0 (4.0 – 4.0)	2 – 6
LIT: Literacy	3.57 (1.24)	4.0 (2.0 – 4.0)	2 – 6
MAT: Mathematics	3.61 (1.16)	4.0 (2.0 – 4.0)	2 – 6

SD: Standard Deviation
IQR: Interquartile Range

Table 4-3. Descriptive statistics for confounders and covariates.

Confounders	N (%)	Mean (SD)	Median (IQR)	Range
Maternal Age (n=11477)	11477	27.34 (5.6)	27.0 (23.0 – 31.0)	14—49
Maternal Education (n=10565)				
≥ A' Levels	4577 (33.0)			
< A' Levels	5988 (43.2)			
Missing	3296 (23.8)			
Maternal Alcohol History (n=11449)				
Yes	3495 (30.5)			
No	7954 (69.5)			
Maternal Smoking History (n=11456)				
Yes	1887 (16.5)			
No	9569 (83.5)			
Index of Multiple Deprivation (n= 11474)				
80-100%	7617 (66.4)			
60-80%	2065 (18.0)			
40-60%	1265 (11.0)			
20-40%	335 (2.9)			
0-20%	193 (1.7)			
Covariates	**N (%)**	**Mean (SD)**	**Median (IQR)**	**Range**
Maternal Ethnicity (n=11453)				
White British	4535 (39.6)			
Pakistani	5176 (45.2)			
Other	1742 (15.2)			
Child Sex (n=13528)				
Male	6554 (48.4)			
Female	6974 (51.5)			
Child Gestational Age (weeks) (n=13529)	13529	39.05 (1.9)	39.0 (38.0 – 40.0)	24—44
Child Birthweight (kg) (n=13527)	13527	3.21 (0.6)	3.22 (2.88 – 3.56)	0.5—5.8

SD: Standard Deviation
IQR: Interquartile Range

Table 4-4. Effects of child mediators on MetS and child outcomes (adjusted model).

(a) MetS on	DE	DE *95% CI*	IE	IE *95% CI*	T-IE	T-IE 95% CI	TE	TE *95% CI*
BPVS (n=13812)	.000	-.028 to .030						
(a) Triglycerides	-.039	-.086 to -.006	.000	-.004 to .002				
(b) Triglycerides	.010	-.047 to .069						
(a) HDL	-.088***	-.118 to -.053	-.005	-.013 to .001				
(b) HDL	.056	-.013 to .124						
(a) LDL	-.002	-.039 to .034	0.00	-.001 to .002	-.004	-.010 to .003	-.004	-.029 to .025
(b) LDL	-0.30	-.090 to -.030						
(a) Adiponectin	-.019	-.057 to .024	0.00	.000 to .004				
(b) Adiponectin	-.021	-.075 to .031						
(a) Leptin	-.054**	-.087 to -.031	.001	-.029 to .025				
(b) Leptin	-.014	-.049 to .042						
LID (n= 13812)	.010	-.026 to .040						
(a) Triglycerides	-.039	-.086 to -.006	.000	-.003 to .002				
(b) Triglycerides	.000	-.062 to .057						
(a) HDL***	-.086	-.115 to -.052	.003	-.002 to .009				
(b) HDL	-.036	-.096 to .026						
(a) LDL	-.004	-.041 to .033	.000	-.002 to .004	.003	-.002 to .010	.014	-.021 to .042
(b) LDL	-.064	-.122 to -.004						
(a) Adiponectin	-.020	-.057 to 0.24	.000	-.003 to .001				
(b) Adiponectin	.008	-.051 to .059						
(a) Leptin**	-.054	-.088 to -.030	.000	-.002 to .002				
(b) Leptin	-.005	-.035 to .043						
COM (n=13832)	-.011	-.027 to .007						
(a) Triglycerides	-.040	-.085 to -.003	-.001	-.005 to .000				
(b) Triglycerides	.025	-.015 to .069						
(a) HDL	-.086***	-.117 to -.052	-.005	-.011 to -.001				
(b) HDL	.059	.009 to .104			-.007*	-.012 to -.002	-.018	-.034 to .000
(a) LDL	-.004	-.042 to .033	.000	-.003 to .001				
(b) LDL	.035	-.019 to .078						
(a) Adiponectin	-.020	-.059 to .020	.001	-.000 to .003				
(b) Adiponectin	-.032	-.072 to .011						
(a) Leptin	-.054**	-.089 to -.031	-.001	-.003 to .000				
(b) Leptin	.019	-.006 to .049						
PSE (n=13832)	-.007	-.024 to .012						
(a) Triglycerides	-.040	-.086 to -.003	-.001	-.004 to .000				
(b) Triglycerides	.018	-.022 to .058						
(a) HDL	-.087***	-.117 to -.053	-.005	-.012 to -.002				
(b) HDL	.062	.014 to .109			-.006*	-.012 to -.002	-.013	-.029 to .004
(a) LDL	-.004	-.042 to .032	.000	-.003 to .001				
(b) LDL	.032	-.014 to .077						
(a) Adiponectin	-.019	-.061 to .019	.000	.000 to .003				
(b) Adiponectin	-.023	-.062 to .019						
(a) Leptin	-.054**	-.090 to -.031	.000	-.029 to .001				
(b) Leptin	.003	-.021 to .031						

PHY (n=13832)	-.011	-.029 to .007						
	-.039	-.086 to -.003	-	-.002 to .001				
(a) Triglycerides			.000					
(b) Triglycerides	.002	-.039 to .045						
	-.087***	-.117 to -.053	-	-.010 to -				
(a) HDL			.005	.001				
(b) HDL	.054	.006 to .100						
(a) LDL	-.004	-.043 to .033	.000	-.002 to .001	-.005	-.032 to .002	-.015	-.010 to -.001
(b) LDL	.027	-.015 to .072						
(a) Adiponectin	-.019	-.059 to .020	.001	.000 to .003				
(b) Adiponectin	-.036	-.074 to .006						
	-.054**	-.088 to -.031	-	-.002 to .001				
(a) Leptin			.001					
(b) Leptin	.010	-.015 to .038						
LIT (n=13832)	-.025*	-.041 to -.008						
	-.040	-.085 to -.003	-	-.004 to .000				
(a) Triglycerides			.001					
(b) Triglycerides	.020	-.022 to .061						
	-.086***	-.117 to -.052	-	-.009 to .000				
(a) HDL			.004					
(b) HDL	.042	-.004 to .091						
(a) LDL	-.004	-.043 to .032	.000	-.003 to .001	-.005	-.010 to -.001	-.030**	-.046 to -.014
(b) LDL	-.019	-.059 to .028						
(a) Adiponectin	-.020	-.060 to .019	.000	.000 to .003				
(b) Adiponectin	.019	-.059 to .028						
	-.054**	-.089 to -.032	-	-.003 to .000				
(a) Leptin			.001					
(b) Leptin	.019	-.004 to .050						
MAT (n=13832)	-.015	-.032 to .004						
		-.087 to -.004	-	-.005 to .000				
(a) Triglycerides	-.040		.002					
(b) Triglycerides	.039	-.011 to .080						
		-.177 to -.052	-	-.008 to .001				
(a) HDL	-.086***		.003					
(b) HDL	.037	-.011 to .083						
(a) LDL	-.004	-.044 to .032	.000	-.003 to .001	-.005	-.012 to -.001	-.020	-.037 to -.003
(b) LDL	.034	-.014 to .075						
(a) Adiponectin	-.019	-.058 to .020	.001	.000 to .003				
(b) Adiponectin	-.040	-.080 to .000						
		-.090 to -.032	-	-.003 to .000				
(a) Leptin	-.054**		.001					
(b) Leptin	.026	.002 to .055						

***DE**: Direct Effect*
***IE:** Indirect Effect*
***T-IE:** Total Indirect Effect*
***TE:** Total Effects (Direct Effect + Indirect Effect)*
(a)Child mediators on METSYN; (b) Child outcomes on child mediators
Note: participant sample sizes ranged from 12,652 (found in unadjusted models) to 13,832 mother-child pairs depending on availability of data

Results

Results in Table 4.1 showed that 21.2% of mothers had high BMI (≥ 30), 57.9% had raised triglycerides levels (>1.7mmol/L), 15.9% with lowered HDL (<1.6mmol/L), 1.5% with raised systolic BP (≥140), 0.5% with raised diastolic BP (≥90), and 3.0% with raised fasting glucose (>5.6mmol/L). 0.9% of mothers was previously diagnosed with hypertension and 3.0% was previously diagnosed with diabetes prior to pregnancy. 4.9% of mothers in this cohort met the IDF classification for maternal metabolic syndrome (Table 4.1). 45.6% of mothers were Pakistani, 39.6% were White British, and 15.2% were classified as other races (Table 4.3). For unadjusted models, sample sizes ranged from n=12,644 to n=13,364 participants. For adjusted models, total sample sizes ranged from n=13,812 to n=13,832 participants, depending on availability of mother-child pairs for specific models (Table 4.4). More descriptive statistics for predictors, outcomes, and confounders and covariates can be found in Tables 4.1—4.3.

The mediation models showed adequate fit according to the fit indices (CFI >.90, TLI>.80, RMSEA=.21, SRMR=.13). All model fits can be found in the Appendix C, Table C1. Statistical significance was set at $p<.05$.

Overall results for the adjusted model found total effects of maternal metabolic syndrome through child mediators on the domains of LIT (B= -.030, 95% CI= -.046, -.014). Direct

effects were found for maternal metabolic syndrome on LIT domain (B= -.025, 95% CI= -.041, -.008). Direct effects for maternal metabolic syndrome were also shown for child mediators of HDL (B= -.086, 95% CI= -.117, -.052) and leptin (B= -.054, 95% CI= -.089, -.032) in all child development domains. The pathway of effect shows that effects of all combined child cord blood markers acted as mediators for maternal metabolic syndrome and child development outcomes, showing total indirect effects. Total indirect effects were found for the COM (B= -.007, 95% CI= -.012, -.002) and PSE domains (B= -.006, 95% CI= -.012, -.002). More specific results can be found in Table 4.4.

The mediation proportion has also been calculated as follows: for the BPVS domain = 100% (--.004/-.004); for the LID domain = 21.4% (.003 / .014); for the COM domain = 38.8% (-.007 / -.018); for the PSE domain = 46.2% (-.006 / -.013); for the PHY domain = 33.3% (-.005 / -.015); for the LIT domain = 16.7% (-.005/-.030); for the MAT domain = 25% (-.005-.020).

More information on both the unadjusted and adjusted models can be found in Table 4.4, the Appendix C, or at https://osf.io/czt87/.

Discussion

The purpose of the present study was to examine child cardiometabolic markers as potential mediators of the links between maternal metabolic syndrome in pregnancy and child developmental outcomes at 5 years old. We found that there were significant total effects of maternal metabolic syndrome on child developmental outcomes in the literacy domain (LIT) at age 5 both before and after adjustments for covariates. Maternal metabolic syndrome was found to affect specific child cord blood markers of lowered HDL and increased leptin levels, displaying these two markers as potential at-risk cord blood biomarkers at birth when maternal metabolic syndrome is present during pregnancy when assessing children literacy outcomes. Total indirect effects also showed that the combined effects of an at-risk profile at birth (using all child cord blood markers) partially mediated the association between maternal cardiometabolic health and children's communication and language (COM), and personal, social, and emotional (PSE) domains at 5 years old.

The above results support the hypotheses of maternal cardiometabolic health being associated with developmental outcomes at 5 years old. Additionally, while the effects of individual cord blood markers were too small to be individually significant, the direct and indirect effects of all combined cord blood markers (HDL, LDL, triglycerides, adiponectin, and leptin) showed significant mediating effects for maternal metabolic syndrome and

child development domains of COM and PSE. Study results were in line with a study using two pregnancy cohorts, where some cord blood markers were seen to be associated with child neurodevelopment at age 3, 5, and 8 years old, specifically for performance and full scale Intelligence Quotient (IQ), and working memory (N. Li et al., 2019). While the previous study only looked at hormones of adiponectin and leptin individually, this study adds to the literature by allowing for closer examination of combined effects of multiple markers to be studied together.

Study results were also consistent with literature on maternal cardiometabolic conditions affecting both cord blood profiles (Mocarzel et al., 2020) and neurodevelopment. Overall findings were in line with research on low-grade, chronic inflammatory processes such as cardiometabolic health in the mother during pregnancy being linked with fetal development (Fitzgerald et al., 2020) and subsequent effects on outcomes such as IQ, socialization, communication, expressive language, physical development, and executive function (Mina et al., 2017; J. R. Thompson et al., 2018; Torres-Espinola et al., 2015; Yamamoto et al., 2019). Closer examination of results showed evidence for complex underlying mechanisms of maternal cardiometabolic profiles being linked with broader domains commonly assessed through education at a starting-school age, such as communication, literacy, and physical development, even when accounting for maternal, environmental, and child covariates and confounders.

Using classification of metabolic syndrome allowed examination of the combined effects of multiple biomarkers. Diabetes and hypertension seem to share similar processes of oxidative stress-mediated regulation cascades and chronic, low-grade inflammation (B. M. Y. Cheung & Li, 2012) with the release of free fatty acids from adipose tissue being linked with higher oxidative stress and maternal endothelial dysfunction (Stump et al., 2005). With this increased metabolic demand and homeostatic disruption during pregnancy, studies found effects on fetal outcomes, in birth or childhood cardiovascular outcomes over time (Leach, 2011; McLaughlin et al., 2018; Sobrevia et al., 2011). In addition, the cord blood marker of lowered HDL, also classified as an oxidative stress marker (Bhatt et al., 2020), presents an early insight into how it can be associated with a child's personal, social and emotional domain, with studies supporting associations when examining oxidative stress dysregulation being found in patients with depression and even subsequent suicide attempts (Lehto et al., 2008; T. Liu et al., 2015). The current study results are supported by previous research and adds a further dimension, that is, it found that combined effects of lowered child health at birth mediated the negative effects of maternal metabolic syndrome on development. This is consistent with the inflammatory cascade hypothesis that postulates inflammation during pregnancy affecting not only early-life programming, but also subsequently showing negative effects on child development (Camerota et al., 2022).

Study Implications

This study demonstrates how maternal cardiometabolic health may contribute to later child developmental difficulties. Maternal metabolic syndrome classification, a constellation of metabolic risk factors, seem to not only affect the pregnancy process but is also linked with specific developmental delays in communication, literacy, and personal, social, and emotional development at 5 years old. This is a critical period for learning and subsequent educational attainment.

Moreover, this study further adds to the literature on gestational biology mechanisms not only affecting fetal health, but also a newborn's health, and essential child developmental milestones. It is often difficult to justify early clinical intervention for children with no clear prognostic factor during pregnancy. This research provides a theoretical basis for interventions even before developmental delays are formally identified in the child through considering maternal metabolic syndrome classification during pregnancy to be a risk marker when considering child development outcomes. A clinical implication from our findings showed that while both maternal and child cardiometabolic markers seemed statistically non-significant when examined individually, but significant when examined together. This displays the importance of not looking for excessive values in any one marker, but to examine both a mother and child's cardiometabolic health as a combined

profile when assessing future risk. Further, results imply that health and educational organisations should be better informed of these potential long-term effects of maternal cardiometabolic health on child developmental milestones. In particular, the start of formal education can possibly consider having extra screening or monitoring systems for affected children at future risk for having special education needs.

Strengths and Limitations

Study strengths include using a large, high quality and ethnically diverse cohort sample. A comprehensive set of cardiometabolic markers was taken from clinical data collected during pregnancy. Further, the classification of metabolic syndrome using a standardized classification according to the International Diabetes Federation definition allows for future replicability. While some studies (Forbes et al., 2015; Ormazabal et al., 2018) have described associations between pregnancy cardiometabolic markers and childhood health-related outcomes, it still remains unclear whether the associations are predominantly due to intrauterine mechanisms or other external confounders such as birth outcomes or socioeconomic levels. The mediation models in this study provides closer examination of maternal-child associations with added mediators before any environmental influence.

This study had several limitations. First, this prospective cohort had a limited sample size that met the requirement for metabolic syndrome classification (n=494), in addition to missing data for the child cord blood markers when comparing mother-child pairs. In addition, the measure of diabetes taken by the study team did not differentiate between type I or type II diabetes in the mother. Maternal gestational diabetes was also not included as part of the analysis, due to possible epigenetic etiology (Yahaya et al., 2020). Next, maternal physical activity, a possible protective mechanism that might mitigate the effect of diabetes and hypertension, was not included as a possible study confounder as there was no standardized measure available from the dataset. Obesity-susceptible single nucleotide polymorphisms (SNP), a component of persistent central obesity and metabolic syndrome also not included as a study factor that could possibly lead to adverse childhood outcomes (C. Y. Y. Cheung et al., 2011). Lastly, while data was taken from a more diverse area, results may not be reflective of pregnancy cohorts from lower income countries.

