The impact of intrauterine exposures on neurodevelopmental outcomes in 8–10 year old children within a disadvantaged population

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Abstract

Introduction: Intrauterine exposures can have lasting impacts on offspring neurodevelopment. The aim of this thesis was to investigate the associations of antenatal depression and pregnancy complications on child cognitive and mental health at 8–10 years of age.

Method: This is a follow-up study of the SCreening fOr Pregnancy Endpoints (SCOPE) cohort. During pregnancy, women completed a number of questionnaires, including the Edinburgh Postnatal Depression Scale (EPDS) at 15 weeks' and 20 weeks' gestation, and pregnancy complications recorded. Women were contacted 8–10 years after delivery for assessment of their child's neurodevelopment. Cognitive testing utilised five tests from the Cambridge Neuropsychological Test Automated Battery, focusing on executive function, memory and reaction time. Mothers completed the Depression, Anxiety and Stress Scale (DASS-42) to assess their own mental health, and the Spence Children's Anxiety Scale (SCAS) and the Child Anxiety Life Interference Scale (CALIS) to assess their child's anxiety. Children completed the SCAS and CALIS questionnaires along with the Center for Epidemiological Studies Depression scale for Children (CES-DC).

Results: Data were available for 273 mother-child pairs. Thirty-eight mothers scored ≥13 on the EPDS and were classed as having high antenatal depression, with the remainder classed as having low antenatal depression. For children of the high antenatal depression group, both the parent and to a lesser extent the child report, demonstrated increased likelihood of anxiety symptoms and anxiety interference. Children in this group were also at increased risk of errors on learning memory and spatial working memory task, and longer motor movement times. There were no

differences in any other reaction time measures, delayed memory measures, or executive functioning or in risk of child self-reported depression symptoms between the groups.

Next, groups were assigned based on the presence of one of the five major complications of pregnancy; preeclampsia (PE; n=38), small for gestational age (SGA; n=34), preterm birth (PTB; n=26), gestational diabetes mellitus (GDM; n=22) and gestational hypertension (GH; n=20) and developmental outcomes compared with controls (n=166). Children born following PE and/or SGA were most vulnerable to cognitive deficits, with poorer performance on executive functioning and memory tasks. Children born following GDM had better learning memory performance compared to controls. Children born SGA or after GH had longer movement and reaction times, respectively. Children born after PE reported higher anxiety and anxiety interference. Children born SGA were at increased risk of reporting anxiety interference. Interestingly, children born preterm had decreased likelihood of self-reported anxiety symptoms, while children born after GDM were at decreased risk of anxiety interference, including anxiety interference outside the home. Exposure to pregnancy complications had no effect on child depressive symptoms.

Conclusion: Maternal antenatal depression and pregnancy complications are associated with neurodevelopmental outcomes in 8–10-year-old children. This has lifelong implications, reducing future job opportunities and socioeconomic success. Similarly, poor mental health in childhood and adolescence is associated with increased risk of long-term mental health problems. Recognition of factors that contribute to deficits in cognition and mental health provides opportunities for early interventions to improve long-term health and social outcomes.

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

I give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Presentations and abstracts arising from this thesis

Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'The impact of preeclampsia and being small for gestational age on neurodevelopmental outcomes in children aged 8-10 years'
Invited speaker at Lyell McEwin Hospital Research Meeting (Adelaide, November 2018)

Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'The impact of preeclampsia and being small for gestational age on neurodevelopmental outcomes in children aged 8-10 years'
Poster presentation at Florey Postgraduate Conference (Adelaide, September 2018)

Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'Early life adversity and neurodevelopmental outcomes in 8-10 year old children'
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Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'Sex differences in parent-reported anxiety in 8-10 year old children following maternal depression during pregnancy'
Oral and poster presentation at Developmental Origins of Health and Disease Conference (Sydney, July 2018)

Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'Maternal depression in pregnancy and behavioural differences between 8-10 year old male and female children'
Poster presentation at Developmental Origins of Health and Disease Conference (Sydney, July 2018)

Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'Poor mental health during pregnancy and neurodevelopmental outcomes in 8-10 year old children'
Invited speaker for Healthy Development Adelaide and Australian Association for Infant Mental Health joint event (Adelaide, June 2018)

Roberts C, **Garrett A**, Plummer M, Loughhead B, Bianco-Miotto T, Hodyl N, Dekker G & Andraweera P.
'Maternal factors in pregnancy that impact child neurodevelopment assessed at 8 – 10 years of age'
Invited speaker presentation for Growing Minds: The Early Origins of Mental Health and Disorder conference (Adelaide, October 2017)

Garrett A, Plummer M, Loughhead B, Andraweera P, Roberts C & Hodyl N.
'The impact of preeclampsia and preterm birth on neurodevelopmental outcomes in children aged 8-10 years'
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Garrett A, Plummer M, Andraweera P, Roberts C & Hodyl N.
'Neurodevelopmental outcomes in children born to mothers following pregnancy complications'
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Garrett A, Andraweera P, Roberts C & Hodyl N.
'Developmental outcomes in children born to mothers with preeclampsia'
Poster presentation at Florey Postgraduate conference (Adelaide, September 2016)

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ADHD	Attention Deficit and Hyperactivity Disorder
AGA	Appropriate for Gestational Age
AST	Attention Switching Task
BMI	Body Mass Index
CALIS	Child Anxiety and Life Interference Scale
CANTAB	Cambridge Neuropsychological Test Automated Battery
CES-DC	Center for Epidemiological Studies Depression scale for Children
DASS	Depression, Anxiety and Stress Scale
DOHaD	Developmental Origins of Health and Disease
DMS	Delayed Matching to Sample
EPDS	Edinburgh Postnatal Depression Scale
GDM	Gestational Diabetes Mellitus
GH	Gestational Hypertension
HPA	Hypothalamic Pituitary Adrenal
IQ	Intelligence Quotient
NZSEI	New Zealand Socioeconomic index
LGA	Large for Gestational Age
MDI	Mental Development Index (Bayley Scales)
ms	Milliseconds
PAL	Paired Associative Learning
PDI	Psychomotor Development Index (Bayley Scales)
PE	Preeclampsia
PTB	Preterm Birth
RTI	Reaction Time task
SCAS	Spence Children’s Anxiety Scale
SCOPE	Screening for Pregnancy Endpoints
SEI	Socioeconomic Index
SES	Socioeconomic Status
SGA	Small for Gestational Age
STAI	State Trait Anxiety Inventory
SWM	Spatial Working Memory

Chapter 1:

Literature Review

Neurodevelopment refers to the growth and development of the central nervous system, which is composed of the brain and spinal cord. These two parts are key to functioning within the world. The brain controls our thoughts, memory, speech, our behaviour and other bodily functions.

1.1 Formation of the brain

The formation of the central nervous system begins very early after conception. The neural tube, the structure from which the brain and spinal cord are derived, forms during the third week of gestation, and closes by week seven [1]. The neural tube contains 3 main regions which go on to become the fore, mid and hind brain. Further differentiation sees the differentiation of the cerebrum, cerebellum, brain stem, and hypothalamus. During the fetal period, development of the brain depends mostly on neuron proliferation, migration and differentiation [1]. These processes are driven somewhat by the genetic make-up of the embryo, however, can also be altered by environmental influences [2, 3]. There are many vulnerable periods during development that can impact on neurodevelopment [4, 5].

1.2 Early life exposures can influence development of the brain

The Developmental Origins of Health and Disease (DOHaD) hypothesis was first suggested by David Barker, and states that events during early development program an individual's risk for future adult chronic disease [6]. This claim was originally supported mainly by cohort studies in which pregnant women faced malnutrition due to factors such as famine, which resulted in poor health outcomes in their children [7-11]. Genome-wide association studies have found strong associations with many disease outcomes, however, only account for small amount of their

occurrence [12-14], therefore suggesting that the environment has an important role in development. Mechanisms that contribute to the DOHaD phenomenon may include epigenetics, where there is modification of gene expression, rather than a change to the genetic code itself. Epigenetic changes are important for cellular differentiation and developmental plasticity, and are influenced by the environment [15]. This highlights the importance of environmental impacts on the development of fetus and subsequent development and health of the child.

Much of the previous research has focused on how early life adverse events can result in poor physical health, such as cardiovascular disease and poor metabolic health later in life. However, more recent research has focused on the impact these early life adverse events have on other aspects of well-being, specifically, neurodevelopment and mental health. Given that the brain is developing rapidly during this time, it is no surprise that the uterine environment during gestation may not only have long lasting impacts on physical health, but also on brain development.

A number of different early life adverse factors, including socioeconomic disadvantage, maternal mental health and pregnancy complications (such as preeclampsia (PE), small for gestational age (SGA) and preterm birth (PTB)), have been associated with an increased risk of poor neurodevelopment and mental health outcomes in offspring. Poor cognitive and mental health status have been associated with poor academic success in children, and also behavioural and social difficulties [16]. These difficulties may not only affect outcomes in childhood, but can also continue into adulthood, creating differences in emotional, relationship, employment and socioeconomic domains. The increased prevalence of these poor outcomes after early life adverse events is key evidence highlighting the vulnerability of the brain both *in utero* and in early childhood. Possible biological mechanisms, such as genetic

variants, may also mediate these outcomes [e.g. 17, 18, 19]. The next step is determining which biological and psychosocial factors are most relevant and/or reliable to predicting poor neurodevelopment and mental health outcomes. This will allow us to provide early interventions to target the most appropriate pathways to improve outcomes for children in the future.

1.3 Impact of socioeconomic status on child development

One of the most important contributing factors to poor developmental outcomes is low socioeconomic status (SES). Overall, people from low SES backgrounds are at higher risk of poor health, have higher rates of illness and disability, and live shorter lives. For example, from 2001-2007, an Australian survey showed estimated difference in life expectancy was six years between the poorest and the richest income quintiles [20]. Low SES can be reflected by a number of factors including low education, single parental household and low household income [21]. One comparison investigated those in the lowest socioeconomic income and highest socioeconomic income in Australia based on income, educational attainment, unemployment and occupation [22]. Those in the lowest socioeconomic group were more likely to smoke, consume inadequate amount of fruit and vegetables, and have impaired fasting glucose [22]. They also had a higher incidence of chronic disease: they were 2.6 times more likely to have diabetes, and 2.2 times more likely to have coronary artery disease and/or stroke [22]. In addition to health outcomes, low SES has also been associated with poor neurodevelopment and educational achievement in children [Reviewed in 23]. Together these demonstrate that people living with low SES are at increased risk of poor outcomes. Hence, in order to improve outcomes, research needs to focus on low SES populations.

1.3.1 *Relationship between socioeconomic status and cognitive outcomes*

Studies have found lower cognitive performance in children of varying age ranges living in socially disadvantaged conditions, including low income [24, 25], unemployment [26] and low parental education [27, 28]. More specifically, children from low SES backgrounds demonstrate smaller vocabularies [29, 30], reduced attentional control [31], poorer executive function and memory [32-34] compared to those from high SES backgrounds. Additionally, Noble et al. [35] found a significant association between SES and brain volume of the hippocampus and amygdala, brain regions which are important for memory, decision making and emotional responses. This difference was seen in children aged 5 to 17 years, and was not explained by sex, race or intelligence quotient (IQ). Children from low SES areas are also more likely to fail courses and drop out of school compared to their high SES counterparts [36]. This in turn reduces job opportunities for those with low SES, leading to intergenerational disadvantage and associated health concerns. Interestingly, the level of social disadvantage at birth has been demonstrated to be a strong predictor of poorer cognitive abilities in adolescence, particularly in the domains of working memory and general intellectual ability [37]. This is consistent with research suggesting health, behavioural and educational differences are established in early childhood, and therefore may be important determinants of future adult health [38].

1.3.2 *Relationship between socioeconomic status and mental health and behavioural outcomes*

In Australia in 2016, people residing in low SES areas were 1.4 times more likely to have behavioural and mental health problems than those from high SES areas [22]. Low SES has also been associated with an increased risk of behavioural and

attention problems in children [23], and this risk is amplified with increasing levels of social disadvantage [39]. Furthermore, those who live in socially disadvantaged areas are more likely to be affected by mental illness, particularly anxiety and depression [40]. This research highlights the importance of early life adversity on development, cognition and mental health and hence the need for early identification and intervention, particularly for those living with socioeconomic disadvantage.

1.4 Maternal mental health during pregnancy and child outcomes

Present research demonstrates that maternal mental health during the perinatal period is also an important factor in child neurodevelopment. Studies suggest that between 12 - 20% of women suffer from poor mental health at some point during pregnancy [41, 42]. Children of women who are depressed, anxious or stressed during pregnancy are more likely to experience many different adverse neurodevelopmental outcomes, including poorer cognitive function, increased likelihood of behavioural issues, and increased risk of anxiety and/or depression in the offspring [Reviewed in 43, 44]. This suggests if research can highlight what factors of maternal mental health are most relevant to predicting outcomes, then these can be used to identify for whom, when and how to intervene.

1.4.1 *Maternal antenatal depression and child cognition*

Most research into associations between antenatal maternal anxiety and depression, and child cognitive outcome has been undertaken in infants. Stress, anxiety and depression during pregnancy have been associated with subsequent decreased cognitive functioning in infants. For example, an average decline of eight points in mental development index (MDI) and psychomotor development index (PDI) scores (as measured by the Bayley Scales of Infant and Toddler Development) was found in

infants born to stressed mothers eight months after birth [45]. Lower scores in Bayley MDI have also been demonstrated at 14 months of age [46] and at two years old [47] in children whose mothers were stressed during pregnancy. Antenatal depression has also been associated with poor outcomes, where children whose mothers had antenatal depression had decreased MDI and PDI scores on the Bayley at 18 months [48]. Findings also suggest a cumulative effect of stress on development: the number of stressful life events was found to be inversely proportional to MDI measured by the Bayley Scales [46]. While this evidence suggests maternal mental health impacts on Bayley MDI and PDI scores, recent evidence suggests that while the Bayley Scales may indicate differences in individual functioning, scores do not necessarily correlate with future performance [49]. Therefore, further studies are needed to investigate whether these differences still exist at older ages.

Few studies have investigated the relationship between antenatal depression and cognition at older ages, and results of existing research are varied. For example, one study by Barker et al. [50] found those children exposed to maternal antenatal depression had decreased verbal IQ at 7-8 years compared to those children whose mothers did not have antenatal depression. In contrast, Evans et al. [51] found that antenatal depression was not associated with IQ score at eight years old. While both studies controlled for similar confounders such as current maternal mental health, the differences found using slightly different measures of IQ suggest that different areas of cognition may be differentially impacted by poor maternal mental health during pregnancy. Few studies investigate the impact of maternal mental health state on specific cognitive domains of children. One study suggests antenatal anxiety, but not antenatal depression, was associated with decreased executive function (inhibition task) in 6 to 9 year old in girls only [52]. These findings also demonstrated antenatal

anxiety and depression were both associated with lower visuospatial working memory in both males and females. Additionally, antenatal depression has been associated with decreased motor skills at 16 months [53] and increased child attention problems at age three [54]. Taken together, these results suggest that differences may exist within different cognitive domains following maternal mental health issues, and therefore these warrant further investigation.

1.4.2 *Maternal antenatal and child mental health and behaviour*

Antenatal anxiety, depression, and stress have also been associated with offspring behaviour, such as a more difficult infant temperament [45, 46, 55-60]. Research in infants has also demonstrated how males and females are differentially impacted by antenatal maternal mood states, highlighting the need to consider sex differences [61-63]. Children exposed to maternal stress or anxiety during gestation also demonstrate increased rates of conduct, emotional and behavioural problems [44, 64-75]. For example, data from the Avon Longitudinal Study of Parents and Children (ALSPAC) demonstrated that mothers who were in the highest 15% on scores for anxiety had double the risk of having children with emotional and behavioural problems at age four years [66] and also at seven years of age [67], even after controlling for multiple potential confounders.

These problems appear to continue into adolescence, with increased rates of behavioural issues found in 13 year olds whose mothers had antenatal anxiety or depression [70]. High maternal anxiety and stress during pregnancy has also been associated with subsequent disorders such as attention deficit hyperactivity disorder (ADHD), and also higher anxiety in children [68, 75]. Adolescents who were exposed *in utero* to stressors such as the Chernobyl disaster in 1986, were twice as likely to

have higher depressive symptoms, or fulfil the criteria for major depressive disorder at age 14 years than those who were not exposed [76].

Although these previous findings suggest antenatal stress and anxiety are associated with child behavioural and mental health outcomes, there is less evidence on the impact of antenatal depression on child mental health. Maternal antenatal depression was associated with increased internalising and externalising behaviours at three years old [77], and in two to six year old children [41] compared to those not exposed to antenatal depression. One study demonstrated that eight year old children exposed to maternal depression *in utero* had increased externalising behaviours compared to children not exposed [74]. While this demonstrates an association between antenatal depression and problem behaviour, the extent to which this association may contribute to child mental health outcomes has yet to be investigated. Adults who were exposed to antenatal depression are at increased risk of anxiety disorders at age 18 years [78], and also depression at both age 16 years [79] and 18 years [80] compared to those not exposed to maternal antenatal depression. This suggests that antenatal depression exposure confers an increased risk of mental health disorders. However, currently it is unknown whether these poorer mental health outcomes can be detected at younger ages. Earlier detection of symptoms would allow for early intervention to reduce the risk of progression into mental health disorder, and hence improve long-term mental health outcomes.

1.4.3 *Postnatal maternal mental health and child outcomes*

Evidence suggests that postnatal maternal mental health symptoms may also impact upon child outcomes [48, 81-83]. For example, depressed mothers demonstrate less interaction, less responsiveness and are less vocal with their infants [84, 85],

which may lead to long-term effects on child interaction and development. However, antenatal mental health symptoms can predict child outcomes independently of postnatal symptoms [48, 51, 66, 86, 87]. In addition, child deficits appear to persist even after controlling for postnatal complications including continuing or new onset anxiety or depression [43], and studies also demonstrate associations with antenatal maternal mood are stronger than with paternal antenatal mood [78, 80]. This suggests that investigation of maternal mental health symptoms during pregnancy may be a more reliable way to investigate child outcomes and allow for earliest possible intervention.

1.4.4 *Maternal antenatal mental health and child outcomes: biological mechanisms*

The exact mechanism for transmission of maternal mental health issues to child outcomes is unknown, although several different mechanisms have been proposed. Programming in fetal brain in response to stress signals is likely to have previously provided an evolutionary benefit in preparing the fetus to protect itself from real external physical danger [88]. One possible mechanism for maternal mental health to impact on child outcomes is alterations in maternal and fetal hypothalamic-pituitary-adrenal (HPA) axes [44, 69], including factors such as increased exposure to the hormone cortisol. Glucocorticoids (such as cortisol) are important for fetal development including the brain [89]. Depression is associated with higher levels of circulating cortisol in pregnant women [90]. These increased levels of cortisol can then cross the placenta and enter fetal circulation, leaving the fetus overexposed [91], which can in turn impact development of biological stress system of the child [92, 93]. This phenomenon has been demonstrated in rat studies. Rats that were exposed to stress *in utero* have higher circulating glucocorticoids in baseline conditions [94-96]. These rats

also exhibit faster [97], stronger [96, 98] and/or more prolonged [99] stress responses to stress than control rats, suggesting a programming effect. This is also likely the case in humans, where children exposed to antenatal anxiety and/or depression have exaggerated cortisol responses to stress [64, 100, 101]. Additionally, programming effects may occur via increased cortisol exposure of the fetus, but without increases in the mother's cortisol. The placenta is extremely important in regulating cortisol exposure of the fetus, and therefore overexposure to cortisol could be caused by changes in placental function. The enzyme 11-beta hydroxysteroid dehydrogenase type II (11β-HSD2) expressed by the placenta converts cortisol to its inactive form, cortisone. Therefore lower placental expression of this enzyme, could result in higher fetal exposure to cortisol even if mother's cortisol is not increased. Supporting evidence in rats exposed to prenatal stress shows they down regulate placental 11β-HSD2 [102]. More recent evidence also suggests maternal antenatal anxiety and depression is associated with downregulation of placental 11β-HSD2 in humans [103], suggesting these children could be exposed to increased cortisol without any direct changes in mothers' cortisol levels. Additional research suggests that cortisol levels present in the maternal circulation are not necessarily associated with subjective maternal mental health scores [104, 105], and therefore this may provide a mechanistic pathway for transmission.

Other evidence suggests that biological factors other than cortisol may be involved. For example, one study asked pregnant women to participate in a stressful computer task while their fetus's heart rate was monitored [106]. They found fetal heart rate increased, but only in mothers who rated themselves as anxious. The effects of this task would be too quick to be caused by cortisol, which would take 10-20

minutes to rise and impact on fetal heart rate [91]. This suggests alternative factors may impact fetal development.

Another possible mechanism is epigenetic changes, which may play a role in the transfer of maternal mental health state to child outcomes. Epigenetic changes refer to changes in gene expression without changes to the genetic code, and include methylation and histone modification. Epigenetic changes can be caused by environmental exposures, and therefore may underlie programming effects [91] and hence impact on child cognition, behaviour and mental health. For example, prenatal stress has been shown to cause epigenetic changes on the DNA encoding the receptor that binds cortisol (glucocorticoid receptor) in rats [107]. More recent research has also shown methylation changes to the glucocorticoid receptor gene of children whose mothers were exposed to partner violence during pregnancy [108].Together, these findings suggest epigenetic factors may also contribute to differences in outcomes.

Other sources have also suggested environmental factors which may also contribute to increased risk of poor outcomes in children exposed to antenatal depression. For example, one study found that maternal antenatal depression was associated with lower levels of healthy nutrition and higher levels of unhealthy nutrition, each of which was prospectively associated with reduced cognitive function in the child at eight years old [50]. Depression during pregnancy is also associated with increased rates of smoking [109], which is in turn associated with poorer cognitive function in children [110]. These findings suggest other environmental impacts should be considered or controlled for in future studies.

1.5 Placenta

The placenta is a highly specialised organ that supports the development and growth of the growing fetus during pregnancy. Its primary role is to exchange nutrients and waste products between maternal and fetal circulation [111]. The placenta is often implicated in pregnancy complications that compromise maternal and fetal/infant health.

1.6 Pregnancy complications

Pregnancy complications are disorders that occur during pregnancy. These include gestational diabetes mellitus (GDM), gestational hypertension (GH), preeclampsia (PE), preterm birth (PTB) or a small for gestational age (SGA) baby. These complications can impact the health of either mother or baby, or both. Low SES has been associated with an increased risk of pregnancy complications [112-115].

1.7 Preeclampsia and Gestational Hypertension

Hypertensive disorders in pregnancy include both GH and PE. Normal physiological changes during pregnancy include increases in cardiac output and blood volume, and decrease in blood pressure [116]. Throughout pregnancy, blood pressure normally decreases during first trimester, and then returns to normal pre-pregnancy levels during the third trimester [117]. GH is characterised by new onset hypertension (≥140mmHg systolic, and/or ≥90mmHg diastolic blood pressure) present after 20 weeks' gestation [118]. PE is characterised by GH, and additionally proteinuria and/or other organ involvement and/or a SGA baby [118]. GH impacts approximately 6 to 8% of pregnancies [119], while PE complicates between 2 and 8% of pregnancies [120].

Both PE and GH have been associated with outcomes in children's long-term neurodevelopment.

1.7.1 *Preeclampsia, gestational hypertension, and child cognitive outcomes*

Several studies have demonstrated poorer cognitive function in infants born after preeclamptic pregnancies, compared to those born after non-preeclamptic pregnancies, on the Bayley MDI [121-124]. In contrast, other studies have found no differences scores on the Bayley Scales following PE [125, 126]. Toddlers who were born after PE pregnancies had significantly lower IQ scores (mean 10 points lower), as measured by the Stanford Binet IQ test at 3 years when compared to those not exposed to PE [127].

Further research suggests that GH and PE during pregnancy can result in cognitive deficits continue into childhood. Morsing and Marsal [128] investigated the impact of PE in relation to PTB and intrauterine growth restriction, and found those children exposed to PE in addition to PTB and growth restriction had significantly lower IQ scores at 5-8 years old compared to those born preterm and growth restricted but not exposed to PE. A more recent study investigated children with intrauterine growth restriction, and suggested no differences in IQ or school achievements in children aged 9-10 years exposed to PE or GH compared to the normotensive group [129]. However, while these studies demonstrate that PE confers neurodevelopmental disadvantage, it is difficult to determine whether this disadvantage only occurs when children were also preterm and growth restricted at birth. When looking solely at PE, a small pilot study (n=10) by Ratsep et al. [130] found that term-born children who were exposed to PE had impaired working memory at age eight years old compared to those

not exposed to PE. However, further research is needed to determine whether this difference exists in other cognitive domains.

Further studies in children offer comparisons between GH, PE and normotensive pregnancy outcomes in relation to child development. One study on British children at age seven years found that children exposed to PE *in utero* had better cognitive function than those exposed only to GH [131]. In contrast, recent findings from the Raine cohort from Western Australia found no difference in cognitive function on a test of Raven's Progressive Matrices at 10 years old between those exposed to PE or GH compared to those not exposed to PE or GH [132]. Differences in findings may be due to the nature of cognitive test used, different reference groups for PE and GH comparison used or different definitions of PE. However, these findings do suggest differential impacts of PE and GH, which highlights the importance of investigating these complications individually.

The impact of PE has also been shown to be long-term. One study of adult Danish men found that men born after intrauterine exposure to PE had a modest reduction in cognitive performance [133]. Another study demonstrated that while there is a slight decrease in IQ in those born after PE pregnancies, IQ scores are still within a normal range [134]. These findings demonstrate long-term impacts of hypertensive disorders on cognitive outcomes. Further research would benefit from investigating different cognitive domains, and also at earlier age time points, to see when differences begin to occur.

1.7.2 *Preeclampsia, gestational hypertension, and child mental health outcomes*

PE and GH have also been associated with subsequent mental health outcomes in offspring. PE has been associated with a range of negative mental health concerns

such as eating disorders [135], schizophrenia [136] and depression [137]. A study on 14 year old children found those exposed to GH had significantly more internalising and externalising behaviours, while PE was not associated with either of these outcomes, compared to those whose mothers were normotensive [138]. Studies in adults have more varied findings. One study from Norway found no difference in self-reported levels of anxiety and depression in adults aged 20 to 30 years old [139] between those born after PE compared to those not exposed to PE. In contrast, another study demonstrated that those born after PE had 30% higher depressive symptom scores compared to those born after normotensive pregnancies at 60 to 63 years old [137]. However in this same cohort, males born after PE were found to be at lower risk of severe mental health disorders requiring hospitalisation than their normotensive counterparts, while females were unaffected [140]. These findings highlight a connection between PE and GH during pregnancy and long-term mental health outcomes in offspring, suggesting further investigation into mental health following hypertensive disorders is needed.

1.7.3 *Preeclampsia, gestational hypertension and child outcomes: Mechanisms of action*

There is little known about the mechanism by which PE or GH may impact upon brain functioning. PE involves interactions between placenta, immune and cardiovascular systems [141], and it is associated with impaired early placentation, dysfunctional trophoblast development, impaired placental angiogenesis, and exaggerated maternal systemic inflammatory response [142-145]. All of these factors have been postulated to contribute to placental insufficiency, which results in restricted nutrients and oxygen exchange between placenta and fetus, and hence may contribute to poor neurodevelopmental outcomes in those children exposed to PE. For example,

magnetic resonance imaging (MRI) studies have demonstrated that at least five brain regions, including the cerebellum, right and left amygdala, brain stem and temporal lobe, were larger in those children born after PE compared to controls [146]. The authors also found lower blood flow to parietal and occipital lobes in children born after PE compared to controls, with the authors suggesting these differences in brain vasculature preceded the structural changes. This may provide a plausible mechanism for how PE may impact long-term brain development.

Also, a recent study focused on the role of proangiogenic factors vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), which are both important regulators of vascular and neurological development [147]. The authors propose that alterations in circulating concentrations of these factors in the mother during pregnancy may impact both fetal cerebrovascular function and subsequent neurodevelopment.

Additionally, genetic mechanisms have also been suggested as a pathway to poor neurological outcomes [148]. Women who have a family history of PE are at increased risk of developing PE than those who do not have a family history [149], and PE is also associated with long-term vascular changes in the mother [150]. This may suggest a genetic predisposition to difference in vasculature, which could impact the brain, and therefore neurological outcomes.

1.8 Small for Gestational Age

Small for gestational age (SGA) usually refers to a birthweight below the 10th percentile relative to the child's sex and gestational age. It is often, but not always, associated with low birthweight, which refers to those born less than 2500 grams. In line with the DOHaD hypothesis, size at birth has been associated with long-term

health outcomes such as increased risk of cardiovascular disease [151]. Recent evidence also suggests being born SGA is also associated with cognitive impairments and poor mental health in later life [Reviewed in 152, 153].

1.8.1 *Small for gestational age and cognitive outcomes*

Evidence shows the impact of SGA on child's cognitive function is evident from an early age. For example, one study found children born at term but SGA had significantly lower scores on the Bayley Scales cognitive, language and motor outcomes at two years old, compared to those born appropriate for gestational age (AGA) [154]. A cohort study of term born children at five years old also found those born small (<15th percentile) had significantly lower IQ compared to their AGA counterparts, even after controlling for factors such as SES [155].

Studies in older children suggest that those born SGA have poorer school performance and experience more learning difficulties than control counterparts [156-159]. Findings also demonstrate children born SGA have significantly lower IQ scores than AGA counterparts, although these are still within a normal range [160-162]. This highlights the importance of investigating specific cognitive domains to further elucidate in which specific areas these deficits occur, which few studies have done. At age 13, children in a Swedish birth cohort were found to have lower verbal, spatial and numerical test scores compared to AGA counterparts [163]. More specifically, O'Keeffe et al. [164] found children born SGA (<10th percentile) had significantly lower executive function, attention and language when assessed at 14 years old when compared to controls born AGA. These deficits appear to continue throughout childhood, with evidence that those born SGA had consistently lower academic achievement across ages five, 10 and 16 years old compared to those born AGA [165].

However, there are also some studies that suggest SGA is not associated with poorer outcomes. One longitudinal study on seven year old children from New Zealand found no difference in IQ of term born children when comparing those born SGA and AGA [166]. Additionally, a study of over 13,000 term born infants found that those born SGA did not have an increased risk of IQ <85 points, or any difference in academic achievement compared to AGA counterparts [160]. Differences in findings of these studies may be explained by the definition of SGA used, or the inclusion of children exposed to other complications such as PE or PTB.

Differences have also been shown in adults. Those born SGA have lower IQ at ages 19 – 28 years old compared to adults born AGA [167, 168]. Although again IQs were within a normal range, those born SGA also demonstrated significantly lower scores on domains of learning and memory at 21 to 28 years of age [168]. Further studies have demonstrated those born SGA <5th percentile were less likely to have professional or managerial occupations, and were instead more likely to work as unskilled, semiskilled or manual labourers at age 26, and this lead to a significant difference in income between SGA and AGA groups [165]. Interestingly, a more recent study in a Swedish cohort found there was no significant difference in educational attainment at 48 years old between those born SGA and AGA [163]. Together, these findings suggest that while differences between those born SGA and AGA may be minor, they may potentially have long-term implications for future outcomes such as socioeconomic success.

One possible reason for differences in outcomes is the definition of SGA that is used in the study. The World Health Organisation recommends anyone born below the 10th population percentile should be classified as SGA. However, previous studies have also defined SGA as <2.5th percentile [159], <5th percentile [165] and also <15th

percentile [169]. SGA is often, but not always, a sign of intrauterine growth restriction. Smaller mothers are more likely to have smaller babies, and therefore while these babies may be small in relation to population centiles, they are not necessarily growth restricted. Children born <2.5th percentile and <5th percentile, while SGA, are also likely to be growth restricted and of low birthweight. Utilisation of centiles corrected for mother's height, weight, ethnicity, gestational age, parity and child sex may be more accurate to determine those who are growth restricted from those who are just small.

1.8.2 *Small for gestational age and mental health outcomes*

Being born SGA and having a low birthweight have also been associated with an increased risk of behavioural and attention problems, including anxiety, inattention, attention deficit hyperactivity disorder (ADHD) and internalizing and externalizing behaviours [170, 171]. One of the earliest studies to demonstrate these phenomena showed that children born SGA as a result of the Dutch Hunger Winter of 1944-1945, were at significantly increased risk of developing schizophrenia in later life [10].