Conclusion

Maternal cardiometabolic risk during pregnancy is associated with child developmental outcomes and newborn health examined through cord blood markers partially mediates this. These findings held after accounting for external variables to distinguish between the direct impact of gestational biology and indirect environmental influence through controlling for maternal, child, and environmental factors. Study outcomes were specifically selected as they are part of a nationwide framework that assesses developmental milestones. These findings highlight a public health need to further understand the mechanistic pathways in which maternal health during pregnancy affects children's health and subsequent development, which further support preventative or interventions as early as possible. As shown in this study, as child cord blood markers are associated with children's development. Healthcare services can therefore consider adding them as prognostic risk biomarkers as part of continuing clinical care. Study findings also indicate a need for early monitoring in children born to mothers with metabolic syndrome classification during pregnancy due to a higher at-risk profile both at birth (seen in cord blood) and age 5 development. More research needs to be done to further understand if these associations are affected by the presence of other pregnancy risk mechanisms and if developmental outcomes persist beyond 5 years old.

Future research could include closer examination of ethnic differences, epigenetic effects, and environmental factors contributing to maternal cardiometabolic health and child developmental outcomes. Future research should also look at trimester-based risk for further understanding of inflammation processes when intrauterine stress is present during early, mid, or late pregnancy (Parker & Douglas, 2010).

Chapter 5a and 5b: Analgesic Drug Exposure During Pregnancy on Child ASD and ADHD Outcomes

Synopsis

This chapter consists of a protocol paper (Chapter 5a) an umbrella review paper (Chapter 5b) providing an evidence synthesis on how analgesic drug use during pregnancy is linked with ASD and ADHD outcomes. The protocol paper stated data extraction techniques and criteria for selection of review, while the review paper synthesised high-quality reviews on effects of paracetamol use on ADHD outcomes in children. Two quality assessments were used for overall evaluation, risk of bias, and heterogeneity. A narrative synthesis showed significant associations between maternal prenatal acetaminophen (paracetamol) use and ADHD outcomes, with a potential dose-dependent relationship. This review provided high-level evidence on how potential endocrine disruption from medication exposure can influence a mother's biochemistry, have effects on fetal development process, and subsequently affect child neurodevelopmental diagnosis.

Dissemination status:

Protocol paper (5a) has been published in *BMC Systematic Reviews*:
https://doi.org/10.1186/s13643-020-01465-9.
Umbrella review (5b) has been published in *Neuroscience and Biobehavioral Reviews:*
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Authors' contributions

I conceptualised and designed the study, conducted analysis, interpretated the data, drafted and revised the manuscripts' drafts and revisions, and submitted the papers for publication. Dr H. A. Hall (for both protocol and review paper) and Ms E. Luedecke (review paper only) contributed to data extraction and inter-rater assessment, analysis and interpretation, and manuscript revisions. Dr B. Auyeung contributed to data interpretation and manuscript reviews. Dr A. L. Murray provided feedback throughout all stages of the process; study design, data analysis and write-up, manuscript revision, and the journal submission process.

The manuscript has been slightly modified for the purpose of this thesis.

Chapter 5a - Protocol Paper:

The Association Between Analgesic Drug Use in Pregnancy and Neurodevelopmental Disorders: Protocol for an Umbrella Review

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List of Study Abbreviations

ASD: Autism Spectrum Disorder

ADHD: Attention-Deficit Hyperactivity Disorder

AMSTAR 2: A MeaSurement Tool to Assess systematic Reviews (2nd edition)

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (5th edition)

FDA: Food and Drug Administration (United States)

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO: international prospective register of systematic reviews

Abstract

Background: Maternal prenatal health has been shown to be an important influence on children's developmental outcomes, which has led to an increased emphasis on providing more information to support clinical decisions in pregnancy. Several systematic reviews suggest that analgesic drug use during pregnancy may have neurodisruptive properties. However, no firm conclusions have yet been drawn on the associations between prenatal analgesic drug use and children's long-term development of neurodevelopmental disorders such as autism spectrum disorder (ASD) or attention deficit hyperactivity disorder (ADHD). Therefore, an umbrella review is proposed for the purpose of examining the associations between maternal analgesic drug use during pregnancy and diagnoses of neurodevelopmental disorders.

Method: Included systematic reviews will consist of studies examining the effect of maternal prenatal analgesic drug use, specifically ibuprofen, acetaminophen, aspirin, naproxen, diclofenac, and ketoprofen, on children's neurodevelopmental disorder status. Examined drugs were restricted to those readily accessible and frequently used by pregnant women, and with characteristics that allow them to cross the placenta and directly affect fetal development. Outcomes will be restricted to formal clinical diagnoses of ASD and/or ADHD. Two reviewers will independently identify eligible reviews from six databases (e.g., PubMed, EMBASE, PsychINFO) from inception dates of databases to the date of data extraction, and conduct manual searches of reference lists, consultation with field experts, and scan of pre-print archives. Extracted data will also include short qualitative summaries by both reviewers. As part of quality assessment, a standardized measurement tool to assess systematic reviews (AMSTAR 2) will be used. A narrative synthesis is proposed to integrate findings from different, potentially methodologically heterogeneous, studies.

Discussion: This umbrella review of associations between maternal prenatal use of analgesic drugs and children's neurodevelopmental disorders could allow for firmer conclusions to be drawn through the synthesis of all relevant published research. The synthesis of findings using high-quality evidence could provide more accurate healthcare information on how analgesic drugs is associated with neurodevelopment. This review will also allow gaps and methodological differences in the literature to be identified, informing recommendations for future research.

Systematic review registration: PROSPERO registration number CRD42020179216.

Keywords: *Umbrella review, analgesics, medication, painkillers, pregnancy, maternal, autism, ADHD*

Background

Recent years have shown an increased emphasis on the effects of maternal prenatal health on children's long- term development. Decisions made during pregnancy should be as well-informed as possible to understand possible long-term effects, such as on children's neuro- development. Since 1990, there has been global increased awareness of neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), with the worldwide prevalence of ASD being 0.17–0.62% (Elsabbagh et al., 2012) and 5.29–7.20% for ADHD (Polanczyk et al., 2007; Thomas et al., 2015). Currently, 56% of pregnant women are reported to use analgesic drugs (Lupattelli et al., 2014). With this prevalence rate, it is worthwhile to examine the effects of prenatal drug use on a child's long-term development.

With increased cardiac output and blood flow that occurs as part of the physiological changes during pregnancy, drug absorption also increases (Feghali et al., 2015). This bioavailability creates complex chemical changes in both the mother and fetus. Studies on pharmacokinetic changes in pregnancy show how placenta transfer occurs between maternal and fetal blood circulatory systems (Sachdeva et al., 2009). Some pharmacological characteristics of drugs that cross the placenta include soluble lipids, unbound drugs that are lower of degree of ionization and have a molecular weight of less than 500 g/mol (S. K. Griffiths & Campbell, 2015). Drugs that fall under this category

include aspirin, ibuprofen, naproxen, and acetaminophen (paracetamol). With hormonal changes in pregnancy and increased lipid levels diminishing the binding capacity of drugs (Gedeon & Koren, 2006), a fetus may experience large concentrations of drug doses, possibly affecting the developing brain.

Some medications of interest in this review, such as acetaminophen and naproxen, are also antipyretic drugs. Antipyretic drugs are prostaglandin antagonists which affect the hypothalamus and decrease body temperatures during an episode of fever. Untreated fever in pregnancy has been associated with malformations in children, particularly neural tube defects, heart defects, and oral clefts (Dreier et al., 2014). While there is some evidence that antipyretic medication has a protective effect, some pregnant women may use these medications without considering potential long-term effects on their child's development neurodevelopment (Dreier et al., 2014). As some women avoid mild analgesics/antipyretics during pregnancy (Twigg et al., 2016), women therefore need to carefully weigh the risks of untreated fever against the risk of using mild analgesics/antipyretics.

During pregnancy, drugs may be used for a wide variety of reasons, such as to alleviate pain, improve health, or increase well-being. While previous research has suggested neurodisruptive properties of certain drugs on the fetus (Masarwa et al., 2018), some of these drugs are still not recognised as human teratogens and are readily accessible to the

public. Current studies show that prenatal use of drugs is frequent in pregnant women, with around 90% of them taking some form of medication during pregnancy (Mitchell et al., 2011). With analgesic drugs recorded as the most commonly-recommended class of drugs to be used during pregnancy, it is possible that pregnant women are engaging in this type of drug use without being aware of potential long-term effects on their child. Recognizing that there was insufficient information to guide clinical decisions, the US Food and Drug Administration (FDA) established new pregnancy exposure registries in 2002 in order to encourage the use of prospective studies to obtain relevant data (*Guidance for Industry on Establishing Pregnancy Exposure Registries; Availability*, 2002). This registry is similar to those in other countries, such as the Swedish Medical Birth Register, which was established in 1973, and has collected information on drugs used during pregnancy since 1995 (*Swedish National Medical Birth Register | European Health Information Portal*, n.d.). However, at the time of writing, neither of these registers have produced re- search with firm conclusions regarding prenatal exposure to analgesic drugs and their association with children's neurodevelopmental outcomes.

Since January 2016, the FDA also proposed changing medication labels in order to provide more information for pregnant women. Despite having shown that analgesic drugs cross the placenta, most of them have been placed under either FDA categories:

category B:

"Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women, or animal studies have shown adverse effects, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester,"

or category C:

"Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well- controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks,"

or category D:

"There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life- threatening situation or for a serious disease in which safer drugs cannot be used or are ineffective)" (R. A. Black & Hill, 2003; Pernia & DeMaagd, 2016).

This illustrates that current clinical guidelines are still based on limited and inconsistent evidence regarding the long-term effects of these drugs on the fetus.

Research has suggested that prenatal drug use is associated with increased behavioural symptoms such as conduct problems and hyperactivity at age 7 (Liew et al., 2014). Further,

a systematic review of nine studies suggested that prenatal exposure to analgesic drugs such as acetaminophen was associated with an increased risk of neurodevelopmental disorders between 18 months and 3 years (Bauer et al., 2018). These results are consistent with another systematic review of seven retrospective cohort studies (Masarwa et al., 2018) that found a significantly increased risk of ASD and ADHD in children with age ranges of 3 to 12 years old, in relation to prenatal acetaminophen use. However, other reviews question conclusions on links between prenatal analgesic drug use and neurodevelopmental disorders in children and suggest that findings may be influenced by unmeasured confounding (de Fays et al., 2015; Masarwa et al., 2020). The above studies and national registries imply that current research or government initiatives are not yet sufficient in nature to understand long-term effects of prenatal analgesic drug use on a child's development. Thus, an umbrella review is needed to provide a comprehensive overview of the existing evidence in this field.

Systematic reviews have long been held as the gold standard in contributing to evidence-based healthcare by informing decision-making processes (Aromataris et al., 2015). The next step in conducting an umbrella review offers valuable insight through providing an overall summary of multiple systematic reviews; effectively synthesizing, comparing, and contrasting results of published systematic reviews and meta-analyses. Umbrella reviews are conducted in line with the same principles as systematic reviews, in terms of, for

example, predefined search strategies, quality assessment, and reporting guidelines. However, the subject of an umbrella review is existing systematic reviews and meta-analyses, rather than original research studies (Aromataris et al., 2015; Hartling et al., 2012). The objectives the proposed umbrella review also align with Cochrane's overview of reviews, consisting of (1) a clearly formulated objective to answer a specific research question, (2) inclusion of only systematic reviews, (3) explicit and reproducible methods of identification and risk/quality assessment, (4) collection and presentation of data from studies (description of systematic reviews, risk of bias, quantitative outcome data, certainty of evidence using a clinical outcome framework such as GRADE assessments), and (5) discussion of findings related to specific research questions (i.e., summary of main results, completeness, applicability and quality of evidence, agreements, and/or disagreements with other studies) (*Overview of Reviews - Chapter V*, 2020). The topic of associations between maternal prenatal use of analgesic drugs and children's neurodevelopmental disorders has reached a level of maturity where it can benefit from this form of synthesis, further allowing for firmer conclusions to be drawn through an overall examination of published research.

The aims of the proposed umbrella review are to (a) summarize and synthesize findings from systematic re- views or meta-analyses on links between analgesic drug use in pregnancy and children's diagnoses of neurodevelopmental disorders, specifically ASD

and ADHD; (b) use high-quality evidence to provide firm conclusions from current literature, in order to inform healthcare guidance for pregnant women; and (c) identify gaps and methodological weaknesses in the literature to inform recommendations for future research in this area.

Methods

Registration and reporting information

The umbrella review protocol is being reported in accordance with the reporting guidance provided in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement (Moher et al., 2009), found in the online supplement (https://doi.org/10. 1186/s13643-020-01465-9). This protocol has also been registered within the International Prospective Register of Systematic Reviews (PROSPERO) database (registration ID: CRD42040179216).

Inclusion criteria

Included studies will be based on the following eligibility criteria:

Population

Study populations will include pregnant women and the children resulting from their pregnancies. No age limit is set for the pregnant women nor their offspring.

Exposures

Only systematic reviews or meta-analyses examining the effects of analgesic drugs will be included in this review. Drugs reviewed will fulfil the criteria of easy access and common usage (Thorpe et al., 2013) and have characteristics that allow them to cross the placenta and directly affect the development of the fetus (Sachdeva et al., 2009). This umbrella review will focus on reviews of the following specific medications: ibuprofen, acetaminophen, aspirin, naproxen, diclofenac, and ketoprofen. ASD and ADHD assessed by any means (e.g., clinical diagnoses, parent- or teacher-report) (Masarwa et al., 2018) will be included in this review. All types of autism spectrum disorders (e.g., pervasive developmental disorder (not otherwise specified) and Asperger's disorder) will be included in this review. All types of attention deficit hyperactivity disorders (e.g., attention deficit disorders, hyperkinetic disorders) will be included in this review.

Setting

Healthcare settings will include both hospital and community data. The study will cover the analgesic drugs taken during the period of pregnancy only.

Outcomes

All reviews which draw on indications of ASD, ADHD, or co-occurring ASD and ADHD, assessed by any means, as outcomes will be included, as will gender-specific reviews. No upper age limit restrictions will be applied for study outcomes.

Study design

Only reviews of studies which include human offspring will be considered for this review. Only reviews of quantitative studies will be included. The review will be restricted to systematic reviews and meta-analyses but will not be restricted to reviews of studies of a particular design (e.g., longitudinal or cross-sectional). Methodological differences will be discussed in the umbrella review.

Language

Limits will be set to only meta-analysis and systematic reviews in the English language due to the language capabilities of the study team.

Exclusion criteria

Excluded studies will be based on the following criteria:

Population

Studies on non-human mammals only will be excluded.

Exposures

Reviews focusing on non-analgesic drugs or illegal drugs will not be included in this review, neither will studies examining neurodevelopmental disorders other than ASD or ADHD.

Study design

Articles that are not relevant to the review's scope of prenatal use of analgesic drugs or children's ASD or ADHD will be excluded. Types of articles which will be excluded are primary or original research, non- systematic reviews (e.g., narrative or scoping reviews), case studies or qualitative reviews, and reviews that draw on published opinion or theoretical studies as a primary source of evidence.

Two reviewers will assess studies against the inclusion and exclusion criteria.

Search strategy

A search will be performed through major repositories of systematic reviews and meta-analyses, namely the following databases: Embase, Maternity and Infant Care, PsycINFO, PsycARTICLES, PubMed, and Cochrane Library. Boolean operators of "AND" and "OR" will be used for search terms and adapted for different data- bases. Search filters will be employed and presented sequentially for the databases with key terms searched for in

the title or abstract fields. Relevant subject headings will also be used in addition to keywords (e.g., "Prenatal exposure drugs neurodevelopment" in the EMTREE the- saurus, or "Prenatal drugs effect ASD" in the MeSH thesaurus).

A list of example search terms is included in Appendix D, Table D1. Search periods will extend from the inception dates of the databases to the date of data extraction. The reference manager Zotero will be used to store records and identify duplicates.