More recent research has demonstrated that at three years old, there were no significant differences in behavioural, including emotional, problems between those born SGA and AGA as rated by the parent [172]. Similarly, a study by Hall and Wolke found no association between emotional problems and being born SGA in a cohort aged between six and 13 years old [173]. These findings are also in line with a Canadian study which found that although children born SGA had increased internalising and externalising behaviours as reported by the parent, this difference was not significant compared to those born AGA [174]. At 14 years old, children born SGA were found to have higher psychiatric symptoms than controls, but again the

difference was not statistically significant [175]. In contrast to these studies, Yi et al. [161] found children aged between eight and 16 years old born SGA had significantly higher anxiety and depression scores compared to their AGA counterparts. This is also in line with a study on adults which demonstrated that those born SGA have increased mood disorders including anxiety and depression at age 20 to 30 years old compared to those not born SGA [139]. A recent review and meta-analysis, however, suggested that being born SGA was not associated with adult depression [176].

1.8.3 *Small for gestational age and child outcomes: Mechanisms of action*

In SGA babies, a suboptimal intrauterine environment causes underdevelopment of the body and the brain [177, 178]. SGA may be caused by placental insufficiency, which is the most common cause of intrauterine growth restriction [178]. Animal studies demonstrate histopathological changes in brains of those offspring born SGA, demonstrating a direct link between SGA and brain development [179]. Human studies demonstrate structural changes in the brains of those born SGA at 12 months old [180], during childhood [181], and during adolescence [182]. These differences include lower total brain volumes, and reduced cerebral and cerebellar gray and white matter volumes in those born SGA [181-183]. A recent study using functional MRI also demonstrated less activation in the hippocampal region in children born SGA compared to those born AGA, and this was associated with deficits in memory [162]. All of these factors may be contributing factors to the associations seen between SGA and cognitive and mental health outcomes.

1.9 Preterm birth

In developed countries, 6-12% of births are preterm (<37 completed weeks' gestation) [184], and number of survivors has increased due to technological advancements in antenatal and neonatal intensive care [185]. This is cause for concern as children who are born very preterm also tend to be low birthweight (ie. under 2500 grams). Children born preterm have overall more problems at school, less advanced cognitive ability, more behavioural problems and higher prevalence of mental issues when compared to children born at full term [Reviewed in 186].

1.9.1 *Preterm birth and cognitive outcomes*

Infants born preterm have demonstrated significantly lower cognitive abilities compared to full term counterparts at age two years (corrected), as measured by the Bayley MDI [125]. At four years, very preterm (≤33 weeks) children also have an increased risk of cognitive delay and language delay, and were three times as likely to have impairments within multiple domains, including cognitive and language delays [187].

As they age, children born preterm still exhibit differences from their term born peers. A number of studies have demonstrated children born preterm have significantly lower IQ than their term born counterparts [188-190]. Conversely, other studies have found little association between PTB and IQ [191]. In more specific cognitive tests, preterm born children have deficits in reading, spelling, arithmetic and attentional difficulties [190]. School-age children were also at an increased risk of executive function deficits [192-195] and deficits in sensorimotor skills (such as visual-motor integration) [196] and also fine and gross motor development [197].

Differences in cognitive ability are also long lasting, with scores on the Weschler adult intelligence test being significantly lower in extremely preterm (<28 weeks) born adolescents, at age 18 years, compared to matched term born individuals [198]. However, in this study, both groups still had average scores within the normal range. Results from a longitudinal study demonstrated that those born early preterm (<32 weeks) had lower IQ scores than their term born counterparts throughout childhood, and this difference was still apparent at 26 years [199]. Investigations into more specific areas of cognition in adolescents also show deficits in measures of executive function [198, 200-203] and memory [37, 202]. Importantly, preterm born adolescents who go home to greater social disadvantage demonstrate lower scores on tests of general intellectual ability, compared to those who go home to less social disadvantage [37]. This suggests that the early life environment plays an important role in long-term neurodevelopment, highlighting a potentially modifiable factor and the importance of the home environment after PTB.

A recent meta-analysis demonstrated differences in cognitive function between preterm born and term born children has not improved overtime with recent advances in medicine, and also does not improve as children age [204]. These findings highlight the importance of early intervention to improve outcomes for preterm born children.

1.9.2 *Preterm birth and mental health outcomes*

Preterm born children are also at increased risk of behavioural and mental health disorders compared to their term born counterparts. In early childhood, preterm birth is associated with more internalising and externalising behaviours increased attention problems, and emotional problems [187, 188, 205-208]. At seven years old, very preterm born children (<30 weeks) had three times the odds of meeting the

criteria for diagnosis of any psychiatric illness compared to those children born at term [209]. A recent study demonstrated children who were born extremely preterm (<28 weeks) without severe disabilities had increased risk of anxiety and obsessive compulsive disorder compared to term born counterparts at 11 years old [210]. This is also supported by a recent meta-analysis that found adolescents aged from 11-20 years who were very preterm (<32 weeks) and with very low birthweight had nearly double the risk of developing clinically significant anxiety problems compared to a group born at term with normal birthweight [211]. These findings are of concern as mental illness during adolescence has been shown to precede the development of subsequent mental illness in adulthood [212-214]. Interestingly, a recent review demonstrated PTB was not associated with depression in later life [176], suggesting there may be different impacts of PTB on later life anxiety and depressive symptoms. If these symptoms can be identified early, this could lead to early intervention for those children born preterm.

Much of the research into preterm birth focuses on those born very preterm (<32 weeks), often with low birthweight as a compounding factor. While those born earliest are at greatest risk of poor neurodevelopmental outcomes, those born late preterm still may be at increased risk for mental health disorders [215]. Therefore, studies should also include late preterm born children in order to investigate differences between preterm and term borns.

Findings also suggest that SES compounds the impacts of preterm birth on mental health. In a Dutch longitudinal study of preterm born children, behaviour and emotion were measured in four year old children by completion of the child behaviour checklist, and SES was determined based on family income, occupation level of parents and their highest education level [216]. Results suggested that those born preterm had an increased risk of behaviour problems compared to term born [216].

These findings were compounded by SES, with those preterm children who were born into low SES having a significantly higher chance of higher total problems scores than those born preterm into high SES [216]. This suggests those PTB children in low SES may have very different outcomes to those born in high SES, highlighting the importance of investigating cohorts in low SES areas.

Majority of these studies investigate the mental health of the child on scales rated by a parent, generally the mother. However, parent report of child anxiety can be impacted by the parent's own experience of mental health issues, and therefore this may lead to parents over or under rating their child's mental health or behavioural symptoms [217]. A recent study in term born adolescents aged 16 to 17 compared self-reported to parent reported levels of anxiety in a cohort of preterm born adolescents [218]. Results demonstrated that mothers of adolescents born preterm reported significantly higher anxiety symptoms, particularly in social phobia domain, compared to mothers of adolescents born at term. However, there was no significant difference in anxiety symptoms when reported by the child themselves [218]. This suggests that the child and mother's interpretation of anxiety may be different, and hence the child's own perception of their own anxiety symptoms should be taken into account.

1.9.3 *Preterm birth and child outcomes: Mechanisms of action*

PTB is associated with alterations in brain development due to developmental and destructive mechanisms including inflammation of the brain and ischaemia, which can cause brain injuries including white matter lesions, ventricular dilation, reduced white matter volume, smaller hippocampal volume, and atrophy of the corpus callosum [219-223]. These brain injuries may lead to altered brain development with persistent changes in brain networks [224, 225], and this may in turn limit the

neuroplasticity of the brain [226]. Even at 34 weeks' gestation, which is considered late preterm birth, the cortical volume of the brain is approximately 50% and total brain volume is approximately 65% of the term brain, with much of the structural maturation yet to occur [227]. This demonstrates even those children born late preterm have underdeveloped brains compared to those born at term, suggesting a plausible mechanism for reduced cognitive function and increased risk of behavioural and mental health issues in preterm born children. Significant positive correlations between gestational age and brain volume at age 8–10 years suggest these structural differences are long-term [189]. PTB has also been associated with changes in frontal and temporal lobes, areas of the brain which affect attention, memory and executive function [228, 229].

1.10 Gestational Diabetes Mellitus

GDM is defined as elevated glucose in the blood during pregnancy, which usually resolves after birth. It currently affects approximately 12% of pregnancies in Australia [230]. GDM has been associated with increased risk of adverse pregnancy outcomes such as macrosomia, large for gestational age (LGA) babies, caesarean section, neonatal hypoglycaemia, shoulder dystocia or birth injury and admission to neonatal care unit [231]. Women are at greater risk of GDM if they carry excess weight, specifically a body mass index (BMI) over 30, have a mother or sister who had GDM, if their age is greater than 25, or if they are not Caucasian. Treatment for diabetes often involves diet modification, with insulin if needed. More recently, metformin has also been used as a treatment in place of insulin. Metformin is easier to take as it is tablet form, as opposed to insulin which needs to be injected, and there is no difference in perinatal complications when compared to insulin [232]. A large

number of epidemiological studies have demonstrated links between GDM in mothers and an increased risk of these mothers developing type 2 diabetes later in life [233]. GDM has also been associated with adverse future health outcomes in children, such as an increased risk of obesity and type 2 diabetes in later life [234]. These findings suggest that intrauterine exposure to GDM may impact long-term development.

1.10.1 *Gestational diabetes mellitus and cognitive outcomes*

More recently, GDM has also been associated with neurodevelopmental outcomes in offspring [Reviewed in 235]. Children born following GDM in pregnancy demonstrate poorer scores on the Bayley MDI at two years of age [236-238]. Results investigating long-term impacts on child neurodevelopment are more inconclusive. One study found children aged five to 12 years born after GDM had slightly lower IQ, but not significantly different to controls whose mothers did not have GDM [239]. However, a larger study from the Avon Longitudinal Study of Parents and Children (ALSPAC) study found those children exposed to GDM had significantly lower IQ at age eight, even after controlling for factors such as child sex, maternal age, smoking during pregnancy and maternal education [240]. Another study on an Indian cohort of children aged 8-10 found that children exposed to GDM actually had better learning, long-term memory retrieval, and verbal ability compared to controls who were not exposed to GDM after controlling for factors such as child age, child sex, gestational age at birth, maternal age and parent's education and SES [241]. Differences between these studies could be due to differences in study location or SES between cohorts, or also the definition of GDM. Ornoy et al. [239] and Fraser et al. [240] utilised the World Health Organisation definition of GDM, whereas Veena et al. [241] defined GDM using the Carpenter-Coustan criteria. A recent review and meta-analysis also

concluded that while infants born to women with GDM demonstrate lower mental and psychomotor development, evidence is more scarce in adolescents [235]. Two studies have investigated the impact of GDM on long-term school achievement outcomes, and found those children exposed to GDM had lower average school grades compared to those adolescents who were not exposed to GDM [240, 242]. Cognitive functioning between those who were and were not exposed to GDM were similar in adult male conscripts [243].

1.10.2 *Gestational diabetes mellitus and mental health outcomes*

There has been very little research investigating the impact of exposure to GDM on long-term mental health. Some previous research has suggested that children born following GDM have an increased risk of mental health conditions such as schizophrenia [136, 244]. GDM was not associated with internalising or externalising behaviours after adjustment at two years of age [245]. However, children who were exposed to GDM were found to be at increased risk of ADHD diagnosis at age six, but this increased risk was only seen in low SES individuals [246]. This highlights the importance of investigating impacts of complications in those most at risk populations, such as low SES groups.

1.10.3 *Biological mechanisms of gestational diabetes mellitus*

The exact mechanisms that underlie the relationship between GDM and subsequent child cognitive function are unknown. Several factors may be involved in imbalanced developmental growth of the fetus, including maternal insulin and glucose. In diabetic pregnancies, hyperglycaemia (high blood sugar) in the mother results in the fetus being exposed to higher amounts of glucose. Animal studies demonstrate those with poor glucose control are at increased risk of damage to certain brain regions

including the hippocampus (important for memory) because of fetal iron deficiency, chronic hypoxia and hypoglycaemia [236, 237], which suggests GDM is associated with impaired brain development in at least one area of the brain. Furthermore, a study in humans investigated the impact of glucose ingestion in pregnant women and the association with fetal brain activity [247]. Results suggested that fetal brain responses were slower in offspring of women with GDM compared to fetuses of women with normal glucose-tolerance [247]. This suggests that GDM is associated with differences in brain development, and therefore may provide reason for the link between GDM and future neurodevelopmental outcomes.

Interestingly, one study has suggested that GDM effects on offspring outcomes are due to familial characteristics rather than an intrauterine mechanism. This study investigated educational achievement at age 16 years, and IQ at 18 years, comparing siblings and non-siblings. They found among non-siblings, those who were exposed to GDM *in utero* had lower cognitive scores, even after adjustment for factors including maternal age at birth and education [248]. However, when comparing cognitive function of those exposed to GDM within siblingships, there was no difference found. This suggests that other factors such as SES and genetics may play a large part in the outcome of those children exposed to GDM.

GDM can be treated with diet control, insulin and/or metformin. If undiagnosed and untreated in time, GDM can result in macrosomia, or a large for gestational age baby [249]. However, recent evidence suggests that treatment of GDM is associated with decreased birthweight and less macrosomia among other outcomes [250, 251]. Furthermore, a study investigating neurodevelopment of infants exposed to GDM found no significant difference in their mental or psychomotor development at age two years in those who were treated with insulin or those treated with metformin

[252]. Together, these findings suggest that any treatment of GDM would potentially decrease the likelihood of neurodevelopmental deficits.

1.11 Limitations of previous studies

While these studies suggest early life adversity is associated with poorer neurodevelopment, there are a number of limitations. Firstly, many of these studies investigate overall cognition, or only one specific domain of cognitive functioning. General measures of cognition, such as IQ, can provide a broad measure of cognitive functioning, however, cognition is a broad construct that contains various domains, including executive function, attention and memory, and each of these areas of functioning may be selectively intact or impaired [253]. Findings demonstrate that although children can have normal IQs, they can have poorer working memory and cognitive flexibility which is associated with difficulties in maths [254]. Difficulties in reading and writing have also been associated with poor inhibitory control and working memory [255-257]. This shows how deficits in particular domains of cognitive function may impact upon overall academic achievement. Ideally, multiple different domains of cognitive functioning would be tested in the same cohort to investigate differences between different domains of cognition within the same group of participants. Secondly, often only one or two pregnancy complications are investigated within a cohort. If multiple complications were investigated within the same cohort, then this would provide greater information on which complications were the most relevant to predicting poor neurodevelopmental outcomes. Thirdly, reports of child mental health are most often reported by the mother of the child. Since previous research suggests that the parent's mental health may impact their scores of their child's behaviour, this highlights the importance of also considering the child's self-

reported mental health symptoms. Finally, many cohort studies focus on participants from a broad range of SES backgrounds. Due to low SES compounding the impacts of early life adverse events, it is important to further investigate participants who are in low SES circumstances, as they may benefit the most from early interventions.

1.12 The SCOPE cohort

The SCreening fOr Pregnancy Endpoints (SCOPE) cohort was an international, multicentre prospective cohort study aimed at developing screening tests for risk for pregnancy complications PE, SGA and spontaneous PTB. In total, 1164 nulliparous pregnant women with singleton pregnancies were recruited from September 2005 to September 2008 at the Lyell McEwin Hospital in Adelaide (see Chapters 2 and 3 for further details). Participants in the study had relatively low SES, with a median of 25 on the scale which ranges from 10-90, with higher scores indicating higher SES levels. There were also a high percentage of pregnancy complications, with approximately 40% of all pregnancies having at least one of the five major complications of pregnancy. Mental health issues were also overrepresented in this cohort, with antenatal depression (17%) and anxiety (25%) levels reported being much higher than those of the national average (approximately 10%) [258]. These factors make this cohort ideal to investigate the associations between maternal antenatal depression, pregnancy complications and child cognitive and mental health outcomes.

1.13 Aims and hypotheses

The aim of this thesis is to investigate the impact of early life adverse factors (poor maternal mental health during pregnancy and pregnancy complications) on child

anxiety and cognitive function at 8–10 years old in a low socioeconomic birth cohort. Specifically, the research in this thesis aims to:

1. Investigate the association between maternal antenatal depression and child mental health (namely anxiety and depression), and investigate differences between mother reported and child reported anxiety and depression
2. Investigate associations between maternal antenatal depression and child cognitive function, specifically in separate cognitive domains including executive function, memory and reaction time
3. Investigate associations between pregnancy complications (PE, SGA, PTB, GDM and GH) and child cognitive function, again in separate cognitive domains of executive function, memory and reaction time
4. Investigate associations between pregnancy complications (PE, SGA, PTB, GDM and GH) and child self-reported anxiety and depression

Based on previous literature, it was hypothesised that:

1. Antenatal depression would be associated with increased child anxiety and depression scores
2. Antenatal depression would be associated with decreased child cognitive functioning
3. Pregnancy complications would be associated with decreased child cognitive functioning
4. Pregnancy complications would be associated with an increase in child anxiety and depression scores

Chapter 2:

Methods

2.1 Participants

Participants were from the Adelaide arm of the SCreening fOr Pregnancy Endpoints (SCOPE) birth cohort. SCOPE was an international, multicentre prospective cohort study which aimed to develop screening tools to predict risk for pregnancy complications including preeclampsia (PE), small for gestational age (SGA) and spontaneous preterm birth (PTB). In total, 1380 nulliparous pregnant women with singleton pregnancies were recruited between September 2005 and September 2008 at the Lyell McEwin Hospital in Adelaide, South Australia of whom 1164 women had ongoing pregnancies at 20 weeks' gestation. Women were excluded from the study if they were deemed to be at high risk of developing a pregnancy complication due to other underlying health conditions such as chronic hypertension, diabetes or systemic lupus, if they had previously had three miscarriages and/or terminations, if their pregnancy was complicated by a major fetal anomaly, or if they received any intervention which may impact on pregnancy outcome (e.g. aspirin or progesterone).

Women were initially recruited and interviewed by SCOPE research midwives at 15±1 weeks' gestation and then again at 20±1 weeks' gestation. Data obtained included demographics, smoking, height, weight, medical and obstetric history, and systolic and diastolic blood pressure. The socioeconomic status (SES) of the participants was measured using the socioeconomic index (SEI), which was calculated using the New Zealand SEI. This gave a validated measure of the participant's socioeconomic level, and was derived from the occupation of the participant. The scale ranged from 10-90, with lower scores indicating lower SEI, and hence greater disadvantage [259]. The Edinburgh Postnatal Depression Scale (EPDS) was administered at both 15±1 and 20±1 weeks' gestation as these were the time points for SCOPE visits (Appendix A). The EPDS is not a diagnostic tool, but rather a screening

tool for depression. Although this scale was originally developed for use during the postnatal period, it has since been validated for use during the antenatal period [260], and this scale has been used at the Lyell McEwin Hospital for approximately 18 years during routine antenatal care. Scores on the EPDS range from 0–30, with higher scores indicating greater levels of depression. Scores of 13 or more indicate a high likelihood of depression, and warrant further investigation [261]. Participants were then followed up prospectively, with research midwives recording pregnancy outcome and birth outcomes. Further methods of the SCOPE study are detailed here [262, 263].

For the follow-up of the SCOPE cohort presented in this thesis, contact with the women was attempted 8-10 years after the delivery of the first child. The study team who were involved in recruitment and testing was comprised of two PhD candidates, including the current candidate. Women were invited to be part of the new study, and attend a follow-up appointment. Contact through phone calls was attempted three times for each woman. This was done at different times of the day over a number of weeks. If women could not be contacted over the phone, a text message was sent to the most recently available active mobile number briefly describing the follow-up and asking them to return the text/call if they were interested. Of the 1164 participants in the initial SCOPE study, 25 participants were removed from the contact list for various reasons (further detailed in Chapter 3, Figure 3.1). Of the remaining 1139 participants available to call, 505 participants could not be contacted. This resulted in 634 participants who were spoken to, of which 420 booked appointments, with 270 attending appointments. The most common reasons for not booking an appointment were not being interested in taking part in research, or having moved interstate/outside of the Adelaide area. Three of the participants expressed an interest in participating although had moved away from Adelaide, and therefore could not attend in person.

These women were sent questionnaires to complete and return to the study co-ordinators. This resulted in data being collected from a total of 273 mother-child pairs.

During the follow-up appointment, women and children provided written consent and assent, respectively, to take part in the study (Appendices B and C, respectively). The follow-up appointment was approximately two hours, and included cardiovascular measures (not presented in this thesis), collection of demographic information and neurodevelopmental assessments. As part of the neurodevelopmental follow-up, both mothers and children participated in cognitive testing and filled out a number of questionnaires (further detailed below). The current candidate was responsible for administration of all cognitive tests and mental health questionnaires.

A total of 270 participants attended appointments in person, while three completed only the questionnaires. Completion of the cognitive tests and questionnaires required the child to understand the tests and questions, respectively. Of those involved in the follow-up, three (1.1%) children were unable to complete any of the cognitive tasks or questionnaires due to autism. A further six (2.2%) did not complete one or more of the cognitive tasks due to technological issues (n=2, 0.7%), difficulty reading (n=2, 0.7%) or autism (n=2, 0.7%). A further nine children (3.2%) had incomplete data for one or more of the questionnaires, thus totals could not be created, and therefore were excluded from further analysis.

2.2 Demographic information at follow-up

Demographic information was collected via interviews with participants. Mothers were asked to report their current marital status, education level, occupation, employment status and family income. Details on obstetric history, medical history, physical activity and current intake of smoking alcohol and drugs were also collected.

Mothers were also asked to report on their child's current school grade, medical history and physical activity. Height and weight of both mother and child were measured at the appointment.

2.3 Cognitive testing

Cognitive performance was assessed using five tests from the standardised Cambridge Neuropsychological Test Automated Battery (CANTAB) connect system [264]. This system has been validated for use in children, and has demonstrated good applicability for evaluating children who may have weak verbal skills [265]. The CANTAB has high sensitivity, and has been used previously to discriminate between those with mild cognitive impairment and controls with normal cognitive performance [266]. The CANTAB battery included tests of executive function, memory and reaction time. The CANTAB system utilises a touch screen tablet, with automated administration of tests to ensure standardised testing across participants. Participants were seated at a desk with the tablet in front of them, where they were instructed to complete a series of five tests in a pre-set sequential order. The tests took approximately 35 minutes to complete.

2.3.1 *Test 1: Attention Switching Task*

The attention switching task (AST) was used to measure executive function, namely attention and cognitive flexibility. In the first block, participants were presented with an arrow in the middle of the screen, with a single word instruction, "direction", centrally positioned above the arrow at the top of the screen (Fig. 2.1A). Two 'buttons' were positioned at the bottom of the screen. The arrow appeared, randomly pointing left or right, and participants were instructed to press the button

corresponding to the direction the arrow was pointing. That is, to press the left button if the arrow was pointing left, and vice versa. This block included eight practice assessments with feedback.

In block two, participants were again presented with the instruction “direction” at the top of the screen, although this time the arrow appeared on the left or right hand side of the screen (Fig. 2.1B). Participants were instructed to again press left or right depending on the direction the arrow was pointing, ignoring the position of the arrow on the screen. This block included eight practice trials with feedback, followed by 40 assessed trials.

In block three, participants were presented with the same arrow stimulus, but this time the instruction at the top read “side” (Fig. 2.1C). Participants were instructed to ignore the direction of the arrow, and press left or right depending on which side of the screen the arrow now appeared. This block included eight practice trials with feedback, followed by 40 assessed trials.

In block four, the instruction randomly switched between “direction” and “side”, and participants were instructed to respond accordingly. This block included 10 practice trials and 80 assessed trials. Throughout the task, participants were instructed to go as fast as they could without making mistakes. Outcomes of interest were side only block errors, direction only block errors, total correct (over all assessed trials), median latency across all assessed trials, switching block errors and switching block median latency.

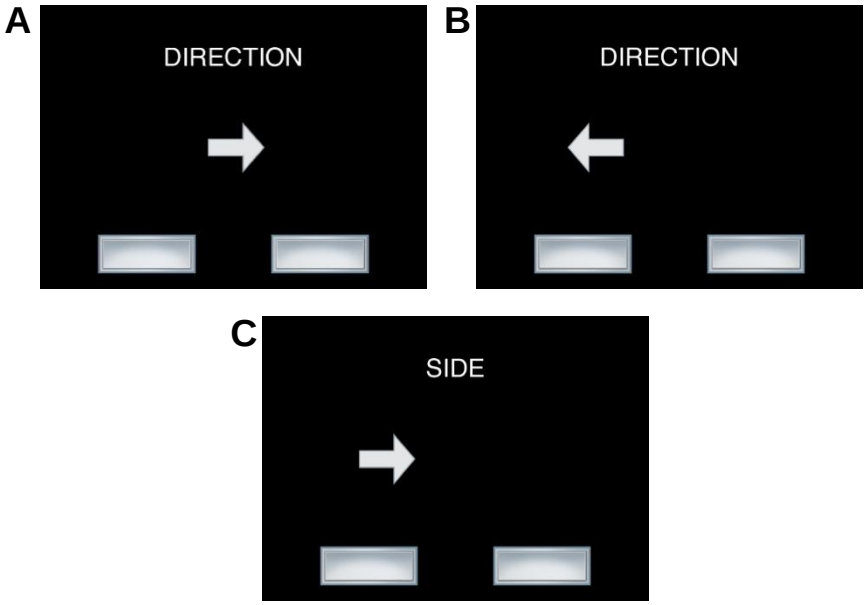

Figure 2.1 Attention switching task screenshots. (A) The first practice block where the arrow appeared in the middle of the screen, and the participant was asked to press left or right depending on which direction the arrow was pointing; (B) Participant was presented with 'direction' instruction, and had to press the left or right button depending on which direction the arrow was pointing; (C) Participant was presented with 'side' instruction, and had to press the left or right button depending on which side of the screen the arrow appeared on.

2.3.2 *Test 2: Delayed Matching to Sample task*

The delayed matching to sample (DMS) task was used to assess visual delayed memory. Participants were presented with a target pattern (Fig. 2.2A) and instructed to remember the pattern. Four patterns then appeared in the boxes across the bottom of the screen, each with different shapes or colours (Fig. 2.2B). Participants were instructed to select which box displayed the pattern that matched the original target pattern by touching the corresponding box, and were given feedback on their performance (Fig. 2.2C). When the correct pattern had been selected, the next trial began. This trial presented another target pattern, which disappeared before the presentation of the four boxes displaying possible responses below (Fig. 2.2D). If an incorrect pattern was selected, participants had to keep selecting until the correct pattern had been identified. Four other practise trials were presented similarly: the target and potential responses were presented simultaneously, and the target and presentation boxes were presented with delays of 0, 4 and 12 seconds between target and possible responses.

After the practise sessions, the assessment block began. This comprised the random presentation of all sequences completed in the practise trials (ie. simultaneous and delayed presentations). Each sequence was presented five times in random order, so the participant was unaware how long they would need to remember the next pattern. Outcomes of interest on this task were the total correct across all trials, total correct on each of the simultaneous, 0 second, 4 second and 12 second delays, and the median correct latency (ie. the latency between the presentation of the response options and the participant selecting the correct box on their first attempt).

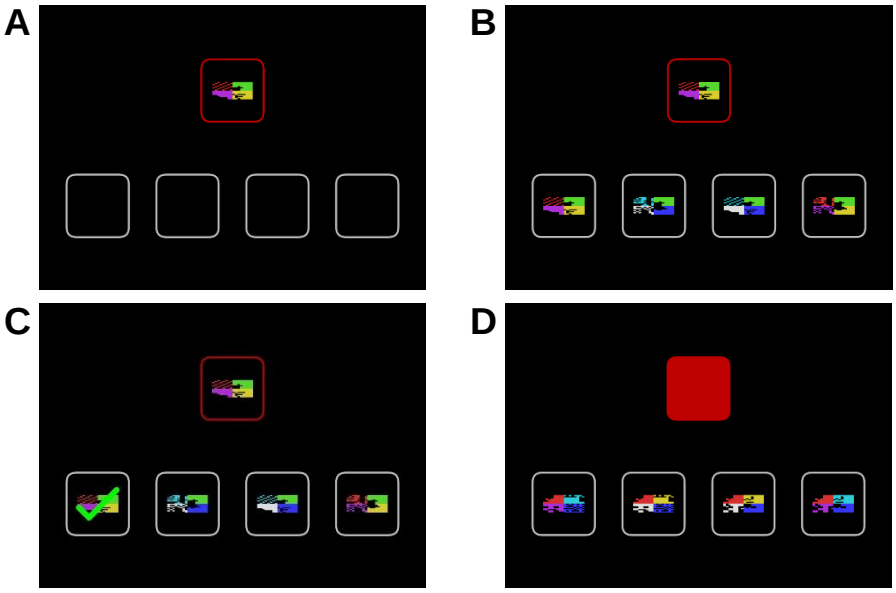

Figure 2.2 Delayed matching to sample task screenshots. (A) The initial presentation of the target pattern; (B) Participants then had to identify the matching pattern from the choices presented in the lower row; (C) The participant received feedback for a correct response. (D) In more complex trials, the target pattern was covered prior to the pattern options appearing in the row below after delays of either 0, 4 or 12 seconds.

2.3.3 *Test 3: Paired Associates Learning task*

The paired associates learning (PAL) task was administered to measure visual memory and new learning. Participants were presented with boxes around the edge of screen which opened and closed in random order, one at a time, to reveal different patterns (Fig. 2.3A). Each pattern then appeared in the centre of the screen (Fig. 2.3B), and participants were asked to touch the box on the screen which corresponded to that pattern. This task became more difficult, with the number of boxes (and patterns) increasing from two, to 4, 6, and 8 patterns. Participants advanced to the next level when they successfully identified the location of each pattern. If the incorrect location was selected at any time, the level was repeated for a maximum of four attempts, before the task ended. Performance was assessed by the number of correct boxes selected on the first attempt, the total number of errors for the whole task and total errors made on each level (both adjusted for levels reached) and number of levels completed.

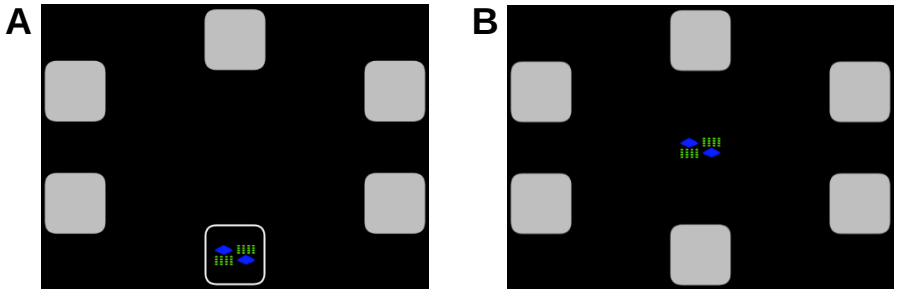

Figure 2.3 Paired associates learning task screenshots. (A) Boxes around the screen opened one by one revealing patterns inside, and participants were instructed to remember which pattern was in which box; (B) Patterns were then presented in the middle of the screen to be matched with the box in which it appeared.

2.3.4 *Test 4: Spatial Working Memory task*

The spatial working memory (SWM) task was used to measure spatial working memory. Participants were presented with a screen of coloured boxes, with a column down the right hand side (Fig. 2.4A). Participants were instructed to find tokens "hidden" under each box, however, only one token was hidden at a time. Once found, a token would not be found again under that box, necessitating the participant to remember the boxes were tokens had been found previously. The participant then commenced the 'search' for the tokens, by touching the boxes on the screen, one at a time. Once a token was found (Fig. 2.4B), the participant selected the home bar to collect the token, and this was repeated until all tokens had been discovered (Fig. 2.4C). The task contained a practice trial, with three boxes, before the assessed levels containing 4-, 6- and 8-box problems. The outcomes of interest were the total number of between errors (the number of times a participant incorrectly revisited a box where a token had already been found) across all trials, and between errors separately on the 4-, 6- and 8-box problems. A strategy score was also generated, which reflected the degree to which the participant had adopted a strategy to remember the boxes where tokens had been found.

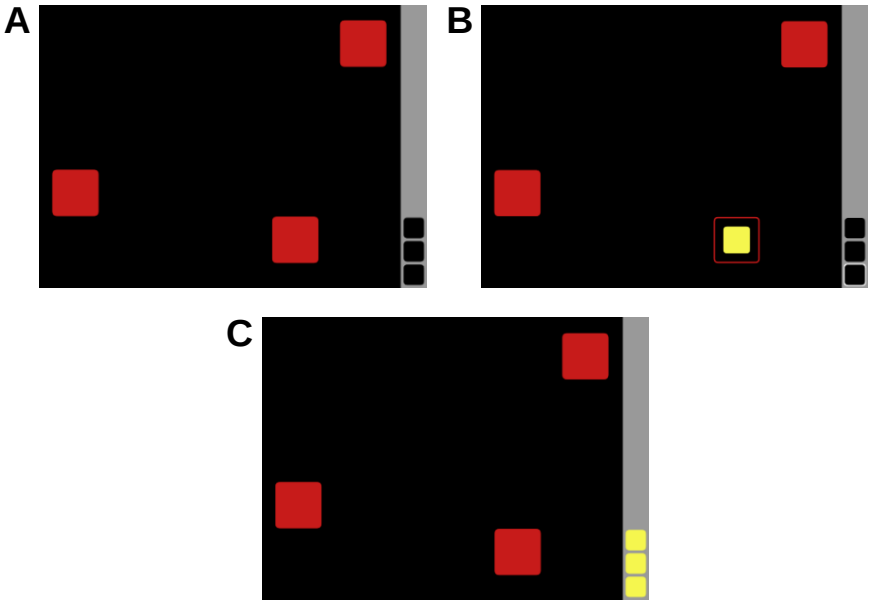

Figure 2.4 Spatial working memory task screenshots. (A) Participants initially presented with this screen and were instructed to search under the red boxes for tokens by touching on each box one at a time; (B) When the correct box was touched, the yellow token appeared and was moved to the bar on the right of the screen. For the rest of this trial, no token will appear under this box again; (C) Once all tokens were collected in the home bar (right of screen), participants moved on to the next level.

2.3.5 *Test 5: Reaction Time task*

The reaction time (RTI) task measured reaction latency and movement time. This task contained two levels: a simple and a five choice reaction time task. Firstly, the participants were shown a button on the bottom of the screen and a circle at the top of the screen (Fig. 2.5A). They were instructed to hold their finger on the bottom button until the circle at the top flashed yellow (Fig. 2.5B). They were then instructed to move their finger as quickly as possible to touch inside the circle. Participants were first presented with a practice block of 10 presentations, followed by 30 assessed presentations. In the simple reaction time, the stimulus always appeared in the same place, however, in the five-choice task the stimulus could appear in any one of five circles (Fig. 2.5C). Performance outcomes for this task included the median 'reaction time', with reaction time defined as the duration of time between the presentation of the yellow circle and the release of the button. The median 'movement time' was also assessed, with movement time defined as the time taken to touch the yellow spot after the release of the button.

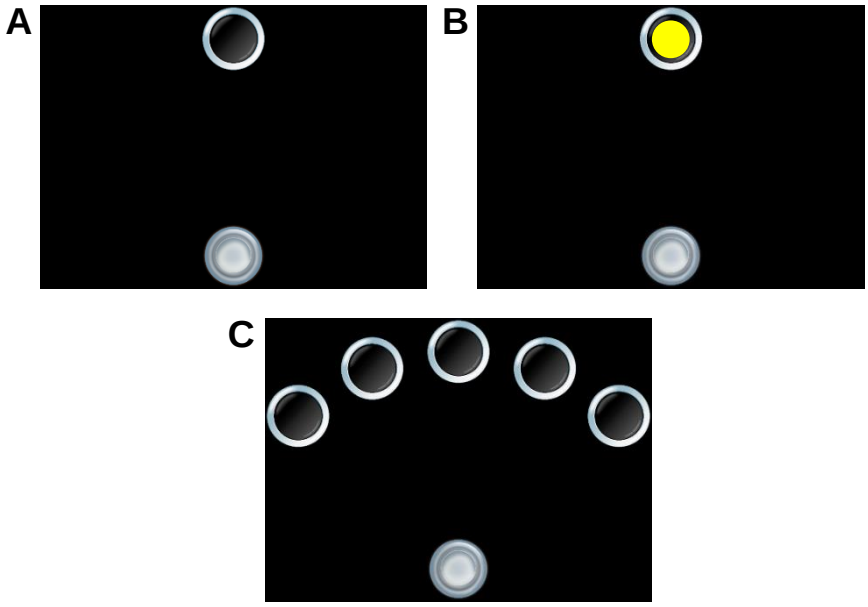

Figure 2.5 Reaction time task screenshots. (A) Participants were instructed to hold their finger on the button at the bottom of the screen and wait for a yellow dot to appear; (B) When the yellow dot appeared, participants had to release the button and touch the yellow dot as fast as they could; (C) This same process was then repeated with the yellow dot appearing in one of five locations, as a five-choice reaction time test.

2.4 Mental Health Questionnaires

Questionnaire data were collected from the mothers and children after cognitive testing was complete. Each participant was presented with questionnaires in paper format in the same order. Mothers and children completed questionnaires separately to avoid discussion of answers. The mother completed the Spence Children's Anxiety Scale (SCAS) and the Child Anxiety Life Interference Scale (CALIS) about their child, and completed the Depression, Anxiety and Stress Scale (DASS) about themselves. Children completed the SCAS, CALIS and the Center for Epidemiological Studies Depression Scale for Children (CES-DC) about themselves. The candidate assisted children with reading of words where necessary.

2.4.1 *Spence Children's Anxiety Scale*

The Spence Children's Anxiety Scale (SCAS) provides a measure of child anxiety symptoms by both parent report (Appendix D) and child report (Appendix E). This questionnaire has been validated for use in children aged 8-12 [267, 268], and has been previously used to distinguish clinically anxious children from non-anxious children [269]. The scale assessed six domains of anxiety, including panic/agoraphobia, separation anxiety, physical injury fears, social phobia, obsessive compulsive behaviours, and generalised anxiety (Table 2.1). Parent and child reports contain parallel items with questions regarding "my child" or the "self" respectively. The parent report contained 38 items. The child scale contained 44 items, however, six items were not scored as they were positive items included to reduce negative response bias. Each item was rated on a scale of 0-3, where 0 was "never", 1 was "sometimes", 2 was "often" and 3 was "always". The maximum possible total score was 114, with higher scores indicating increased anxiety.

Table 2.1 Subscales of the Spence Children's Anxiety Scale (SCAS) questionnaire with example questions. See Appendices D and E for full scales.

Subscale	**Example question from child questionnaire**	**Maximum score for subscale**
Panic/Agoraphobia	I suddenly start to tremble or shake when there is no reason for this	27
Separation Anxiety	I worry about being away from my parents	18
Physical Injury fears	I am scared of being in high places or lifts (elevators)	15
Social Phobia	I worry what other people think of me	18
Obsessive Compulsive	I have to keep checking that I have done things right (like the switch is off, or the door is locked)	18
Generalised Anxiety	I worry about things	18

2.4.2 *Child Anxiety Life Interference Scale*

The Children's Anxiety Life Interference Scale (CALIS) assessed the impact of the child's fears and worries with their daily life. The CALIS was developed to investigate the impact of anxiety on different aspects of children's lives such as home life, school, social life and involvement in activities. It has been validated for use in children aged 6-17 years old, and demonstrates good internal consistency, and good convergent and divergent validity [270]. This scale included both a parent report (15-item; Appendix F) and a child report (9-item; Appendix G). Both parent and child reports included nine identical items, which referred to 'your child' or 'you' respectively. The parent report also included six extra items to assess the impact the child's anxiety had on the parent's life. Each item was rated on a 5-point Likert scale, where 0 was "not at all", and 4 was "a great deal". Scores were calculated for total anxiety interference, as well as subscales of child anxiety inside the home, outside the home and parent life (parent report only; see Table 2.2). Child total scores ranged from 0-36, while parent total scores ranged from 0-64, with higher scores indicating greater anxiety interference.

Table 2.2 Subscales of the Child Anxiety Life Interference Scale (CALIS) with example questions. See Appendices F and G for full scales.

Subscale	**Example item from scale**	**Maximum score for subscale**
At home	Do fears and worries upset you?	16
Outside home	How much do fears and worries make it difficult for you to do the following things; Be with friends outside of school?	20
Parent life (parent report only)	How much do your child's fears and worries interfere with your everyday life in the following areas; Your relationship with your partner or a potential partner?	28

2.4.3 *Center for Epidemiological Studies Depression scale for Children*

The Center for Epidemiological Studies of Depression scale for Children (CES-DC) was used to measure child depressive symptoms (Appendix H). This scale is a modified version of the Center for Epidemiological Studies of Depression scale, originally developed by Radloff et al. [271] to measure depressive symptoms in adults. The CES-DC demonstrates high reliability and validity [272, 273]. The CES-DC is a 20-item self-report, with each item scored on a 4-point Likert scale. Responses ranged from "not at all" to "a lot". Scoring on 16 of the items referred to the presence of a depressive symptom during the past week, while scoring on the remaining four statements referred to positive items, which were therefore reversed scored. Total scores ranged from 0-60, with higher scores indicating higher depressive symptoms.

Developers of the CES-DC suggest scores above 15 indicate significant depressive symptoms in children [272, 273]. At time of consent, mothers were asked to provide the name of their child's general practitioner (GP) should their child's scores indicate they may benefit from professional help. Therefore, a letter (Appendix I) was sent to the GP of any child who scored 15 or above and whose GP details had been given to study co-ordinators.

2.4.4 *Depression, Anxiety and Stress Scale*

The 42-item Depression, Anxiety and Stress Scale (DASS) was used to assess depression, anxiety, and stress symptoms in the mother (Appendix J). The DASS has been validated for use in adults [274]. There are a total of 42 questions on the DASS, where depression, anxiety and stress each correspond to 14 items each (example items, Table 2.3). Each item was rated on a 4-point Likert scale, where 0 was "did not apply to me at all", and 3 was "applied to me very much, or most of the time". Total scores ranged from 0-42 for each domain. Scores were created for each of the three subscales, with higher scores on each domain indicating increased severity of symptoms. At time of consent, women were asked to provide the name of their GP should they wish for them to be contacted if their score may suggest they could benefit from professional help. Women who provided their GP's name and scored high enough to be classed within the severe or extremely severe category for any of depression (scores of 21 and over), anxiety (scores of 15 and over) or stress (scores of 26 and over) domains had letters sent to their GP (Appendix K). All women were also provided with a copy of National Helplines (Appendix L) at the beginning of the appointment as a precaution in case the questionnaires completed at the appointment brought up any issues for either themselves or their child.

Table 2.3 Example items from different domains of the Depression, Anxiety and Stress Scale (DASS). See Appendix J for full scale.

Domain	**Example item**
Depression	I felt I had nothing to look forward to
Anxiety	I found myself in situations that made me so anxious I was most relived when they ended
Stress	I found it hard to wind down

2.5 Ethical Approval

Ethics approval for the SCOPE follow-up project was granted by the University of Adelaide Human Research Ethics Committee (approval number: HREC/15/WCHN/126). Site specific approval was granted for Lyell McEwin Hospital (approval number: SSA/15/NALHN/88). All women provided written consent for themselves (Appendix A) and their child (Appendix B), and children provided written assent (Appendix B) before participating in the follow-up.

2.6 Statistics

Participants were given the same ID number as they were given in the initial SCOPE study; mothers had an 'M' added to the number, while children had a 'C' added. This allowed for easy distinction between mother and child outcomes, and also simple linkage with de-identified data from initial recruitment. Cognitive data were stored on the CANTAB secure cloud based platform. This was subsequently downloaded onto an excel spreadsheet and transferred to SPSS. Questionnaire data were entered onto Redcap for secure storage. Data were analysed using SPSS v25.

Normality of the data were assessed using histograms and Q-Q plots. Categorical variables were compared between groups using Chi-square and Fisher's exact tests. Univariate analysis of normally distributed data between two groups was analysed using t-tests, while non-normally distributed data were analysed using Mann-Whitney U and Kruskal Wallis tests. For multivariate analysis, normally distributed data were analysed using linear regressions. The majority of questionnaire and cognitive outcome data were found to follow Poisson distributions, therefore were analysed using Poisson regressions.

Chapter 3:

Recruitment of participants for the SCreening fOr Pregnancy Endpoints (SCOPE) follow-up study

3.1 Abstract

Introduction: Cohort studies can be subject to attrition bias overtime. The SCreening fOr Pregnancy Endpoints (SCOPE) study recruited women during pregnancy. This chapter analyses the cohort at the 8-10 year follow-up to assess differences between the original and follow-up cohorts to assess for potential attrition bias.

Method: The SCOPE study recruited 1164 pregnant women at 15±1 weeks' gestation between September 2005 and September 2008. Data collected included information on demographics, smoking status, alcohol and drugs consumption. Women were invited back to participate in follow-up study via phone 8-10 years after the birth. We therefore compared birth demographics between those who *attended* the follow-up, those who were *contacted but did not attend*, and those who were *uncontactable*, to investigate bias due to non-participation.

Results: Those who attended the follow-up study were older at the birth of their child, and had higher socioeconomic status than those who were *contacted but did not attend*, and those who were *uncontactable.* Those who *attended* were also more likely to be Caucasian, overweight or obese, engaged in full or part-time work, and less likely to be smoking or taking drugs at 15 weeks' gestation. They were also had lower rates of depression compared to the *uncontactable* and *contacted but did not attend* groups. There were no significant differences in infant demographics between the three groups, including in infant sex, gestational age, birthweight or birthweight centile.

Conclusion: The SCOPE study had attrition bias similar to those described by other follow-up studies. However, due to the fact that all participants recruited in this study are from low socioeconomic backgrounds, this cohort can still provide valuable insight into which early life adverse factors may be most relevant to predicting future outcomes within a disadvantaged population.

3.2 Introduction

The SCreening fOr Pregnancy Endpoints (SCOPE) study was an international, multi-centre prospective cohort study with the primary aim of developing screening tests to predict risk for pregnancy complications such as preeclampsia (PE), small for gestational age (SGA) babies and spontaneous preterm birth (PTB). Nulliparous pregnant women were recruited from November 2004 to February 2011 from Auckland (New Zealand), Cork (Ireland), Leeds (UK), London (UK), Manchester (UK) and Adelaide (Australia) (n=5628). There were 1164 mother-baby dyads enrolled in the Adelaide cohort between September 2005 and September 2008. Women were initially recruited and interviewed by SCOPE research midwives at 15±1 weeks' gestation. Data obtained included demographics, smoking, height, weight, medical and obstetric history and blood pressure (Further detailed in Chapter 2).

Previous follow-up studies have demonstrated that those who continue to be followed up are more likely to have higher socioeconomic status (SES) and be less disadvantaged [275, 276]. Recruitment is an important and time consuming part of any follow-up study. In this chapter, the original cohort is detailed, as well as the recruitment process and numbers. The primary aim is to assess whether women who attended the follow-up study were representative of the original SCOPE cohort.

3.3 Original SCOPE cohort recruited at 15±1 weeks' gestation

The mean age at SCOPE study recruitment was 24 years (Table 3.1). Overall, participants had a relatively low socioeconomic index (SEI), with a median SEI of 25 on a scale ranging from 10-90, where higher scores indicate higher SEI levels. The majority had only high school level education, were Caucasian and had a partner (Table 3.1). Almost a quarter of participants were still smoking at 15 weeks' gestation,

and just over 4% were still consuming alcohol and/or using illicit drugs at 15 weeks' gestation (Table 3.1).

Table 3.1 Demographic characteristics of participants in the Adelaide SCOPE cohort at recruitment

Characteristic	**Details at recruitment (15±1 weeks' gestation) (n=1164)**
Age, years mean (SD)	24 (5)
SEI	25 (20-30)
≤12 years' education	859 (73.8%)
Caucasian	1067 (91.7%)
With partner	990 (85.1%)
BMI, kg/m^2	26 (22-31)
Continuing to smoke	278 (23.9%)
Still consuming alcohol	51 (4.4%)
Using other drugs[a]	50 (4.3%)

Data presented as median (IQR) or n (%) unless otherwise stated.
SEI Socioeconomic Index (derived from the NZSEI; see Chapter 2); *BMI* Body Mass Index.
[a]Other drugs based on self-reported use of marijuana, cocaine/crack, amphetamines, substance P, XTC, opiates, hallucinogens, binge alcohol (≥6 units a session) and/or herbal highs.

Mothers in the SCOPE cohort were younger during their first pregnancy compared to the national average for first birth (mean age SCOPE 24 versus 29.7 years in 2005 in Australia [230]). The median SEI of the entire cohort was 25 (IQR: 20-30), indicating a disadvantaged population. There was also a higher level of smoking during pregnancy compared to the national average (23.9% in SCOPE at 15 weeks vs. Australian average 9.9% at any time during pregnancy in 2016 [230]). It is estimated that in areas of social disadvantage, adversity may impact up to 50% of the population [277]. This makes the SCOPE participants an ideal cohort in which to investigate the impact of early life adverse factors on developmental outcomes.

3.4 Recruitment of participants for follow-up

When women were enrolled in the SCOPE study during pregnancy, they provided their current home and mobile numbers for contact by the study team. In some instances, an additional phone number of a partner or parent was provided to facilitate contact with the woman should her contact details change. Due to the follow-up being 8-10 years after the initial cohort recruitment, ethical approval was gained to access participant's most recently listed phone numbers on the clinical information system (OACIS) at the Lyell McEwin Hospital. OACIS is updated every time a person presents to a public hospital within Adelaide, and therefore contains the most up-to-date contact information available. Majority of participants had two phone numbers listed on OACIS, therefore, majority of women had four numbers which could potentially be used to contact them.

Out of the 1164 women initially enrolled in SCOPE, 25 women were removed from the contact list. This was due to five who had previously withdrawn from the study, three women who had miscarriages, and four due to stillbirths. Seven women had terminations after enrolment, while two babies died in the neonatal period. Two women did not give permission to be contacted for future follow-up, and two women had infants who had died between 12-18 months of age. This resulted in 1139 women remaining who were eligible to be contacted for the follow-up study (Figure 3.1). The follow-up study was coordinated by this PhD candidate along with another PhD candidate. Together, the two candidates recruited participants and ran testing appointments.

We attempted to contact all 1139 participants by phone. Each woman was called three times over a number of weeks. If the women did not answer any of these calls and a mobile number was available, a text message was sent to the woman providing

information about the study, and requesting a reply from those interested in taking part.

Of the 1139 women, 203 were found to have all available phone numbers disconnected. We spoke to 634 of the original participants, of whom 420 booked in appointments to participate in the follow-up. Of these, 270 attended appointments in person. Three women expressed an interest in participating, but had moved outside of Adelaide. These women and their children filled in hard copies of the questionnaires and returned them via post. A total of 273 participants completed the follow-up assessments (Figure 3.1). The most common reasons for women not booking an appointment after they were contacted were not being interested or living outside of Adelaide.

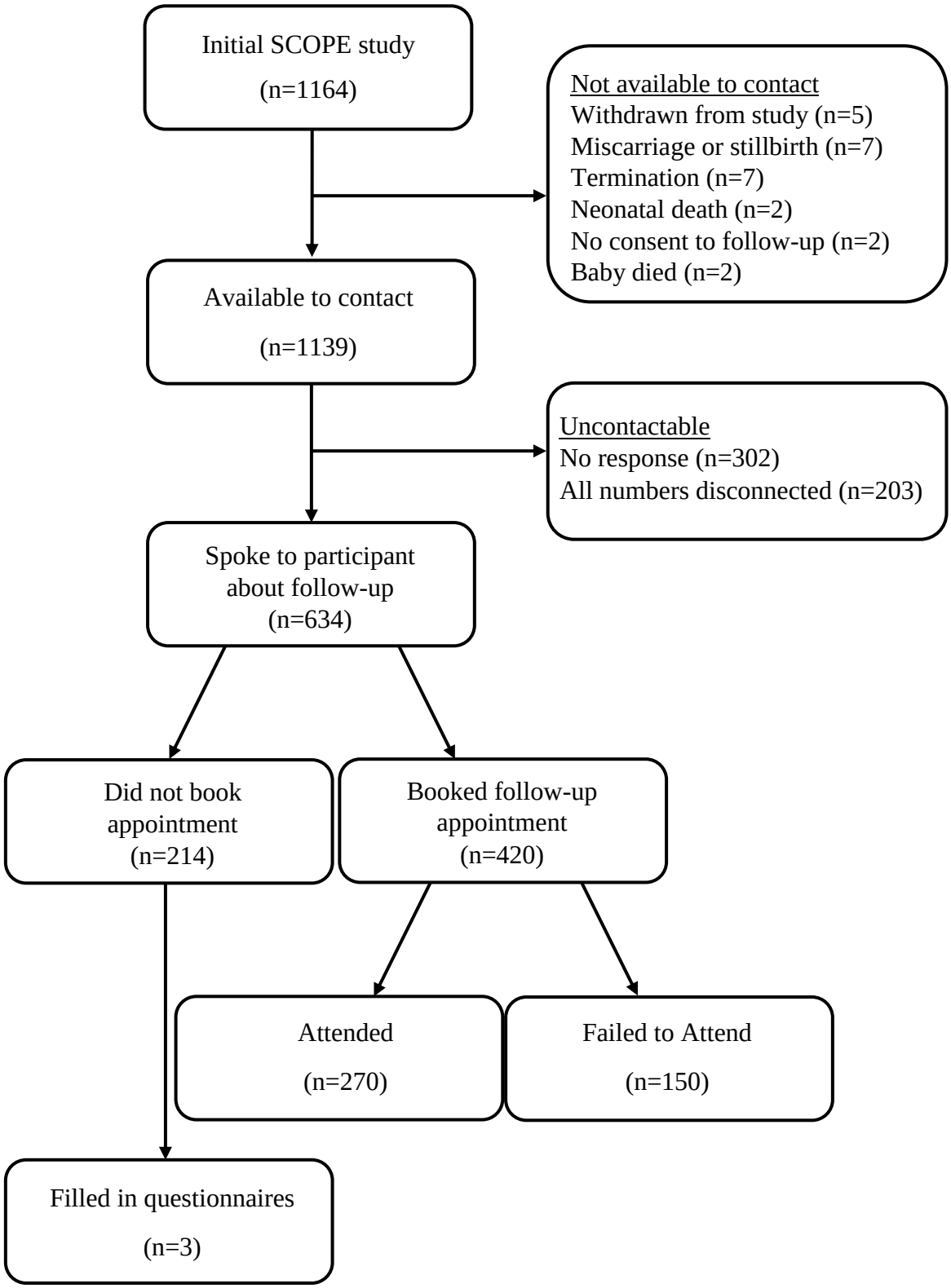

Figure 3.1 Recruitment of participants to SCOPE follow-up study

As one of our aims was to investigate the impact of pregnancy complications on child outcomes, we attempted to contact all participants from each pregnancy complication group. Pregnancy complication groups were assigned based on the presence of one of the five major complications of pregnancy; preeclampsia (PE), small for gestational age (SGA), preterm birth (PTB), gestational diabetes mellitus (GDM) and gestational hypertension (GH). If a participant had two or more pregnancy complications (e.g. PE and SGA), they were placed in both groups (i.e. both PE and SGA groups). Any participant who did not have one of these five complications was designated a control. Of those who were spoken to, attendance percentages ranged from 33% in the GH group, to 55% in the GDM group (Table 3.2). Therefore, of the 273 women and children who participated in the follow-up, 38 (14%) women had PE during their first pregnancy, 34 (13%) children were born SGA, and 26 (10%) were born preterm (PTB; Table 3.2). Twenty-two women (8%) had GDM, and 20 (7%) had GH.

Table 3.2 Recruitment numbers for each pregnancy complication group

Pregnancy Complication	**Available to call**	**Attempted to contact**	**No numbers**	**Spoken to participant**	**Booked in**	**Attended, n (% of 273)**
Control	745	745	116	387	249	166 (61)
PE	117	117	21	78	57	38 (14)
SGA	135	135	39	79	56	34 (13)
PTB	83	83	18	50	38	26 (10)
GDM	59	59	9	39	26	22 (8)
GH	91	91	16	61	42	20 (7)

PE Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.
Note: Pregnancy complications were not mutually exclusive, and some women had two or more complications, thus they were counted in two or more groups.

3.5 Statistical analysis

Following recruitment, all initial SCOPE participants who were contacted (n=1139) were classified into three groups. These were *Uncontactable* (n=505), those who had all numbers disconnected, or did not respond to calls and/or messages; *Contacted but did not attend* (n=361), where the original participant was spoken to directly, but they did not wish to book an appointment, or they booked an appointment and did not attend; and *Attended* (n=273), those who booked and attended the follow-up appointment, including the three participants who completed and returned questionnaires. Kruskal Wallis tests were used to compare continuous data between the three groups. Post-hoc analysis was performed using Mann-Whitney U tests with the critical *p*-value adjusted for multiple comparisons. Chi-square tests were used to compare categorical data between the three groups, where *p*-value <0.05 was considered significant.

3.6 Results

3.6.1 *Maternal demographics at recruitment (15±1 weeks' gestation)*

Table 3.3 summarises maternal demographics at initial SCOPE recruitment (15±1 weeks' gestation) by those who were *Uncontactable, Contacted but did not attend* and *Attended*. There were significant differences in mother's age and SEI between the three groups (all $p<0.001$). Post-hoc analyses demonstrated mothers in the *Uncontactable* and *Contacted but did not attend* groups were significantly younger and had lower SEI compared to the *Attended* group ($p<0.001$). There were no significant differences between any of the three groups in completion of at least 12 years' education. There was a difference in ethnicity between groups ($p=0.029$), with more Caucasian women in the *Attended* group. There were more participants in the *Attended*

group who were married, and fewer were defacto (p<0.001). However, there was no significant difference in the number of women with a partner between the three groups. There was a significant difference in body mass index (BMI) between groups (p=0.001), with fewer underweight and healthy weight participants in the *Attended* group and a higher prevalence of overweight and obese in the *Attended* group. There were also differences in employment between the three groups, with higher percentages of full and part-time workers in the *Attended* group compared to the other two groups (p<0.001). Those who were *Uncontactable* and *Contacted but did not attend* smoked and consumed other drugs more frequently at 15 weeks' gestation compared to the *Attended* group (both p<0.01) but had no significant difference in consumption of alcohol. Those who were *Uncontactable* and *Contacted but did not attend* also had higher levels of depressive symptoms as rated by the EPDS compared to the *Attended* group (Table 3.3). This difference was significant at 15, but not at 20, weeks' gestation. While there was a higher frequency of EPDS scores ≥13 in the non-attended groups compared to the *Attended* group, this difference was not significant.

3.6.2 *Infant demographics*

There were no significant differences between the three groups in regards to child sex, gestational age, birthweight or birthweight centile (Table 3.4).

Table 3.3 Maternal demographics at initial SCOPE recruitment (15±1 weeks' gestation) by those who were uncontactable, contacted but did not attend and attended

	Uncontactable (n=505)	**Contacted but did not attend (n=361)**	**Attended (n=273)**	***p*-value[a]**
Mum Age, Years, mean (SD)	23 (5)[b]	24 (5)[b]	26 (5)	**<0.001**
SEI median (IQR)	22 (20-30)[b]	24 (20-33)[b]	27 (22-34)	**<0.001**
Education level, <12 years school, n (%)	385 (76.2)	262 (72.6)	193 (70.7)	0.203
Ethnicity, n (%)				**0.029**
1. Caucasian	442 (87.5)	339 (93.9)	264 (96.7)	**<0.001[c]**
2. Maori	3 (0.6)	1 (0.3)	1 (0.4)	
3. Pacific Islander	1 (0.2)	0 (0)	0 (0)	
4. South East Asian	30 (5.9)	7 (1.9)	4 (1.5)	
5. Indian Sub-Continent	2 (0.4)	1 (0.3)	1 (0.4)	
6. African Ancestry	3 (0.6)	1 (0.3)	0 (0)	
7. Middle Eastern	2 (0.4)	3 (0.8)	0 (0)	
8. Hispanic	2 (0.4)	0 (0)	1 (0.4)	
9. Aboriginal	14 (2.8)	5 (1.4)	1 (0.4)	
10. Other	6 (1.2)	4 (1.1)	1 (0.4)	
Marital status, n (%)				**<0.001**
Single	80 (15.8)	46 (12.7)	41 (15.0)	
Married	121 (24.0)	114 (31.6)	112 (41.0)	
De facto	301 (59.6)	201 (55.7)	120 (44.0)	
Separated/divorced	2 (0.4)	0 (0)	0 (0)	
Same sex partner	1 (0.2)	0 (0)	0 (0)	
Partner, yes, n (%)	423 (83.8)	315 (87.3)	232 (85.0)	0.360
BMI group, n (%)				**0.001**
Underweight (<18.5)	21 (4.2)	9 (2.5)	5 (1.8)	
Healthy (18.5-24.9)	235 (46.5)	145 (40.2)	94 (34.4)	
Overweight (25-29.9)	116 (23.0)	100 (27.7)	99 (36.3)	
Obese (≥30)	133 (26.3)	107 (29.6)	75 (27.5)	
Employment, n (%)				**<0.001**
Full time	158 (31.3)	170 (47.1)	148 (54.2)	
Part time	134 (26.5)	98 (27.1)	87 (31.9)	
Student	31 (6.1)	14 (3.9)	6 (2.2)	
Home maker	24 (4.8)	9 (2.5)	4 (1.5)	
Unemployed	152 (30.1)	67 (18.6)	21 (7.7)	
Sickness beneficiary	2 (0.4)	3 (0.8)	4 (1.5)	
Other (e.g. voluntary work)	4 (0.8)	0 (0)	3 (1.1)	

(Table 3.3 continued next page)

Table 3.3 continued. Maternal demographics at initial SCOPE recruitment (15±1 weeks' gestation) by those who were uncontactable, contacted but did not attend and attended

	Uncontactable (n=505)	**Contacted but did not attend (n=361)**	**Attended (n=273)**	***p*-value[a]**
Currently smoking, yes, n (%)	155 (30.7)	79 (21.9)	39 (14.3)	**<0.001**
Consuming alcohol, yes, n (%)	27 (5.3)	12 (3.3)	9 (3.3)	0.237
Taking other drugs[d], yes, n (%)	31 (6.1)	10 (2.8)	6 (2.2)	**0.009**
15 week EPDS score, median (IQR)	6 (3-10)[a]	7 (3-10)[a]	5 (2-9)	**0.002**
20 week EPDS score, median (IQR)	5 (2-10)	5 (2-9)	4 (2-9)	0.169
EPDS ≥13 at either 15 or 20 weeks, n (%)	103 (20.4)	72 (19.9)	38 (13.9)	0.065

SEI Socioeconomic Index (derived from NZSEI); *BMI* Body Mass Index; *EPDS* Edinburgh Postnatal Depression Scale.

[a]*p*-value between denotes differences between three groups;.[b]denotes significantly different from "*attended*" group in post-hoc analysis (at $p<0.017$ level); [c]*p*-value from comparison of Caucasian and all "other" ethnicities between the three groups; [d]Other drugs include marijuana, cocaine/crack, amphetamines, substance P, XTC, opiates, hallucinogens, binge alcohol (≥6 units a session) and herbal highs.

Table 3.4 Demographics of infants born to SCOPE women

	Uncontactable (n=505)	**Contacted but did not attend (n=361)**	**Attended (n=273)**	***p*-value[a]**
Sex, male, n (%)	262 (51.9)	173 (47.9)	121 (44.3)	0.121
Gestational Age, weeks	40 (38-40)	39 (38-40)	39 (38-40)	0.713
Birthweight, grams	3370 (3050-3720)	3370 (3080-3720)	3470 (3076-3755)	0.511
Birthweight centile	43 (21-69)	46 (21-73)	49 (20-72)	0.730

Data presented as median (IQR) or n (%).

[a]*p*-value between denotes differences between three groups.

3.7 Discussion

Of participants enrolled in the original SCOPE study, those who participated in the follow-up tended to be less disadvantaged during pregnancy. The *Attended* group tended to be older at the time of their first pregnancy, have a higher SEI, and were more frequently Caucasian. They were more frequently employed in full or part-time work. The *Attended* group were also less likely to have smoked, consumed alcohol and/or drugs at 15 weeks' gestation, and had lower depression scores. However, there were no significant differences in infant outcomes between groups demonstrating no difference in early life birth factors for children who were followed-up compared to those who were not.