In order to provide a comprehensive search, reference lists of selected reviews, reviews in-press (derived from scanning pre-print archives or discussion with field experts), will form part of the supplementary search strategy and recorded under "additional records." These include contacting study authors, manual searches of grey literature (such as Open Grey, Virtual Health Library), and preprint platforms (such as arXiv.org, medRxiv.org, PsyArXiv.com, Open Science Framework [OSF] preprints).

Screening and selection procedure

Data extraction

Data extraction and coding will be independently carried out by two researchers. All articles identified from the literature search will be independently screened by two researchers. First, titles and abstracts of articles will be screened based on the eligibility

criteria as outlined above. Second, full texts will be examined in detail and screened for eligibility. Third, references of all considered articles will be searched manually to identify any relevant reports that may have been missed in the initial search strategy. Any disagreements will be resolved through discussion by the researchers to meet a consensus, if necessary. Information extracted from each study will include first author, year of publication, reported a protocol, objective(s), reported strategies to search literature, number of databases searched and date of last search, inclusion/exclusion criteria, population, main outcomes of interest, type of study designs included (e.g., observational studies), number of included studies, number of studies reporting data for meta-analyses, effect metric(s) reported (e.g., risk ratio), methods to assess study risk of bias, additional analyses, metabias assessment (e.g., publication bias across studies), funding source, and conflicts of interest. Extracted data will be stored in spreadsheets which will be used to determine eligibility for inclusion in the umbrella review.

Any discrepancies will be solved through discussion until consensus is achieved, with the assistance of the third researcher if needed. Studies with missing essential information such as participant data or search strategies will not be included in the final review. A PRISMA flow diagram showing the number of studies included and excluded at each stage of the study selection process will be provided (Moher et al., 2009) (found in online

supplement: https://doi.org/10. 1186/s13643-020-01465-9.) The umbrella re- view will undergo a full pilot process using a small sample of papers before a full review is initiated.

Quality assessment

A proposed quality assessment, the AMSTAR 2 (A MeaSurement Tool to Assess systematic Reviews-2) (Shea et al., 2017) will be used for this umbrella review (online supplement: https://doi.org/10. 1186/s13643-020-01465-9). This updated version of a critical appraisal tool was chosen for rapid quality assessments of systematic reviews in healthcare. The AMSTAR 2 tool consists of 16-items addressing search strategies, data extraction techniques, bias risk, appropriate methodology, and interpretation and discussion of results. Seven domains within the AMSTAR 2 are regarded as "critical" and flaws in these domains are deemed to affect the validity of the review (assessed by items 2, 4, 7, 9, 11, 13, 15). The AMSTAR 2 authors propose a scoring scheme which categorizes the confidence in the results of each review into "High," "Moderate," "Low," and "Critically low." We will use this scheme and reviews which we rate as "Critically low" (the study has more than one critical flaw) will be excluded from the data synthesis. Studies which we deem "Low" (one critical flaw) will be included, but their conclusions are given less weight.

The AMSTAR 2 not only allows for future replicability, but also provides reviewers with little epidemiological training with a standardized template, for a more in-depth appraisal

of the literature. It consists of detailed questions. This tool is in line with advised guidelines on the assessment of systematic reviews based on identifying methodological features such as how well the research question is defined, use of a systematic search strategy, possible publication or funding bias, selective reporting, previous quality ratings, and presence of information synthesis and conclusion (Fusar-Poli & Radua, 2018). The AMSTAR 2 will be modified to suit the topic for this umbrella review through reducing the emphasis of randomized control trials in the quality assessment process.

Data synthesis

A narrative synthesis method is proposed for this umbrella review. Included studies will be tabulated with an overall summary. We will provide a narrative synthesis of the findings from each review, supported by a table showing the results of the critical appraisal based on included studies (as assessed by the modified AMSTAR 2 approach). The table will include a description of key features, findings, variations of re- search, and supplemented with graphics if relevant. A meta-analysis will not be performed. This method was primarily chosen due to the lack of firm conclusions on prenatal analgesic drug use and potential heterogeneity of data from multiple systematic reviews and meta-analyses. A narrative synthesis provides flexibility due to its qualitative rather than quantitative nature of the analysis. The purpose of this narrative synthesis is to examine and integrate ideas from multiple different reviews to provide a clear overview of the effects of analgesic drugs on neurodevelopmental diagnoses. Variations or discrepancies in findings will be explored

by comparing methodological features between reviews (e.g., eligibility criteria, outcomes definitions).

Confidence in cumulative evidence

The strength of the body of evidence will be assessed through the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) certainty ratings. Using GRADE guidelines (Fusar-Poli & Radua, 2018), the researchers will examine the following domains for a decrease in certainty: risk of bias, imprecision of true effects, inconsistency of effects, indirectness of outcomes, and publication bias.

Discussion

The purpose of this umbrella review is to elucidate the associations between prenatal use of analgesic drugs and children's neurodevelopmental disorder diagnoses through the synthesis of relevant published research. Findings from this review will provide a clearer direction for clinical decisions made during pregnancy in relation to the use of analgesic drugs. A small sample of papers will be selected to conduct at the pilot as an initial stage of the umbrella review, including search strategies, inclusion/exclusion criteria, data extraction, and quality assessments. The results of the pilot will be used to refine data extraction in the full umbrella review or if necessary, modification of the scope of the review before proceeding with the full review.

Potential practical issues may present proposed search terms producing irrelevant results, in which the team will then redefine current search strategies. If key variables are missing from our data extraction plan, all amendments to the protocol will be documented and reported thoroughly. All amendments to the protocol will be documented in a separate summary sheet, which will be submitted in the final umbrella review.

A potential limitation of this review could involve difficulties in synthesizing information due to methodological differences of original studies leading to heterogeneous results in the selected reviews. Another limitation could arise from the emphasis of AMSTAR 2; due

to its original focus of being a tool for randomized controlled clinical trials of interventions, several items in the AMSTAR 2 are not entirely relevant to this umbrella review, such as question 8 where the description of studies in adequate detail had to have "interventions" as an option to fulfil the criteria of "Yes" (Additional File 2). To mitigate this, the AMSTAR 2 will be modified to suit the topic of our umbrella review.

However, this also offers an opportunity to discuss these methodological differences and provide clear suggestions for future research. Using synthesized information on analgesic drugs and their association with neurodevelopmental outcomes, there are several strengths of this proposed review. A strength of the proposed review lies in the added value of synthesising findings from previous reviews on the effects of prenatal use of analgesic medications on children's long-term neurodevelopment. To our knowledge, no such review has been conducted on this topic as of yet. Findings could help refine clinical practices for the prenatal period and increase the quality of available information which future decisions in healthcare policy are based on.

Chapter 5b - Umbrella Review Paper:

Analgesic Drug Use in Pregnancy and Neurodevelopment Outcomes: An Umbrella Review

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Abstract

Background: Emerging evidence from reviews suggests that analgesic drug exposure during pregnancy may contribute to child neurodevelopment outcomes. A comprehensive overview of existing evidence is needed for firm conclusions to inform clinical guidelines. This umbrella review aims to synthesise high-quality evidence on prenatal analgesic drug exposure and risk of ASD and ADHD in children.

Methods: Seven databases were searched from inception to May 2021 to identify relevant reviews of any design. The AMSTAR 2 and the GRADE quality assessments were used to evaluate risk of bias and heterogeneity. A narrative synthesis approach was used to summarise findings. Five systematic reviews and meta-analyses met the inclusion criteria.

Results: All reviews reported significant associations between maternal prenatal acetaminophen use and ADHD outcomes (risk ratio range: 1.08 to 1.34; no pooled incidence rate), with a potential dose-dependent relationship. Potential sources of heterogeneity included usage timing and dosage.

Conclusion: Findings suggest minimisation of prenatal acetaminophen exposure due to risk for ADHD outcomes. Future studies should include assessing potentially interacting mechanisms associating acetaminophen use with future neurodevelopmental outcomes.

Background

Literature suggests that around 90% of women take some form of medication during pregnancy (Elsabbagh et al., 2012; Thomas et al., 2015), with approximately 56% of women reporting using analgesic drugs during pregnancy (Lupattelli et al., 2014), making them the most common class of drugs used during pregnancy (Henry & Crowther, 2000; Servey & Chang, 2014). Given its widespread use, it is critical that there is clarity on the potential harms of analgesic drug use during pregnancy. The purpose of the current study is to synthesise the evidence from existing meta-analyses and systematic reviews, to provide a comprehensive overview of the evidence on the links between prenatal maternal analgesic use and key neurodevelopmental outcomes: autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). This study aims to summarise findings in the form of a narrative review on how analgesic drug use during pregnancy affects risk for ASD and ADHD outcomes.

Drug absorption, also known as bioavailability, is dependent on systemic circulation, which in this context is the mother's cardiac output and blood flow (Feghali et al., 2015; Sachdeva et al., 2009). This bioavailability then leads to some unbound drugs with characteristics of lipid solubility, lower ionization, and lower molecular weight (<500g/mol) crossing the placenta and entering the fetal blood circulatory system in large concentrations, directly affecting the fetal brain (Gedeon & Koren, 2006; S. K. Griffiths &

Campbell, 2015). Drugs within this category include aspirin, ibuprofen, naproxen, and acetaminophen (paracetamol). While previous research has suggested neurodisruptive properties of certain drugs on the fetus (Masarwa et al., 2018), some of these drugs are still not classified human teratogens and are easily accessible to the public. Current clinical guidelines are still based on dated and limited evidence regarding the long-term effects of these drugs on the fetus (Guidance for Industry on Establishing Pregnancy Exposure Registries; Availability, 2002).

It is critical to examine how drugs such as acetaminophen, which are easily accessible and commonly found over the counter, can potentially affect child neurodevelopmental outcomes. Increasing clinical evidence suggests that prenatal exposure to medication could have lasting effects on fetal development, such as neurological, reproductive, and urogenital disorders (Bauer et al., 2021). A recent review suggested that medications such as acetaminophen can act as an endocrine disruptor and has associations with variety of risks ranging from genital malformations (Mazaud-Guittot et al., 2013), cognitive and behavioural difficulties (Rifas-Shiman et al., 2020), and hormonal disruption causing early puberty onset during adolescence (Bauer et al., 2021). Within this review, positive associations were found in 26 out of 29 studies of 220,000 mother-child pairs when examining maternal acetaminophen use and potential adverse neurodevelopment effects

such as ADHD, ASD, decreased IQ and conduct disorders. In 16 out of 19 studies within the review, possible dose-response associations were found.

Other reviews have found links between maternal prenatal analgesic drug use and increased risk of neurodevelopmental disorders between the ages of 18 months and 12 years old (Bauer et al., 2018; Masarwa et al., 2018). However, bias analyses performed to studies that failed to adjust for relevant confounders such as parental ADHD and maternal migraine found no such link. Findings may therefore be influenced by unmeasured confounding. As the existing evidence on links between maternal use of analgesic drugs in pregnancy and children's neurodevelopmental outcomes seems mixed, the aims of this umbrella review are to: a) examine and synthesise findings from the current literature of systematic reviews or meta-analyses on links between analgesic drug use in pregnancy and neurodevelopmental disorders in children, specifically ASD and ADHD; b) use high-quality evidence to inform guidelines and clinical practices regarding the use of analgesic drugs in pregnancy and neurodevelopmental outcomes of ASD and ADHD; and c) to identify possible gaps in the literature providing further opportunities to better inform recommendations for future research in this area.

Methods

Study design

An umbrella review examining the associations between analgesic drug use during pregnancy and ASD or ADHD outcomes was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement. The study protocol was previously published (Kwok et al., 2020) and has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020179216).

Search Strategy and Selection Criteria

A search was performed by one reviewer through the following major databases: Embase, Global Health, PsycINFO, PsycARTICLES, PubMed, and Cochrane Library from inception to 30 May 2021 (Appendix D, Table D1) Boolean operators of "AND" and "OR" were used for linking search terms, with specific syntax adapted for different databases. Search filters were employed and presented sequentially, with key terms searched for in the title or abstract fields. Relevant subject headings were also included in the search such as using MeSH ID numbers. These included analgesics (D000700), aspirin (D001241), acetaminophen (D000082), ibuprofen (D007052), naproxen (D009288), diclofenac (D004008), ketoprofen (D007660). Reference lists of selected reviews, reviews in-press (derived from scanning pre-print archives or discussion with field experts), manual searches of grey literature (such as Open Grey, Virtual Health Library), and preprint

platforms (such as arXiv.org, medRxiv.org, PsyArXiv.com, Open Science Framework [OSF] preprints) were also scanned for articles fitting the eligibility criteria.

Articles included systematic reviews and meta-analysis examining associations between analgesic drugs and the outcomes of ASD, ADHD or ASD and ADHD in human offspring. Animal models were not included in this review. Reviews were not restricted to those containing primary studies of a particular research design, such as longitudinal or cross-sectional designs. Rather, methodological differences are highlighted and discussed. Only the main analysis of meta-analysis or systematic reviews articles that were relevant to the topic of this umbrella review were considered. Opinion articles, primary empirical articles or non-systematic reviews were excluded. Articles published in languages other than English were also excluded due to the language capabilities of the team. More details on the inclusion and exclusion criteria can be found in the registered PROSPERO protocol (CRD42020179216) and the published protocol (Kwok et al., 2020).

Data extraction

One reviewer (JK) searched the databases for titles or abstracts that fit the eligibility criteria. Two reviewers (JK and EL) independently compared each extracted article to make sure eligibility criteria were met before assessing all the articles. A third reviewer (HAH) was available if consensus was not reached by the two reviewers or to resolve any discrepancy during this process.

The following data were extracted from all eligible reviews: first author, publication year, standard identifier of PMID and DOI, study title, database name, number of participants, and data extraction approach. Reviewers independently used a standardised coding sheet to record further details on article methodology: data synthesis method (quantitative, qualitative, or mixed), any missing essential information, presentation format (descriptive, graphical, table, or other types), study design type, and if publication bias was present. Next, reviewers used the eligibility criteria stated previously to determine whether each review was to be included for final analysis and stated reasons if it was not included.

All reported effect sizes (odds ratios, hazard ratios, relative risk, standardised mean difference) were converted to risk ratios, as well as their corresponding 95% confidence intervals. Additionally, it was noted for each review whether articles adjusted for confounding variables.

Quality Assessments

A quality assessment of each review was first assessed independently by both reviewers, followed by a meeting where reviewers came to a consensus about the study quality scores. The quality assessment was based on the AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews). The AMSTAR 2 tool consists of 16 items which evaluate search

strategies, data extraction techniques, risk of bias, appropriate methodology, and the interpretation and discussion of results.

The AMSTAR 2 tool was modified to suit this umbrella review topic through critical appraisal of meta-analysis and systematic reviews instead of randomised control trials. Seven domains in the AMSTAR 2 were identified as critical in affecting the validity of the review. These were items 2, 4, 7, 9, 11, 13, 15, with a maximum score of 11 points for meta-analyses, and 9 points for systematic reviews. A scoring scheme was also designed to categorise confidence in results, consisting of 'High', 'Moderate', 'Low' and 'Critically Low'. Articles rated as 'Critically Low' signified two or more critical flaws in the review article and was included but given significantly less weight in the narrative synthesis. Articles rated as 'Low' signified one critical flaw and were included in the synthesis, with conclusions given less weight. Meta-analyses were scored on a strict scale due to emphasis on methodology: "High = 9-11", "Moderate = 7-8", "Low = 5-6", "Critically Low = <5". Systematic reviews were scored using the following scale: "High = 7-9", "Moderate = 4-6", "Low = 3-4", "Critically Low = <3". For systematic reviews, more emphasis was placed on data synthesis in the discussion or conclusion section in order to fulfil study aims of providing a scoping review involving not only methodological appraisal, but also interpretation and conclusions of results.

Data synthesis

A narrative synthesis method was used in this umbrella review. Included articles are placed in an overall descriptive table (Appendix D, Table D3). These tables include key features for both the data extraction process and methodology (i.e., variations in data selection, study designs, indication of bias present, adjustments for covariates or confounders). Separate tables are provided for the AMSTAR 2 and GRADE assessments (Appendix D, Table D4 and D5) and key findings (Table 5.1). A narrative synthesis was carried out with the purpose of providing a clear and integrated summary of the combined literature of qualitative and quantitative reviews on the topic of the effects of analgesic drugs on ASD and ADHD diagnosis.