Some cohort studies have higher follow-up rates, such as the Dunedin longitudinal study with 95% follow-up rate up to the age of 35 years, which results in smaller impacts of attrition bias. However, it is also not uncommon for follow-up studies to have lower attendance rates, which therefore results in greater differences between participants and non-participants. For example, Strandhagen [275] found their follow-up cohort was biased with those who participated being older with higher incomes. An analysis of the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort also found that loss to follow-up was associated with lower SES, and this in turn was associated with an underestimation of inequality in the cohort [276]. This suggests analyses using this follow-up data may underestimate the impact of social disadvantage within the SCOPE cohort. However, while participants who came back did have higher average SEI during pregnancy compared to the whole original cohort, they still represent a disadvantaged population compared to the wider Adelaide population.

One limitation of recruitment for follow-up was that many participants were uncontactable, as all phone numbers had been disconnected, or participants did not respond to text or phone messages left on message banks. This is likely due to the long gap between recruitment and follow-up (8-10 years), where participants had not been contacted, despite the fact that the most up-to-date phone numbers were available. To reduce selection bias, every participant was called three times and text messages were sent to all valid mobile numbers to ensure as many participants as possible had opportunity to participate.

There were also a number of participants who were contacted but did not want to attend appointments in person due to child behavioural or health issues. This may have also biased outcomes, with those children who were followed-up having less cognitive, mental health and/or behavioural impairments. To reduce the likelihood of this bias, questionnaires were sent via postage to parents unable to attend to complete at home.

It is important to acknowledge that these differences in demographics between the original and follow-up cohorts may result in an underestimation of poor outcomes in 8-10 year old children, and may therefore not be entirely representative of the disadvantage within the entire SCOPE cohort. However, these analyses will provide an indication of the most relevant early life adverse factors that may impact upon long-term cognition and mental health. Cognitive, behavioural and mental health impairments in childhood increase the risk of future neurodevelopmental deficits. This may lead to differences in academic performance, and lead to poor job opportunities and therefore decreased socioeconomic success. These findings may inform interventions to target the entire low SEI population within the Lyell McEwin Hospital catchment area to improve long-term outcomes for all children.

Chapter 4:

The impact of maternal antenatal depression on parent and child reported anxiety and depression in 8-10 year old children

4.1 Abstract

Introduction: Maternal antenatal depression has been associated with increased risk of mental health issues in adulthood. However, there is little evidence as to whether this depression impacts on child mental health, and whether this is different between mother- and child-reported symptoms.

Method: Women involved in the SCreening fOr Pregnancy Endpoints (SCOPE) study completed the Edinburgh Postnatal Depression Scale (EPDS) at 15 weeks' gestation. At follow-up 8-10 years after delivery, both mother and child completed the Spence Children's Anxiety Scale (SCAS) and the Child Anxiety Life Interference Scale (CALIS). Children also completed the Center for Epidemiological Studies Depression Scale for Children (CES-DC).

Results: Mothers who scored ≥13 on the EPDS were classed as having high antenatal depression (n=38) and scores <13 indicated low antenatal depression (n=235). In the final analysis adjusted for factors including current maternal depression, mothers who had high antenatal depression had higher risk of rating their children as having higher anxiety (adjusted risk ratio, aRR:1.31 95% CI: 1.22-1.41) and increased risk of anxiety life interference (aRR:1.52, 1.39-1.66). These differences were also seen to a lesser extent with respect to child self-reported risk of anxiety symptoms (aRR:1.10, 1.03-1.17) and risk of everyday anxiety interference (aRR:1.16, 1.03-1.30). This increased risk was seen in all anxiety subscales in the mother's report, but only seen in the panic/agoraphobia and social phobia scales, and risk of anxiety outside the home in the child report. There was no association between antenatal depression and depression symptoms of children.

Conclusion: Maternal antenatal depression is associated with increased likelihood of child anxiety in both mother and child-reported anxiety and anxiety life interference compared to those with low antenatal depression. This finding highlights the need for specific interventions to reduce the long-term risk of mental health issues.

4.2 Introduction

Maternal depression is one of the most common complications of the antenatal period [278]. A recent review including low, middle and high income countries demonstrated that approximately 12% of women may experience perinatal depression [279]. Women in Australia who suffer from depression are more likely to be younger, smokers, from lower income households and be overweight or obese [258]. Depressive symptoms during pregnancy have been associated with smoking [109], and also with higher incidence of pregnancy complications such as preeclampsia (PE), small for gestational age (SGA) and preterm birth (PTB) [280-283]. The fact that maternal depression commonly occurs within social contexts such as low socioeconomic status (SES), unemployment and family stress suggests the importance of investigating effects of antenatal depression on children within these contexts.

Both maternal antenatal anxiety and depression have been associated with long-term outcomes in children [43, 44, 91, 284]. Antenatal anxiety has been associated with conduct disorders, emotional and behavioural problems in children [44, 64, 65, 67-70]. Similarly, antenatal depression has been associated with both internalising and externalising behaviours in three year olds [77], and also a higher risk of child attention problems at 3-4 years [54]. Barker et al. [74] found no associations between antenatal depression and internalising behaviours, but found there was an association between antenatal depression and externalising behaviour in eight year old children. These findings demonstrate associations between antenatal depression and subsequent child behaviour. However, less research has focused on the association between antenatal depression and child mental health. One study following 151 mother-child pairs found children exposed to antenatal maternal depression were four times more likely to suffer from depression at 16 years old [79]. Moreover, both pre- and postnatal

depression have been associated with an increased risk of depression at 18 years old [80]. While these findings demonstrate associations between antenatal depression and behavioural outcomes in adolescence, there is no consistent data that would suggest a causal relationship, or to suggest these symptoms first appear in childhood.

Much of the previous research in children of younger ages utilises parental report of child mental health symptoms, however, this may be a source for discrepancy Evidence suggests that mothers with current depression may over report their child's symptoms, depending on their own symptomology [217], while another study suggests that depressed parents may in fact report more accurately about their child due to their increased awareness of mental health symptomology [285]. For example, when comparing child behaviour ratings of mothers and teachers, Leis et al. [72] found associations between mother's antenatal depression and child behaviour, but no association between mother's antenatal depression and the teacher's report of child behaviour. Additionally, Robinson et al. [286] demonstrated how different contextual factors for the parent such as depression, stress and low income can increase the discrepancy between parent and child report of the child's behaviour. Together, this evidence demonstrates the importance of considering what impact the mother's mental health may have on her rating of the child's behaviour, and also the importance of considering the child's own view of their mental health.

In the current study, we assessed mental health status of 8-10 year old children who were born in the Adelaide birth cohort of the SCreening fOr Pregnancy Endpoints (SCOPE) study. The Adelaide SCOPE cohort was from a low socioeconomic background and had a high proportion of women with antenatal depression. The women in SCOPE were followed throughout pregnancy, and hence antenatal depression data are available. Given that mother's current maternal mental health can

impact on her rating of child behaviour, children were asked to rate their own anxiety and depression symptoms. Mothers were also asked to rate their child's anxiety symptoms, as well as completing a questionnaire about their own current mental health. The primary aim of this study was to investigate how mothers' antenatal depression symptoms were related to child mental health outcomes. The secondary aim was to compare differences in outcomes in parent reported and child reported outcomes at age 8-10 years.

4.3 Methods

4.3.1 *Participants*

This study was part of a 10 year follow-up of the Adelaide SCOPE cohort. In brief, the Adelaide SCOPE cohort consisted of 1164 nulliparous pregnant women and their partners recruited between September 2005 and September 2008 at the Lyell McEwin Hospital in Adelaide, South Australia. It is part of an International cohort study conducted in Adelaide, Australia; Auckland, New Zealand; London, Leeds and Manchester, UK; and Cork, Ireland with a total of 5628 women recruited [262, 263]. The main aim of the SCOPE study was to develop screening tools to predict risk for pregnancy complications. Data collected included the woman's medical history, obstetric history, and standard mental health antenatal screening and pregnancy outcomes.

In the current study, Adelaide women were contacted by phone 8-10 years after the first pregnancy to participate in a follow-up study. A large number of participants (n=530) could not be contacted: 23 due to the loss of a baby (either late miscarriage, stillbirth or infant death), two did not originally provide consent to be followed up for future studies, 202 were no longer contactable on the same phone number and 227 did

not answer. Of the 634 participants who could be reached, 420 (66%) booked appointments and 270 attended appointments (64% of those who booked appointments). Three of the SCOPE women were interested in participating but had moved outside of the Adelaide area, therefore they were sent hard copy questionnaires to complete and return via post. This resulted in a total of 273 mother-child pairs participating in the follow-up study.

At the follow-up appointment, women and children provided written consent and assent, respectively. Children underwent cognitive testing and completed questionnaires during a two hour session. During the same session, the child's mother completed the questionnaires about herself and her child. Both mother and child were placed in separate rooms for answering questionnaires to avoid collusion. In three cases, the questionnaires about the child's anxiety were completed by a guardian other than the mother. Nine children (3.2%) had incomplete data for one or more of the self-reported questionnaires, thus totals could not be created, and therefore were excluded from further analysis.

4.3.2 *Measures*

4.3.2.1 *Maternal mental health*

In the SCOPE study, depression during pregnancy was measured using the Edinburgh Postnatal Depression Scale (EPDS) [261] at both 15±1 and 20±1 weeks' gestation (Appendix A). The EPDS is a 10-item questionnaire, with higher scores indicating increased depressive symptoms. Although this scale was originally developed for use during the postnatal period, it has since been validated for use during pregnancy [260]. A cut off score of ≥13 is recommended to suggest significant depressive symptoms that likely indicate depression [261]. In this study, high antenatal

depression was defined as EPDS score of ≥13 at either 15 or 20 week time point. All participants who scored <13 at both time points were therefore the low antenatal depression group.

At the follow-up appointment, the Depression, Anxiety and Stress Scale (DASS-42) was used to assess maternal mental health (Appendix J). This measure includes three 14-item scales measuring depression, anxiety and stress [274]. Participants were presented with a description and asked to rate how much the statement applied to them during the past week. Each item was rated on a 4-point Likert scale, ranging from 0 ("did not apply to me at all") to 3 ("applied to me very much, or most of the time"). Scores ranging from 0 to 42 were created for each of the three subscales of depression, anxiety and stress, with higher scores on each subscale indicating increased severity of symptoms in that domain. For more details, see Chapter 2 (Section 2.4.4).

4.3.2.2 *Child Anxiety*

The Spence Children's Anxiety Scale (SCAS) is a 38-item measure of overall anxiety, as well as sub-domains of anxiety such as panic/agoraphobia, social anxiety, separation anxiety, obsessive compulsive behaviours, physical injury fears and generalised anxiety [267] . This scale can be completed by child self-report (Appendix E) or by a parent (Appendix D). The parent scale contains 38 items and the child scale contains 44 items. However, six responses on the child report are not scored as they are positive items included to reduce negative response bias. Both child and parent scales contain parallel items, with questions regarding the "self" or "my child" respectively. Each item was rated on a scale of 0-3, where 0 was "never" and 3 was "always". The maximum possible total score was 114, with higher scores indicating increased anxiety.

The Children's Anxiety Life Interference Scale (CALIS) questionnaire assesses the impact of a child's fears and worries on their daily life. This scale was completed separately from both the perspective of the mother (15-item; Appendix F) and the child (9-item; Appendix G), and contained subscales for anxiety interference at home, outside the home, and parent life (parent report only). Both parent and child reports contained nine parallel items, with the parent form containing an extra six items to assess the 'parent life' subscale. Each item was rated on a 5-point Likert scale, where 0 was "not at all", and 4 was "a great deal" [270]. The maximum score for the mother's form was 64, while the child's maximum total was 36, with higher scores indicating higher anxiety interference.

4.3.2.3 *Child depression*

The Center for Epidemiological Studies of Depression scale for Children (CES-DC) is a 20-item self-report designed to measure depressive symptoms in children (Appendix H) [273]. Each item of the CES-DC was scored on a 4-point Likert scale, with responses ranging from "not at all" to "a lot". The questionnaire specifically references feelings during the past week. Sixteen of the statements refer to the presence of a depressive symptom, while the remaining four questions refer to positive items and were hence reverse scored. Total scores ranged from 0-60, with scores above 15 indicating significant depressive symptoms [273].

4.3.3 *Data analysis*

Data were analysed using SPSS v25. T-tests and Mann-Whitney U tests were used for comparison of demographics between the groups. Correlations between depression and anxiety outcomes were performed using Spearman correlations. Mann-

Whitney U tests were performed to compare scores on the parent and child reported questionnaires between those in the low and high antenatal depression (EPDS) groups. Multivariate analyses utilised Poisson regressions to analyse the impact of antenatal depression (low or high EPDS group) on child mental health outcomes for both the parent and child reports. Regression modelling was conducted to adjust for the potential influence of other factors known to affect child anxiety and depression. Model 1 was adjusted for mother's smoking status at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's education level (years), child age; Model 2 included all factors in Model 1 plus child sex, and Model 3 included all factors in Model 2 plus mother's current depression score (at follow-up). Data on confounding factors used in the models were available for all participants who attended the follow-up.

4.4 Results

4.4.1 *Demographics*

Table 4.1 shows the demographic characteristics of the whole follow-up cohort at recruitment to the SCOPE study, and separated into those women with low (n=235), and high antenatal depression (n=38) based on their EPDS score. Between those with low and high antenatal depression, there were no statistically significant differences in the mother's age, socioeconomic index (SEI), body mass index (BMI), ethnicity, partner status, education level, job status or alcohol consumption at 15 weeks' gestation. There were significantly more women who were smoking at 15 weeks' gestation in the high antenatal depression group compared to the low antenatal depression group ($p<0.05$). By definition, scores on the EPDS were significantly higher in those women with high antenatal depression compared to those with low

antenatal depression at both 15 and 20 weeks' gestation (Table 4.1). There was no difference in pregnancy complications between the low and high antenatal depression groups.

Table 4.1 Characteristics of SCOPE follow-up participants during pregnancy and according to low and high antenatal depression groups

	All n=273	**Low antenatal depression n=235**	**High antenatal depression n=38**	***p*-value[a]**
Age of mother at recruitment, years, mean (SD)	26 (5)	26 (5)	25 (5)	0.081
SEI	27 (22-34)	27 (22-34)	28 (20-33)	0.894
BMI, kg/m^2	26.6 (23.7-30.6)	26.30 (23.7-30.6)	26.75 (22.9-29.7)	0.953
Ethnicity, Caucasian	264 (96.7%)	228 (97.0%)	36 (94.7%)	0.464
Married or defacto	232 (85.0%)	201 (85.5%)	31 (81.6%)	0.527
Education level at recruitment, years	12 (11-13)	12 (11-13)	12 (11-12)	0.107
Job Status at recruitment, full time	148 (54.2%)	132 (56.2%)	16 (42.1%)	0.110
Smoking at 15 weeks	39 (14.3%)	**27 (11.5%)**	**12 (31.6%)**	**0.001**
Consuming alcohol at 15 weeks	9 (3.3%)	7 (3.0%)	2 (5.3%)	0.364
EPDS score at 15 weeks' gestation	5 (2-9)	**4 (1-7)**	**15 (11-16)**	**<0.001**
EPDS score at 20 weeks' gestation	4 (2-9)	**4 (2-7)**	**13 (12-15)**	**<0.001**
Complicated pregnancy[b]	107 (39.2%)	92 (39.1%)	15 (39.5%)	0.970

Data presented as median (IQR) or n (%) unless otherwise stated.

SEI Socioeconomic Index determined using NZSEI (see Chapter 2); *BMI* Body Mass Index; *EPDS* Edinburgh Postnatal Depression Scale.

[a]*p*-value from comparison between low and high antenatal maternal depression groups

[b]*Complicated pregnancy* included participants with any of the major complications of pregnancy including preeclampsia, small for gestational age, preterm birth, gestational diabetes or gestational hypertension.

Table 4.2 shows characteristics from the SCOPE follow-up cohort at time of follow-up. Mothers who had high antenatal depression during pregnancy also had significantly higher depression scores on the DASS at follow-up compared to those women who had low antenatal depression (Table 4.2). At follow-up, there were no significant differences in the age or sex of the children between antenatal depression groups.

Table 4.2 Characteristics of women and children at follow-up, and divided by low and high antenatal depression groups

	All (n=273)	**Low antenatal depression (n=235)**	**High antenatal depression (n=38)**	***p*-value[a]**
DASS Depression score, median (IQR)	2 (0-5)	**1 (0-5)**	**4 (2-11)**	**0.002**
Child age at follow-up, years, mean (SD)	9.6 (0.6)	9.6 (0.6)	9.5 (0.5)	0.151
Child sex, Male, n (%)	121 (44.3%)	106 (45.1%)	15 (39.5%)	0.517

DASS Depression, Anxiety and Stress Scale.
[a]*p*-value calculated between low and high antenatal depression groups.

4.4.2 *The association between antenatal depression, and maternal depression and child anxiety 8-10 years later*

Table 4.3 present correlations between mental health questionnaires scores. Maternal antenatal depression at both 15 and 20 week time points in pregnancy were strongly, positively correlated. Mother's current depression was also moderately positively correlated with depression score at both 15 and 20 weeks' gestation. Maternal antenatal depression was also moderately associated with parental report of child anxiety (as measured on the SCAS) and child anxiety life interference (as measured on the CALIS). Maternal antenatal depression at 15 and 20 weeks' gestation were weakly, but significantly, related to child anxiety scores as measured on both the

SCAS and CALIS. Maternal antenatal depression at 15 or 20 weeks' gestation was not associated with child depression scores, or current maternal depression scores as measured by the DASS.

4.4.3 *The association between current levels of maternal depression and child anxiety at age 8-10 years*

Mother's current depression (DASS-D) was only weakly associated with parental report of child anxiety on the SCAS and CALIS, but was not associated with child reported anxiety on the SCAS or child reported anxiety interference on the CALIS (Table 4.3). Mother's current depression was also not associated with child depression score.

Table 4.3 Associations between mental health questionnaire scores (Spearman's correlations)

	EPDS at 15 weeks	**EPDS at 20 weeks**	**DASS-D**	**SCAS (Parent report)**	**CALIS (Parent report)**	**SCAS (Child self-report)**	**CALIS (Child self-report)**	**CES-DC**
EPDS at 15 weeks	1.0	-	-	-	-	-	-	-
EPDS at 20 weeks	**0.699****	1.0	-	-	-	-	-	-
DASS-D	**0.384****	**0.437****	1.0	-	-	-	-	-
SCAS (Parent report)	**0.268****	**0.261****	**0.350****	1.0	-	-	-	-
CALIS (Parent report)	**0.341****	**0.291****	**0.382****	**0.668****	1.0	-	-	-
SCAS (Child self-report)	**0.221****	**0.163****	0.099	**0.270****	**0.198****	1.0	-	-
CALIS (Child self-report)	**0.177****	**0.162****	0.068	0.990	0.065	**0.579****	1.0	-
CES-DC	0.119	0.078	0.032	**0.220****	**0.216****	**0.615****	**0.557****	1.0

**Significant at $p<0.01$ level.

EPDS Edinburgh Postnatal Depression Scale; *DASS-D* Depression, Anxiety and Stress Scale – Depression score; *SCAS* Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale; *CES-DC* Center for Epidemiological Studies Depression Scale for Children.

4.4.4 *Univariate analysis of antenatal depression and child mental health*

Mothers with high antenatal depression reported their children as having significantly more overall anxiety compared to those women with low antenatal depression (Table 4.4; $p<0.001$). This difference was seen in the SCAS subscales of panic/agoraphobia, separation anxiety, social phobia, obsessive compulsive and generalised anxiety (all $p<0.05$), but not in physical injury fears, with mothers with high levels of antenatal depression consistently reporting higher scores in these areas. Mothers with high antenatal depression also scored their children as having significantly more total anxiety interference compared to those mothers who had low scores on the EPDS (Table 4.4; $p<0.001$). This difference was observed for on all of the parent reported CALIS subscales, including at home, outside the home and parent life (all $p<0.05$).

In the child self-report, there was no significant difference in scores between children of mothers in the low or high antenatal groups for total anxiety or the subscales as measured by the SCAS (Table 4.4). There was also no difference in child-reported anxiety inference between antenatal depression groups. Although children of mothers with high antenatal depression had higher median scores on the depression questionnaire compared to those whose mothers had low antenatal depression, this difference was not significant.

Table 4.4 Comparisons of child anxiety and depression scores of those women with low or high antenatal depression during pregnancy, based on parent and child reports

	Parent report			**Child report**		
	Low antenatal depression (n=235)	**High antenatal depression (n=38)**	***p*-value**	**Low antenatal depression (n=235)**	**High antenatal depression (n=38)**	***p*-value**
SCAS						
Total	**15 (10-24)**	**23 (14-36)**	**<0.001**	29 (18-41)	35 (22-43)	0.123
Panic/agoraphobia	**0 (0-2)**	**2 (0-4)**	**0.001**	3 (1-6)	4 (2-7)	0.075
Separation anxiety	**3 (1-5)**	**5 (2-8)**	**0.004**	5 (3-8)	6 (3-8)	0.274
Physical injury fears	3 (2-5)	4 (2-6)	0.085	4 (2-6)	4 (2-7)	0.501
Social phobia	**4 (3-6)**	**6 (4-8)**	**0.013**	4 (2-7)	5 (3-8)	0.159
Obsessive compulsive behaviour	**1 (0-2)**	**2 (1-3)**	**0.006**	6 (3-9)	7 (5-8)	0.267
Generalised anxiety	**3 (2-5)**	**5 (3-8)**	**0.005**	6 (4-8)	6 (5-8)	0.349
CALIS						
Total	**8 (4-15)**	**14 (8-32)**	**<0.001**	7 (4-14)	10 (5-14)	0.161
At home	**3 (2-5)**	**6 (2-9)**	**0.001**	4 (2-7)	5 (2-8)	0.247
Outside home	**3 (1-6)**	**6 (2-10)**	**0.032**	3 (1-6)	3 (1-8)	0.412
Parent life	**2 (0-5)**	**5 (3-13)**	**<0.001**	-	-	-
CES-DC	-	-	-	12 (8-20)	15 (7-21)	0.628

Data presented as median (IQR).

EPDS Edinburgh Postnatal Depression Scale; Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale; *CES-DC* Center for Epidemiological Studies Depression Scale for children.

4.4.5 *Associations of antenatal depression on child anxiety symptoms (as measured by the SCAS)*

After adjusting for the potential effects of mother's smoking status, mother's age, mother's education, child age in Model 1, mothers with high antenatal depression were 41% more likely to rate their children as having higher total anxiety symptoms (Table 4.5). This likelihood did not change in Model 2 with the addition of child sex. After the inclusion of mother's current depression score in Model 3, the likelihood of rating anxiety symptoms in the child decreased slightly to 31%, but was still significant. A similar trend was seen in the anxiety subscales, where the addition of mother's current depression scale reduced the likelihood of parent-reported child symptoms compared to Model 1 and 2. However, those mothers with high antenatal depression consistently had increased risk of rating their children as having increased anxiety symptoms compared to those mothers with low antenatal depression in all SCAS subscales (Table 4.5).

After controlling for mother's smoking status, mother's age, mother's education, child age in Model 1 for the child anxiety self-report, children of mothers with high antenatal depression had 12% increased risk of reporting higher anxiety symptoms compared to those whose mothers had low antenatal depression (Table 4.5). Adjusting for child sex in Model 2 slightly reduced this risk (11%), and adding mother's current depression in Model 3 lead to a slight further reduction to the risk (10%). There were no significant differences in risk in child-reported anxiety symptoms on any of the sub-scales, except for panic/agoraphobia, where high antenatal depression was associated with a 23% increased risk of symptoms in Model 3 (Table 4.5).

4.4.6 *Associations of antenatal depression and child anxiety life interference (as measured by CALIS)*

After adjusting for effects of mother's smoking status, mother's age, mother's education, child age in Model 1, mothers with high antenatal depression were 70% more likely to rate their children as having anxiety interference (total) relative to their low antenatal depression counterparts (Table 4.5). After the addition of child sex to this model (Model 2), the likelihood increased slightly to 73%. In the final model with the addition of mother's current depression score in Model 3, mothers who had high antenatal depression had increased risk of parent reported anxiety interference (total) of 52% compared to their low antenatal depression counterparts. Mothers with high antenatal depression also had rated their children as having increased likelihood of anxiety interference at home, outside the home and parent life subscales, relative to those mothers with low antenatal depression (Table 4.5).

In the analysis of the child reported symptoms, Model 1 demonstrated those children with mothers who had high antenatal depression were at a significantly higher risk (18%) of anxiety interference (total) relative to their low antenatal depression counterparts (Table 4.5). Once child sex and mother's current depression score was adjusted for (Model 3), those who mothers had high antenatal depression were still at 16% increased risk of self-reported anxiety interference (Table 4.5). When looking at the child self-reported subscales, there was no difference in risk of at home interference between groups, but in the final model (Model 3), those children whose mothers had high antenatal depression were at 20% increased risk of anxiety interference outside the home compared to those whose mothers had low antenatal depression (Table 4.5).

4.4.7 *Antenatal depression was not related to child self-reported depression*

All three regression analyses were run to investigate the association between antenatal depression and child self-reported depressive symptoms at 8–10 years old. The outcomes of these analyses indicate there was no difference in risk for child depressive symptoms between high and low antenatal depression groups (Table 4.5).

Table 4.5 Adjusted relative risks (aRR) of child anxiety and depression symptoms in children exposed to high levels of maternal antenatal depression compared to those exposed to low antenatal depression

	Parent report aRR* (95% CI)			**Child report aRR* (95% CI)**		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
SCAS						
Total	**1.41 (1.31, 1.51)**	**1.41 (1.31, 1.51)**	**1.31 (1.22, 1.41)**	**1.12 (1.00, 1.19)**	**1.11 (1.04, 1.18)**	**1.10 (1.03, 1.17)**
Panic/Agoraphobia	**1.90 (1.49, 2.42)**	**1.95 (1.53, 2.48)**	**1.71 (1.34, 2.20)**	**1.23 (1.05, 1.46)**	**1.22 (1.04, 1.44)**	**1.23 (1.04, 1.45)**
Separation Anxiety	**1.47 (1.26, 1.73)**	**1.48 (1.26, 1.73)**	**1.39 (1.18, 1.63)**	1.13 (0.97, 1.31)	1.12 (0.96, 1.29)	1.10 (0.95, 1.28)
Physical Injury fears	**1.26 (1.06, 1.51)**	**1.26 (1.05, 1.50)**	**1.22 (1.02, 1.46)**	1.11 (0.93, 1.31)	1.09 (0.91, 1.29)	1.01 (0.90, 1.28)
Social Phobia	**1.22 (1.05, 1.42)**	**1.22 (1.05, 1.42)**	**1.17 (1.01, 1.36)**	**1.18 (1.01, 1.36)**	1.16 (1.00, 1.35)	**1.17 (1.00, 1.36)**
Obsessive Compulsive	**1.66 (1.29, 2.12)**	**1.69 (1.32, 2.16)**	**1.39 (1.07, 1.79)**	1.09 (0.95, 1.25)	1.08 (0.94, 1.24)	1.05 (0.92, 1.21)
Generalised Anxiety	**1.36 (1.15, 1.59)**	**1.36 (1.15, 1.59)**	**1.27 (1.07, 1.49)**	1.04 (0.90, 1.20)	1.03 (0.90, 1.18)	1.03 (0.90, 1.19)
CALIS						
Total	**1.70 (1.56, 1.85)**	**1.73 (1.59, 1.89)**	**1.52 (1.39, 1.66)**	**1.18 (1.06, 1.32)**	**1.17 (1.05, 1.31)**	**1.16 (1.03, 1.30)**
At home	**1.58 (1.36, 1.84)**	**1.60 (1.37, 1.86)**	**1.46 (1.25, 1.71)**	1.16 (1.00, 1.36)	1.16 (0.99, 1.35)	1.12 (0.96, 1.32)
Outside home	**1.43 (1.23, 1.66)**	**1.47 (1.26, 1.71)**	**1.33 (1.14, 1.55)**	**1.20 (1.03, 1.41)**	**1.19 (1.02, 1.40)**	**1.20 (1.02, 1.40)**
Parent life	**2.16 (1.87, 2.49)**	**2.21 (1.91, 2.55)**	**1.81 (1.56, 2.10)**	-	-	-
CES-DC						
Total	-	-	-	1.00 (0.91, 1.10)	1.00 (0.91, 1.09)	0.99 (0.91, 1.09)

*aRR: For those exposed to high levels of antenatal depression (n=38); Reference category is low maternal antenatal depression (n=235).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life interference scale; *CES-DC* Center for Epidemiological Studies Depression scale for Children.
Model 1 included smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's depression score at follow-up.

4.5 Discussion

This study, assessing the potential impact of antenatal depression on child anxiety and depression 8-10 years later, found high levels of antenatal depression were associated with increased risk of child anxiety symptoms and difference in risk of how much this anxiety impacts on the child's everyday life. This relationship was consistently reported by the mothers of children, but to a much lesser extent by the children themselves, and was evident even after adjusting for a variety of other factors known to impact on child anxiety, such as maternal smoking during pregnancy, child sex, child age and current maternal depression. These results indicate a potential long-lasting effect of antenatal depression on child anxiety, but also demonstrate the perceived magnitude of anxiety differs between mother and child.

Previous studies have investigated associations between antenatal depression and child behaviour. Velders et al. [77] found antenatal depression was associated with increased internalising and externalising behaviour in children at three years old, while Barker et al. [74] found increased risk of externalising problems at eight years old. This study adds a unique perspective by investigating the impact of antenatal depression on child anxiety at 8-10 years old. In this study, antenatal depression was associated with increased risk of anxiety symptoms and increased risk of impact regarding both the parent report and child self-report. These differences remained after controlling for current maternal depression, supporting the "programming hypothesis", whereby depression during pregnancy has some association with child anxiety that is not explained solely by current maternal depression. However these differences were seen to a lesser extent and seen on fewer subscales in the child self-report compared to the parental report, even after adjustment for factors such as maternal age at

recruitment, maternal education years, smoking status at 15 weeks' gestation, child's age at testing, child sex and mother's depression score at follow-up.

Much of the previous research has demonstrated associations between maternal depression and child behaviour relies on maternal report data to rate children's behaviour or mental health [41, 72]. This could potentially be a problem due to the fact that a mother's own perception and bias of her child's abilities may not accurately reflect how the child is feeling themselves. In the present study, we used validated, parallel questionnaires to assess anxiety symptoms of 8-10 year old children, rated on the same scale by both the parent and child themselves. Total scores of parent-reported child anxiety symptoms (SCAS) were positively associated with child self-reported scores. However, there was no association between parent and child reported total scores on the anxiety interference scale (CALIS), suggesting that mothers and children have some agreement in their amount of anxiety, but disagree with how much the child's anxiety impacts their everyday life. Previous research has found poor concordance between parent and child reported anxiety rated at three separate time points across three years in participants aged 8–13 years old [287]. This suggests the most accurate picture of a child's mental health can be determined by looking at reports from multiple informants such as mothers, fathers, primary caregivers and teachers, in addition to the child [288]. This difference highlights the importance of assessing both mother and child reported symptoms separately.

Current maternal depression symptoms may impact upon the child's mental health, and previous research has suggested this may be problematic as a mother's current mental state may impact her rating of her child. One study suggested that mothers with current high levels of depressive symptoms have less accurate perceptions of their children's mental health which may lead them to over report their

children's problems [217]. In contrast, another study suggested that depressed mothers have more accurate perceptions of their children [285], and non-depressed parents may be less aware of their children's mental health problems, and hence non-depressed parents tend to under-report their child's problems. In this study, we found that children were at an increased risk of anxiety symptoms (total) and anxiety interference (total) in both the parent-reported and self-report, after controlling for other factors including mother's current anxiety. This is consistent with studies of the Avon Longitudinal Study of Parents and Children, which found antenatal depression was associated with increased risk of attention problems at age three [54] and emotional and behavioural issues at age 10-11 [72], also after controlling for mother's current depression. Together, these findings support the idea that antenatal depression does impact upon long-term outcomes for children, and that this difference is not solely explained by the mother's current depressive symptoms.