Confidence in cumulative evidence

Confidence in the cumulative evidence was assessed through Grading of Recommendations, Assessment, Development and Evaluations (GRADE) certainty ratings guidelines. Each review was carefully assessed and assigned two ratings 1) certainty rating ("Very Low" = true effect different from estimated effect"; "Low" = true effect possibly different from estimated effect; "Moderate" = true effect close to estimated effect, and "High" = true effect similar to estimated effect), and 2) decision making ("Critical = 7-9", "Important but Not Critical = 4-6", and "Of Limited Importance = 1-5"). The following domains were assessed for certainty of evidence: risk of bias, publication bias, imprecision of true effects, inconsistency of effects, and indirectness of outcomes. As per the GRADE

guidelines, certainty was either down-rated or up-rated based on the above-mentioned several domains. Scores were then summed, and decision-making importance was assigned to one of the following categories: “Critical”, “Important but not critical”, “Of limited importance”. The domains for certainty and decision-making importance are stated in Appendix D, Table D2.

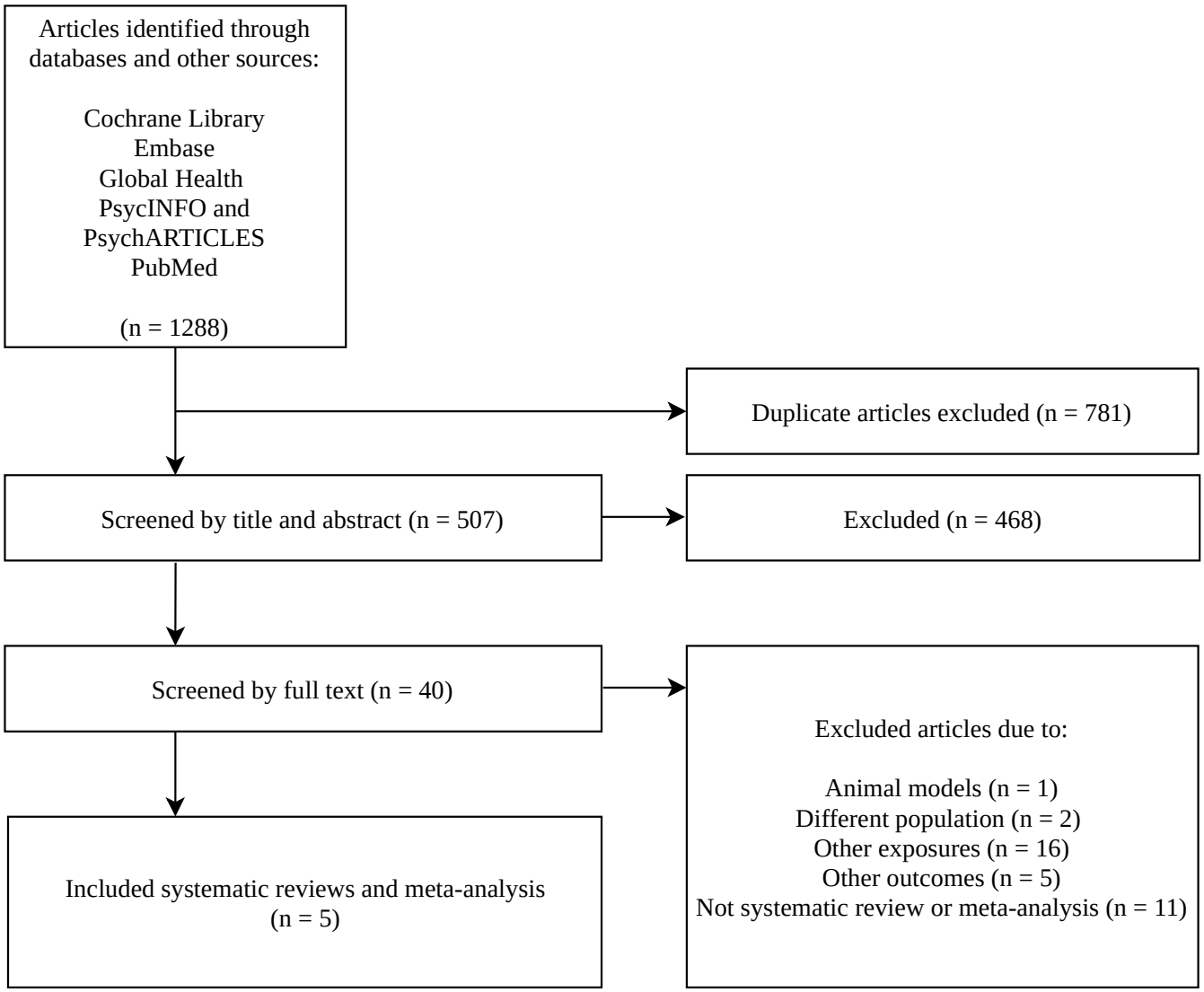

Figure 5-1. Flowchart of Selected Review Articles

Table 5-1. Findings of included reviews.

Author (Year)	Primary results	Risk Ratio for ADHD Outcomes (95% CI)	Risk Ratio for ASD Outcomes (95% CI)	AMSTAR 2 Category	GRADE certainty ratings	GRADE (decision-making)
Hoover et al. (2015)	Small associations found between prenatal acetaminophen exposure and ADHD symptoms during childhood. However, included studies in this review were limited inconclusions due to not controlling for variables such as prenatal use of acetaminophen for pain relief and fever, previously associated with negative pregnancy outcomes. Associations remained after adjustments for confounders such as maternal pyrexia or psychiatric illness.	Not stated	Not stated	Critically Low	0	Of limited importance
Bauer et al. (2018)	Associations were found between only prenatal acetaminophen drug exposure and neurodevelopmental risk outcomes, but not ibuprofen or other analgesic drugs. Review also noted that the included studies controlled for exposure across all pregnancy trimesters, indications for acetaminophen use (e.g. fever, headache/migraine, infection, pain). All included studies used prospective design and statistically controlled for confounders such as selection or recall bias.	Not stated	Not stated	High	2	Critical
Masarwa et al. (2018)	Associations were found between prenatal acetaminophen exposure and increased risk of ADHD and ASD outcomes (20-30%). As included studies controlled for covariates and confounders of both maternal and child factors, the review noted that associations were moderated by exposure duration, maternal age, and age of follow-up for the child.	1.34	1.19	High	1	Important but not critical
Gou et al. (2019)	Consistent associations were found between prenatal acetaminophen exposure and increased risk of ADHD outcomes (25%) using prospective cohort studies. Prenatal acetaminophen use was also linked to higher risk when taken in the third trimester as compared to the first and second trimester. Included studies adjusted for acetaminophen use due to infection/inflammation during pregnancy, but not other conditions such as pain relief. Some studies within this review controlled for the wide range of confounds using negative control comparison or sibling-controlled analysis.	1.28 (any exposure) 1.08 (third trimester) 1.63 (≥ 28 days)	Not stated	Moderate	1	Important but not critical
Alemany et al. (2021)	Associations found between prenatal acetaminophen exposure and risk of ADHD symptoms (12.2%). Associations also found between acetaminophen exposure and Autism Spectrum Conditions (ASC) (12.9%). Slightly stronger associations were found for males for ASD and ADHD outcomes, as compared to females. A common set of confounders was used with harmonised exposure and outcome measures across all the cohort studies.	1.088 (OR=1.21; Females OR=1.18 Males OR=1.23)	1.093 (OR = 1.19; Females OR=1.06 Males OR=1.28)	Low	1	Important but not critical

NS: Not Stated

Results

A total of 1288 articles were identified through six databases and grey literature searches. After duplicates were excluded, and with articles screened by title, abstract, and full text, forty articles remained. A further thirty-five articles were excluded due to one of the following classifications: animal models, different population, other exposures or outcomes, and non-systematic reviews or meta-analysis. A total of five systematic reviews and meta-analysis met the inclusion and exclusion criteria and were included as the final review (Appendix D, Table D3).

Four out of the five articles included sample sizes, with a range of 61,601 to 244,940 participants in each review. Two articles used a qualitative systematic review method, two articles used a quantitative meta-analysis method, and one article used a combination of both methods. Four reviews included in this study used a cross-sectional study design. Population age ranges were from 1.5 years to 13.5 years.

All five articles included acetaminophen drug use as exposures during pregnancy and examined ADHD as outcomes that were relevant to the review. Three out of the five articles examined ASD outcomes. Only acetaminophen drug use was reviewed due to insufficient power for the other analgesic drugs of aspirin, ibuprofen, naproxen, diclofenac, and ketoprofen in the selected articles regarding ADHD and ASD outcomes.

Three articles used a narrative summary method, and four articles adjusted for covariates and confounders. Confounders include purpose of usage such as pain relief or maternal fever, of which the latter has been shown to distort observed associations and have adverse pregnancy outcomes. In addition to this, the reviews also noted that women sought relief from pain or fever also were more likely to use other medications apart from acetaminophen, which then presents a further confounding effect on mechanisms affecting the foetus. Some confounders that were adjusted for within reviewed studies from the selected articles included variables such as socioeconomic status, maternal education, nicotine and alcohol intake, psychiatric illness, infection or inflammation during pregnancy, and child's birth weight, and child's gestational age. Certain residual confounding such as selection bias raised some potential concerns. To adjust for these confounding effects, authors of the primary studies used multiple methods to minimise their effects such as using prospective designs on large clinical datasets or using propensity score matching or power analysis to control for these variables.

AMSTAR 2 quality ratings were "High" for two articles (Bauer et al., 2018; Masarwa et al., 2018), "Moderate" for one article (Gou et al., 2019), "Low" for one article (Alemany et al., 2021), and "Critically Low" for one article(Hoover et al., 2015). Identified issues were failing to use a comprehensive literature search strategy (Alemany et al., 2021; Bauer et al., 2018; Gou et al., 2019; Hoover et al., 2015), to provide a list of excluded studies and justify the exclusions (Alemany et al., 2021; Hoover et al., 2015;

Masarwa et al., 2018), and to use a satisfactory technique for assessing the risk of bias (Hoover et al., 2015). Only one review registered a written protocol prior to review conduct (Masarwa et al., 2018). Adhering to a predefined, well-developed methodology minimises the risk of bias in the conduct and reporting of research and prevents unnecessary duplication of work (Tawfik et al., 2020).

GRADE was used as reproducible and transparent framework to show certainty of evidence. This review showed selected articles have a score range of 0 – 2; two articles were downrated for risk of bias present, two articles were uprated for including a dose-response gradient, and all articles discussed possible confounding on estimated effects. For decision-making scores based on GRADE, one article was rated "Of limited importance", three articles were rated "Important but not critical", and one article was rated "Critical". Five out of six articles were rated as important, pointing towards recommendation for clinical decision making as per the GRADE guidelines.

Risk ratios were also calculated for ADHD and ASD outcomes in three articles. Masarwa et al., (2018) found that acetaminophen exposure showed a RR of 1.34 for ADHD outcomes (95% CI, 1.21, 1.47) and 1.19 for ASD outcomes (95% CI, 1.14, 1.25). Gou et al., (2019) found that acetaminophen exposure showed a RR of 1.26 for ADHD outcomes for exposure in the third trimester (95% CI, 1.08, 1.47), and RR of 1.63 for ADHD outcomes if the dose exceeded 28 consecutive days (95% CI, 1.23, 2.16). Alemany et al., (2021) found that acetaminophen exposure showed a RR of 1.09 for

ADHD outcomes for any exposure across 3 pregnancy trimesters (95% CI, OR = 1.21, 1.07, 1.36), and RR of 1.09 in ASD outcomes (95% CI, OR =1.19, 1.07, 1.33).

Narrative Synthesis

Primary results from the included reviews generally showed associations between maternal prenatal acetaminophen use and ADHD outcomes. Other analgesic drugs of interest such as aspirin, ibuprofen, naproxen, diclofenac, and ketoprofen were not examined due to insufficient evidence in the selected reviews when looking at our outcomes of interest. Upon examination of the AMSTAR and GRADE categories, studies that fell within the higher categories showed similar results of prenatal acetaminophen exposure being associated with neurodevelopmental risk, particularly for ADHD outcomes. The study designs included in this umbrella review consisted of cross-sectional, longitudinal, randomised control trials, case-control studies, register-based studies, and cohort studies.

One review attempted to control for ibuprofen and aspirin use, but there was insufficient statistical power to detect associations as the usage rates were low (Bauer et al., 2018). This was reflective of limited studies examining other analgesic drugs and neurodevelopmental outcomes, possibly due to lack of drug accessibility or medical records. Some reviews did not adjust for variables such as timing of exposure, purpose, duration, or frequency of use. However, those that did provided valuable insight into factors involved in examining maternal drug use and its effects. While effects were seen to be slightly moderated by maternal and child confounds such as age[10,15,17], the direction and strength of association were largely similar across the articles. In

addition, there is a possibility that the effects of acetaminophen involve a dose-dependent relationship or a trimester-based relationship where the third trimester presented the highest risk for increased ADHD outcomes (Alemany et al., 2021; Gou et al., 2019). Findings regarding differences in ADHD outcomes due to gender have been inconclusive, with one study suggesting that males are at a slightly higher risk than females (Alemany et al., 2021), while another study arguing that effects may be stronger amongst girls (Gou et al., 2019). Effect sizes for gender differences were, however, too small to draw any firm conclusions.

The selected reviews did not provide any direct evidence on the mechanisms; however, one hypothesis for potential mechanisms underlying this association is that acetaminophen directly affects physiological mechanisms (Bauer et al., 2018; Gou et al., 2019). For example, acetaminophen use indirectly activates the maternal immune system and fetal endocannabinoid system, which have been implicated in both ASD and ADHD aetiology (Alemany et al., 2021; Blecharz-Klin et al., 2017). Animal studies have also found links between exposure to acetaminophen and lower levels of brain-derived neurotrophic factor (BDNF) in the striatum in male rats, with alterations in the metabolism of dopamine identified as well (Blecharz-Klin et al., 2017). A decrease in BDNF and dopaminergic dysfunction are thought to be highly relevant in the pathogenesis of ADHD and ASD outcomes (Liew et al., 2014). Further, an imaging study by Baker et al., (2020) found that prenatal acetaminophen exposure affected frontoparietal brain connectivity in children and was associated with an increased risk

of ADHD at ages 6 to 7 years. As the study measured prenatal acetaminophen use using meconium collected from newborns instead of maternal self-reports, these results provide a different methodological angle in supporting the findings of articles included in this review that relied on mothers' self-reports. Evidence for a trimester-based association of acetaminophen and ADHD could also be due to the processes of rapid brain growth and structural differentiation during the third trimester being disrupted (Bauer et al., 2018).

Heterogeneity and potential bias

Studies selected for this review showed some evidence of heterogeneity in both study measures and outcomes. Alemany et al., (2021) found substantial between-study heterogeneity when examining exposure to acetaminophen and ASD symptoms among girls using hospital diagnosis (I^2 = 68.37%, $p<.001$). Masarwa et al., (2018) found evidence of significant heterogeneity between study estimates of ADHD outcomes (I^2 = 93%, $p<.001$) and hyperactivity symptoms (I^2 = 72%, $p<.03$). The study acknowledged that variability of exposure times (first 20 weeks to any point in pregnancy), and exposure duration (4-28 days, to ≥ 28 days) possibly contributed to heterogeneity of observed effects. Gou et al., (2019) found heterogeneity for estimates of ADHD outcomes (I^2 = 26%, $p<.03$). Study adjustments were made for previously associated maternal factors (e.g. age, psychiatric illness, intelligence, behavioural scores). Masarwa et al., (2018) also noted the possible presence of ecological fallacy for the factor of a dose-response effect, where there was possibly no link between

exposure duration and outcomes on an individual level, due to the wide range of exposure duration, which may have contributed to heterogeneity. Study results were consistent with previous research (Ystrom et al., 2017) in showing observed significant associations with ADHD and ASD. Two out of the five studies (Bauer et al., 2018; Hoover et al., 2015) did not use meta-analytic methods to provide summary estimates of effects. Variability across these reviews suggests that the mechanisms behind a dose-response relationship of acetaminophen exposure and child neurodevelopment outcomes are still not fully understood.