Interestingly, EPDS scores at 15 and 20 weeks' gestation were not significantly associated with child depression score at 8-10 years, nor was the mother's current level of depression. Previous findings have reported associations between antenatal depression and increased risk of depression in children at 16 years old [79] and at 18 years of age [80]. In the current study, children at age 8-10 years old born to mothers who had high antenatal depression had higher depression scores compared to their low antenatal depression counterparts, but this difference was not statistically significant. There was also no difference in risk of depressive symptoms after controlling for various factors including current maternal depressive symptoms. Taken together with the previous findings, those from the present study suggest that there may be a window of opportunity between childhood and adolescence to intervene to reduce the risk of developing depression in adolescence.

Previous studies have suggested that sex differences are important when assessing anxiety outcomes as, in general, female children tend to be more anxious than males [289, 290]. One study suggests that female children are more susceptible to depressive symptoms at 18 years of age compared to males if their mothers had antenatal depression [291]. However, these authors found no effect of child sex on depression at 12 years of age, suggesting that different biological processes are involved in brain development through adolescence, which may also be more influenced by programming. This may explain why the addition of sex made little difference to risk of anxiety or depressive symptoms.

One of the most well described biological mechanisms for the effect of antenatal depression on child development is alterations of maternal and fetal hypothalamic pituitary adrenal (HPA) axes [44, 69]. Antenatal depression has been linked with higher levels of the stress hormone, cortisol, during pregnancy [100]. Increased cortisol may also reduce placental enzyme 11-beta hydroxysteroid dehydrogenase type II (11β-HSD2) [103]. This enzyme is responsible for the conversion of cortisol to its inactive form, cortisone. Therefore, a decrease in 11β-HSD2 may result in more cortisol available in fetal circulation. This exposure to higher cortisol may lead to perturbations in the development of the child's HPA axis. Children born to mothers with antenatal depression demonstrate increased cortisol in response to acute stress [64, 100, 101, 292]. Maternal depression may also directly, or indirectly, influence blood flow or nutritional supply to the fetus, and this may in turn impact upon child outcomes [50, 54]. This offers biologically plausible mechanisms that may contribute to the effects seen in the present study.

The hospital from which the SCOPE participants were recruited serves a socioeconomically disadvantaged population. Previous studies have suggested that

those with lower SES are more likely to have depression [40]. However, in the present study we found no significant differences in SES between those with high or low levels of antenatal depression. However, most participants had low SES. Other studies include participants from a wider range of economic backgrounds which may explain their disparate findings in this regard. Investigating a cohort who are all low SES adds to the understanding of how antenatal depression impacts children who are all similarly exposed to a low SES environment. This may lead to new understandings of what factors lead to resilience in children.

This study had a number of limitations. Firstly, data on maternal mental health were only available from pregnancy and at 8-10 years post-delivery. This meant we could not investigate factors that happened after the birth, such as postnatal depression, and the impact they may have had on child mental health outcomes. However, although postnatal depression has been associated with a range of behavioural deficits in children [293-295] and also mental health problems [296, 297], EPDS scores during pregnancy have been associated with the development of postnatal depression. Therefore antenatal EPDS scores may serve as a marker of the development of depression for women in future. Additionally, we controlled for current maternal depression to limit the impact this may have on findings. Secondly, attrition bias may have affected our results. Women who did not attend the follow-up or could not be contacted had significantly higher depression scores at 15 weeks' gestation compared to those who attended (See Chapter 3, Table 3.3). This may suggest an underestimation of poor outcomes in the follow-up. Finally, we did not address any biological measures of anxiety or depression. Given that previous studies have shown varying associations between subjective (i.e. questionnaire data) and objective (e.g. biomarkers such as cortisol) data, future studies should investigate the link between these.

This study also had a number of strengths. Firstly, this study was a follow-up of a richly phenotyped cohort, with prospective data available on a variety of factors. We also not only investigated the impact that antenatal depression had on anxiety, but also how much this anxiety interfered with the child's everyday life. Secondly, we investigated anxiety of the child from both the mother and child perspective. Thirdly, participants were generally from low socioeconomic backgrounds. Low SES has been shown to be a major contributor to poor outcomes in children. Therefore, if findings can help to identify early on which children are most at risk of poor developmental outcomes, then this information can be used to create interventions to help those who are most disadvantaged. Finally, although we did not utilise objective biomarkers of depression (ie. cortisol), we identified depression through scores on the EPDS. The EPDS is routine for all women who attend the hospital to complete at the first antenatal appointment, which is usually at similar time points which are defined as "high antenatal depression" at in this study. This means findings here can be easily translated to other women to identify those most at risk of poor outcomes, and therefore allow for early intervention.

Overall, we found that maternal antenatal depression increased the risk of child anxiety and how much these anxiety symptoms interfere with the child's life in parent and child reports. However, this difference is rated as much larger for parents and in different subscales compared to when rated by children. Poor mental health in childhood has been associated with increased risk of mental health disorders in adolescence and in adulthood, therefore this finding highlights the need for early interventions to prevent or stop the development of these disorders in future. In contrast, we found no association between maternal antenatal depression, and child reported depression symptoms at 8-10 years old. However, given previous research has

found associations between antenatal depression and depressive symptoms in offspring at adolescence and adulthood, these findings highlight a window of opportunity for early intervention in childhood to avoid the development of depressive disorders.

Chapter 5:

The impact of maternal antenatal depression on child cognitive function at 8-10 years old

5.1 Abstract

Introduction: Increasing evidence links poor maternal mental health during pregnancy with poor child outcomes. However, few studies have looked at the impact of maternal antenatal depression on child cognitive function in mid childhood. We investigated the impact of antenatal depression on cognitive domains in 8-10 year old children.

Method: Women in the SCreening fOr Pregnancy Endpoints (SCOPE) study completed the Edinburgh Postnatal Depression Scale (EPDS) at 15 weeks' gestation. Women and children were contacted 8-10 years after delivery to attend a follow-up appointment. Children's cognitive assessments were conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB), investigating cognitive domains of executive function, memory and reaction time.

Results: Mothers who scored ≥13 on the EPDS were classed as having high antenatal depression (n=38) and scores of <13 indicated low antenatal depression (n=235). After adjustment for maternal age at recruitment, maternal education, maternal smoking at 15 weeks' gestation, child age, child sex and current maternal depression, those whose mothers had high antenatal depression had higher likelihood of errors on the 6-box problem of the new learning memory task (adjusted risk ratio, aRR: 1.35, 95%CI 1.08-1.68) and also increased likelihood of errors on the 6-box problem of the spatial working memory task (aRR: 1.23, 1.05-1.44). However, there was no difference in likelihood of errors on the harder 8-box problems. Those children whose mothers had high antenatal depression during pregnancy also had significantly longer movement times on the simple reaction time task, although this difference was small (β:18.61; 95%CI 4.05-33.17). There was no difference between the low and high antenatal depression groups on any other reaction time outcomes or on the executive functioning task.

Conclusion: Antenatal depression is associated with memory deficits and motor movement time deficits at 8-10 years old. This highlights the importance of intervention to reduce depressive symptoms during pregnancy, and also to provide interventions to reduce the risk of poor neurodevelopment in children.

5.2 Introduction

Maternal antenatal depressive symptoms affect up to 20% of pregnant women [41], with families living in low socioeconomic households disproportionately affected by poor mental health [40]. Increasing evidence from prospective cohort studies demonstrates children exposed to poor maternal mental health during pregnancy including depression, anxiety or stress have more adverse outcomes compared to children not exposed to poor maternal mental health [43, 44, 69, 298, 299].

Recent evidence has suggested that antenatal depression may be more relevant to predicting future developmental outcomes in children, and predicts adverse child outcomes, independently of postnatal depression [48, 51, 86, 87]. The impact of antenatal depression on infant cognitive abilities has been studied in a number of settings with mixed results. For example, Koutra et al. [48] found that antenatal depression predicted child neurological development as measured by the Bayley Mental Development Index (MDI) at 18 months old, independent of postnatal depression. In contrast, some studies have suggested that there is no relationship between antenatal depression and infant cognitive development at age three years [300], or even that child neurodevelopment is better following antenatal depression as measured by the Bayley MDI at two years old [301]. Although there are mixed findings, recent research suggests that while the Bayley Scales are a good indicator of infant development between individuals, scores are not associated with future school performance [49]. This suggests the importance of investigating potential associations of antenatal depression on child outcomes at older ages.

Few studies have followed up children at older ages to investigate long-term neurodevelopmental impacts of maternal antenatal depressive symptoms on child cognitive function with varying findings. In the Avon Longitudinal Studies of Parents

and Children (ALSPAC) cohort, maternal antenatal depression was associated with lower intelligence quotient (IQ) in eight year old children, but this difference disappeared after controlling for confounders such as maternal age, smoking during pregnancy and education [51]. In contrast, studies by Barker et al. [50, 74] demonstrated those children exposed to maternal antenatal depression had lower IQ scores than those not exposed to antenatal depression. However, IQ is composed of different cognitive domains including executive function and memory, and while these findings demonstrate antenatal depression may impact IQ, there is little evidence on which underlying cognitive domains of IQ are most impacted. Few studies have investigated impact of antenatal depression and specific cognitive domains. One study found antenatal depression was associated with poorer visuospatial working memory in 6 to 9 year old children, but not associated with executive function [52], while other studies found associations with increased attention difficulties [54, 72] and lower fine motor development [53]. This suggests different aspects of cognition may be differentially impacted, and hence should be investigated separately.

Given that previous research has focused on young infants and global IQ measures in children, we sought to investigate the impact of antenatal depression on different cognitive domains in school aged (8-10 year old) children. This study took advantage of the detailed prospective data collected from the Adelaide arm of the SCOPE cohort, which included measures of antenatal depression on the Edinburgh Postnatal Depression Scale (EPDS) at 15 and 20 weeks' gestation. This cohort resides in an area characterised by low socioeconomic status (SES), allowing us to explore those most impacted by antenatal depression, who are most disadvantaged. To assess children's neurodevelopment, we utilised an automated cognitive testing battery completed on an iPad with which the children were familiar. This allowed us to

objectively measure each child's cognitive function including executive function, memory and reaction time. Due to this follow-up being 8-10 years after the birth, we also controlled for the mother's current depression by including measures to assess mother's current depression symptoms, as previous research has shown current maternal depression can impact child cognitive function. We hypothesised that those children exposed to maternal antenatal depression would have deficits in cognition aged 8-10 years.

5.3 Methods

5.3.1 *Participants*

Participants were from the Adelaide arm of the SCreening fOr Pregnancy Endpoints (SCOPE) cohort. SCOPE was a prospective cohort study which aimed to develop screening tools to predict risk for pregnancy complications [262, 263]. In brief, 1164 nulliparous pregnant women were recruited between September 2005 and September 2008 at the Lyell McEwin Hospital in Adelaide, South Australia. Women were initially recruited, interviewed and examined by SCOPE research midwives at 15±1 weeks' gestation, and then again at 20±1 weeks. Women were excluded from the study if they were deemed to be at higher risk of developing a pregnancy complication due to other underlying health conditions such as chronic hypertension, diabetes or systemic lupus. Participants were followed up prospectively throughout pregnancy, with research midwives recording pregnancy outcome and measurements of the baby. For follow-up of the SCOPE participants, women were contacted by phone 8-10 years after the first pregnancy and asked to attend a follow-up appointment.

At the follow-up appointment, women and children provided written consent and assent, respectively. Children underwent cognitive testing and completed

questionnaires during a two hour session. During the same session, the children's mothers took the same cognitive tests and answered questionnaires about themselves and their child.

5.3.2 *Measures*

5.3.2.1 *Maternal mental health*

Depression during pregnancy was measured using the Edinburgh Postnatal Depression Scale (EPDS) [261] at both 15 and 20 weeks of gestation (Appendix A). The EPDS is a 10-item questionnaire used for screening for depression, with higher scores indicating increased depressive symptoms. Although this scale was originally developed for use during the postnatal period, it has since been validated for use during the antenatal period [260]. A cut off score of ≥13 is recommended to suggest significant depressive symptoms that likely indicate depression [261]. In this study, high antenatal depression was defined as EPDS score of ≥13 at either the 15 or 20 week time point. All participants who scored <13 at both time points therefore comprised the low antenatal depression group.

At follow-up, mothers completed the Depression, Anxiety and Stress Scale (DASS-42; Appendix J). This measure includes three 14-item scales measuring depression, anxiety and stress independently [274]. Participants were asked to rate how much each item applied to them during the past week. Items were rated on a 4-point Likert scale, ranging from 0 ("did not apply to me at all") to 3 ("applied to me very much, or most of the time"). Scores were created for each of these three subscales, with scores ranging from 0-42 for each subscale, and higher scores indicating increased severity of symptoms in that domain.

5.3.2.2 *Cognitive function*

Cognitive performance was assessed using five tests from the standardised Cambridge Neuropsychological Test Automated Battery (CANTAB) connect system [264]. The CANTAB system utilises a touch screen tablet, with automated administration of tests to ensure standardised testing across participants. Participants were seated at a desk with the tablet in front of them, where they were instructed to complete a series of five tests. These tests were specifically chosen to assess components of reaction time, executive function, memory and reaction time, and took approximately 35 minutes. All participants completed the tests in the same order.

Attention switching task

The attention switching task (AST) was used to measure executive function, namely cognitive flexibility. Participants were initially presented with an arrow in the middle of the screen, with the word 'direction' at the top of the screen, and asked to press the buttons according to which direction the arrow was pointing (Fig. 5.1A). In more complex trials, the arrow was presented on either side of the screen either pointing left or right, and instructions of either 'direction' or 'side' appeared across the top of the screen. The participant was asked to press a corresponding button, either left or right, depending on which direction the arrow was pointing (Fig. 5.1B), or which side of the screen the arrow was on (Fig. 5.1C). Each block began with eight practice trials. The participants were first presented with a 40 trial 'direction' only block, then a 40 trial 'side' only block, before a final block of 80 trials that randomly switched between instructions. Throughout the task, participants were instructed to go as fast as they could without making mistakes. Outcomes of interest were side block errors, direction block errors, total correct and median latency over all assessed trials, switching block

errors and switching block median latency. For more details, see Chapter 2 (Section 2.3.1).

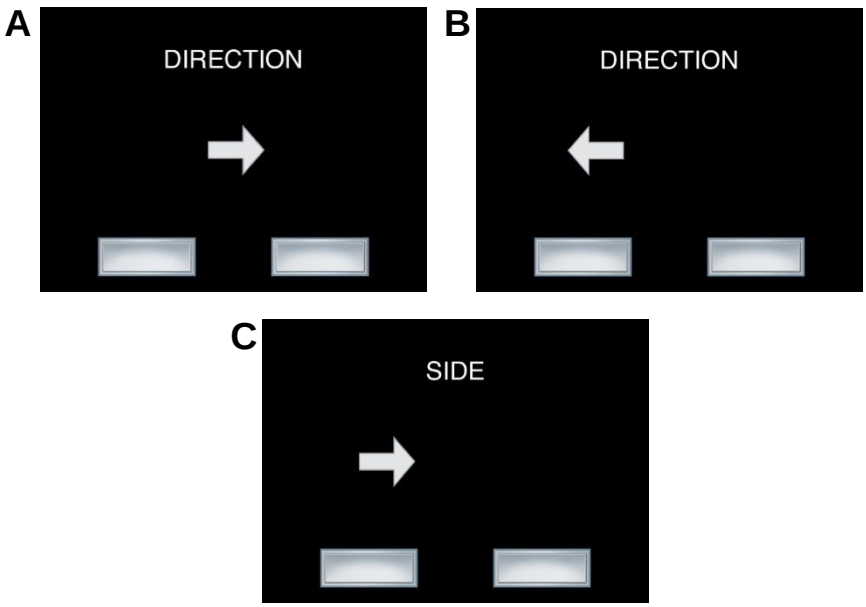

Figure 5.1 Attention switching task screenshots. (A) The first practice block where the arrow appeared in the middle of the screen, and the participant was asked to press left or right depending on which direction the arrow was pointing; (B) Participant was presented with 'direction' instruction, and had to press the left or right button depending on which direction the arrow was pointing; (C) Participant was presented with 'side' instruction, and had to press the left or right button depending on which side of the screen the arrow appeared on.

Delayed matching to sample task

The delayed matching to sample (DMS) task was used to assess visual delayed memory. Participants were first presented with a target pattern and instructed to remember the pattern (Fig. 5.2A). They were then presented with a choice of four patterns underneath, which included the target pattern and three decoys (Fig. 5.2B). Participants received feedback on responses (Fig. 5.2C). In more complex trials, the target pattern was covered before the choices of patterns appeared below (Fig. 5.2D). This task presented these patterns either simultaneously, or after a delay of 0, 4, or 12 seconds, and these delays were randomised for each trial so the participant did not know for how long they would need to remember the next pattern. Performance was assessed by the total number of correct over all trials, total correct on each level of the delays, and total median latency (milliseconds). For more details, see Chapter 2 (Section 2.3.2).

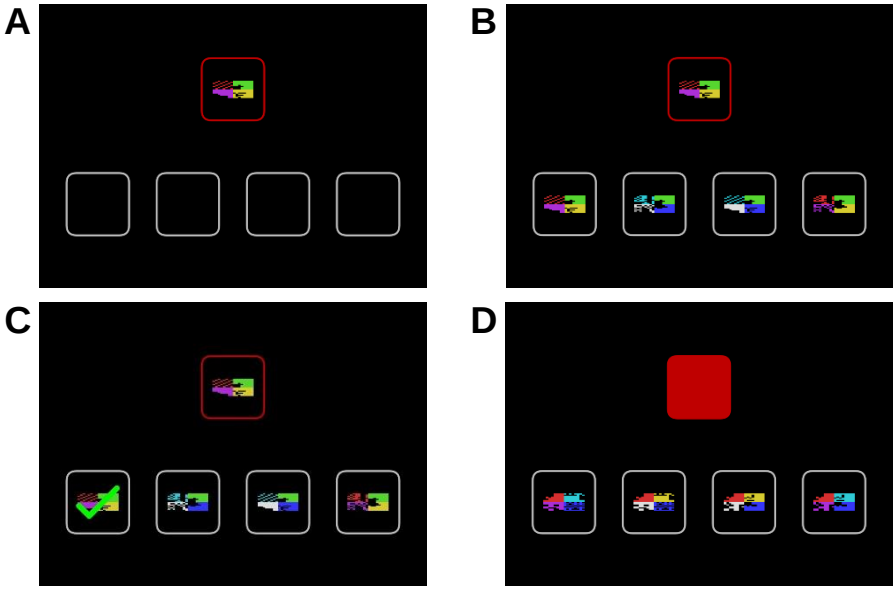

Figure 5.2 Delayed matching to sample task screenshots. (A) The initial presentation of the target pattern; (B) Participants then had to identify the matching pattern from the choices presented in the lower row; (C) The participant received feedback for a correct response. (D) In more complex trials, the target pattern was covered prior to the pattern options appearing in the row below after delays of either 0, 4 or 12 seconds.

Paired associates learning task

The paired associates learning (PAL) task was administered to measure visual memory and new learning. Participants were presented with six to eight white boxes around the edge of screen, which opened in a randomised order, one at a time, to reveal different patterns (Fig. 5.3A). Participants were then presented with each pattern in the centre of the screen, and asked to touch the box where that pattern appeared (Fig. 5.3B). The level of difficulty of this task increased, starting from two patterns, and increasing to 4, 6, and 8 different patterns. Participants advanced to the next level when they successfully identified the location of each pattern. If they chose incorrectly, the same level was repeated for a maximum of four attempts. Outcomes of

interest were the number of correct boxes selected on the first attempt, the total number of errors for the whole task and total errors made on each level (both adjusted for levels reached) and number of levels completed. For more details, see Chapter 2 (Section 2.3.3).

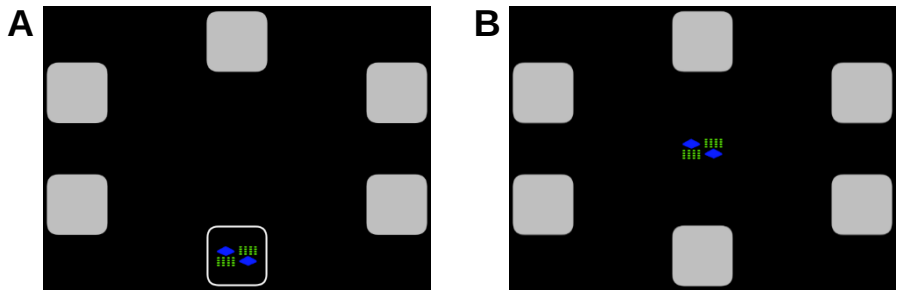

Figure 5.3 Paired associates learning task screenshots. (A) Boxes around the screen opened one by one revealing patterns inside, and participants were instructed to remember which pattern was in which box; (B) Patterns were then presented in the middle of the screen to be matched with the box in which it appeared.

Spatial working memory task

The spatial working memory (SWM) task was used to measure memory. Participants were presented with a screen of coloured boxes, and were told that they had to find a token under each box, but only one token would be hidden at a time (Fig. 5.4A). Therefore once a token had been found in a box (Fig. 5.4B), participants were instructed to not look in that box again. Once participants had found all the tokens (Fig. 5.4C), they moved on to the next level. The task contained a practice with three boxes, and then advanced on to 4-, 6- and 8-box problems. The outcomes of interest were the total number of between errors (the number of times a participant incorrectly revisits a box where a token has already been found) across all trials, and between errors separately on the 4-, 6- and 8-box problems. A strategy score was also

generated, which reflected the degree to which the participant had adopted a strategy to remember the boxes where tokens had been found. For more details, see Chapter 2 (Section 2.3.4).

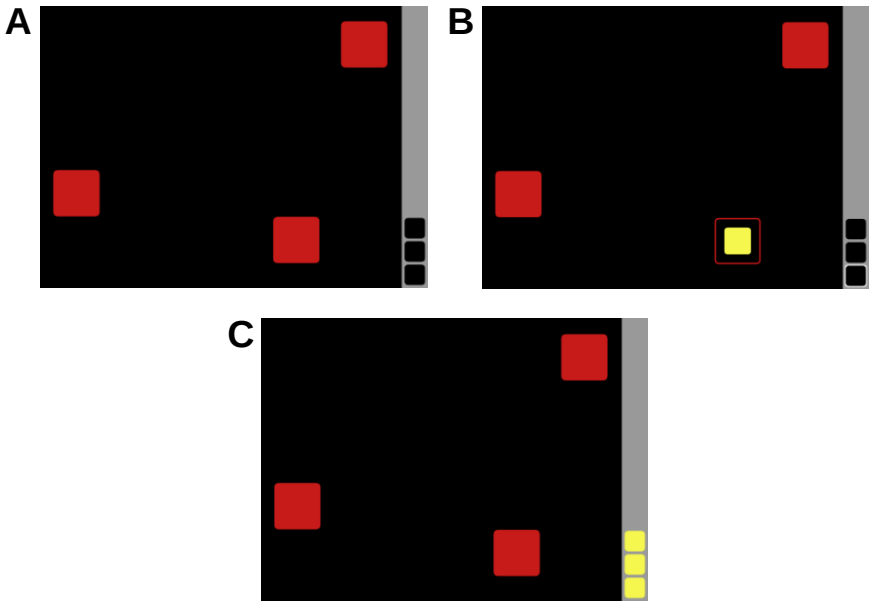

Figure 5.4 Spatial working memory task screenshots. (A) Participants initially presented with this screen and were instructed to search under the red boxes for tokens by touching on each box one at a time; (B) When the correct box was touched, the yellow token appeared and was moved to the bar on the right of the screen. For the rest of this trial, no token will appear under this box again; (C) Once all tokens were collected in the home bar (right of screen), participants moved on to the next level.

Reaction time task

The reaction time (RTI) task was used to measure reaction latency and movement time. The participant was shown a button on the bottom of the screen, with a circle at the top of the screen (Fig. 5.5A). They were instructed to hold down the bottom button until the circle at the top became yellow (Fig. 5.5B). They were then instructed to move their hand as quickly as possible to touch inside the yellow circle.

In the simple reaction time, the stimulus always appeared in the same place, however, in the five-choice task the stimulus could appear in one of five circles (Fig. 5.5C). Outcomes of interest for both simple and five-choice tasks were reaction time (duration of time between the presentation of the yellow spot and the release of the button), and movement time (the time taken to touch the yellow spot after the release of the button). For more details, see Chapter 2 (Section 2.3.5).

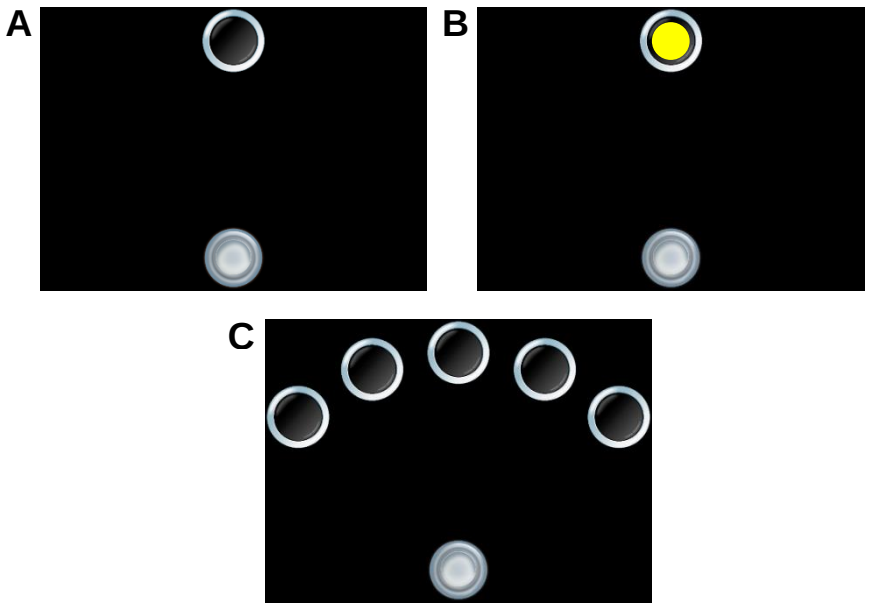

Figure 5.5 Reaction time task screenshots. (A) Participants were instructed to hold their finger on the button at the bottom of the screen and wait for a yellow dot to appear; (B) When the yellow dot appeared, participants had to release the button and touch the yellow dot as fast as they could; (C) This same process was then repeated with the yellow dot appearing in one of five locations, as a five-choice reaction time test.

5.3.3 *Data analysis*

Data were analysed using SPSS v25. T-tests and Mann-Whitney U tests were used for analysis of demographics for continuous variables between groups. Chi-square and Fisher's exact tests were used to compare categorical variables between the groups. Mann-Whitney U tests were used to assess cognitive function of children comparing between those mothers with low and high antenatal depression (EPDS) groups. T-tests were used for univariate analysis of latencies and reaction times. Regression models were conducted to adjust for the potential influence of other factors known to affect child anxiety and depression, including mother's smoking status, mother's age, mother's education, child age, child sex, and mother's current depression score. Poisson regression models were used for score and count data, while linear regressions were used for latency outcomes. Model 1 included mother's smoking status, mother's age, mother's education, child age; Model 2 included all factors in Model 1 plus child sex; Model 3 included all factors in Model 2 plus mother's current depression score at follow-up. Data on confounding factors used in the models were available for all participants who attended the follow-up.

5.4 Results

5.4.1 *Demographics*

A large number of participants (n=530) could not be contacted; 23 due to loss of baby, two did not originally consent to be followed up for future studies, 202 had no valid phone numbers, and 227 did not answer. Of the 634 participants who could be reached, 420 (66%) booked appointments and 270 (43%) attended appointments. Three children (1.1%) were unable to complete any of the cognitive tests due to autism. A further six (2.2%) did not complete one or more of the cognitive tests due to

technological issues (n=2, 0.7%), difficulty reading (n=2, 0.7%) and/or autism (n=2, 0.7%).

Table 5.1 shows the demographic characteristics of the whole follow-up cohort, and separated into those women with low and high levels of antenatal depression. There were no statistically significant differences in the mother's age at recruitment, socioeconomic index (SEI), body mass index (BMI), ethnicity, partner status, education level, job status or alcohol consumption at 15 weeks' gestation between the two groups. There were significantly more smokers in the high antenatal depression group compared to the low antenatal depression group (p=0.001). As expected, scores on the EPDS were significantly higher for those women with high antenatal depression compared to those with low depression scores at both 15 and 20 weeks' gestation (both p<0.001). There was no difference in the incidence of pregnancy complications between the groups.

Table 5.2 shows characteristics of participants at follow-up. Mothers who had high antenatal depression also had significantly higher depression scores on the DASS at follow-up compared to those who had low antenatal depression (p=0.002). There were no significant differences in the age or sex of the children between the groups at follow-up.

Table 5.1 Characteristics of SCOPE women during pregnancy and divided into those with low and high antenatal depression

	All (n=273)	**Low antenatal depression (n=235)**	**High antenatal depression (n=38)**	***p*-value**
Age of mother at recruitment years, mean (SD)	26 (5)	26 (5)	25 (5)	0.081
SEI	27 (22-34)	27 (22-34)	28 (20-33)	0.894
BMI, kg/m^2	26.60 (23.70-30.60)	26.30 (23.70-30.60)	26.75 (22.90-29.70)	0.953
Ethnicity, Caucasian	264 (96.7%)	228 (97.0%)	36 (94.7%)	0.464
Married or defacto	232 (85.0%)	201 (85.5%)	31 (81.6%)	0.527
Education level at recruitment, years	12 (11-13)	12 (11-13)	12 (11-12)	0.107
Employment at recruitment, full time	148 (54.2%)	132 (56.2%)	16 (42.1%)	0.110
Smoking at 15 weeks	39 (14.3%)	**27 (11.5%)**	**12 (31.6%)**	**0.001**
Consuming alcohol at 15 weeks	9 (3.3%)	7 (3.0%)	2 (5.3%)	0.364
EPDS score at 15 weeks	5 (2-9)	**4 (1-7)**	**15 (11-16)**	**<0.001**
EPDS score at 20 weeks	4 (2-9)	**4 (2-7)**	**13 (12-15)**	**<0.001**
Complicated pregnancy[a]	107 (39.2%)	92 (39.1%)	15 (39.5%)	0.970

Data presented as median (IQR) or n (%) unless otherwise stated.

SEI Socioeconomic Index (determined using NZSEI [see Chapter 2]); *BMI* Body Mass Index; *EPDS* Edinburgh Postnatal Depression Scale.

[a]Complicated pregnancy – refers to those with any of the major complications of pregnancy including preeclampsia, small for gestational age, preterm birth, gestational diabetes mellitus or gestational hypertension.

Table 5.2 Characteristics from all participants at follow-up, and divided into those with low and high antenatal depression

	All (n=273)	**Low antenatal depression (n=235)**	**High antenatal depression (n=38)**	***p*-value**
Mother's DASS Depression score, median (IQR)	2 (0-5)	**1 (0-5)**	**4 (2-11)**	**0.002**
Child age at follow-up, years mean (SD)	9.6 (0.6)	9.6 (0.6)	9.5 (0.5)	0.151
Child sex, Male, n (%)	121 (44.3%)	106 (45.1%)	15 (39.5%)	0.517

DASS Depression, Anxiety and Stress Scale.

5.4.2 *Univariate analysis of maternal antenatal depression and child cognitive outcomes*

Table 5.3 shows univariate analysis of child cognitive outcomes between those whose mothers had low and high antenatal depression. There were no significant differences in scores for any measures of child executive function as measured by the AST between those children whose mothers had low or high antenatal depression.

In the DMS memory task which measured visual delayed memory, there were no significant differences in overall total correct score between those children whose mothers had low or high antenatal depression. There were no differences in scores for the simultaneous, 0 or 4 second delays. However, children whose mothers had high antenatal depression scored significantly more correct on the 12 second delay problems compared to those whose mothers had low antenatal depression ($p<0.05$), indicating better performance.

There was no difference in child performance on any visual memory and new learning outcomes as measured by the PAL task between the low and high antenatal depression groups.

In the SWM task which measured spatial working memory, there were no differences in total between errors. For between errors on individual levels, there was no difference in between groups on the 4- and 8-box problems. However, those children whose mothers had high antenatal depression made significantly more errors on the 6-box problem ($p<0.05$), indicating poorer performance. There was no difference in SWM strategy score.

Those children whose mothers had high antenatal depression had significantly longer latencies in both simple reaction time and simple movement time (both $p<0.05$), indicating slower reaction and motor movement times on the reaction time task (RTI).

In the five choice task, the high antenatal depression group again had longer latencies in both the reaction and movement times, however, only the movement time was significant ($p<0.05$).

Table 5.3 Raw cognitive outcomes with unadjusted analysis from children whose mothers were classed as having low antenatal depression, compared to outcomes of children whose mothers had high antenatal depression

	Low antenatal depression (n=235)	**High antenatal depression (n=38)**	***p*-value**
Attention switching task			
Side block errors	1 (0-2)	0 (0-2)	0.997
Direction block errors	3 (1-6)	3 (1-5)	0.359
Switching block errors	10 (6-15)	8 (6-17)	0.498
Switching block, latency, ms, mean (SD)	836.35 (162.80)	838.68 (162.26)	0.936
Total correct	143 (133-149)	143 (131-150)	0.579
Latency, ms, mean (SD)	723.64 (122.74)	726.95 (105.35)	0.877
Delayed matching to sample			
Total correct			
Overall	16 (14-17)	17 (14-18)	0.294
Simultaneous	5 (4-5)	5 (5-5)	0.541
0s delay	4 (3-5)	4 (3-5)	0.610
4s delay	4 (3-5)	4 (3-5)	0.781
12s delay	**3 (3-4)**	**4 (4-5)**	**0.043**
Latency, ms, mean (SD)	2988.19 (833.66)	3181.45 (904.42)	0.457
Paired associative learning			
First attempt memory score	15 (13-18)	15 (13-17)	0.818
Total errors (adjusted)			
Total	5.5 (3-10)	6 (3-9)	0.808
4 box problem	0 (0-1)	0 (0-0)	0.388
6 box problem	1 (0-3)	2 (0-4)	0.158
8 box problem	3 (1-6)	3 (1-6)	0.905
Number of problems reached	8 (8-8)	8 (8-8)	0.668
Spatial working memory			
Between errors			
Total	17 (12-21)	16.5 (11-23)	0.529
4 box problem	0 (0-1)	0 (0-1)	0.973
6 box problem	**4 (1-7)**	**6 (3-8)**	**0.026**
8 box problem	12 (8-15)	11.5 (7.5-14)	0.573
Strategy score	9 (8-10)	9 (8-10)	0.901
Reaction time *milliseconds, presented as mean (SD)*			
Simple reaction time	**372.70 (43.20)**	**388.35 (49.23)**	**0.046**
Simple movement time	**175.67 (39.96)**	**197.88 (42.16)**	**0.002**
Five choice reaction time	431.45 (56.23)	442.57 (58.48)	0.268
Five choice movement time	**210.45 (44.09)**	**228.65 (40.14)**	**0.019**

Data presented as median (IQR) unless otherwise stated.

5.4.3 *Antenatal depression was not associated with executive function in children*

After adjustment for mother's smoking status, mother's age, mother's education, child age (Model 1), there was no significant difference in risk of errors or correct scores on the executive function task between those whose mothers had high or low antenatal depression (Table 5.4). After adding child sex (Model 2) and then mother's current depression score (Model 3), there were still no differences in risk of errors or correct outcomes in the executive function task.

Table 5.4 Increased or impaired executive function in children exposed to high antenatal depression in reference to those whose mothers had low antenatal depression

Attention switching task outcomes			
	Model 1	**Model 2**	**Model 3**
Side block errors	0.74 (0.53, 1.03)	0.75 (0.54, 1.04)	0.84 (0.68, 1.04)
Direction block errors	0.95 (0.81, 1.11)	0.95 (0.81, 1.11)	0.92 (0.78, 1.07)
Switching block errors	0.91 (0.82, 1.01)	0.91 (0.82, 1.01)	0.94 (0.85, 1.05)
Switching block latency[a]	-6.65 (-64.21, 50.92)	-7.43 (-64.82, 49.96)	-9.90 (-68.34, 48.54)
Total correct	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)	1.01 (0.98, 1.04)
Overall latency[a]	-6.68 (-48.80, 35.44)	-7.75 (-49.22, 33.72)	-7.95 (-50.20, 34.30)

Results presented as adjusted relative risks (aRR; 95% CI) or [a]from linear regression (β; 95% CI) for high antenatal depression group (n=38); Reference category is low maternal antenatal depression (n=235).

Model 1 adjusted for smoking status at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's current depression score.

5.4.4 *Antenatal depression was associated with learning and spatial working memory in children*

After adjustment, there was no difference in risk of errors on the DMS task, nor any difference in latency between the low and high antenatal depression groups (Table 5.5).

Following adjustment for mother's smoking status, mother's age, mother's education, and child age (Model 1), those children whose mothers had high antenatal depression had significantly higher risk of errors on the 6-box problem of the PAL task compared to those whose mothers had low antenatal depression (Table 5.5). This risk remained stable across models, with the final model (Model 3) resulting in 35% increased risk of errors. There was no difference in risk of total errors or errors on other levels of the PAL task between groups.

After adjustment for mother's smoking status, mother's age, mother's education, and child age (Model 1), those children with mothers who had high antenatal depression had significantly increased risk (19%) of between errors on the 6-box problem of the SWM task (Table 5.5). This difference increased after controlling for child sex and mother's current depression (Model 3), suggesting a 23% increase in risk of errors compared to their low antenatal depression counterparts. There was no difference in risk of between errors on any other levels, or strategy score, between groups.

Table 5.5 Increased or impaired memory in children exposed to high antenatal depression in reference to those whose mothers had low antenatal depression

	Model 1	Model 2	Model 3
Delayed Matching to Sample			
Total correct			
Overall	1.04 (0.95, 1.13)	1.03 (0.95, 1.13)	1.04 (0.95, 1.09)
Simultaneous	1.03 (0.87, 1.21)	1.03 (0.87, 1.21)	1.03 (0.87, 1.22)
0s delay	1.02 (0.85, 1.22)	1.02 (0.85, 1.22)	1.01 (0.84, 1.21)
4s delay	0.99 (0.82, 1.19)	0.99 (0.82, 1.19)	1.00 (0.82, 1.20)
12s delay	1.12 (0.93, 1.34)	1.11 (0.93-1.34)	1.12 (0.92, 1.35)
Median latency[a]	141.87 (-160.09, 443.82)	35.94 (-169.78, 443.30)	140.37 (-167.44, 448.18)
Paired Associative Learning			
First attempt memory score	0.98 (0.99, 1.08)	0.98 (0.90, 1.08)	0.98 (0.89, 1.08)
Total errors adjusted			
Total	1.08 (0.96, 1.22)	1.09 (0.96, 1.23)	1.09 (0.97, 1.24)
4 box problem	0.83 (0.55, 1.24)	0.83 (0.55, 1.24)	0.80 (0.53, 1.20)
6 box problem	**1.35 (1.08, 1.67)**	**1.36 (1.09, 1.68)**	**1.35 (1.08, 1.68)**
8 box problem	1.01 (0.59, 1.18)	1.01 (0.86, 1.19)	1.03 (0.88, 1.21)
Spatial Working Memory			
Between errors			
Total	1.04 (0.95, 1.14)	1.04 (0.95, 1.14)	1.05 (0.96, 1.15)
4 box problem	1.07 (0.70, 1.64)	1.07 (0.70, 1.64)	1.11 (0.72, 1.71)
6 box problem	**1.19 (1.02, 1.39)**	**1.19 (1.02, 1.39)**	**1.23 (1.05, 1.44)**
8 box problem	0.99 (0.89, 1.11)	0.99 (0.89, 1.11)	0.99 (0.89, 1.11)
Strategy score	0.99 (0.88, 1.12)	0.99 (0.88, 1.12)	0.99 (0.88, 1.13)

Results presented as adjusted relative risk (aRR; 95% CI) or [a]from linear regression (β; 95% CI); Differences in those exposed to high levels of antenatal depression (n=38); Reference category is low maternal antenatal depression (n=235).

Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's current depression score.

5.4.5 *Antenatal depression was associated with movement time but not reaction time*

After adjustment, there were no differences in simple reaction time, or five choice reaction or movement times between groups (Table 5.6). However, children whose mothers had high antenatal depression had significantly longer simple movement time compared to those children only exposed to low antenatal depression.

Table 5.6 Differences in reaction time in children exposed to high antenatal depression in reference to those whose mothers had low antenatal depression

Reaction time task outcomes			
	Model 1 **β* (95% CI)**	**Model 2** **β* (95% CI)**	**Model 3** **β* (95% CI)**
Simple			
Reaction time	12.91 (-2.62, 28.45)	12.55 (-2.89, 28.00)	13.74 (-1.93, 29.40)
Movement time	**19.00 (4.52, 33.48)**	**18.55 (4.25, 32.86)**	**18.61 (4.05, 33.17)**
Five choice			
Reaction time	7.37 (-12.57, 27.31)	6.76 (-12.94, 26.46)	7.28 (-12.72, 27.28)
Movement time	14.96 (-0.73, 30.65)	14.52 (-1.02, 30.06)	14.30 (-1.51, 30.12)

*β: Differences in those exposed to high levels of antenatal depression (n=38); Reference category is low maternal antenatal depression (n=235).
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's current depression score.

5.5 Discussion

This study sought to explore the relationship between antenatal depression and cognitive function in a prospective cohort of children aged 8-10 years. Previous research has demonstrated associations between antenatal depression with behavioural outcomes and IQ, hence this study sought to investigate the impact antenatal depression had on specific cognitive domains. We found associations between antenatal depression and visual learning and spatial working memory, and performance on a simple motor task, after adjustment for various confounding factors. These findings support that intrauterine mechanisms may play a role in long-term child development.

There was an association between antenatal depression and memory 8-10 years later. Interestingly, children whose mothers had high antenatal depression had increased risk of errors in the visual learning and spatial working memory tasks for 6-box problems, but not on more challenging 8-box problems. This finding may suggest issues with complexity of the 8-box problem, whereby the task becomes too challenging for 8-10 year old participants. This finding may also suggest that children in the high antenatal depression group have shorter memory spans, therefore "fatigue" more quickly during the task, and then both groups perform comparably for the 8-box task. There is also evidence that demonstrates antenatal anxiety is associated with impulsivity in children [302]. This may suggest that as the task gets harder, children whose mothers had high antenatal depression become more impulsive more quickly, meaning they get more incorrect on 6-box problems, but then perform comparably on the hardest level ie. when there are eight boxes. Taken together, these findings do give some support to an intrauterine mechanism for cognitive deficits to visual learning and spatial working memory. After adjustment for several confounding factors including

current maternal depression, these differences in memory remained domains. Interestingly, differences in delayed memory that suggested children whose mothers had high antenatal depression had better memory after a 12 second delay were attenuated in the adjusted models. This suggests that some areas of memory, such as visual learning and spatial working memory may be more susceptible to intrauterine exposures.

Executive functions are controlled predominantly by the prefrontal cortex. Previous findings have suggested an association between high maternal antenatal anxiety and lower prefrontal cortical volumes in children [303]. However, few studies have investigated the influence of antenatal depression on prefrontal functioning or executive functioning specifically. A study by Buss et al. [52] assessed maternal depression throughout pregnancy, and found that this was not associated with child executive functioning at 6-9 years old as measured by an inhibitory control task. Similarly in the current study, we found no association between maternal antenatal depression and performance on an executive function (attention switching) task. While both these tasks measured broader executive functioning, they measured different aspects of executive function. Taken together, these findings suggest that antenatal depression does not impact on child executive functioning.

The present study assessed child cognitive function in separate domains to assess differences in specific areas of cognition. Previous research has associated antenatal depression with general cognitive outcomes, such as scores on the Bayley MDI [48] and IQ measures. Barker et al. [74] found those children whose mothers had antenatal depression had lower IQ scores at eight years old, while Evans et al. [51] found there was no difference in IQ of eight year old children after adjustment for maternal age, smoking, drinking, maternal education, income, child sex, birthweight and

breastfeeding. In these studies, there is no association with IQ after adjustment, or the difference in IQ scores is very minimal, with both groups scoring within a normal IQ range. There have been very few studies that address the impact of antenatal depression on specific cognitive domains. The present study found increased risk of deficits specifically in the cognitive domain of memory, and a small increase in motor movement time in those children exposed to antenatal depression. It is important to investigate separate cognitive domains instead of just on IQ, as IQ relies on different aspects of cognitive functioning. If deficits in specific cognitive domains can be identified, then specific interventions can be used to target those specific domains to reduce deficits, and hence in turn improve overall IQ.

Previous evidence suggests that other factors, such as child sex, play important roles in child neurodevelopment. For example, Murray et al. [81] found differences in child's academic scores at age 16 following postnatal depression, but this difference was only seen in boys and not girls. In the present study, there was little change in the impact of antenatal depression on cognitive outcomes after adjustment for child sex. One difference between the study by Murray et al. and the present study, is the difference in SES of the participants. Murray et al. included participants from low to high SES, and also found associations independently between SES and academic performance. The participants in the current study were all relatively low SES. SES has proven to be an important factor in predicting cognitive function [35-37, 304], therefore this may suggest that within low SES cohorts all participants are disadvantaged equally, and therefore there are little sex differences at 8-10 years old. Sex differences in brain organisation also become accentuated during adolescence, suggesting hormonal effects of puberty play a large role in brain function [305]. Therefore, these differences may not be as pronounced in 8-10 year old children.

Previous research has explored the impact of antenatal mental health on child motor development with varying results. Mid-pregnancy self-reported stress has been associated with lower performance on the Bayley Psychomotor Development Index at eight months [306]. In another study, where stress, anxiety and depression measures during pregnancy were used to create a composite measure of maternal distress, it was found that maternal distress was associated with reduced fine motor development at 16 months old [53]. However, one study that investigated specifically maternal depression during mid-pregnancy (measured by the EPDS) found that depression score was not associated with visual motor performance of three year old children [307]. Our results suggest that after adjustment, antenatal depression during pregnancy was associated only with speed of motor movement time on a simple (one choice) reaction time task, but not with reaction time or any measures on a more complex five choice reaction task. Differences in findings may be due to ages of participants, as these differences may be very subtle and become more apparent at older ages. However, it is also worth mentioning that the average difference seen in our study was only 20 milliseconds. While this is statistically significant, there is arguably little clinical relevance of a difference this small.

There are a number of limitations in this study. Firstly, the number of women who had antenatal depression and attended the follow-up was relatively small. These women were also more likely to have moderate rather than severe levels of depression, given those with severe depressive symptoms more frequently did not return for the follow-up appointment (See Chapter 3, Table 3.3). This could mean the current results are a conservative reflection of the true impact of maternal antenatal depression. Secondly, data were only available from pregnancy and then at 8-10 years old, and therefore we had limited information about other factors that may have impacted on

child cognition between initial recruitment and follow-up. For example, maternal depression trajectories throughout childhood have been associated with child development [308, 309], and suggest that exposure to maternal depression throughout the child's life may have a larger impact than only at one time point. However, we did attempt to account for this by controlling for current maternal depressive symptoms in our final analyses, and also controlling for other factors that may influence long-term outcomes such as maternal smoking during pregnancy. Furthermore, previous findings have demonstrated a correlation between antenatal scores on the EPDS and postnatal EPDS scores, suggesting those with high levels of antenatal depression are at the greatest risk of being diagnosed with postnatal depression. Finally, we did not account for parent's cognitive function in relation to child's cognitive function. Some research suggests that in adults, depression is associated with cognitive impairment [310, 311]. This may suggest that mothers with high depressive symptoms have decreased cognitive ability, and therefore this provides another plausible pathway for transmission of cognitive impairment to the child. However, if we can use antenatal depression scores to identify areas of cognitive deficits, we can seek specific interventions to improve deficits in those specific domains.

This study also had a number of strengths. Firstly, the EPDS is a standard screening tool that is quick and easy to administer. If women whose children may be at increased risk of neurodevelopmental deficits can be easily identified, we can use specific interventions to target both depression in the mother and cognitive deficits in the children. Secondly, all participants were from a prospective cohort study from a low SES background. Low SES is associated with greater disadvantage, and these individuals are therefore at an increased risk of poor outcomes compared to their high SES counterparts. Investigating differences in this cohort provides details on where

change can be implemented to reduce the risk of poor outcomes. Finally, we utilised a cognitive testing battery that tested multiple cognitive domains. These findings therefore demonstrated which cognitive domains were most vulnerable following antenatal depression, and therefore allows for targeted interventions to improve specific outcomes.

In summary, we found that antenatal depression was associated with an increased risk of errors on visual learning and spatial working memory tasks in 8-10 year old children. There was also a small, but significant, increase in motor movement time on a reaction time task. There were no differences in any other reaction time measures or executive functioning (attention switching). Poor cognitive function can lead to poor academic performance, which may then lead to decreased job opportunities and lower socioeconomic success. Being able to pinpoint exact cognitive domains that are impacted by antenatal depression, particularly in a disadvantaged population, will allow specific interventions to target these domains, and therefore improve long-term outcomes.

Chapter 6:

Associations between pregnancy complications and cognitive outcomes in 8-10 year old children

6.1 Abstract

Introduction: Pregnancy complications such as preeclampsia (PE), gestational hypertension (GH), small for gestational age (SGA), preterm birth (PTB) and gestational diabetes (GDM) have been associated with long-term impacts on offspring cognitive function. We sought to investigate the impact these complications had on specific domains of cognitive functioning in 8–10 year old children.

Method: This study was a follow-up of the SCreening fOr Pregnancy Endpoints (SCOPE) study. Children completed a neurodevelopmental assessment at 8-10 years old. Cognitive assessments were conducted using the Cambridge Neuropsychological Test Automated Battery (CANTAB) investigating cognitive domains of executive function, memory and reaction time. For analysis, children were divided into groups based on pregnancy complication of their mother: PE (n=38), SGA (n=34), PTB (n=26), GDM (n=22), GH (n=20) and controls (n=120).

Results: Children born following PE and/or SGA were the most vulnerable to cognitive deficits. Children born following PE, SGA and PTB showed deficits in executive function, as evidenced by decreased total correct (adjusted risk ratio, aRR: 0.95, 95% CI 0.91-0.98; aRR: 0.96, 0.93-0.96; aRR: 0.96, 0.93-0.99, respectively) compared to controls. There were no differences in the delayed or spatial working memory tasks. However, children born after PE and/or SGA had more errors on the new learning memory task (aRR: 1.37, 1.19-1.57; aRR: 1.35, 1.18-1.54 respectively). Interestingly, children who were exposed to GDM had better memory performance on this task, with decreased likelihood of errors (aRR: 0.79, 0.66-0.95). Children born SGA had longer movement time (β:18.99, 95%CI 1.47, 36.50), while children born following GH had longer reaction time (β:21.87, 95%CI 4.00, 39.74) compared to controls.

Conclusion: These data suggest that different complications have differential impacts upon domains of cognitive functioning. Recognition of the specific neurodevelopmental consequences of pregnancy complications provides opportunities for early interventions for children to improve long-term outcomes.

6.2 Introduction

Pregnancy complications such as preeclampsia (PE), gestational hypertension (GH), small for gestational age (SGA), preterm birth (PTB) and gestational diabetes mellitus (GDM) collectively affect up to 25% of pregnancies. These complications have been associated with an increased risk of future cardiovascular disease in both mother [312-314] and child [315]. However, recent evidence has also suggested that these complications can lead to deficits in child neurodevelopment [Reviewed in 152, 235, 316-318].

Hypertensive disorders during pregnancy such as PE and GH have been associated with poor cognitive outcomes in children, including lower scores on the Bayley Mental Developmental Index (MDI) [122, 123, 125], poorer memory [130], executive function [319] and lower intelligence quotient (IQ) [127, 128, 133, 134, 320, 321]. These cognitive deficits also continue into adulthood, with adults exposed to PE and/or GH in utero having more self-reported cognitive impairment 70 years later [322]. Despite all of this evidence, there is little research which looks into which specific aspects of cognitive function are most affected by pregnancy complications.

Two of the most well-research complications in association with cognitive function are SGA and PTB. Children born SGA have demonstrated poorer performance at school and experience more learning difficulties compared to children not born SGA [156-158]. Children born SGA were also found to have lower attention, executive functioning and language at 14 years old compared to those born appropriate for gestational age (AGA) [164]. They also demonstrate an 18 point lower IQ than AGA children, although this is generally still within a normal range [168]. PTB has similarly been shown to precede poor cognitive outcomes in children. PTB has been associated with decreased performance on the Bayley MDI at two years old [125]

There have also been differences shown in IQ in adulthood, whereby PTB adults have IQs up to 16 points lower than their term born counterparts [198, 199], however, scores are often still within a normal range if excluding those with major cognitive impairments [198, 199, 323]. In more specific cognitive domains, eight month old preterm born children had poorer executive function [193], and adolescents who were born preterm had poorer memory compared to their term born counterparts [37]. Often these studies only investigate those children born extremely preterm, and one study investigating differences in IQ of children aged 8-11 years found no differences in IQ in moderate to late preterm born children compared to term-born children [191]. Therefore, further research is needed to elucidate differences within different cognitive domains.

There have been varying reports on the impact of GDM on child cognitive outcomes. Some studies have suggested GDM is associated with poorer cognitive function in very young children compared to those whose mothers did not have GDM [239, 240, 246, 324], while some studies suggest there is no difference in cognitive function between children whose mothers did or did not have GDM [236, 325]. Most of these studies have looked at children under the age of two, and there is limited evidence about whether these differences are seen long-term. One study of the Avon Longitudinal Study of Parents and Children cohort from the UK found eight year old children born after GDM had on average a five point lower overall IQ compared to those not exposed to GDM [240]. However, another study done in India investigated differences in cognitive functioning within different cognitive domains in 9-10 year old children, and found those born after GDM actually had better learning and long-term retrieval memory compared to controls [241]. Again, this study is one of the very few that do not investigate IQ as a whole, and instead looks at separate aspects of

cognitive function that may impact upon these deficits in IQ. This is important because different domains of cognitive functioning impact upon IQ score, and therefore IQ does not give an accurate indicator of where cognitive deficits lie. Investigating specific domains of cognitive functioning would allow for these domains to be targeted to improve overall IQ.

Very few studies have investigated the impact of pregnancy complications on specific aspects of cognitive function in children. Discrepant findings between studies may be due use of different cognitive assessments, or children being tested across different ages for assessment of different cognitive domains. This means it is currently unclear whether all cognitive domains are equally affected by different pregnancy complications. Using rich phenotypic data from a prospective cohort, we investigated the impact of pregnancy complications, including PE, SGA, PTB, GDM and GH, on child cognitive functioning at 8-10 years old. We utilised an automated cognitive testing battery to investigate separate domains of cognition including tests of executive function, memory and reaction time.

6.3 Methods

6.3.1 *Participants*

Participants were children born from mothers who took part in the Adelaide cohort of the SCreening fOr Pregnancy Endpoints (SCOPE) study. SCOPE was an international, multi-centre prospective cohort study with centres in Auckland, NZ; Leeds, London and Manchester, UK; Cork, Ireland and Adelaide, Australia. This primary aim of SCOPE was to develop screening tools to predict pregnancy complications. Further methods are detailed in previous SCOPE publications [262, 263]. In brief, 1164 nulliparous pregnant women were recruited between September

2006 and September 2008 at the Lyell McEwin Hospital in Adelaide, South Australia. Women were initially recruited and interviewed by SCOPE research midwives at 15±1 weeks' gestation, and then again at 20±1 weeks. Women were excluded from the study if they were deemed to be at higher risk of developing a pregnancy complication due to other underlying health conditions such as chronic hypertension or systemic lupus. Participants were followed up prospectively, with research midwives recording pregnancy and neonatal outcomes.

Of the 1164 women involved in the initial SCOPE study, 1139 participants were available to call, and 273 participants took part in the follow-up (Further recruitment details in Chapter 3).

Women and children provided written consent and assent. Children underwent cognitive testing and completed questionnaires during a two hour follow-up session. During the same session, the children's mothers took the same cognitive tests and answered questionnaires about their child. A total of 270 participants attended appointments in person, while three filled out questionnaires, giving a total of 273 mother and child pairs.

6.3.2 *Measures*

6.3.2.1 *Definitions of pregnancy complications*

GH was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two or more measurements at least six hours apart after 20 weeks' gestation. PE was defined using the revised International Society for the Study of Hypertension in Pregnancy definition of GH or postpartum hypertension with proteinuria (24-hour urinary protein of 300 mg or spot urine protein/creatinine ratio of ≥30 mg/mmol creatinine or urine dipstick protein ≥ ++) or any multisystem

complication of PE or uteroplacental dysfunction as evidenced by intrauterine growth restriction [118]. SGA was defined as birthweight below the 10th percentile on a customised scale, adjusted for maternal height, weight, ethnicity, parity, and gestational age at delivery and infant sex [326]. PTB was defined as birth at <37 weeks' gestation. GDM was defined according to the World Health Organisation classification: fasting glucose ≥5.1 mmol/L or a two hour level of ≥8.5 mmol/L following an oral glucose tolerance test [327]. At the time of initial recruitment to the SCOPE study, the screening glucose levels for GDM were different, therefore all participants involved in the follow-up were reclassified due to new guidelines. The control group was any participant who was not classified as having any of the above pregnancy complications.

6.3.2.2 *Cognitive function*

Cognitive performance was assessed using five tests from the standardised Cambridge Neuropsychological Test Automated Battery (CANTAB) connect system [264]. The CANTAB system utilises a touch screen tablet, with automated administration of tests to ensure standardised testing across participants. Children were seated at a desk with the tablet in front of them, where they were instructed to complete a series of five tests. These tests were specifically chosen to assess components of executive function, memory and reaction time, and took approximately 35 minutes. All participants completed the tests in the same order.

Attention switching task

The attention switching task (AST) was used to measure executive function, namely cognitive flexibility. Participants were initially presented with an arrow in the middle of the screen, with the word ‘direction’ at the top of the screen, and asked to press the buttons according to which direction the arrow was pointing (Fig. 6.1A). In more complex trials, the arrow was presented on either side of the screen either pointing left or right, and instructions of either ‘direction’ or ‘side’ appeared across the top of the screen. The participant was asked to press the corresponding button, either left or right, depending on which direction the arrow was pointing (Fig. 6.1B), or which side of the screen the arrow was on (Fig. 6.1C). Each block began with eight practice trials. The participants were first presented with a 40 trial ‘direction’ only block, then a 40 trial ‘side’ only block, before a final block of 80 trials that randomly switched between instructions. Throughout the task, participants were instructed to go as fast as they could without making mistakes. Outcomes of interest were number of errors in the side only block, direction only block, switching block, and total number of correct trials over all of the assessed trials. Performance was also assessed by median latency to response (milliseconds) in the switching block and across all assessed blocks (total). For more details, see Chapter 2 (Section 2.3.1).

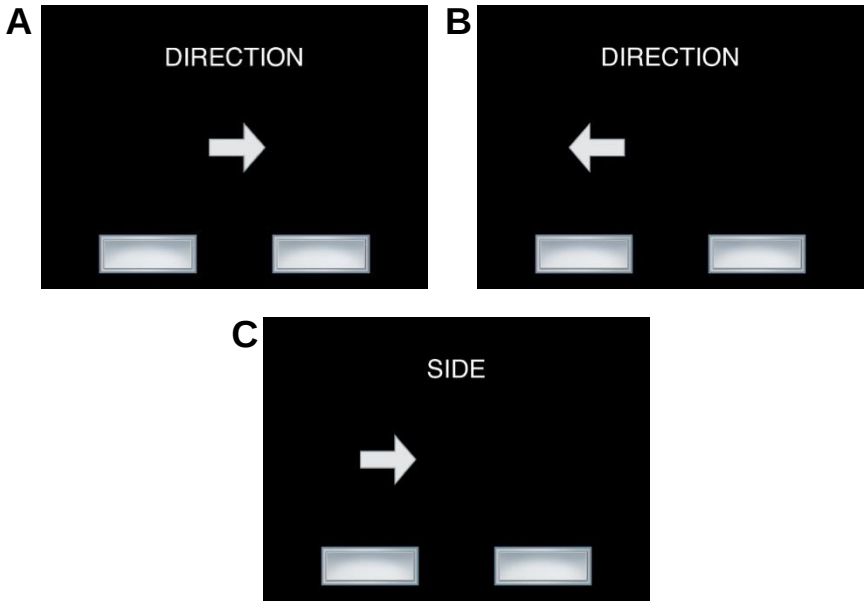

Figure 6.1 Attention switching task screenshots. (A) The first practice block where the arrow appeared in the middle of the screen, and the participant was asked to press left or right depending on which direction the arrow was pointing; (B) Participant was presented with 'direction' instruction, and had to press the left or right button depending on which direction the arrow was pointing; (C) Participant was presented with 'side' instruction, and had to press the left or right button depending on which side of the screen the arrow appeared on.

Delayed matching to sample task

The delayed matching to sample (DMS) task was used to assess visual delayed working memory. Participants were first presented with a target pattern and instructed to remember the pattern (Fig. 6.2A). They were then presented with a choice of four patterns underneath, which included the target pattern and three decoys (Fig. 6.2B). Participants received feedback following their response (Fig. 6.2C). In more complex rounds, the pattern was covered before the presentation of the four boxes displaying possible responses below (Fig. 6.2D). This task presented patterns either simultaneously, or after a delay of 0, 4, or 12 seconds, and delays were randomised for each trial so the participant did not know how long they would need to remember the

next pattern for. Performance was assessed by the total number of correct over all trials, total correct on each level of the delays, and total median latency (ms). For more details, see Chapter 2 (Section 2.3.2).

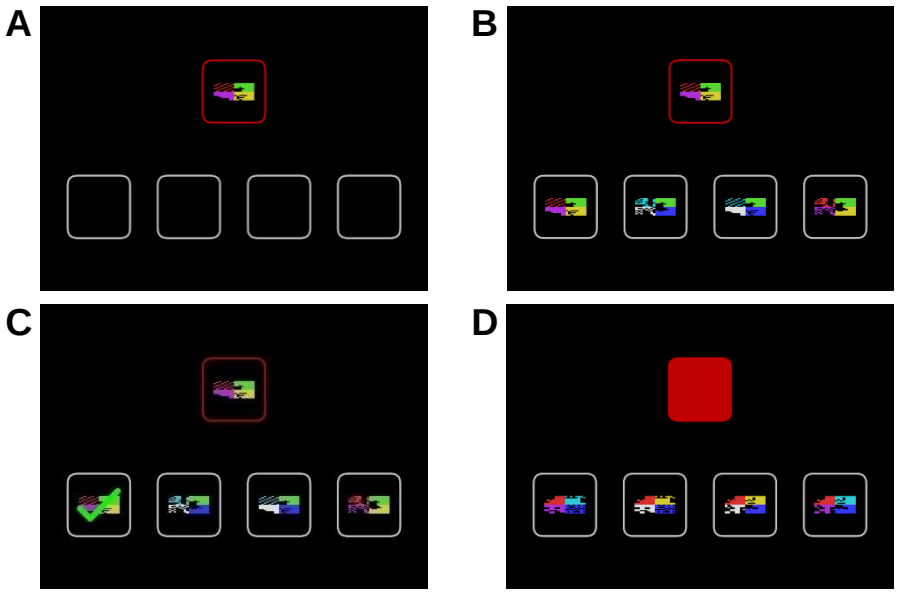

Figure 6.2 Delayed matching to sample task screenshots. (A) The initial presentation of the target pattern; (B) Participants then had to identify the matching pattern from the choices presented in the lower row; (C) The participant received feedback for a correct response. (D) In more complex trials, the target pattern was covered prior to the pattern options appearing in the row below after delays of either 0, 4 or 12 seconds.

Paired associates learning task

Paired associates learning (PAL) task was administered to measure visual working memory and new learning. Participants were presented with six white boxes around the edge of screen (Fig. 6.3A), which opened in a randomised order one at a time to reveal different patterns. Participants were then presented with each pattern in the centre of the screen (Fig. 6.4B), and asked to touch the box that previously

contained that pattern. The level of difficulty of this task increased, starting from two patterns, and increasing to 4, 6, and 8 different patterns. Participants advanced to the next level when they successfully identified the location of each pattern. If they chose incorrectly, the same level was repeated for a maximum of four attempts. If the participant still did not respond correctly on the fourth attempt, the task ended. Outcomes of interest were the number of correct boxes selected on the first attempt, the total number of errors for the whole task and total errors made on each level (both adjusted for levels reached) and number of levels completed. For more details, see Chapter 2 (Section 2.3.3).