Three out of the five studies (Alemany et al., 2021; Gou et al., 2019; Masarwa et al., 2018) used standard random-effects models to account for unexplained heterogeneity and account for study variability in outcomes (Appendix D, Table D4). These three studies also carried out subgroup analyses to either identify potential sources of heterogeneity or examine the contribution of relevant covariates. Acetaminophen frequency, timing, and duration of use, age of follow-up, and maternal age, were seen as significant moderators in the association between prenatal acetaminophen use and the risk of ADHD outcomes. Significant moderators in the association between prenatal acetaminophen use and the risk of ASD were identified as timing and prolonged exposure. Acetaminophen exposure during the second trimester and exposure of more than 28 days presented a marginally higher risk of ASD with HKD symptoms (Bauer et al., 2018).

Limitations

Study conclusions are limited according not only to the quantity of articles fitting the eligibility criteria, but also the comprehensiveness of data within the articles. Measures used to assess ADHD and ASD outcomes were varied, most were not based on validated instruments with specific cut-offs for clinical symptoms; instruments used included parent or teacher-based questionnaires (Alemany et al., 2021; Bauer et al., 2018; Gou et al., 2019; Hoover et al., 2015), trained psychologist assessment questionnaires (Gou et al., 2019), clinical diagnoses (Bauer et al., 2018; Hoover et al., 2015; Masarwa et al., 2018) and hospital admission registries (Alemany et al., 2021; Gou et al., 2019). This increased risk for outcome misclassification. In addition, the duration of exposure to acetaminophen, gestational week at exposure, children's age at follow-up, and maternal age varied between articles included in each review, possibly contributing the heterogeneity of observed effects. It should also be noted that the individual articles often only included participants of European descent and so results are potentially limited in generalisability. This is important because pharmaceutical research has identified ethnic differences in drug metabolism, therapeutic responses, and side effects (Peacock & Patel, 2008). This review is also limited by different methods of evaluation regarding drug exposures (such as dosage) and ASD and ADHD outcomes (such as standardised forms of diagnosis). However, most of the included studies used the Newcastle-Ottawa Scale, a scoring system that assesses study quality and risk of bias for observational studies. In addition, this study used two quality assessments to establish stricter criteria firstly for initial inclusion of articles, followed

by weighted conclusions according to the quality assessment scores. Higher scores were given more weight in the discussion.

Conclusion

Analgesic drugs are commonly used by pregnant women for a wide variety of reasons (Elsabbagh et al., 2012; Henry & Crowther, 2000; Lupattelli et al., 2014; Servey & Chang, 2014; Thomas et al., 2015), suggesting low hesitancy about these drugs despite not knowing long-term effects on the foetus. It has been suggested that that awareness amongst health professionals about long-term risks of prenatal acetaminophen should be increased (Bauer et al., 2021). Findings of this umbrella review reinforce this and suggest that health professionals should advise women early in pregnancy to use acetaminophen only when needed. Guidelines on the appropriate use of acetaminophen should not only be available to all women, but also include information on the lowest effective dose for the shortest possible duration, while balancing out more immediate benefits of acetaminophen use such as for pain relief or fever. Pregnant women who use acetaminophen should be closely monitored across all trimesters of pregnancy, with emphasis placed on reducing excessive use due to links with risk of neurodevelopmental difficulties.

Future research should aim to gain a better understanding of the various potentially interacting mechanisms exploring associations between acetaminophen use in pregnancy with offspring neurodevelopmental outcomes. This will provide valuable insights for proper use of acetaminophen, or possible development of alternative safer analgesics to be taken during pregnancy. Studies should record acetaminophen exposure at different time points in pregnancy and include details such as timing,

duration, dose, and frequency of use. Examination of other types of analgesic drugs could also provide further insight to the mechanisms of fetal development. Outcomes could include cord or clinical biomarkers such as hair analysis directly from the foetus could also provide further understanding of analgesic drug exposure metabolization in the fetus.

In addition, closer examination of other drugs which can possibly counteract the effects on the fetus can be studied. Measuring direct fetal exposure to acetaminophen in meconium or through cord plasma acetaminophen (APAP) metabolites will aid in accurately capturing the dose of acetaminophen that reaches the foetus and subsequently isolate unique effects on development (Bauer et al., 2018; Laue et al., 2019). Other methods such as polygenic risk scores or sibling control designs can also be used to account for genetic confounding. Due to the difficulty of conducting experimental research to understand how much analgesic drug exposure in pregnancy impacts neurodevelopmental outcomes, use of empirical designs like counterfactual statistical approaches can possibly help to rule out confounding; for example, matching based methods. Other methods to increase accuracy could also include biomarkers of analgesic drug exposure taken during pregnancy rather than retrospective self-reports from mothers. Lastly, examined outcomes can be expanded to test for associations between analgesic drugs and neurodevelopmental disorders or psychopathology onset in adulthood. This is especially important considering recent evidence that suggests that ADHD symptoms may not always manifest at a clinically

significant level until later in development that is traditionally recognised (Murray et al., 2021). Therefore, caution should be given by healthcare professionals regarding the dosage and duration of acetaminophen drug use during pregnancy and its potential effects on fetal neurodevelopment.

Chapter 6: Discussion

Synopsis

This chapter summarises empirical chapters 2 to 5 and synthesises their findings to provide an overall discussion with strengths, limitations, and future research directions. The empirical chapters in this thesis used multiple statistical methodologies of regression, mediation, and growth curve models to define and examine how maternal inflammation affects children's development from an age range of 18 months up to 16 years old. Overall, the findings have indicated that maternal inflammatory processes during pregnancy may have small but significant effects on children's cognitive, socio-behavioural, and neurodevelopmental outcomes. Additionally, trimester-based effects of maternal inflammation in pregnancy related to oxidative stress processes show varying effects on children's developmental outcomes. Due to the complex nature of maternal pregnancy processes on fetal growth and development, it seems that different methodological approaches are needed for further understanding of how biological mechanisms driving pregnancy processes affect a child's cognitive, socioemotional, and behavioural development, while also considering maternal, child, and environmental influences over time.

The aim of this thesis was to examine associations between maternal inflammation during pregnancy, and children's developmental outcomes. This thesis used data from cohort studies and existing review studies to examine how maternal inflammation risks defined as immune, metabolic, or endocrine risk during pregnancy, were associated with children's cognitive, socio-emotional, and neurodevelopmental outcomes.

This thesis' specific aims were to:

a) explore effects of maternal metabolic health risk during pregnancy and child and adolescence socio-emotional development when adjusting for external factors (Chapter 3)

b) examine if child cord blood markers mediate any effects of maternal metabolic health risk during pregnancy on child development (Chapter 4)

c) whether there are trimester effects of maternal inflammation during pregnancy (as defined as infections or metabolic risk in this thesis) on children's development (Chapter 2 and Chapter 3)

d) if medication taken during pregnancy affects children's neurodevelopmental outcomes (Chapter 5)

The research hypotheses are as follows:

1. Maternal metabolic health risk during pregnancy affects developmental outcomes in childhood and adolescence.
2. Cord blood markers displaying metabolic risk will have mediating effects on maternal metabolic risk during pregnancy and child development outcomes.
3. Maternal inflammation occurring at later pregnancy trimesters will have negative effects on children's developmental outcomes.
4. Negative effects of maternal metabolic health risk during pregnancy will still hold for childhood and adolescent outcomes even after controlling for other external factors.
5. Prenatal medication exposure of analgesic drugs will negatively affect children's neurodevelopmental outcomes.

General summary

General findings from the empirical papers of this study provide necessary information to show proof of concept that maternal processes linked to inflammation are associated with lowered child cognitive and psychological outcomes. To broaden our understanding of how maternal health risk affects child development outcomes, empirical chapters in this thesis give complimentary insights into pregnancy mechanisms and child outcomes, including developmental trajectories. In addition, each empirical chapter controlled for confounders and covariates of maternal factors (smoking, alcohol, psychiatric history, education, age), child factors (birthweight, gestation, sex), and socioeconomic factors (deprivation indices). An umbrella review was also included in this thesis as an added supplement for a narrative review on examining gestational biology processes in the context of neurodevelopmental disorder diagnosis.

A review of the literature in Chapter 1 has shown that maternal inflammatory processes related to oxidative stress on child neurodevelopment outcomes is still a relatively underexplored topic in human studies. In Chapter 2, third trimester maternal infections during pregnancy were associated with lower child cognitive outcomes at 8 years old. In Chapter 3, maternal metabolic markers of HDL, LDL, triglycerides, and fasting glucose taken during pregnancy were found to be associated with increased hyperactivity and conduct problems from 4 to 16 years old. These associations still held after controlling for maternal, child, and socioeconomic factors. The research

question (Question 2) of whether cord blood makers of metabolic health risk is associated with child development outcomes was examined further in Chapter 4, where child cord blood markers of LDL, HDL, triglycerides, adiponectin, and leptin were added as mediators to the maternal-child path model. Findings showed maternal metabolic risk being associated with child mediators of lowered HDL and increased leptin levels. The combined effects of all child mediators also were associated with lowered scores in the communication and language domain, and personal, social, and emotional domain at age 5. This suggests that cord blood markers mediated the association between maternal metabolic health risk and some child development outcomes. The above findings support hypotheses one and two, showing that when maternal metabolic health risk is present during pregnancy, it has a cascade effect, with newborn health acting as a mediator (cord blood), followed by effects on child development (essential developmental domains and socio-emotional behaviour), possibly even stretching into adolescence. It should be noted that despite findings showing statistical significance, effects were seen to be small, possibly due to controlling for multiple variables when examining the cohort studies. Methodologically, while many studies conventionally favour large effect sizes to guide conclusions, there is now caution against reflexive categorisation such as 'small' or 'large' effects, with emphasis on how 'small' effect sizes can still demonstrate pervasiveness of a condition relative to the type of examined variables (e.g. health risk), study design, and sample sizes. It has also been argued that small effect sizes can be

profound and substantial in nature and still be used to justify strong conclusions (Lance & Vandenberg, 2009).

Findings from Chapters 3 and 4 are in line with prior studies that examined effects of maternal markers of metabolic health during pregnancy on possible negative future consequences on child health. A recent study emphasised on optimising maternal health (BMI, blood pressure, cholesterol, glucose levels) at 28 weeks of pregnancy due to found associations with child cardiovascular health using the same markers at 10 to 14 years old (Perak et al., 2021). Chapter 3 models developmental outcomes stretching over time, and Chapter 4 helps to address the large time-gap limitation between pregnancy and 10-14 years old of this prior study, through examining newborn markers and early childhood outcomes, which allowed for more direct associations to be drawn due to less influence of common environmental factors such as parenting styles after birth or peer relationships. The thesis's empirical chapters demonstrated the importance of understanding how pregnancy mechanistic pathways work to influence childhood cognitive and socioemotional outcomes.

One possible explanation for why maternal metabolic health seems to have a significant effect on children's health is likely due to the short-chain fatty acids (SCFA) process, which contribute to hepatic lipid metabolism playing an essential role in the pregnancy process (Ziętek et al., 2021). Research has found evidence that lower serum levels of SCFAs assessed in the first and third trimester of pregnancy were linked with

better infant neurodevelopment, including language, psychomotor development, behaviour, mood, and temperament (Hernández-Martínez et al., 2022). This shows that lowered levels of these markers are associated with better outcomes at a young age. Turning to the question of trimester-specific effects of maternal inflammation during pregnancy on developmental outcomes, our hypothesis of inflammation occurring in early pregnancy trimesters having negative effects on children's development was only partially supported. Study findings in Chapters 2 and 4 showed that both the first and third trimester of pregnancy seem to be potential critical windows for children's cognitive and socioeconomic outcomes, implying differential effects of maternal inflammation timing and type during pregnancy on children's development. Other recent studies have also found that inflammation occurring either during pregnancy or within early infant life has been associated with reduced brain structure or function, and lowered cognitive outcomes (Kuban et al., 2019; Rudolph et al., 2018; Xie et al., 2019).

Possible mechanistic pathways of risk

One possible explanation for how maternal infection affects child development is the hypothesis of cytokine production affecting fetal brain development when maternal inflammation occurs in incidences such as fever (Wilkerson et al., 2002; Zerbo et al., 2013). This increased production affects the fetal inflammatory response through transfer of cytokines such as interleukin-6 to the placenta (Zaretsky et al., 2004), leading to more adverse neurological outcomes. This can be seen through Chapter 2

showing how maternal infections, linked with inflammation, leads to lowered child cognitive outcomes, and Chapter 4 showing a biological path of how maternal inflammation affects placenta and cord blood, and subsequent child development outcomes.

In theory, mechanisms behind the effects of inflammation have been explained using DNA telomere biology, a marker of cellular ageing (Armanios, 2013). Stress has been found affect cell telomere length, causing a cascade in inflammatory processes leading to damage to cell tissue that accumulates over time (Shalev, 2012). The shortening of telomere shows accelerated cell ageing and declining tissue integrity, which has been associated with physiological and psychiatric outcomes such as cardiovascular disease (P. Liu et al., 2019) or affective disorders such as depressive episodes or bipolar disorder (Elvsåshagen et al., 2011). Further adult studies have shown that there is a potential role of maternal systemic stress to initially set or destabilise the fetal telomere system (Moreno-Palomo et al., 2014; Send et al., 2017), with a clear separation from genetic heritability when looking at mother-offspring versus father-offspring correlation (Broer et al., 2013).

As evidenced by literature, heightened inflammation is not only a key pathway to future physiological health risks but is also postulated to trigger inflammation in the fetal brain (Graham et al., 2022), even potentially influencing treatment response (Réus et al., 2015). Prenatal exposure to inflammation has been associated with reductions

in the cortical grey matter volume area involved with neurotransmitter systems associated with ADHD (Dunn et al., 2019), which could explain findings from Chapter 3 where maternal metabolic risk showed increased conduct and hyperactivity problems over time. Immune-mediated neurodevelopmental models also show links with disrupted dopaminergic activity and deficits in sensorimotor gating, memory, and social interaction (Luchicchi et al., 2016). A proinflammatory cytokine, Interleukin-6 (IL-6), was associated with fronto-limbic white matter tracts changes and cognitive functioning at age 2, with implications for future effects on both brain development and cognition (Rudolph et al., 2018). Potential effects of pro-inflammatory cytokines have also been found on brain structure pertaining to language and communication. Prior study results found continuous maternal immune activation being associated with reduced cerebellar volume in neural circuits pertaining to language and social processing, which may underlie autism spectrum disorder symptoms such as social interaction and repetitive behaviour (Suleri et al., 2022). In addition, increased parietal-occipital functional connectivity has been hypothesised as a maladaptive response to systemic inflammation during critical growth periods of a fetus' brain development and has been associated with lowered cognitive outcomes (Bach et al., 2022). This could explain why lowered child development outcomes in Chapter 3 upon exposure to maternal metabolic risk were seen across cognitive domains of literacy and communication and language through both direct and indirect exposures of maternal risk and cord blood marker risk.

Another potential linking mechanism of how maternal health affects child development is exploring the idea of maternal gut microbiota. While this thesis did not directly examine gut microbiota, the interplay of maternal obesity is found to influence microbial colonisation during pregnancy, further associating with offspring phenotypic traits after birth such as impaired neurodevelopment (Madore et al., 2016; Zhou & Xiao, 2018). Other studies have also found evidence for metabolic complications during pregnancy being associated with maternal and infant microbiota (Calatayud et al., 2019). Maternal-to-infant gut microbiota, when studied in interaction with other factors such as prenatal or postnatal stress, or drug exposure (Codagnone et al., 2019) shows further influences on child brain development and behaviour (Dawson et al., 2021). Possibly relevant to chapter 2 of the thesis that examined maternal infections in pregnancy, maternal gut microbiota during maternal immune activation has been linked with atypical brain development associated with neuropsychiatric disorders in both preclinical models and human studies (Minakova & Warner, 2018; Vlasova et al., 2021). These above mechanisms suggest a crosstalk between maternal metabolic or endocrine disruption, immune activation response, and gut microbiota in pregnancy having links with neurodevelopmental etiology.

Medication exposure as an important consideration

As reviewed in the introduction section, medication exposure is an important factor when examining the long-term effects of maternal processes on child development. Medication use during pregnancy is commonly recommended as a form of

intervention to regulate specific biological processes or to provide pain relief. This thesis included an umbrella review in Chapter 5 to explore a different perspective of how controlling for potential maternal inflammation can also potentially disrupt fetal development and subsequently have real-life consequences such as ADHD outcomes. The exposure of interest in this chapter was paracetamol (APAP) due to its general availability and common usage. Findings from the review partially supported hypothesis 5 where analgesic drugs, specifically APAP, was associated with children's neurodevelopmental outcomes of ADHD, but not autism spectrum disorder (ASD). A hypothesis for possible mechanisms related to acetaminophen use and fetal neurodevelopment includes the increase of oxidative stress and immunologic pathways that are involved in microglia development, endocannabinoid systems (ECS) influencing ASD ethology (Schultz et al., 2021), disruption of maternal hormones, and possible alteration of brain-derived neurotrophic factors (BDNF) (Bauer et al., 2018). Results from Chapter 5 were supported by another review of 16 studies that found long-term and higher doses of acetaminophen use being more strongly associated adverse neurodevelopmental disorders, with strong evidence for attention/hyperactivity symptoms (Khan et al., 2022).

Strengths

The chapters in this thesis had several strengths. First, different analyses across the chapters provided complementary insights when examining how maternal health affects child development outcomes. Child development outcomes included a broad range, from functional developmental outcomes used by educational providers to assess development and school readiness, to developmental trajectories ranging into adolescence, providing important insight for persisting symptomology over time. Overall, this thesis adds to the current literature through further support for neurodevelopmental disruption or disorder etiology to be complex and multifactorial in nature.

Next, predictors identified in this thesis also showed similar incidence rates to the population when examining maternal conditions during pregnancy, such as infection rates (Collier et al., 2009) or maternal metabolic risk (Bartha et al., 2008), allowing for comparisons with other cohort studies also looking at mother-child associations. Further, for the empirical chapters, most of the analysed maternal biomarkers apart from infections (Chapter 2; maternal self-reported) were from medical records, which were then analysed in combination with data from interviews by the research team. Having biomarker information is valuable due to less susceptibility for bias and more replicability as compared to self-report measures. In addition, longitudinal and cross-sectional collection of biomarkers can help yield better discrimination when examining variables in relation to disease etiology, contributing to higher prognostic value. Using

multiple methods of data collection is usually linked to increased data quality and generalisability of the results.

In 2021, the UK government published a review recognising the importance of assessing early child development processes across domains, which included cognitive, emotional, and social capabilities formed within the first 1,001 critical days (HM Government, 2021). Based on available cohort data, this thesis examined varying breadth and depth of child developmental outcomes. Chapter 2 explored child cognition using 3 developmental and intelligence assessments, Chapter 3 explored national key stage assessments used by the UK government to determine child developmental milestones, Chapter 4 used a standardised questionnaire that has shown sufficient evidence for reliability and validity (Kersten et al., 2016; Riso et al., 2010; Speyer et al., 2022), while chapter 5 examined evidence for child neurodevelopmental diagnosis risk. The above outcomes were therefore selected for their relevance to aid scientists and policy makers in future decision-making.

This thesis shows benefits of using large-scale community ascertained cohorts. This method is not only more representative, but also achieves good power and precision when examining longitudinal associations. Characteristics of neurodevelopmental or mental health tend to be under-estimated as risk when adopting a traditional disease-oriented approach. However, by analysing cohort study data, this thesis shifts the current focus of maternal inflammation and child outcomes to a more population-

oriented approach (Bauman & Van de Water, 2020), which potentially produces a significant impact even with marginal shifts in outcomes, affecting economic and health policy decisions and resource allocation.

Limitations

The chapters in this thesis had several main limitations. First, conceptualisation of the empirical chapters was heavily theorised on preclinical models. The timing of neurodevelopment processes is seen to differ between mice and humans with neurogenesis and cell migration, differentiation and outgrowth occurring earlier in the gestation process for humans (Gumusoglu & Stevens, 2019). In addition, much of interpreted literature on maternal immune activation models also base their findings on animals, such as proinflammatory cytokine induction in mice being associated with behavioural abnormalities suggestive of autism or schizophrenia (Missault et al., 2014; Smith et al., 2007). This led to limited hypothesis testing and suggestions for interventions in human studies.

Next, biomarker selection and cut points can be somewhat arbitrary with no guidelines to define what is an optimal cut-off value, especially for continuous variables such as leptin or adiponectin levels. Studies have tried to use computational network models to verify biomarkers candidates (Baumgartner et al., 2018), or receiver operating characteristic (ROC) curves to distinguish between optimal or non-optimal biological states. However, in general, clinical reference intervals are usually derived from specific

reference samples that use single time point measurements (Raghavan et al., 2016). While this thesis attempted to account for this limitation through multiple timepoints (e.g., exploring trimester effects), treating predictors as continuous variables where relevant, and using standard deviations as unit comparisons for outcomes, the interpretation of findings are still limited to individual variances from patients' own baselines due to the complex and dynamic nature of pregnancy (e.g. starting off with higher cholesterol with smaller increments over trimesters could be viewed as lower risk, as compared to starting off with normal cholesterol levels but with large increments over trimesters possibly being viewed as higher risk).

Another limitation is using the selected cohort studies. While data was primarily taken from large UK cohorts (ALSPAC and BiB), it should be noted firstly, that there is a time gap for recruitment between the two cohorts. ALSPAC, also known as 'Children of the 90s' recruited pregnant women between 1991 and 1992 (Boyd et al., 2013; Fraser et al., 2013), while BiB recruited pregnant women between 2007 and 2010 (Born in Bradford Collaborative Group & Raynor, 2008). This time gap can present difficulties in comparisons across cohorts. For predictors, factors like environmental changes such as pollution affecting general population health over time can affect epigenetic regulation (Breton et al., 2021), while for outcomes, more awareness of neurodevelopmental disorders may influence diagnostic criteria and assessment of symptoms (Polanczyk et al., 2007). Additionally, these cohorts collected data for

general higher income countries and findings cannot be generalised to low-and middle- income countries.

Next, due to the range of child outcomes assessed by different levels of symptomology using different cohorts, direct comparisons could not be drawn across the chapters. While outcomes included sub-clinical behavioural problems such as hyperactivity, necessarily signal an increased risk of neurodevelopmental conditions or future psychopathology. Therefore, this thesis approached interpretation of future disorder risk in a more conservative manner.

Regarding maternal variables, it should be noted that not all obstetric variables, including for instance maternal preeclampsia, were added as a covariate for the empirical chapters. While a recent study found associations of maternal preeclampsia with elevated child emotional and behavioural problems (Dachew et al., 2021), other cohort studies found no effects (O'callaghan et al., 1997). Overall, mixed results were shown for maternal pre-eclampsia being associated with child psychological outcomes (Tearne et al., 2015), and so while the variable is clinically important when assessing pregnancy complications, it may not be a strong predictor of this thesis' outcomes of interest.

Lastly, this thesis also did not take other important aspects contributing to early childhood development into account when examining maternal-child outcomes, such

as genetic inheritance, sociocultural factors, or other environmental factors such pollutants. Transfer of genetic susceptibility to potential neurodevelopmental risk or future psychopathology was not explored, despite literature showing possible links that antenatal stress or early adversity can affect children with specific genetic vulnerabilities differently (Caspi et al., 2003). However, some maternal exposures measured in this study, such as elevated maternal adiposity on child health have been found to be likely driven by non-genetic factors, which then allows for intervention before development of disease pathology (Inzani & Ozanne, 2022). When examining outcomes in low-and-middle income countries, sociocultural factors were also seen to play an important role in accessing healthcare resources (e.g. lack of psychoeducation or home-based medical services), of which these factors can influence maternal health and parenting, and eventual child outcomes (Kumar et al., 2022). A recent global systematic review on low- middle- and high-income countries also found that high-quality parenting in the first 3 years were associated with improved early childhood development outcomes (Jeong et al., 2021). Lastly, prenatal exposure to environmental pollutants such as per- and polyfluoroalkyl substances (PFAS) has been associated with increased ASD and ADHD risk (Skogheim et al., 2021). While these above factors were not the focus of the thesis, it should be noted that they have also been associated with child development outcomes.

Conclusions

Overall, this thesis provides strong evidence that maternal inflammation in pregnancy affects child development outcomes. The synthesis of current literature with thesis findings, strengths, and limitations supports the idea that maternal inflammatory processes such as infections and dysregulated lipid metabolisation during pregnancy seems to be associated with neurodevelopmental disruption.

Further Research

Prognostic methods during pregnancy

This thesis indirectly displays the importance of using readily available prognostic methods during pregnancy for rapid measurement of how trimester changes in pregnancy biomarkers could be associated with child development outcomes. One suggestion of further research is to continue using biomarker analyses, such as using hair metabolites, which could provide a basis for further understanding of mechanisms, such as cortisol spikes or alterations in in lipid metabolism as pregnancy progresses (Delplancke et al., 2018). This can be useful in differentiating between effects of complicated versus healthy pregnancies on child outcomes, possibly creating broad classification models which could allow for greater insight into mechanisms underlying subclinical symptoms and subsequently, future clinical diagnosis of neurodevelopmental or mental health disorders. Taking a more pragmatic approach, using biomarkers also encourages for a more streamlined and harmonised research

and clinical practices, thereby increasing cost-effectiveness and better guidance for decision-making across disciplines (Coulter et al., 2016).

Another way to further understand linking mechanisms of pregnancy could be to translate neurodevelopmental data from preclinical models to human studies using a neuroinformatics method, such as a database that accounts for cross-species differences of pregnancy and neural development (Clancy et al., 2007). This has been modelled in other subsequent studies corresponding animal to human pregnancy trimesters for nicotine exposure or drug exposure on offspring outcomes (Thompson et al., 2009; Zhang et al., 2018). Other computational methods can include using epidemiological data to create predictive tools for infant mental health and the likelihood of psychopathology development in early childhood (Luby et al., 2019).

Importance of timing of intervention

Based on the theory of stress resilience, preclinical studies tend to draw an overarching conclusion of early intervention being generally beneficial for development outcomes, possibly due to observed morphological and short-term behavioural changes in animals (Arabin et al., 2021). Large-scale reports have also presented theoretical evidence of early prevention and intervention possibly affecting outcomes, but experimental attempts at this have not yet shown to be consistently effective (Dickerson et al., 2016, 2022). Based on this thesis' findings, it is likely that human fetal developmental infrastructure seems to enter not only different but overlapping stages

of vulnerability both prenatally and postnatally. As a suggestion for resource optimisation while considering pragmatic limitations such as attrition, another suggestion for future research would be to consider refining the scope of work to emphasise on timing-specific interventions upon identification of risk during or after pregnancy.

All the above should be taken into consideration to support the pregnancy process and child development outcomes, leading to better overall quality of life for future families.

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Supplementary Materials

Appendix A – Chapter 2

Table A1. Descriptive statistics for predictors and outcomes (n = 6,849).

Maternal Infections*	N	%	
No	3107	45.4	
Yes	3742	54.6	
1st trimester (n = 6,889)			
No	5288	76.8	
Yes	1601	23.2	
2nd trimester (n = 6,860)			
No	4468	65.1	
Yes	2392	34.9	
3rd trimester (n = 7,091)			
No	5588	78.8	
Yes	1503	21.2	
Child scores	**Mean**	**SD**	**Range**
GMDS (Mean age = 1.5 years)			
Hearing /Speech (Verbal)	100	16.1	62 – 114
Performance	113	12.7	64 – 135
Average	108	8.8	65 – 114
WPPSI-RUK (Mean age = 4.1 years)			
Verbal Scale	100	13.6	54 – 152
Performance Scale	108	14.6	55 – 151
Fullscale	104	14.2	52 – 113
WISC-III (Mean age = 8.6 years)			
Verbal Scale	107	16.7	46 – 155
Performance Scale	100	17.1	46 – 151
Total Scale	104	16.5	45 – 151

**Prenatal infections (urinary tract infection, influenza, rubella, thrush, genital herpes, or other infections not stated) occurring any time during pregnancy*

Table A2. Confounders and covariates (n = 7,410).

Confounders		
	Mean (SD)	**Range**
Maternal age at childbirth (years)	29.1 (1.23)	15 – 44
	N	**%**
Maternal education		
(≥ A' levels)	3068	41.3
(< A' levels)	4111	55.5
Missing	231	3.2
Deprivation index		
Highest quintile	1965	26.5
60-80%	1162	15.7
40-60%	1054	14.2
20-40%	885	11.9
Lowest quintile	765	10.3
Missing	1579	21.3
Covariates		
Child Gender		
Male	3740	50.4
Female	3670	49.6
Child Gestation		
≥ 37 weeks	6982	94.2
< 37 weeks	428	5.8
Child Birthweight		
≥ 2500g	6970	94.0
< 2500g	349	4.7
Missing	91	1.3
Maternal psychiatric history		
No	5955	80.4
Yes	829	11.2
Missing	626	8.4
Maternal smoking (any point in pregnancy)		
No	5073	68.5
Yes	1488	20.1
Missing	849	11.4

Appendix B – Chapter 3

Table B1: Descriptive characteristics for maternal predictor variables and child outcome variables.

	N	Mean	SD	Range
Maternal Metabolic Markers				
1st Trimester				
GLU	4495	5.29	0.98	2.57 – 23.14
TRG	4495	1.04	0.71	0.24 – 8.44
LDL	4495	1.47	0.39	0.53 – 3.57
HDL	4495	2.98	0.82	0.39 – 6.62
BMI	5013	26.72	5.39	14.58 – 55.04
2nd Trimester				
GLU	2841	5.29	0.77	3.46 – 18.44
TRG	2845	1.03	0.47	0.25 – 5.96
LDL	2845	3.04	0.74	0.86 – 7.17
HDL	2845	1.57	0.33	0.36 – 3.22
BMI	3000	26.36	5.19	15.18 – 54.16
3rd Trimester				
GLU	2964	5.26	0.93	0.41 – 20.41
TRG	2964	0.99	0.50	0.06 – 6.41
LDL	2964	3.11	0.77	0.91 – 7.23
HDL	2845	1.58	0.35	0.22 – 4.62
BMI	3126	26.46	5.29	16.01 – 54.24
SDQ				
Conduct Scale				
4 years	9473	1.96	1.42	0 – 10
7 years	8421	1.60	1.46	0 – 10
8 years	7783	1.50	1.47	0 – 10
9 years	8056	1.28	1.42	0 – 10
11 years	7346	1.20	1.42	0 – 10
13 years	7046	1.25	1.43	0 – 10
16 years	5663	1.02	1.35	0 – 10
Hyperactivity Scale				
4 years	9479	3.97	2.33	0 – 10
7 years	8397	3.38	2.37	0 – 10
8 years	7781	3.34	2.47	0 – 10
9 years	8056	2.95	2.26	0 – 10
11 years	7328	2.77	2.24	0 – 10
13 years	7046	2.91	2.23	0 – 10
16 years	5663	2.54	2.12	0 – 10
Emotional Scale				
4 years	9479	1.45	1.52	0 – 10
7 years	8411	1.51	1.67	0 – 10
8 years	7780	1.69	1.83	0 – 10
9 years	8040	1.51	1.77	0 – 10
11 years	7329	1.46	1.73	0 – 10
13 years	7049	1.43	1.71	0 – 10
16 years	5653	1.49	1.85	0 – 10

Table B2. Descriptive characteristics for confounders and covariates.

	N	%
Child Sex		
Male	7372	51.1
Female	7050	48.9
Maternal Smoking (1st tri)		
Yes	3235	25.4
No	9504	74.6
Maternal Smoking (2nd tri)		
Yes	2342	21.6
No	8509	78.4
Maternal Smoking (3nd tri)		
Yes	2212	19.7
No	8997	80.3
Maternal Smoking (any tri)		
Yes	3645	24.3
No	7243	48.3
Missing	4121	27.5
Maternal Alcohol (1st trimester)		
Yes	6835	54.4
No	5740	45.6
Maternal Alcohol (3rd trimester)		
Yes	5584	50.1
No	5571	49.9
Maternal Psychiatric History		
Yes	1528	13.6
No	9734	86.4
Deprivation		
80-100%	2248	15.0
60-80%	1425	9.5
40-60%	1325	8.8
20-40%	1106	7.4
0-20%	1022	6.8
Missing	7883	52.5
Child Gestation		
≥ 37 weeks	12584	83.8
< 37 weeks	1398	9.3
Missing	1027	6.9
Child Birthweight		
≥ 2500g	12488	83.2
< 2500g	781	5.2
Missing	1740	11.6

Table B3. Model fits.

	n	CFI	TLI	RMSEA	SRMR
T1 CON	15133	.978	.966	.021	.012
T1 HYP	15132	.973	.958	.028	.015
T1 EMO	15133	.971	.955	.021	.014
T2 CON	15100	.978	.965	.020	.013
T2 HYP	15099	.973	.958	.027	.014
T2 EMO	15100	.971	.955	.020	.014
T3 CON	15101	.978	.964	.019	.011
T3 HYP	15100	.973	.957	.026	.013
T3 EMO	15101	.971	.954	.019	.013
All T CON	15133	.978	.964	.016	.008
All T HYP	15132	.973	.956	.021	.009
All T EMO	15133	.971	.952	.016	.009

T1: Trimester 1, T2: Trimester 2, T3: Trimester 3, All T: All trimesters adjusted
CON: conduct problems, EMO: emotional problems, HYP: hyperactivity problem

Table B4. R2 estimates, Intercept, Slope, Quadratic (unadjusted for covariates).