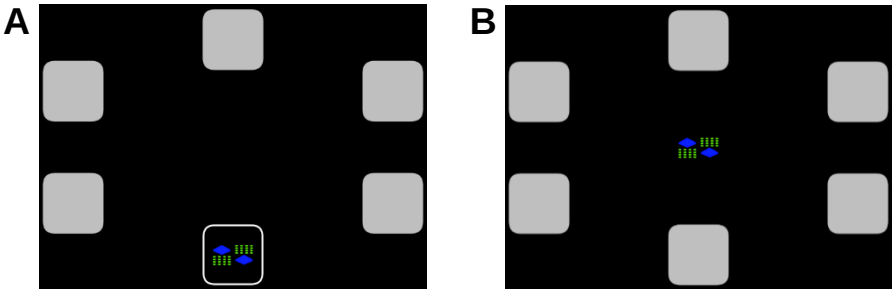

Figure 6.3 Paired associates learning task screenshots. (A) Boxes around the screen opened one by one revealing patterns inside, and participants were instructed to remember which pattern was in which box; (B) Patterns were then presented in the middle of the screen to be matched with the box in which it appeared.

Spatial working memory task

The spatial working memory (SWM) task was used to measure working memory. Participants were presented with a screen of coloured boxes (Fig. 6.4A), where they were told that they had to find a token under each box, but only one token would be hidden at a time. Therefore once a token had been found in a box (Fig. 6.4B), participants were instructed to not look in that box again. Once all tokens had been

found (Fig. 6.4C), participants moved to the next level. The task contained a practice with three boxes, and then advanced on to 4-, 6- and 8-box problems. The outcomes of interest were the total number of between errors (the number of times a participant incorrectly revisits a box where a token has already been found) across all trials, and between errors separately on the 4-, 6- and 8-box problems. A strategy score was also generated, which reflected the degree to which the participant had adopted a strategy to remember the boxes where tokens had been found. For more details, see Chapter 2 (Section 2.3.4).

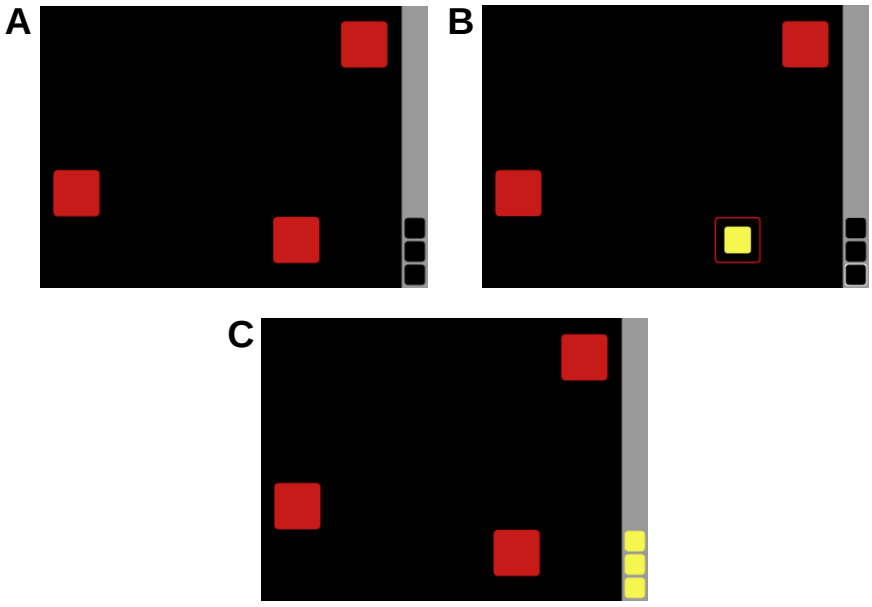

Figure 6.4 Spatial working memory task screenshots. (A) Participants initially presented with this screen and were instructed to search under the red boxes for tokens by touching on each box one at a time; (B) When the correct box was touched, the yellow token appeared and was moved to the bar on the right of the screen. For the rest of this trial, no token will appear under this box again; (C) Once all tokens were collected in the home bar (right of screen), participants moved on to the next level.

Reaction time task

During the reaction time (RTI) task, participants were presented with a button on the bottom of the screen, and a white circle at the top of the screen (Fig. 6.5A). They were instructed to hold down the bottom button until the circle at the top became yellow (Fig. 6.5B). When this happened, they were then instructed to move their hand as quickly as possible to touch inside the yellow circle. The RTI task comprised two sections: a simple reaction time task and a five-choice task. In the simple reaction time task, the stimulus always appeared in the same place, however, in the five-choice task the stimulus could appear in any one of five circles that were presented at the top of the screen (Fig. 6.5C). Outcomes of interest for both the simple and five-choice tasks were reaction time, defined as the duration of time between the presentation of the yellow circle and the release of the button, and movement time, defined as the time taken to touch the yellow spot after the release of the button. For more details, see Chapter 2 (Section 2.3.5).

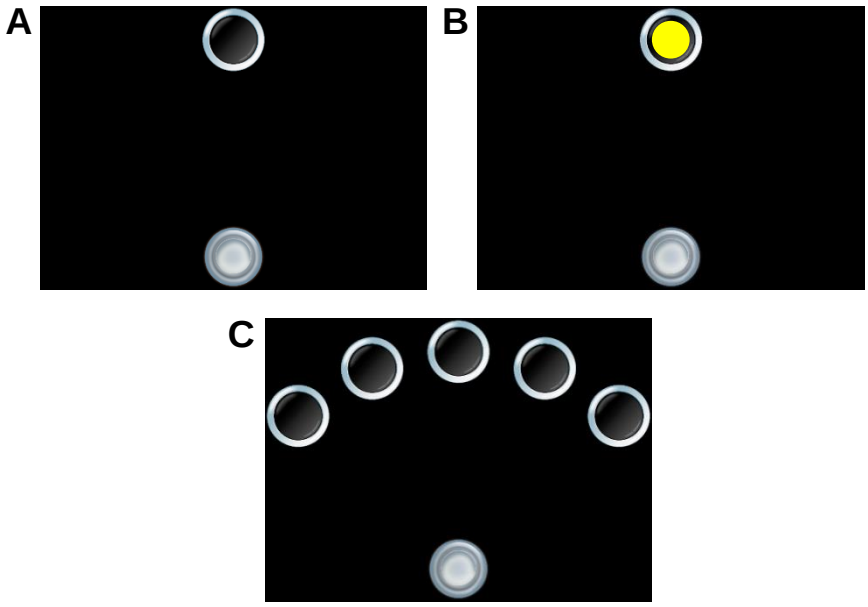

Figure 6.5 Reaction time task screenshots. (A) Participants were instructed to hold their finger on the button at the bottom of the screen and wait for a yellow dot to appear; (B) When the yellow dot appeared, participants had to release the button and touch the yellow dot as fast as they could; (C) This same process was then repeated with the yellow dot appearing in one of five locations, as a five-choice reaction time test.

6.3.3 *Data analysis*

Participants were divided into groups based on the presence of a major complication of pregnancy: PE, SGA, PTB, GDM and GH. Participants without one of these five major complications formed the control group. If a mother had two or more pregnancy complications in her pregnancy, the data was included in both complication groups for analysis. Participant demographics of the control group were compared to each pregnancy complication group using t-tests or Mann-Whitney U tests where appropriate, based on the distribution of the data. Categorical variables were analysed using chi-squared or Fischer's exact analyses. Linear regressions were used to analyse differences in reaction times, while Poisson regressions were used for all remaining

cognitive outcomes. To understand the potential impact of other variables on cognitive outcomes, two multivariate analyses were conducted: the first adjusting for the effects of smoking status at 15 weeks' gestation (yes versus no), mother's age at recruitment, mother's years of education and child age (Model 1); and the second adjusting for all factors included in Model 1 plus child sex (Model 2). Data on confounding factors used in the models were available for all participants who attended the follow-up.

6.4 Results

6.4.1 *Demographics*

Mothers who had GDM and/or GH were significantly older than the control group (Table 6.1). There were no significant differences in socioeconomic index (SEI), ethnicity, partner status or maternal years of education between the control group and any of the complication groups. There were significantly more mothers smoking at 15 weeks' gestation in the SGA group, and significantly more mothers consuming alcohol at 15 weeks' gestation in the PE group (Table 6.1). The children in the PE, SGA and PTB groups were significantly younger than controls at follow-up (Table 6.2). There was no significant difference in child sex between groups. Children born after PE, SGA, PTB or GDM were born at significantly lower gestation compared to controls, with those born after PE, SGA or PTB also having significantly lower birthweights than controls (Table 6.2).

Table 6.1 Characteristics of women at recruitment (15±1 weeks' gestation) within the control and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
Mum age birth, years mean (SD)	25 (5)	26 (4)	27 (5)	26 (5)	**28 (4)***	**28 (4)***
SEI	27 (22-33)	18 (19-33)	22 (19-33)	22 (19-30)	27 (22-34)	30 (22-44)
Ethnicity, Caucasian	163 (98%)	36 (95%)	32 (94%)	26 (100%)	20 (91%)	19 (95%)
With partner	135 (81%)	35 (92%)	32 (94%)	22 (84%)	21 (96%)	18 (90%)
Education, years	12 (11-13)	12 (11-13)	12 (11-12)	12 (11-13)	12 (11-13)	12 (11-13)
Completed at least 12 years education	116 (70%)	24 (63%)	23 (68%)	16 (62%)	14 (64%)	14 (70%)
Currently smoking	23 (14%)	4 (11%)	**10 (30%)***	6 (23%)	2 (9%)	2 (10%)
Consuming alcohol	4 (2%)	**4 (11%)***	2 (6%)	2 (8%)	1 (5%)	0 (0%)

Data presented as median (IQR) or n (%) unless otherwise stated.
*****Significantly different to controls ($p<0.05$).
SEI Socioeconomic Index (derived from NZSEI [see Chapter 2]); *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

Table 6.2 Characteristics of children within the control and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
Child age at testing, years, mean (SD)	9.7 (0.5)	**9.0 (0.5)***	**9.2 (0.5)***	**9.5 (0.7)***	9.6 (0.7)	9.8 (0.5)
Sex, male	76 (46%)	15 (40%)	12 (35%)	12 (46%)	12 (56%)	6 (30%)
Gestational age at birth, weeks	40 (39-41)	**38 (36-39)***	**39 (36-40)***	**34 (33-36)***	**39 (38-40)***	39 (38-41)
Birthweight, grams	3570 (3320-3830)	**2970 (2340-3730)***	**2540 (1960-2770)***	**2040 (1660-2500)***	3460 (2810-3750)	3410 (3280-3700)

Data presented as median (IQR) or n (%) unless otherwise stated.
*****Significantly different to controls (p<0.05).
PE Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

6.4.2 *The impact of pregnancy complications on child executive function*

PE and SGA groups made significantly more errors in the switching block of the AST and significantly less total correct responses overall, indicating poorer executive functioning in these groups compared to controls (Table 6.3). There were no other significant differences in the number of errors between any of the complication groups compared to controls. There were no significant differences in any of the latency measures between any of the groups, except for PTB group who had a significant longer total latency compared to controls (Table 6.3).

In the fully adjusted model (Model 2), children born following PE in pregnancy had an increased likelihood of errors on side and switching blocks compared to controls (Table 6.4). Children born after PE also had significantly shorter latency for the switching block, however, there was no difference in total latency, when compared to the control group. Similar to PE group, children born SGA had significantly increase risk of errors on side and switching blocks, therefore had significantly less risk for total correct, compared to the control group (Table 6.4). Children born SGA also had shorter latencies in the switching block, however, there was no difference in the overall total latency. The PTB group had significantly increased risk of making more side and switching block errors, which resulted in, on average, a lower risk of correct responses when compared to controls (Table 6.4). PTB group had no difference in latency for the switching block trial, but did have longer latency over all assessed blocks compared to controls. Children born after GDM had significantly higher risk of errors in the direction block (Table 6.4). However, there was no significant differences in risk of overall total correct compared to controls. There was no difference in risk of errors in any of the blocks or overall total for GH group compared to controls (Table

6.4). There was also no difference in any latency measures for children born after GDM or GH compared to controls.

Table 6.3 Comparison of child executive function outcomes between controls and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
AST outcomes						
Side block errors	0 (0-1)	1 (0-2)	1 (0-2)	0 (0-2)	1 (0-2)	0.5 (0-1.5)
Direction block errors	3 (1-6.5)	4 (1-6)	4 (1-6)	3 (1-6)	4 (2-5)	3 (2.5-4.5)
Switching block errors	9.50 (6-13.5)	**13 (8-21)***	**14 (6-19)***	13 (6-19)	8 (6-14)	9 (8-13)
Switching block, Latency, ms, mean (SD)	831.47 (150.46)	842.0 (180.49)	810.22 (182.16)	880.50 (184.78)	824.31 (181.54)	884.18 (164.08)
Total correct	144 (135-150)	**137 (123-143)***	**138 (120-148)***	135 (117-149)	143 (136-150)	142.5 (139-147)
Total latency, ms, mean (SD)	710.72 (111.48)	756.17 (153.16)	726.68 (116.70)	**796.81 (139.60)***	729.17 (141.15)	739.73 (118.92)

Data presented as median (IQR) unless otherwise stated.
*****Significantly different from controls ($p<0.05$).
AST Attention Switching Task; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

Table 6.4 Increased or impaired executive function in children exposed to pregnancy complications in reference to controls

	Control (n=166)	**PE (n=38)**		**SGA (n=34)**		**PTB (n=26)**		**GDM (n=22)**		**GH (n=20)**	
	Ref	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
AST outcomes											
Side block errors	1	**2.31 (1.67, 3.20)**	**2.41 (1.74, 3.36)**	**1.98 (1.45, 2.70)**	**2.00 (1.46, 2.73)**	**1.86 (1.37, 2.54)**	**1.86 (1.37, 2.54)**	0.89 (0.55, 1.44)	0.88 (0.54, 1.43)	0.83 (0.51, 1.36)	0.86 (0.52, 1.41)
Direction block errors	1	1.10 (0.98, 1.31)	1.08 (0.90, 1.29)	0.95 (0.79, 1.14)	0.93 (0.77, 1.12)	1.17 (0.98, 1.38)	1.16 (0.98, 1.38)	**1.25 (1.04, 1.49)**	**1.26 (1.05, 1.51)**	0.87 (0.70, 1.08)	0.86 (0.69, 1.07)
Switching block errors	1	**1.50 (1.34, 1.68)**	**1.52 (1.35, 1.70)**	**1.37 (1.22, 1.53)**	**1.38 (1.23, 1.54)**	**1.19 (1.06, 1.34)**	**1.19 (1.06, 1.34)**	0.99 (0.86, 1.14)	0.98 (0.85, 1.13)	1.00 (0.87, 1.15)	1.02 (0.88, 1.17)
Switching block latency[a]	1	-60.51 (-124.06, 3.05)	**-64.54 (-127.80, -1.28)**	**-73.07 (-136.91, -9.23)**	**-76.35 (-140.41, -12.29)**	27.51 (-37.67, 92.69)	27.47 (-37.56, 92.50)	-24.58 (-93.20, 44.05)	-20.95 (-89.28, 47.38)	56.12 (-13.9, 126.17)	50.58 (-19.63, 120.79)
Total correct	1	**0.95 (0.91, 0.98)**	**0.95 (0.91, 0.98)**	**0.96 (0.92, 0.99)**	**0.96 (0.93, 0.99)**	**0.96 (0.93, 0.99)**	**0.96 (0.93, 0.99)**	1.00 (0.96, 1.04)	1.00 (0.96, 1.04)	1.01 (0.97, 1.05)	1.01 (0.97, 1.05)
Total correct latency[a]	1	-0.80 (-50.18, 48.58)	-5.81 (-54.22, 42.61)	-19.28 (-65.27, 26.71)	-24.55 (-70.07, 20.99)	**71.09 (22.49, 119.69)**	**71.03 (23.35, 118.71)**	8.70 (-43.18, 60.57)	13.06 (-37.88, 63.99)	33.67 (-18.18, 85.52)	25.97 (-25.15, 77.10)

Results presented as adjusted relative risks (aRR; 95% CI) or [a]from linear regression (β; 95% CI).
Model 1 adjusted for smoking status at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex.
AST Attention Switching Task; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

6.4.3 *The impact of pregnancy complications on child memory*

Table 6.5 shows comparison of raw cognitive outcomes on the memory tasks between controls and pregnancy complication groups. In the delayed memory (DMS) task, children in the PE group had significantly longer latencies compared to controls, indicating they took longer when they selected the correct pattern as their first response (Table 6.5). There were no other significant differences for DMS outcomes between controls for any of the other pregnancy complications groups. In the new learning memory (PAL) task, the SGA group had significantly lower first attempt memory score compared to controls, indicating they made fewer correct choices in the first round of each trial (Table 6.5). Those born SGA also had more total errors, and more errors on the easiest (4-box) trial of this task. However, these differences were not observed between the SGA group and controls on the harder levels of the PAL task (6- and 8-box trials; Table 6.5). There were no other significant differences between any of the pregnancy complication groups and the controls on any outcomes of the PAL task. On the spatial working memory (SWM) task, the PTB group made significantly more errors than controls in the first assessed, easiest level (4-box problem) (Table 6.5). There were no other differences in the number of total between errors, or on any between errors on subsequent levels (6- or 8-box trials) between controls and any other pregnancy complications. There was a statistically significant difference between controls and PTB group in strategy score (Table 6.5). This was due to increased spread, whereby term born children had increased amount of scores closer to the minimum score of two, with lower scores indicating overall better use of strategy in this task.

Table 6.5 Comparison of child memory outcomes between controls and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
Delayed Matching to Sample (DMS)						
Total correct						
Overall	16 (14-17)	16 (14-17)	15.5 (14-17)	16 (14-17)	16 (14-17)	16 (14.5-17.5)
Simultaneous	5 (5-5)	5 (4-5)	5 (4-5)	5 (5-5)	5 (4-5)	5 (4-5)
0s delay	4 (3-5)	4 (3-4)	4 (3-4)	4 (2-4)	4 (3-5)	4 (3.5-5)
4s delay	4 (3-5)	3.5 (3-5)	4 (3-5)	4 (3-4)	4 (3-5)	4 (3-4)
12s delay	4 (3-4)	3.5 (3-4)	3.5 (3-4)	4 (3-4)	3 (2-4)	4 (3-5)
Latency, ms mean (SD)	2975.53 (867.59)	**3318 (1021.24)***	3113.38 (896.74)	3260.50 (1083.93)	2754.40 (659.41)	3075.03 (730.24)
Paired Associates Learning (PAL)						
First attempt memory score	15 (13-18)	15 (12-17)	**13.5 (10-17)***	15.5 (12-17)	16 (14.5-18)	16 (12.5-17)
Errors (adjusted)						
Total	5 (3-9.5)	6 (4-12)	8 (4-15)	6 (4-10)	4.5 (2-8)	6 (3-11.5)
4 box problem	0 (0-1)	0 (0-1)	**1 (0-3)***	0 (0-1)	0 (0-2)	0 (0-1)
6 box problem	1 (0-3)	2 (0-4)	2 (0-4)	1.5 (0-3)	0.5 (0-3)	2 (0.5-4.5)
8 box problem	3 (1-6)	3 (1-8)	4 (1-9)	3.5 (1-7)	2.5 (0.5-4)	3.5 (2-6)
Spatial Working Memory (SWM)						
Between errors						
Total	16 (11-21)	17 (12-22)	19 (16.5-22)	19 (13-22)	17 (15-21)	17 (13.5-23)
4 box problem	0 (0-1)	0 (0-1)	0 (0-2)	**1 (0-2)***	0 (0-1)	0 (0-2)
6 box problem	4 (1-7)	5 (2-8)	5.5 (3-7)	6 (3-8)	4 (2-7)	4 (0-6.5)
8 box problem	12 (7-15)	12 (9-14)	13 (11.5-14)	12 (10-14)	13 (11-15)	13.5 (9.5-15)
Strategy score	9 (7-10)	9 (8-10)	9 (8-10)	**9 (8-10)***	9 (8-10)	9.5 (7-11)

Data presented as median (IQR) unless otherwise stated.
*****Significantly different from controls at $p<0.05$ level.
PE Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

In the fully adjusted model, there were no significant difference in the risk of poorer memory performance on the DMS task for any of the pregnancy complications in comparison to the control group (Table 6.6).

In the fully adjusted model (Model 2) for outcomes of new learning on the PAL task, children born following PE had a significantly increased risk of errors on the 6- and 8-box problems, which resulted in an average 37% increased risk of total errors compared to controls (Table 6.7). Children born SGA had significantly lower likelihood of errors on their first attempt (first attempt memory score), indicating poorer performance, compared to controls. Those born SGA also had increased risk of errors on the 4-, 6- and 8-box trials (Table 6.7). This resulted in an average of 35% increased risk of total errors (adjusted) in those born SGA compared to controls. There were no differences in outcomes on the PAL task in those born preterm compared to controls. Children born after GDM made less errors on the eight box problem, which resulted in, on average, 22% decreased risk of errors overall when compared to controls (Table 6.7). There were no significant differences in PAL task outcomes when comparing controls and children born after GH (Table 6.7).

There were no significant differences in spatial working memory (SWM) outcomes between any of the pregnancy complication groups and controls (Table 6.8).

Table 6.6 Increased or impaired memory on the delayed matching to sample task in children exposed to pregnancy complications compared to controls

	Control (n=166)	**PE (n=38)**		**SGA (n=34)**		**PTB (n=26)**		**GDM (n=22)**		**GH (n=20)**	
	Ref	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
DMS outcomes											
Total correct											
Overall	1	0.98 (0.88, 1.09)	0.98 (0.93, 1.02)	0.96 (0.86, 1.07)	0.96 (0.86, 1.07)	0.99 (0.89, 1.11)	0.99 (0.89, 1.11)	0.97 (0.86, 1.09)	0.97 (0.86, 1.10)	1.02 (0.91, 1.15)	1.02 (0.91, 1.15)
Simultaneous	1	1.00 (0.82, 1.21)	1.00 (0.82, 1.21)	0.97 (0.80, 1.18)	0.98 (0.80, 1.19)	1.03 (0.85, 1.26)	1.03 (0.85, 1.26)	0.94 (0.75, 1.17)	0.94 (0.75, 1.17)	0.97 (0.78, 1.21)	0.97 (0.78, 1.21)
0s delay	1	0.92 (0.75, 1.15)	0.92 (0.74, 1.15)	0.90 (0.73, 1.13)	0.90 (0.72, 1.12)	0.91 (0.73, 1.14)	0.91 (0.73, 1.14)	1.03 (0.82, 1.30)	1.03 (0.82, 1.31)	1.06 (0.84, 1.34)	1.05 (0.83, 1.33)
4s delay	1	0.99 (0.80, 1.24)	0.99 (0.79, 1.23)	1.00 (0.80, 1.24)	1.00 (0.80, 1.24)	0.99 (0.80, 1.24)	0.99 (0.80, 1.24)	1.03 (0.81, 1.30)	1.03 (0.81, 1.31)	0.98 (0.77, 1.26)	0.97 (0.76, 1.25)
12s delay	1	0.99 (0.79, 1.24)	0.99 (0.79, 1.24)	0.96 (0.77, 1.21)	0.96 (0.77, 1.21)	1.03 (0.83, 1.30)	1.03 (0.83, 1.30)	0.89 (0.69, 1.16)	0.90 (0.69, 1.17)	1.11 (0.87, 1.42)	1.11 (0.87, 1.41)
Latency[a]	1	204.08 (-173.18, 581.33)	207.63 (-174.41, 586.67)	21.94 (-342.06, 385.93)	27.83 (-338.65, 394.31)	209.70 (-174.77, 594.18)	209.74 (-175.81, 595.30)	-268.27 (-663.38, 126.85)	-269.81 (-666.69, 127.08)	86.79 (-319.68, 493.25)	94.11 (-315.75, 503.98)

Results presented as adjusted relative risks (aRR; 95% CI) or [a]from linear regression (β; 95% CI).
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex.
DMS Delayed Matching to Sample; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

Table 6.7 Increased or impaired memory on the paired associative learning task in children exposed to pregnancy complications compared to controls

	Control (n=166)	**PE (n=38)**		**SGA (n=34)**		**PTB (n=26)**		**GDM (n=22)**		**GH (n=20)**	
	Ref	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
PAL outcomes											
First attempt memory score	1	0.92 (0.83, 1.03)	0.92 (0.83, 1.03)	**0.89 (0.79, 0.99)**	**0.88 (0.79, 0.99)**	0.99 (0.88, 1.10)	0.99 (0.88, 1.10)	1.04 (0.93, 1.18)	1.04 (0.93, 1.18)	0.96 (0.84, 1.08)	0.95 (0.84, 1.08)
Errors (adjusted)											
Total	1	**1.34 (1.17, 1.54)**	**1.37 (1.19, 1.57)**	**1.32 (1.16, 1.51)**	**1.35 (1.18, 1.54)**	0.96 (0.83, 1.12)	0.97 (0.83, 1.12)	**0.79 (0.66, 0.95)**	**0.78 (0.66, 0.93)**	1.04 (0.89, 1.22)	1.07 (0.91, 1.25)
4 box problem	1	1.08 (0.69, 1.69)	1.03 (0.66, 1.62)	**1.56 (1.06, 2.29)**	**1.52 (1.03, 2.23)**	0.69 (0.41, 1.16)	0.69 (0.41, 1.16)	0.98 (0.58, 1.67)	1.00 (0.59, 1.71)	0.92 (0.54, 1.60)	0.89 (0.51, 1.53)
6 box problem	1	**1.44 (1.11, 1.86)**	**1.47 (1.13, 1.90)**	**1.30 (1.00, 1.68)**	**1.32 (1.02, 1.72)**	0.99 (0.75, 1.31)	0.99 (0.75, 1.31)	0.86 (0.62, 1.19)	0.85 (0.61, 1.18)	1.18 (0.89, 1.57)	1.22 (0.91, 1.62)
8 box problem	1	**1.33 (1.12, 1.59)**	**1.38 (1.15, 1.65)**	**1.28 (1.07, 1.52)**	**1.32 (1.11, 1.56)**	0.95 (0.79, 1.16)	0.96 (0.79, 1.17)	**0.75 (0.60, 0.95)**	**0.74 (0.59, 0.93)**	1.03 (0.84, 1.26)	1.06 (0.87, 1.30)

Results presented as adjusted relative risks (aRR; 95% CI).
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex.
PAL Paired Associates Learning; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

Table 6.8 Increased or impaired memory on the spatial working memory task in children exposed to pregnancy complications compared to controls

	Control (n=166)	**PE (n=38)**		**SGA (n=34)**		**PTB (n=26)**		**GDM (n=22)**		**GH (n=20)**	
	Ref	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
SWM outcomes											
Between errors											
Total	1	0.97 (0.87, 1.08)	0.98 (0.88, 1.09)	1.07 (0.96, 1.18)	1.08 (0.98, 1.20)	1.10 (0.99, 1.22)	1.10 (0.99, 1.22)	1.11 (0.99, 1.24)	1.10 (0.98, 1.23)	1.06 (0.94, 1.19)	1.08 (0.96, 1.21)
4 box problem	1	0.99 (0.61, 1.63)	1.09 (0.61, 1.66)	1.04 (0.64, 1.69)	1.08 (0.64, 1.75)	1.52 (0.98, 2.36)	1.54 (0.99, 2.39)	1.03 (0.60, 1.77)	1.02 (0.59, 1.74)	1.07 (0.62, 1.84)	1.09 (0.63, 1.89)
6 box problem	1	0.94 (0.78, 1.15)	0.95 (0.78, 1.16)	1.00 (0.83, 1.21)	1.02 (0.84, 1.23)	1.14 (0.94, 1.38)	1.14 (0.94, 1.38)	1.00 (0.80, 1.24)	0.99 (0.79, 1.23)	0.91 (0.72, 1.16)	0.92 (0.72, 1.17)
8 box problem	1	0.97 (0.85, 1.10)	0.98 (0.86, 1.11)	1.10 (0.97, 1.24)	1.11 (0.96, 1.26)	1.05 (0.92, 1.19)	1.05 (0.92, 1.19)	**1.15 (1.01, 1.32)**	1.15 (1.00, 1.31)	1.11 (0.97, 1.27)	1.13 (0.99, 1.29)
Strategy score	1	1.05 (0.91, 1.21)	1.05 (0.91, 1.21)	1.06 (0.92, 1.22)	1.06 (0.92, 1.22)	1.09 (0.95, 1.26)	1.09 (0.95, 1.26)	1.08 (0.92, 1.27)	1.08 (0.92, 1.27)	1.07 (0.91, 1.25)	1.07 (0.91, 1.25)

Results presented as adjusted relative risks (aRR; 95% CI).
Model 1adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex.
SWM Spatial Working Memory; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

6.4.4 *The impact of pregnancy complications on child reaction time*

In the reaction time (RTI) task, PE and GH groups had significantly longer reaction times (by approximately 25 milliseconds) on the simple task compared to controls (Table 6.9). Children born SGA had no difference in reaction time, but had significantly longer movement time compared to controls (Table 6.9). There were no differences in reaction or movement time between the children in the control and other pregnancy complication groups for the simple reaction time task. There were also no significant differences between controls and any pregnancy complication group on the five choice task, either in reaction or movement time.

In the fully adjusted model (Model 2), there were no differences in simple or five-choice reaction or movement times in PE, SGA or GDM groups when compared to controls (Table 6.10). Children born SGA had significantly longer simple movement time after adjustment in both Model 1 and Model 2 (Table 6.10). There were no differences in any other reaction or movement times for the SGA group. Children born after GH had significantly longer simple reaction times compared to controls after adjustment in both Models (Table 6.10). There were no significant differences in any other reaction time outcomes for GH group.

Table 6.9 Comparisons of child reaction times between control and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
RTI outcomes (milliseconds)						
Simple						
Reaction time	367.82 (37.75)	**393.17 (64.75)***	382.54 (51.58)	381.52 (36.67)	380.19 (34.14)	**390.23 (35.57)***
Movement time	175.15 (39.98)	185.80 (40.83)	**196.90 (51.40)***	190.31 (38.26)	162.74 (29.80)	184.85 (38.48)
Five choice						
Reaction time	426.62 (49.77)	444.91 (65.33)	443.46 (73.01)	430.65 (50.43)	446.76 (65.58)	446.45 (52.27)
Movement time	208.87 (40.39)	217.39 (42.01)	226.74 (56.03)	224.21 (44.06)	191.81 (45.82)	222.70 (37.49)

Data presented as mean (SD).
*****Significantly different from controls at $p<0.05$ level.
RTI Reaction Time; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

Table 6.10 Increased or decreased reaction time in children exposed to pregnancy complications compared to controls

	Control (n=166)	**PE (n=38)**		**SGA (n=34)**		**PTB (n=26)**		**GDM (n=22)**		**GH (n=20)**	
	Ref	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2	Model 1	Model 2
RTI outcomes											
Simple											
Reaction time	1	17.19 (-1.20, 35.58)	16.32 (-2.07, 34.70)	6.95 (-9.96, 23.87)	5.51 (-11.38, 22.40)	10.40 (-5.64, 26.44)	10.35 (-5.68, 26.38)	10.22 (-7.22, 27.66)	10.91 (-6.51, 28.33)	**23.30 (5.48, 41.12)**	**21.87 (4.00, 39.74)**
Movement time	1	14.39 (-2.42, 31.20)	12.83 (-3.74, 29.39)	**20.99 (3.32, 38.66)**	**18.99 (1.47, 36.50)**	14.93 (-2.06, 31.92)	14.84 (-1.99, 31.68)	-12.84 (-31.13, 5.45)	-11.64 (-29.73, 6.45)	9.48 (-9.35, 28.31)	7.36 (-11.41, 26.13)
Five choice											
Reaction time	1	7.20 (-15.00, 29.40)	5.60 (-16.45, 27.65)	7.62 (-15.16, 30.40)	5.01 (-17.57, 27.59)	0.45 (-20.89, 21.78)	0.36 (-20.88, 21.60)	17.65 (-6.42, 41.72)	19.25 (-4.55, 43.05)	22.43 (-1.21, 46.06)	19.72 (-3.83, 43.27)
Movement time	1	10.56 (-6.43, 27.54)	9.04 (-7.72, 25.81)	16.52 (-1.67, 34.72)	14.27 (-3.72, 32.26)	14.59 (-2.69, 31.88)	14.50 (-2.61, 31.62)	-15.76 (-34.86, 3.34)	-14.24 (-32.99, 4.52)	14.31 (-4.47, 33.08)	12.41 (-6.35, 31.17)

Results from linear regression presented as β (95%).
Model 1adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex.
RTI Reaction Time; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

6.5 Discussion

This study indicated that pregnancy complications are associated with child cognitive outcomes that are apparent 8-10 years after birth. Different complications of pregnancy affected specific cognitive domains. Following pregnancy complications, executive functioning appeared to be most vulnerable cognitive domain, as evidenced by decreased likelihood of correct scores on the AST task which were seen in children who were born following PE, SGA and PTB. Although there were no differences between controls and pregnancy complications groups in delayed memory, measured by DMS, or spatial working memory, as measured by SWM task, children born following PE and/or born SGA were at increased risk of errors on the visual and new learning memory task (PAL). Interestingly, those children born after GDM were at decreased risk of memory deficits on the PAL task, suggesting children born following GDM are not at increased risk of neurodevelopmental outcomes at 8-10 years old. In regards to the reaction time task, there were few differences in reaction time, with results suggesting children born SGA and following GH may have poorer reaction time compared to controls, as evidenced by a minor increase in reaction and movement times, respectively, following adjustment. Findings suggest that children born following PE and/or SGA may be at the largest increased risk of neurodevelopmental deficits, with deficits in executive function and memory, with SGA children also demonstrating increased movement time.