	R^2 Estimates (SE)			Unstandardised Intercepts (SE)			Standardised Intercepts (SE)		
	I	S	Q	I	S	Q	I	S	Q
Trimester 1									
Conduct	.004 (.002)	.014 (.006)*	.014 (.007)*	1.970 (.014)***	-1.678 (.053)***	.858 (.053)***	1.807 (.033)***	-.585 (.030)***	.336 (.027)***
Hyperactivity	.010 (.004)**	.008 (.005)*	.006 (.005)	3.984 (.023)***	-2.509 (.080)***	1.292 (.076)***	2.148 (.030)***	-.569 (.027)***	.337 (.024)***
Emotional	.004 (.003)	.007 (.005)	.004 (.004)	1.489 (.016)***	.321 (.065)***	-.359 (.063)***	1.297 (.029)***	.088 (.017)***	-.113 (.019)***
Trimester 2									
Conduct	.008 (.005)	.013 (.007)	.014 (.008)	1.969 (.014)***	-1.682 (.053)***	.861 (.053)***	1.806 (.033)***	-.586 (.030)***	.337 (.027)***
Hyperactivity	.006 (.004)	.008 (.006)	.007 (.020)	3.984 (.023)***	-2.512 (.080)***	1.296 (.076)***	2.149 (.030)***	-.570 (.027)***	.339 (.024)***
Emotional	.004 (.003)	.009 (.006)	.005 (.328)	1.490 (.016) ***	.317 (.065)***	-.356 (.063)***	1.297 (.029)***	.086 (.017)***	-.111 (.019)***
Trimester 3									
Conduct	.009 (.005)	.021 (.010)*	.019 (.009)*	1.969 (.014)***	-1.681 (.053)***	.861 (.053)***	1.806 (.033)***	-.586 (.030)***	.337 (.027)***
Hyperactivity	.007 (.004)	.001 (.002)	.002 (.003)	2.984 (.023)***	-2.513 (.080)***	1.296 (.076)***	2.149 (.030)***	-.570 (.027)***	.339 (.024)***
Emotional	.001 (.001)	.007 (.006)	.009 (.008)	1.490 (.016)***	.317 (.065)***	-.357 (.063)***	1.297 (.029)***	.086 (.017)***	-.112 (.019)***
All Trimesters									
Conduct	.014 (.006)*	.029 (.010)**	.025 (.009)**	1.951 (.016)***	-1.666 (.059)***	.861 (.057)***	1.790 (.034)***	-.581 (.031)***	.337 (.028)***
Hyperactivity	.017 (.005)**	.023 (.010)*	.020 (.010)*	3.957 (.026)***	-2.444 (.088)***	1.254 (.082)***	2.133 (.030)***	-.554 (.028)***	.327 (.025)***
Emotional	.011 (.005)*	.012 (.007)	.014 (.009)	1.480 (.017)***	.299 (.072)***	-.352 (.069)***	1.289 (.030)***	.082 (.019)***	-.111 (.021)***

I: Intercept, S: Slope, Q: Quadratic
p<.05, p<.01**, p<.001****

Table B5. Correlations table for maternal metabolic markers, confounders, and covariates.

	T1	T2	T3	T1 Maternal Smoking	T2 Maternal Smoking	T3 Maternal Smoking	T1 Maternal Alcohol	T3 Maternal Alcohol	Maternal Psychiatric History	Deprivation	Gestation	Birthweight
T1												
GLU	-	.709	.710	.056	.071	.072	.000	-.007	-.001	.048	-.022	-.015
BMI	-	.939	.931	.040	.039	.036	-.022	-.052	-.010	.159	.008	-.003
LDL	-	.756	.734	.054	.049	.052	.002	-.007	.014	.031	.016	.004
HDL	-	.818	.771	-.144	-.161	-.154	.063	.152	-.002	-.137	-.033	-.014
TRG	-	.752	.737	.153	.173	.169	.008	-.011	.085	.087	.016	.000
T2												
GLU	.709	-	.698	.071	.085	.089	.020	.002	-.009	.042	-.012	-.003
BMI	.939	-	.960	.053	.053	.040	-.024	-.067	.003	.167	.003	-.008
LDL	.756	-	.800	.024	.045	.036	-.002	.043	.029	-.024	.018	.010
HDL	.818	-	.801	-.121	-.125	-.120	.068	.144	.012	-.143	-.029	-.009
TRG	.752	-	.796	.159	.167	.160	-.005	-.030	.081	.104	.005	-.014
T3												
GLU	.710	.698	-	.073	.066	.078	.026	.011	-.014	.044	-.018	.009
BMI	.931	.960	-	.048	.051	.040	-.023	-.066	.000	.169	.007	-.004
LDL	.734	.800	-	.015	.022	.017	.004	.033	.006	-.019	.026	.026
HDL	.771	.801	-	-.110	-.127	-.124	.076	.149	-.003	-.138	-.014	.015
TRG	.737	.796	-	.154	.161	.165	-.002	-.014	.071	.116	.014	-.003

T1: Trimester 1 corresponding marker, T2= Trimester 2 corresponding marker, T3= Trimester 3 corresponding marker
p<.05, p<.01**, p<.001****
**Data on maternal alcohol intake for second trimester not available*

Appendix C – Chapter 4

Table C1. Model fits (adjusted models).

	n	CFI	TLI	RMSEA	SRMR
BVPS	13812	0.985	0.826	0.021	0.013
LID	13812	0.984	0.812	0.021	0.013
COM	13832	0.987	0.851	0.021	0.013
PSE	13832	0.987	0.847	0.021	0.013
PHY	13832	0.987	0.847	0.021	0.013
LIT	13832	0.987	0.854	0.021	0.013
MAT	13832	0.987	0.845	0.021	0.013

Table C2. Effects of child mediators on MetS and child outcomes (unadjusted models).

(b) MetS on	**DE**	**DE *95% CI***	**IE**	**IE *95% CI***	**T-IE**	**T-IE 95% CI**	**TE**	**TE *95% CI***
BPVS (n=12646)	.005	-.024 to .029						
(a) Triglycerides	-.006	-.053 to .031	.000	-.001 to .003				
(b) Triglycerides	-.027	-.085 to .031						
(a) HDL	-.075***	-.106 to -.040	-.006	-.013 to -.001				
(b) HDL	.073	.003 to .141						
(a) LDL	-.015	-.053 to .017	.000	.000 to .004	-.005	-.012 to .001	.000	-.027 to .024
(b) LDL	-.023	-.083 to .029						
(a) Adiponectin	-.012	-.050 to .031	.000	-.001 to .002				
(b) Adiponectin	-.008	-.059 to .048						
(a) Leptin	-.089***	-.132 to -.059	.000	-.003 to .002				
(b) Leptin	.003	-.028 to .039						
LID (n= 12644)	.008	-.022 to .038						
(a) Triglycerides	-.006	-.053 to .031	.000	-.001 to .002				
(b) Triglycerides	-.005	-.065 to .047						
(a) HDL	-.074***	-.106 to -.037	.000	-.005 to .005				
(b) HDL	.006	-.066 to .064						
(a) LDL	-.016	-.054 to .015	.001	.000 to .005	.012	-.017 to .043	.004	-.003 to 010
(b) LDL	-.058	-.121 to .000						
(a) Adiponectin	-.012	-.050 to .029	.000	-.003 to .001				
(b) Adiponectin	.014	-.039 to .070						
(a) Leptin	-.089***	-.136 to -.061	.004*	.002 to .007				
(b) Leptin	-.043*	-.086 to 0.21						
COM (n= 13364)	-.017	-.034 to .002						
(a) Triglycerides	-.007	-.052 to .031	.000	-.002 to .001				
(b) Triglycerides	.014	-.036 to .052						
(a) HDL	-.075***	-.107 to .042	-.008*	-.014 to -.003				
(b) HDL	.101***	.056 to .150						
(a) LDL	-.016	-.056 to .019	.000	-.004 to .000	-.006	-.011 to .000	-.022*	-.039 to -.003
(b) LDL	.028	-.019 to .075						
(a) Adiponectin	-.012	-.052 to .031	.000	-.001 to .002				
(b) Adiponectin	-.009	-.052 to .031						
(a) Leptin	-.089***	-.133 to -.061	.002*	.001 to .005				
(b) Leptin	-.028*	-.051 to -.007						
PSE (n= 13364)	-.014	-.033 to .004						
(a) Triglycerides	-.007	-.052 to .031	.000	-.001 to .001				
(b) Triglycerides	.006	-.031 to .046						
(a) HDL	-.075***	-.108 to .041	-.008*	-.014 to -.003				
(b) HDL	.102***	.056 to .147						
(a) LDL	-.016	-.056 to .018	.000	-.003 to .000	-.005	-.011 to .001	-.018	-.037 to -.002
(b) LDL	.025	-.023 to .071						
(a) Adiponectin	-.012	-.052 to .031	.000	-.001 to .002				
(b) Adiponectin	-.004	-.042 to .038						
(a) Leptin	-.089***	-.133 to -.061	.003*	.002 to .006				
(b) Leptin	-.037**	-.063 to -.018						
PHY (n= 13364)	-.018	-.036 to .001						
(a) Triglycerides	-.007	-.052 to .032	.000	-.001 to .001				
(b) Triglycerides	-.008	-.047 to .032						
(a) HDL	-.075***	-.108 to -.041	-.007*	-.013 to -.003				
(b) HDL	.095***	.048 to .139						
(a) LDL	-.016	-.056 to .019	.000	-.003 to .000	-.003	-.009 to .002	-.021*	-.039 to -.004
(b) LDL	.019	-.033 to .063						
(a) Adiponectin	-.012	-.052 to .031	.000	.000 to .003				
(b) Adiponectin	-.018	-.057 to .023						
(a) Leptin	-.089***	-.133 to -.061	.004**	.002 to .006				
(b) Leptin	-.043**	-.068 to -.021						

LIT (n= 13364)	-.033**	-.050 to -.015						
(a) Triglycerides	-.007	-.052 to .032	.000	-.002 to .001				
(b) Triglycerides	.018	-.029 to .055						
(a) HDL	-.075***	-.108 to -.041	-.007*	-.013 to -.003				
(b) HDL	.089**	-.040 to .134						
(a) LDL	-.016	-.056 to .018	.000	-.004 to .000	-.005	-.011 to .000	-.037***	-.054 to -.021
(b) LDL	.027	-.022 to .074						
(a) Adiponectin	-.013	-.053 to .031	.000	-.001 to .002				
(b) Adiponectin	-.005	-.047 to .037						
(a) Leptin	-.089***	-.133 to -.061	.003*	.001 to .005				
(b) Leptin	-.030*	-.052 to -.012						
MAT (n= 13364)	-.021	-.039 to -.003						
(a) Triglycerides	-.007	-.052 to .031	.000	-.002 to .001				
(b) Triglycerides	.031	-.012 to .069						
(a) HDL	-.075***	-.107 to -.041	-.005*	-.011 to -.002				
(b) HDL	.071*	.024 to .117						
(a) LDL	-.017	-.057 to .018	-.001	-.004 to .000	-.005	-.011 to .000	-.025*	-.044 to -.008
(b) LDL	.036	-.009 to .081						
(a) Adiponectin	-.012	-.052 to .030	.000	-.001 to .003				
(b) Adiponectin	-.025	-.066 to .016						
(a) Leptin	-.089***	-.133 to -.061	.001	.001 to .003				
(b) Leptin	-.014	-.036 to .006						

p<.05, p<.01*, p<.001**
***DE**: Direct Effect*
***IE:** Indirect Effect*
***T-IE:** Total Indirect Effect*
***TE:** Total Effects (Direct Effect + Indirect Effect)*
(a)Child mediators on MetS; (b) Child outcomes on child mediators
Note: participant sample sizes ranged from 12,652 to 13,832 (found in adjusted models) mother-child pairs depending on availability of data

Table C3. Correlation Table for Child Cord Blood Markers..

		1	2	3	4	5
1	**Triglycerides**	1				
2	**HDL**	.234***	1			
3	**LDL**	.012	-.452***	1		
4	**Adiponectin**	.036	-.037	.051*	1	
5	**Leptin**	.022	-.078	-.081*	.117***	1

p<.05, p<.01**, p<.001****

Table C4. Correlation Table for covariates.

		1	2	3	4	5	6	7	8
1	**Maternal Education**	1							
2	**Maternal Age**	.193***	1						
3	**Maternal Alcohol**	.028**	-.040***	1					
4	**Maternal Smoking**	-.193***	-.221***	.286***	1				
5	**Deprivation Indices**	.193***	.165***	.274***	-.036	1			
6	**Child Sex**	.017	.008	.016	.009***	.005	1		
7	**Gestation**	.022*	-.068***	.051***	-.013***	.022	.022	1	
8	**Birthweight**	.053***	.044***	.138***	-.045***	.096***	.096	.618***	1

p<.05, p<.01**, p<.001****

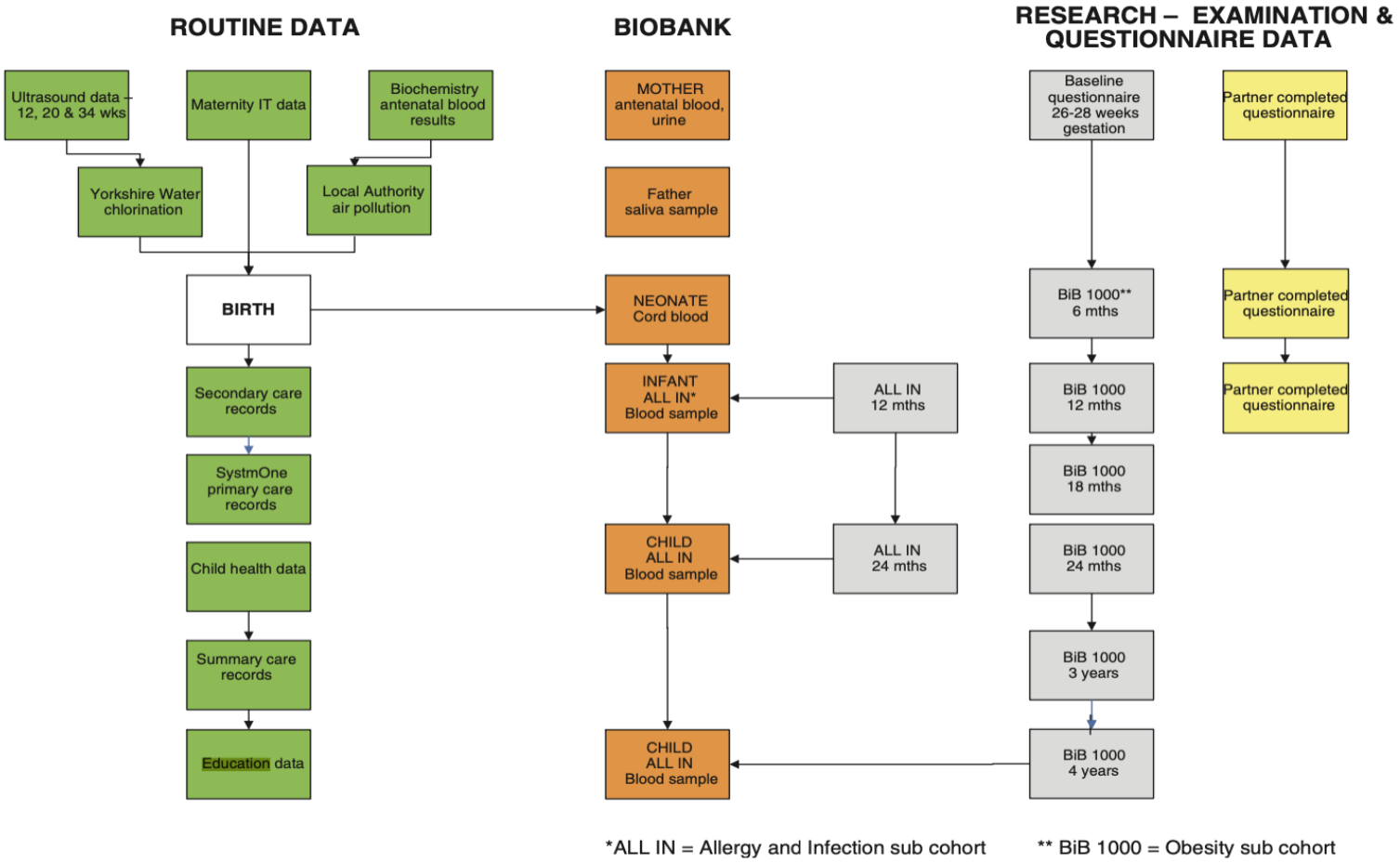

Figure C1. Participant flowchart from BIB research team (doi:10.1093/ije/dys112)[2].

Note: Reliability testing of the growth data measurements by BiB health workers indicated good quality control for inter- and intra-observer technical error of measurements (r=0.96-1.00) (Johnson et al., 2009)[3].

[2] John Wright, Neil Small, Pauline Raynor, Derek Tuffnell, Raj Bhopal, Noel Cameron, Lesley Fairley, Debbie A Lawlor, Roger Parslow, Emily S Petherick, Kate E Pickett, Dagmar Waiblinger, Jane West, on behalf of the Born in Bradford Scientific Collaborators Group, Cohort Profile: The Born in Bradford multi-ethnic family cohort study, *International Journal of Epidemiology*, Volume 42, Issue 4, August 2013, Pages 978–991, https://doi.org/10.1093/ije/dys112

[3] Johnson WO, Cameron N, Raynor P, Dickson P, Seymour C, Wright J. An assessment of routine anthropo- metric data collected on infants by health workers in Bradford, UK: a cross-sectional anthropometric reliability study. Int J Nurs Stud 2009;46:310–16.

Table C5. Data collection details.

Variables	Details
Demographic data	
Singleton births (n=13455)	Medical record
Twins (n=354; 177 sets)	Medical record
Triplets (n=9; 3 sets)	Medical record
Child Biological Samples	
Child cord blood markers (Assay)	13ml; from medical data as extracted from the eCLipse maternity IT system, taken at birth.
Mother Biological Samples (taken at 28 weeks)	
Body Mass Index (BMI)	Weighed and measured at time of recruitment (28 weeks)
Systolic blood pressure	From baseline measure at 28 weeks, taken by clinical staff
Diastolic blood pressure	From baseline measure at 28 weeks, taken by clinical staff
Fasting Glucose	From baseline measure at 28 weeks; 13 mls blood sample, prepared for storage at -80°C: serum, whole blood, plasma, buffy coat and red blood cells
HDL Cholesterol	From baseline measure at 28 weeks; 13 mls blood sample, prepared for storage at -80°C: serum, whole blood, plasma, buffy coat and red blood cells
Triglycerides	From baseline measure at 28 weeks; 13 mls blood sample, prepared for storage at -80°C: serum, whole blood, plasma, buffy coat and red blood cells
Previously diagnosed diabetes	From health services data collected as part of clinical care
Gestational diabetes	Baseline measure, maternity data set; diagnosed by glucose tolerance test based on WHO (WHO/NCD/NCS/99.2) thresholds for impaired glucose tolerance or impaired fasting glucose, (i.e. fasting plasma glucose ≥6.0mmol/l and/or 2-hr post-challenge glucose ≥ 7.8mmol/l) at 26 weeks.
Sociodemographic characteristics	
Deprivation	Taken by research team at baseline questionnaire (28 weeks)
Education - Mother	Taken by research team at baseline questionnaire (28 weeks)
Self-reported health behaviour	
Smoking Status	Self-reported by mothers throughout pregnancy
Mental Health	Self-reported by mothers throughout pregnancy

Appendix D – Chapter 5

Table D1. Data extraction details.

Cochrane Library Advanced Search Manager	**20-May-21**
Search Manager	Select MeSH descriptor (right button) and Look Up MeSH term i.e. Analgesics MeSH descriptor: [term] explode all trees Select Add/Edit search line Add MeSH terms until all filled in
Search Builder:	Search terms in Title/Abstract/Keywords i.e. painkillers Set and Apply limits: Content Type [Cochrane Reviews], Cochrane Library publication date [All dates], Select "Search word variations"
Cochrane Search	((analgesic* OR painkillers* OR drugs* OR medication* OR aspirin* OR acetaminophen* OR ibuprofen* OR naproxen* OR diclofenac* OR ketoprofen* OR NSAIDS* OR antiinflammatory*) AND ((fetus* OR fetal* OR child* OR offspring* OR mother* OR maternal* OR pregnant* OR prenatal* OR antenatal*)) AND ((neurodevelopment* OR child development* OR Autism* OR Asperger* OR attention deficit hyperactivity* OR inattention*OR hyperactivity*OR impulsivity*OR hyperkinetic*OR ASD* OR ADHD*)) AND ((meta analysis* OR systematic review* OR quantitative review* OR research synthesis*))):ti,ab,kw (Word variations have been searched)
PubMed Advanced Search Builder	**20-May-21**
MeSH instructions	Go to MeSH Advanced: "https://www.ncbi.nlm.nih.gov/mesh/advanced" Under Builder, select "MeSH Unique ID" Key in first MeSH ID (i.e. Analgesics is D000700) Select 'OR' and key in next MeSH ID Add rows until all MeSH IDs are filled in
Search Builder:	Search (((((((D000700[MeSH Unique ID]) OR D001241[MeSH Unique ID]) OR D000082[MeSH Unique ID]) OR D007052[MeSH Unique ID]) OR D009288[MeSH Unique ID]) OR D004008[MeSH Unique ID]) OR D007660[MeSH Unique ID]))

PubMed Search	Terms to use: Analgesics [Pharmacological Action] AND "Naproxen"[Mesh] AND "Analgesics"[Mesh] AND "Acetaminophen"[Mesh] AND "Aspirin"[Mesh] AND "Diclofenac"[Mesh] AND "Ibuprofen"[Mesh] AND "Ketoprofen"[Mesh] ("Analgesics"[Pharmacological Action] OR "Naproxen"[MeSH Terms] OR "Analgesics"[MeSH Terms] OR "Acetaminophen"[MeSH Terms] OR "Aspirin"[MeSH Terms] OR "Diclofenac"[MeSH Terms] OR "Ibuprofen"[MeSH Terms] OR "Ketoprofen"[MeSH Terms] OR ("analgesics*"[Title/Abstract] OR "painkillers*"[Title/Abstract] OR "drugs*"[Title/Abstract] OR "medication*"[Title/Abstract] OR "aspirin*"[Title/Abstract] OR "acetaminophen*"[Title/Abstract] OR "ibuprofen*"[Title/Abstract] OR "naproxen*"[Title/Abstract] OR "diclofenac*"[Title/Abstract] OR "ketoprofen*"[Title/Abstract] OR "nsaids*"[Title/Abstract] OR "antiinflammatory*"[Title/Abstract])) AND ("fetus*"[Title/Abstract] OR "fetal*"[Title/Abstract] OR "child*"[Title/Abstract] OR "offspring*"[Title/Abstract] OR "mother*"[Title/Abstract] OR "maternal*"[Title/Abstract] OR "pregnant*"[Title/Abstract] OR "prenatal*"[Title/Abstract] OR "antenatal*"[Title/Abstract]) AND ("neurodevelopment*"[Title/Abstract] OR "child development*"[Title/Abstract] OR "autism*"[Title/Abstract] OR "asperger*"[Title/Abstract] OR "attention deficit hyperactivity*"[Title/Abstract] OR "inattention*"[Title/Abstract] OR "hyperactivity*"[Title/Abstract] OR "impulsivity*"[Title/Abstract] OR "hyperkinetic*"[Title/Abstract] OR "asd"[Title/Abstract] OR "adhd*"[Title/Abstract]) AND ("meta analysis*"[Title/Abstract] OR "systematic review*"[Title/Abstract] OR "quantitative review*"[Title/Abstract] OR "research synthesis*"[Title/Abstract])
EMBASE Advanced Search Manager	**20-May-21**
Search Builder:	Set and Apply limits: limit 1 to (abstracts and (meta analysis or "systematic review") and english and "review")
EMBASE Search	((analgesic* or painkillers* or drugs* or medication* or aspirin* or acetaminophen* or ibuprofen* or naproxen* or diclofenac* or ketoprofen* or NSAIDS* or antiinflammatory*) and (fetus* or fetal* or child* or offspring* or mother* or maternal* or pregnant* or prenatal* or antenatal*) and (neurodevelopment* or child development* or Autism* or Asperger* or attention deficit hyperactivity* or inattention*OR hyperactivity*OR impulsivity*OR hyperkinetic*OR ASD* or ADHD*) and (meta analysis* or systematic review* or quantitative review* or research synthesis*)).mp. [mp=title, abstract, heading word, drug

trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

Search terms:
acetaminophen*
adhd*
analgesic*
antenatal*
antiinflammatory*
asperger*
aspirin*
attention
deficit
hyperactivity*
autism*
child
development*
child*
diclofenac*
drugs*
fetal*
fetus*
ibuprofen*
inattention*or
hyperactivity*or
impulsivity*or
hyperkinetic*or
asd*
ketoprofen*
maternal*
medication*
meta
analysis*

	mother* naproxen* neurodevelopment* nsaids* offspring* painkillers* pregnant* prenatal* quantitative review* research synthesis* systematic
Global Health Search Manager	**20-May-21**
Search Builder: Global Health Search	Set and Apply limits: limit 1 to (abstracts and english language) ((analgesic* or painkillers* or drugs* or medication* or aspirin* or acetaminophen* or ibuprofen* or naproxen* or diclofenac* or ketoprofen* or NSAIDS* or antiinflammatory*) and (fetus* or fetal* or child* or offspring* or mother* or maternal* or pregnant* or prenatal* or antenatal*) and (neurodevelopment* or child development* or Autism* or Asperger* or attention deficit hyperactivity* or inattention*OR hyperactivity*OR impulsivity*OR hyperkinetic*OR ASD* or ADHD*) and (meta analysis* or systematic review* or quantitative review* or research synthesis*)).mp. [mp=abstract, title, original title, broad terms, heading words, identifiers, cabicodes] **Search terms:** acetaminophen* adhd* analgesic* antenatal* antiinflammatory* asperger*

aspirin*
attention
deficit
hyperactivity*
autism*
child
development*
child*
diclofenac*
drugs*
fetal*
fetus*
ibuprofen*
inattention*or
hyperactivity*or
impulsivity*or
hyperkinetic*or
asd*
ketoprofen*
maternal*
medication*
meta
analysis*
mother*
naproxen*
neurodevelopment*
nsaids*
offspring*
painkillers*
pregnant*
prenatal*
quantitative
review*

	research synthesis* systematic
APA PsycInfo and APA PsycArticles Full Text Search Manager	**20-May-21**
Search Builder:	Set and Apply limits: limit to articles with abstracts, english language, human, review articles
PsycInfo and PsycArticles Search	((analgesic* or painkillers* or drugs* or medication* or aspirin* or acetaminophen* or ibuprofen* or naproxen* or diclofenac* or ketoprofen* or NSAIDS* or antiinflammatory*) and (fetus* or fetal* or child* or offspring* or mother* or maternal* or pregnant* or prenatal* or antenatal*) and (neurodevelopment* or child development* or Autism* or Asperger* or attention deficit hyperactivity* or inattention*OR hyperactivity*OR impulsivity*OR hyperkinetic*OR ASD* or ADHD*) and (meta analysis* or systematic review* or quantitative review* or research synthesis*)) **Search terms:** acetaminophen* adhd* analgesic* antenatal* antiinflammatory* asperger* aspirin* attention deficit hyperactivity* autism* child development* child* diclofenac* drugs*

fetal*
fetus*
ibuprofen*
inattention*or
hyperactivity*or
impulsivity*or
hyperkinetic*or
asd*
ketoprofen*
maternal*
medication*
meta
analysis*
mother*
naproxen*
neurodevelopment*
nsaids*
offspring*
painkillers*
pregnant*
prenatal*
quantitative
review*
research
synthesis*
systematic

Table D2. GRADE certainty and decision-making criteria.

Certainty down-rated for	Certainty up-rated for	Decision-making
a) Risk of bias b) Publication bias c) Imprecision d) Inconsistency e) Indirectness	a) Large magnitude of effect b) Dose-response gradient c) Plausible confounding that reduces demonstrated effect d) Possible confounding suggesting spurious effect when actual results show no effect	a. **Critical:** highly likely that results are a reasonable and accurate representation of data b. **Important but not critical:** likely that results are a reasonable and accurate representation of data c. **Of limited importance:** not clear if results are a reasonable and accurate representation of data

Table D3. Descriptive characteristics of included reviews.

Author (Year)	Participants	Databases	Study method	Study Type	Design	Number of studies assessed for eligibility	Final number of studies included
Hoover et al. (2015)	NS	Cochrane Library, PubMed, Embase	Qualitative	Systematic Review	Cross-sectional	NS	4
Bauer et al. (2018)	137,738	Embase	Qualitative	Systematic Review	Longitudinal	64	9
Masarwa et al. (2018)	61,601	Cochrane Library, Embase, Global Health	Quantitative, Qualitative	Meta-analysis and Systematic Review	Cross-sectional	30	7
Gou et al. (2019)	244,940	Embase, Cochrane Library, PubMed	Quantitative	Meta-analysis	Cross-sectional	16	8
Alemany et al. (2021)	73,881	PubMed	Quantitative	Meta-analysis	Cross-sectional	NS	NS

NS: Not Stated

Table D4. Methodological characteristics of included reviews.

Author (Year)	Population age range (years)	Exposures relevant to review	Outcomes relevant to review	Analysis Used	Adjusted for covariates and confounders	Additional analysis performed within review	Heterogeneity I^2 (%)	Significance of heterogeneity (p-value)
Hoover et al. (2015)	3 – 12	Acetaminophen	ADHD	Narrative Review	No	NS	NS	NS
Bauer et al. (2018)	1.5 – 12	Acetaminophen, ibuprofen	ADHD, ASD, HKD	Narrative Review	Yes	Performed in included studies	NS	NS
Masarwa et al. (2018)	3 - 13.5	Acetaminophen	ADHD, ASD, Hyperactivity symptoms	Narrative Review, Random Effects Models	Yes	Sensitivity analysis, moderator analysis for heterogeneity	ADHD: 72 ASD: 14 Hyperactivity symptoms: 93	ADHD: .03 ASD: .31 Hyperactivity symptoms: <.001
Gou et al. (2019)	3 – 11	Acetaminophen	ADHD	Random Effects Models	Yes	Sensitivity analysis, subgroup analysis for heterogeneity	ADHD: 26	.22
Alemany et al. (2021)	4 – 12	Acetaminophen	ADHD, ASD	Meta-analytic Models	Yes	Sensitivity analysis, Cochran's Q test and I2 test for heterogeneity	ADHD: <1 ADHD: 2.4	ADHD: .89 ASD: .5

NS: Not Stated
ADHD: diagnosis classification of Attention-Deficit Hyperactivity Disorder
Hyperactivity Symptoms: hyperactivity-impulsiveness symptoms
Hyperkinetic disorder (HKD); hyperactive behavioural phenotype

Table D5. GRADE certainty overall ratings (downgrading or upgrading of evidence).

Author (Year)	Risk of bias present	Publication bias present	Imprecision (based on 95% CI)	Inconsistency of effects	Indirectness of outcomes	Large effect size (RR/OR/HR: >3.0)	Dose-response gradient	All plausible confounding would reduce a demonstrated effect (increase confidence in estimated effects)	All possible confounding would suggest a spurious effect (for results showing no effect)	Total GRADE rating score
Hoover et al. (2015)	Yes (sampling bias)	No	NA	No	No	No	No	Yes	No	0
Bauer et al. (2018)	No	No	No	No	No	No	Yes	Yes	NA (results show some effect)	2
Masarwa et al. (2018)	Yes	NA (unable to evaluate due to limited studies)	No	No	No	No	Yes	Yes	NA (results show some effect)	1
Gou et al. (2019)	No	No	No	No	No	No	No	Yes	NA (results show some effect)	1
Alemany et al. (2021)	No	No	No	No	No	No	No	Yes	NA (results show some effect)	1

Down-ratings: yes = -1, no = 0, not applicable (NA) = 0
Up-ratings: yes = +1, no = 0, not applicable (NA) = 0