Previous research often describes a negative relationship between pregnancy complications and subsequent child cognitive function, but often studies report only the relationship with measures of overall cognitive function such as Bayley MDI, IQ, or school grades or achievement. In this study, we investigated different domains of cognitive function to understand which pregnancy complications impact which specific

cognitive domains. This allowed a direct comparison between pregnancy complication groups and a consistent control group on a range of cognitive domains. PE has previously been associated with cognitive deficits, particularly in children. This is evidenced by lower IQ in childhood [127, 128, 328], and in poorer cognitive function at army conscription in adulthood [133]. The findings in the present study suggest that children born after PE have specifically an increased risk of executive function and memory deficits when compared to controls, and these deficits may be the reason for deficits in IQ seen at younger ages. Interestingly, one study that investigated executive function between adults who were and were not exposed to PE *in utero* found that there was no association between PE and executive functioning at 60 years old [322]. This finding, in line with the present results, may suggest differences in executive function disappear overtime. However, it should be noted that executive function in Tuovinen et al. [322] was measured by self-report, and not with an objective cognitive test. Further research would benefit from these investigations using objective tests to see if these differences did still exist at older ages. SGA has also previously been associated with poorer cognitive function in younger children [157, 168], and executive function at age 19-20 [329]. Our study suggests that these differences in SGA children's executive function appear early, and can be seen at 8-10 years of age. This would suggest that these deficits begin early and last into adulthood, and therefore children born SGA would benefit from early intervention to reduce differences in cognitive functioning.

Memory is an important component of cognitive function, and forms part of executive functioning. Previous research has demonstrated 7-10 year old children born after PE pregnancies had poorer immediate and delayed working memory performance [130], and term born SGA adults who had significantly lower immediate and delayed

memory performance compared to non-SGA term born control adults [329]. In the current study, we found children born after PE and SGA had increased risk of poorer memory performance in comparison to controls. However, these differences were only seen on the PAL task, which assesses visual memory and new learning, and not in the delayed memory (DMS) or spatial working memory (SWM) outcomes. There was a trend towards PE and SGA groups having lower delayed memory scores compared to controls, but this was not significant. Differences may not have been apparent in the current study due to little variability within results. Current findings suggest that there is only one discreet aspect of memory impacted by these complications at age 8–10 years old. This suggests that specific interventions may be able to target learning and visual memory to improve specifically this domain in these children, and hence reduce differences with controls.

Pregnancy complications, in general, are associated with an increase in inflammation [330]. However, it is important to also consider complications individually as they may have different mechanisms of action. For example, a recent change in definition of PE may explain some of the differences seen here in the PE group. The definition of PE changed in 2014 to include not only those with hypertension and proteinuria, but also pregnancies with hypertension and intrauterine growth restriction as evidenced by an SGA baby. The SGA definition used in this study was calculated based on customised centiles that adjusted for mother's height, weight and ethnicity, which would suggest these children were subject to intrauterine growth restriction. This change in definition may suggest more women are now diagnosed with PE than before the change in definition. This may provide a plausible mechanism for poorer functioning, as reduced nutrients and oxygen going to the fetus may be associated with slower or delayed overall development, including that of the

brain. This may manifest in a number of ways, including poor cognitive function. Evidence suggests that while SGA children demonstrate IQs within a normal range, functional magnetic resonance images have shown differences in brain activation patterns compared to children born AGA at four to seven years old [162]. This difference in brain activation may explain why IQ scores between AGA and SGA children are comparable, but there is a difference in the specific cognitive domain of memory. The differences in children born after pregnancies complicated by PE have been less well researched, and are poorly understood. One study by Ratsep et al. [146] suggests PE leads to differences in cerebral blood flow, which in turn can cause changes in brain volume and structural alterations. This study also demonstrated how children born after PE had differences in brain volume compared to age-matched controls, suggesting that this may be the cause of differences in cognitive function [146]. This may suggest why children born following PE and/or SGA were most vulnerable to cognitive deficits. Future research would benefit from further elucidating differences between PE, SGA and PE+SGA.

PTB has well established associations with poor neurodevelopmental outcomes in children. This is evidenced by lower IQ score [188, 198], memory [202, 331], attention [332] and executive function [192, 193, 204] compared to their term born counterparts. Differences in white matter distribution [198] and brain volume [189] have been found in preterm children when compared to age matched term born children, which may help to explain differences in cognitive function. Our results found that children born preterm also had decreased overall total correct in the executive functioning compared to term born children. Interestingly, in the fully adjusted model, there were no significant differences in memory or reaction time outcomes between control and PTB groups. Previous literature has highlighted

memory and motor impairments in PTB children when compared to term born counterparts [202, 331, 333, 334]. Differences in findings may be due to the fact that the PTB group in this study was generally born during the late preterm period (32 to 36 weeks' gestation). Previous studies have demonstrated that birth at earlier gestational ages increases the risk of neurodevelopment impairment. For example, Schneider et al. [334] found preterm children born less than 28 weeks' gestation had greater impairments than those children born 28-35 weeks' gestation. This would suggest the PTB group in this study may not have as much impact on their development, and hence not have as many deficits as those born very or extremely preterm. Including more children from earlier gestational ages from low socioeconomic backgrounds could help to further investigate these differences.

Previous studies have found varying associations of GDM and child cognitive function, with some studies suggesting poorer [236, 238, 240], better [241], or no difference [243] in cognitive function between children exposed and not exposed to GDM. The present study found children born after GDM had significantly better memory as measured by the PAL task, with no difference in executive function or reaction time. This finding is in line with Veena et al. [241], who demonstrated better learning, long-term retrieval in nine year old children whose mothers had GDM compared to controls. The PAL task involves learning and retrieval of new information, and therefore would involve similar areas of the brain as the task utilised by Veena et al. [241]. However, many previous studies investigating the impact of GDM on infants have found deficits in visual recognition memory at eight months [237] and deficits in delayed recall at 12 months [238, 324], which were not found in this study. Previous research has suggested that there are alterations in the neurologic processes that underpin cognitive function found in those children who have been

exposed to GDM [236, 335], however, there is little research into the biological mechanisms that may cause these differences. Diabetic pregnancy is characterised by hyperinsulinemia, which can in turn lead to hypoxia and iron deficiency [336, 337]. Animal studies demonstrate these factors may have significant impacts on the development of the brain, particularly in areas such as the hippocampus that regulate memory [338]. Findings from the present study in addition to previous findings may suggest that cognitive deficits associated with GDM only exist short term, and that by age 8-10 years, these deficits are no longer apparent. It is also worth noting that GDM is treated with different treatments, which may include diet control, metformin and/or insulin. While previous research has demonstrated no differences on the Bayley MDI at age two depending on treatment with metformin or insulin [252], the present sample was too small to investigate potential differences this may have had on differences in memory performance. The present study also found no difference in motor functioning in the GDM group on a task of reaction time, as has been previously reported [239, 339]. Ornoy et al. [239] found smaller differences in motor ability between older children (9-12 years old) comparing GDM to controls, than between the younger (5-8 years old), suggesting there may be some kind of improvement over time in motor abilities of those born after GDM. This may again suggest differences get smaller overtime, and may help explain why there were no differences found in this study.

Motor performance has previously been related to various pregnancy complications. Being born SGA has been associated with poorer motor performance compared to AGA controls [340, 341], but there is little evidence around effects of GH on psychomotor abilities. The Raine cohort has previously described poorer motor functioning in offspring born after GH [342] and children born after PE [343, 344]. These studies utilised the McCarron Assessment of Neuromuscular Development

[345], which tests fine and gross motor functions with a range of tasks. In line with these previous findings, the current study found children born after SGA or GH had poorer reaction time when compared to controls. However, while this difference was significant, in the fully adjusted model the difference between controls and GH or SGA groups was only approximately 20 milliseconds, and only existed in one outcome of the four motor outcomes. Therefore, these results should be interpreted with caution, and further studies would need to investigate the clinical relevance of these differences.

There were significant differences in the ages of the children between control and the PE, SGA and PTB groups at the time of testing. After adjusting for various factors including child age, there were differences in executive function and memory domains that did not exist in the univariate analysis, but few differences in reaction time outcomes. Previous research suggests that there are differences in cognitive functioning between these ages, in particular, executive function improves with age [346]. Our findings would suggest that different domains of memory may also be influenced by age, however, motor performance did not appear to be influenced by age within the 8 to 10 year old range. Previous research has also demonstrated differences in cognitive abilities between males and females [347], hence child sex was added to model. Controlling for sex of the child had little impact on the overall risk ratios. However, further interaction effects should be explored in order to further investigate this.

One limitation of this study is untangling the effects of each individual pregnancy complication. As this was a case-control study, all participants with a complication were included in that group, and therefore the same participants were at times included in two complication groups (For example, a child exposed to both PE

and born SGA would be included in both complications groups for analysis). Pregnancy complications have a cumulative effect on cognitive performance, with the more complications increasing the risk of cognitive impairment [125]. Future studies could include only those with single complications and investigate separately those with multiple complications in order to disentangle the specific impacts of different pregnancy complications. Secondly, it should be noted that intelligence has been reported to have a direct inheritable component [348], and a socially inherited component. For example, mothers with a higher IQ are more likely to provide an appropriately stimulating and supportive environment to nurture their child's neurodevelopment. However, this study had limited data available on the child's early postnatal environment. Early life maternal factors such as postnatal depression, or reduced maternal cognitive capacity following pregnancy complications may have impacted the early life environment, and hence impacted on child cognitive function. Previous research also suggests that pregnancy complications are associated with cognitive impairment in mothers [349]. Whether this is due to shared genetic predisposition to both pregnancy complications and cognitive decline, or a product of other factors that are also associated with both pregnancy complications and cognitive performance, such as social disadvantage, is unknown. These associations would warrant further investigations in future studies. However, all participants in this sample had relatively low socioeconomic status (SES), particularly compared to population average, which allowed us to explore cognitive function in a similarly disadvantaged SES environment. Further, maternal cognitive function was tested in the current study, with no differences found between the pregnancy complication groups (data not presented). Finally, there were a number of participants who did not have data available for certain tasks due to their inability to participate in the cognitive testing.

Most of these were due to participants not understanding the tasks due to learning difficulties, autism and/or attention deficit hyperactivity disorder. All of these participants were from the control group, which therefore may have led to an overestimation of the control group's abilities. However, the CANTAB is a beneficial assessment tool due to the fact that most tasks use only patterns and not words, which allowed the majority of participants to participate.

Overall, this study demonstrates that pregnancy complications are associated with deficits in certain different domains of cognitive function in 8-10 year old children. Poor cognitive function is associated with poor academic performance, which can lead to reduced future job opportunities and socioeconomic success. Knowing which pregnancy complications are associated with different cognitive domains will allow early interventions to target these specific areas, therefore improving long-term outcomes for children.

Chapter 7:

Impact of pregnancy complications on self-reported anxiety and depression in 8 – 10 year old children

7.1 Abstract

Introduction: Pregnancy complications such as preeclampsia (PE), gestational hypertension (GH), small for gestational age (SGA), preterm birth (PTB) and gestational diabetes (GDM) have been associated with poor mental health in adulthood. We aimed to investigate whether these complications were associated with child self-reported anxiety and depression at 8-10 years of age.

Method: Participants were part of the SCreening fOr Pregnancy Endpoints (SCOPE) study, and a total of 273 mother-child pairs were followed up. Children were divided into groups based on pregnancy complication of their mother: PE (n=38), SGA (n=34), PTB (n=26), GDM (n=22), GH (n=20) and controls (n=166). At follow-up, children completed the Spence Children's Anxiety Scale, Child Anxiety Life Interference Scale and the Centre for Epidemiological Studies Depression Scale for Children.

Results: After adjusting for factors including current maternal depressive symptoms, children born after PE pregnancies had higher likelihood of reporting anxiety symptoms (adjusted risk ratio; aRR, 95% CI:1.14, 1.06-1.23) and anxiety interference (aRR:1.58, 1.39-1.80), including anxiety interference both at home (aRR:1.21, 1.01-1.45) and outside the home (aRR:2.10, 1.75-2.51) compared to controls. Children born SGA were more likely to report higher anxiety life interference (aRR:1.33, 1.16-1.52) and interference outside the home (aRR:1.73, 1.44-2.07) compared to controls. Children born preterm were less likely to report anxiety symptoms (aRR:0.90, 0.83-0.98), and children born after GDM were less likely to report anxiety interference (aRR:0.80, 0.67-0.95), including anxiety interference outside the home (aRR:0.73, 0.56-0.95), than controls. There were no significant differences in any anxiety measures between controls and children born after GH. There were also no significant differences in child depressive symptoms between controls and any pregnancy complication group.

Conclusion: Mental health issues in childhood are associated with the development of mental health disorders in the future. Recognition of early life factors such as pregnancy complications that may be associated with future mental health provides opportunities for early interventions for children to improve long-term health and social outcomes.

7.2 Introduction

Emotional and behavioural issues impact up to 20% of children under the age of two years [350]. This is important as psychological disturbances in childhood and adolescence are major risk factors for the development of psychiatric disorders in adulthood [212, 351]. Given mental health problems affect one in five adults in Australia [352], identifying and understanding the contributing factors may help towards alleviating these conditions.

Early life adverse exposures, such as pregnancy complications, have been associated with the future development of mental health issues. Preeclampsia (PE) is defined as gestational hypertension (GH) with proteinuria and/or a small for gestational age (SGA) baby, and it affects 2-8% of pregnancies [120, 353]. Exposure to PE *in utero* has been associated with negative psychological outcomes such as depression and schizophrenia in adulthood [136, 137, 140]. Other studies, however, have shown no differences in the frequency of mental health conditions in adults [354], with one study even reporting that children born of preeclamptic pregnancies have decreased internalising and externalising behaviours at age 14 years [138]. Gestational hypertension (GH) alone has also been associated with poor outcomes in some studies, but this appears to depend on the outcome of interest. For example, at age 14 years, children exposed to GH *in utero* have demonstrated increased internalising behaviours compared to controls [138]. However, no differences in depression symptoms have been found in adulthood compared to adults whose mothers did not have GH [137].

Previous research has also suggested that offspring born SGA demonstrate higher psychiatric symptoms in adolescence [175] and increased risk of mental health disorders in adulthood compared to children born an appropriate size for gestational age (AGA) [10, 355]. Another pregnancy complication, preterm birth (PTB), has also

been associated with poor neurodevelopmental outcomes, with children demonstrating more frequent behavioural issues than their term born peers, such as increased emotional problems at 11 years old [356] and increased internalising and externalising behaviours throughout childhood and adolescence [357, 358]. More recently, PTB has been associated with increased anxiety symptoms at preschool age [359], and at 11 years of age [210]. A recent review, however, demonstrated that neither PTB nor being born SGA were associated with adult depression [176]. The pregnancy complication gestational diabetes mellitus (GDM) has also been associated with increased risk of mental health disorders in offspring [136, 244]. Children born after exposure to GDM had increased internalising and externalising behaviours at two years of age, although differences were no longer significant after adjustment [245].

Associations between pregnancy complications and poor mental health in children support the development origins of health and disease (DOHaD) hypothesis [6], suggesting the *in utero* environment can impact on the long-term mental health of the child. Differences in findings between studies from different complications may be caused by differences in socioeconomic status (SES), diet, environment, age of fetus at exposure, and the age of offspring at assessment. Previous studies have investigated differences in mental health outcomes between cases exposed to one or two pregnancy complications compared to controls. However, few studies have looked at a prospective pregnancy cohort follow-up study to investigate numerous complications within the same cohort. Conducting this analysis in a large, geographically- and socioeconomically-similar sample could help elucidate which pregnancy complications are most relevant to predicting outcomes for these children.

SES may also be an important modulating factor in the association between early life exposures and child outcomes. Children from low SES communities are at

significantly higher risk of emotional problems than their higher SES counterparts [216, 360]. Other studies have also suggested that while having a pregnancy complication may confer certain vulnerabilities, factors such as SES may compound and lead to even more negative outcomes [173, 216]. Given that previous evidence suggests that low SES children are more at risk of poor outcomes, this highlights the importance of assessing these associations in communities with low SES.

Furthermore, previous studies relating early life adversity to child anxiety and behaviour rely on parental reports of child mental health. A recent study demonstrated that while anxiety was higher in preterm born children compared to term born children when reported by the mother, there was no difference when comparing child-reported symptoms [218]. Mothers who have depression themselves may under or over report child symptoms [217, 285], and therefore this may not necessarily be an accurate reflection of how the child feels, or the true incidence of child depression. Studies assessing child psychological issues from the perspective of the child are scarce. Given that rates of mental health disorders are reported to be as prevalent in childhood as adolescence [350], early identification of factors that may increase the risk of poor mental health could provide opportunity for intervention.

Due to the fact that different studies have investigated mental health in offspring at different ages, using different measures and utilising parental reports, it is difficult to compare outcomes to investigate which pregnancy complications may be most relevant in predicting mental health outcomes in children. Since children of low SES are at the greatest risk of poor outcomes, further studies are needed to compare neurodevelopmental impacts of pregnancy complications within disadvantaged cohorts. In this study, rich phenotypic data from a low SES cohort were utilised to investigate the impact of pregnancy complications on self-reported anxiety and

depression scores among 8-10 year old children to determine which complications are most relevant to predicting poor mental health outcomes.

7.3 Methods

7.3.1 *Participants*

Participants were children born from mothers who took part in the Adelaide arm of the SCreening fOr Pregnancy Endpoints (SCOPE) cohort. SCOPE was an international, multi-centre prospective cohort study with centres in Auckland, NZ; Leeds, London and Manchester, UK; Cork, Ireland and Adelaide, Australia. The primary aim of SCOPE was to develop screening tools to predict risk for pregnancy complications. Further methods are detailed in previous SCOPE publications [262, 263]. Briefly, 1164 nulliparous pregnant women were recruited between September 2005 and September 2008 at the Lyell McEwin Hospital in Adelaide, South Australia. Women were initially recruited and interviewed by SCOPE research midwives at 15±1 weeks' gestation, and then again at 20±1 weeks. Demographic information recorded at 15 weeks' gestation included education level, smoking and alcohol consumption. Women were excluded from the study if they were deemed to be at higher risk of developing a pregnancy complication due to other underlying health conditions such as chronic hypertension or systemic lupus. Participants were followed up prospectively, with research midwives recording pregnancy and neonatal outcomes.

Of the 1164 women involved in the initial SCOPE study, 634 were able to be contacted, and 273 mother-child pairs subsequently participated in the follow-up study (for further details about recruitment see Chapter 3).

At the follow-up appointment, women and children provided written consent and assent respectively. Children underwent cognitive testing and completed

questionnaires lasting approximately one hour. During the same session, the children's mothers took the same cognitive tests and answered questionnaires about their child. For analysis, data were divided into groups based on the presence of a major complication of pregnancy: PE, SGA, PTB, GDM and GH.

7.3.2 *Measures*

7.3.2.1 *Definitions of pregnancy complications*

GH was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two or more measurements at least six hours apart after 20 weeks' gestation. PE was defined using the revised International Society for the Study of Hypertension in Pregnancy definition of GH or postpartum hypertension with proteinuria (24-hour urinary protein of 300 mg or spot urine protein/creatinine ratio of ≥ 30 mg/mmol creatinine or urine dipstick protein ≥ ++) or any multisystem complication of PE or uteroplacental dysfunction as evidenced by intrauterine growth restriction [118]. SGA was defined as birthweight below the 10^{th} percentile on a customised scale, adjusted for maternal height, weight, ethnicity, parity, and gestational age at delivery and infant sex [326]. PTB was defined as birth at <37 weeks' gestation. GDM was defined according to the World Health Organisation classification: fasting glucose ≥ 5.1 mmol/L or a two hour level of ≥ 8.5 mmol/L following an oral glucose tolerance test. At the time of initial recruitment to the SCOPE study, the screening glucose levels for GDM were slightly different, therefore all participants involved in the follow-up were reclassified due to new guidelines [327]. If a participant had two or more complications, they were placed into each applicable complication group for analysis. The control group included any participant who was not classified within the PE, GH, SGA PTB, or GDM complication groups.

7.3.2.2 *Child Anxiety*

The Spence Children's Anxiety Scale (SCAS) was used to assess overall anxiety symptoms, as well as sub-domains of anxiety such as panic/agoraphobia, social anxiety, separation anxiety, obsessive compulsive behaviours, physical injury fears and generalised anxiety (Appendix E) [267]. The SCAS was completed by the child without the presence of the mother. The scale contains 44 items, however, six responses were not scored as they are positive items included to reduce negative response bias. Each item was rated on a scale of 0-3, where 0 was "never" and 3 was "always". The maximum possible total score was 114, with higher scores indicating increased anxiety.

The Children's Anxiety Life Interference Scale (CALIS) questionnaire assessed the impact that the child's fears and worries had on their daily life (Appendix G) [270]. The child report included nine items, with subscales 'at home' and 'outside home' anxiety interference. Each item was rated on a 5-point Likert scale, where 0 was "not at all", and 4 was "a great deal". The maximum total score was 36, with higher scores indicating higher anxiety interference.

7.3.2.3 *Child depression*

The Center for Epidemiological Studies of Depression scale for Children (CES-DC) is a 20-item self-report designed to measured depressive symptoms in children (Appendix H) [273]. Each item was scored on a 4-point Likert scale, with responses ranging from "not at all" to "a lot". Scoring on 16 of the statements referred to the presence of a depressive symptom during the past week, while scoring on the remaining four questions referred to positive items and were hence reversed scored. Total scores ranged from 0-60, with scores above 15 indicating significant depressive

symptoms [273]. At time of consent, mothers were asked to provide details of their child's general practitioner (GP) should scores on this questionnaire indicate their child may benefit from professional help. Therefore a letter (Appendix I) was sent to the GP of any child who scored over 15.

7.3.2.4 *Maternal mental health*

During their pregnancy, mothers completed both the State Trait Anxiety Inventory (STAI) and Edinburgh Postnatal Depression Scale (EPDS) at 15 and 20 weeks' gestation. STAI scores range from 20 – 80, with higher scores indicating increased levels of anxiety. The EPDS scores range from 0 – 30, with higher scores indicating greater levels of depression [261]. At follow-up, mothers completed the Depression, Anxiety and Stress Scale (DASS; Appendix J). For more details on the DASS, see Chapter 2 (Section 2.4.4). Due to the fact that mother's depression has been shown to moderate the relationship between pregnancy complication and child mental health [359], current maternal anxiety or depression was included in the final models.

7.3.3 *Data analysis*

Univariate analyses were performed to compare scores on the anxiety and depression scales between the control group and each pregnancy complication group using Mann-Whitney U tests. Multivariate analysis utilised Poisson regression to compare the control group to each of the pregnancy complication groups. To understand the potential contribution of other variables on anxiety and depression outcomes, three multivariate analyses models were used: Model 1 adjusting for the effects of smoking status at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age; Model 2 adjusting for all

factors included in Model 1 plus child sex; Model 3 adjusting for all factors in Model 2 plus mother's anxiety at 15 weeks' gestation and current anxiety for child anxiety outcomes, or mother's depression at 15 weeks' gestation and current depression for child depression outcomes. Data on confounding factors used in the models were available for all participants who attended the follow-up.

7.4 Results

7.4.1 *Demographics*

Table 7.1 shows demographics of controls and pregnancy complication groups. Mothers who had GDM and/or GH during pregnancy were significantly older than the control group. There were no significant differences in socioeconomic index (SEI), ethnicity, has a partner (yes or no) or maternal years of education between the control group and any of the complication groups. There were significantly more mothers smoking at 15 weeks' gestation in the SGA group, and significantly more mothers still consuming alcohol at 15 weeks in the PE group. There were no significant differences between the control and complication groups in regards to depression or anxiety score during pregnancy. Children in PE, SGA and PTB groups were significantly younger than controls at follow-up. There were no significant differences in sex of the child between groups. Children born after PE, SGA, PTB or GDM were born at significantly lower gestation, with those born after PE, SGA or PTB also having significantly lower birthweights compared to controls.

Table 7.1 Characteristics of participants within the control and pregnancy complication groups.

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
Maternal demographics at recruitment (15±weeks' gestation)						
Age, years, mean (SD)	25 (5)	26 (4)	27 (5)	26 (5)	**28 (4)***	**28 (4)***
SEI	27 (22-33)	18 (19-33)	22 (19-33)	22 (19-30)	27 (22-34)	30 (22-44)
Ethnicity, Caucasian	163 (98%)	36 (95%)	32 (94%)	26 (100%)	20 (91%)	19 (95%)
With partner	135 (81%)	35 (92%)	32 (94%)	22 (84%)	21 (96%)	18 (90%)
Education, years	12 (11-13)	12 (11-13)	12 (11-12)	12 (11-13)	12 (11-13)	12 (11-13)
Education level, Completed at least 12 years	116 (70%)	24 (63%)	23 (68%)	16 (62%)	14 (64%)	14 (70%)
Currently smoking	23 (14%)	4 (11%)	**10 (30%)***	6 (23%)	2 (9%)	2 (10%)
Consuming alcohol	4 (2%)	**4 (11%)***	2 (6%)	2 (8%)	1 (5%)	0 (0%)
EPDS score	5 (2-9)	6 (2-9)	5 (1-8)	7 (3-8)	5 (1-8)	6 (1-9)
STAI score	30 (23-40)	30 (20-40)	28 (23-37)	32 (23-37)	32 (23-40)	27 (20-40)

(Table 7.1 continued on next page)

Table 7.1 continued. Characteristics of participants within the control and pregnancy complication groups.

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
Child Outcomes						
Age, years, mean (SD)	9.7 (0.5)	**9.0 (0.5)***	**9.2 (0.5)***	**9.5 (0.7)***	9.6 (0.7)	9.8 (0.5)
Sex, male	76 (46%)	15 (40%)	12 (35%)	12 (46%)	12 (56%)	6 (30%)
Gestational age at birth, weeks	40 (39-41)	**38 (36-39)***	**39 (36-40)***	**34 (33-36)***	**39 (38-40)***	39 (38-41)
Birthweight, grams	3570 (3320-3830)	**2970 (2340-3730)***	**2540 (1960-2770)***	**2040 (1660-2500)***	3460 (2810-3750)	3410 (3280-3700)

Data presented as median (IQR) or n (%) unless otherwise stated.
*Significantly different to controls ($p<0.05$).
SEI Socioeconomic Index, (derived from NZSEI [See Chapter 2]); *EPDS* Edinburgh Postnatal Depression Score; *STAI* State Trait Anxiety Inventory; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

7.4.2 *Univariate analysis of pregnancy complications and child mental health outcomes*

There were no significant differences in child reported anxiety symptoms as measured by the SCAS (either total scores or subscale scores) for any of the pregnancy complications compared to the controls (Table 7.2). In relation to anxiety interference (CALIS), children born after PE reported significantly higher total anxiety interference compared to the controls, and this difference was seen in the anxiety interference 'outside home' subscale (Table 7.2). Children born SGA also reported significantly higher anxiety interference on the 'outside home' subscale, but there was no difference in the total score (Table 7.2). There were no significant differences in child self-reported anxiety interference for PTB, GDM or GH groups when compared to controls. There were no significant differences in depression symptoms (measured by the CES-DC) between controls and any of the pregnancy complications groups.

Table 7.2 Scores on anxiety and depression questionnaires based on child report by control and pregnancy complication groups

	Control (n=166)	**PE (n=38)**	**SGA (n=34)**	**PTB (n=26)**	**GDM (n=22)**	**GH (n=20)**
SCAS						
Total	29 (17-40)	35 (20-48)	31 (21-40)	31 (23-40)	29 (17-37)	29 (19-48)
Panic/Agoraphobia	3 (1-6)	4 (1-6)	4 (1-6)	4 (2-6)	1.5 (1-6)	4 (1.5-7.5)
Separation Anxiety	5 (3-8)	5 (3-8)	6 (3-8)	4 (3-7)	3.5 (2-7)	4 (3-7.5)
Physical Injury	4 (2-6)	4 (2-7)	3 (2-6)	4.5 (1-6)	3.5 (3-6)	5 (3-7.5)
Social Phobia	4 (3-7)	5 (2-7)	5.5 (3-7)	5 (3-9)	5 (2-7)	4 (1.5-8.5)
Obsessive/Compulsive	6 (3-8)	7 (5-9)	6 (4-9)	6 (4-7)	6.5 (2-8)	6 (4.5-8.5)
Generalised Anxiety	6 (4-8)	6 (4-9)	6 (4-7)	6 (4-7)	5 (4-7)	7 (5-9.5)
CALIS						
Total	7 (4-14)	**12 (6-20)***	10 (5-14)	6 (4-10)	7 (2-12)	7 (4-14)
At home	5 (2-7)	5 (3-7)	4 (2-6)	3 (2-6)	4 (2-6)	4 (3-7)
Outside home	3 (1-6)	**7 (3-9)***	**6 (3-9)***	2 (1-3)	3 (1-7)	3 (1-7)
CES-DC	13 (8-20)	13 (9-22)	13 (7-22)	12 (9-18)	14 (5-21)	12 (7-20)

Data presented as median (IQR).
*****Significantly different to controls ($p<0.05$).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale; CES-DC Centre for Epidemiological Studies Depression scale for Children; *PE* Preeclampsia; *SGA* Small for Gestational Age; *PTB* Preterm Birth; *GDM* Gestational Diabetes Mellitus; *GH* Gestational Hypertension.

7.4.3 *Children born after preeclampsia have increased anxiety symptoms and anxiety interference*

In the fully adjusted model (Model 3), children born after PE had 14% increased likelihood of anxiety symptoms (total score) compared to controls (Table 7.3). There was a significant increased risk of separation anxiety symptoms in children born after PE in Model 1, however, this disappeared after the addition of child sex to Model 2. There was no increased likelihood of anxiety found on any of the other subscales. In the final model (Model 3), the PE group also had a 58% increased risk of anxiety interference (total score), with significantly higher risk of anxiety interference on the 'at home' and 'outside home' subscales compared to controls (Table 7.3).

Table 7.3 Adjusted relative risks (aRR) of child self-reported anxiety symptoms following exposure to preeclampsia in utero compared to controls

	Child report (aRR*; 95% CI)		
	Model 1	Model 2	Model 3
SCAS			
Total	**1.18 (1.10, 1.27)**	**1.13 (1.05, 1.22)**	**1.14 (1.06, 1.23)**
Panic/ Agoraphobia	1.04 (0.85, 1.28)	1.00 (0.82, 1.24)	1.01 (0.82, 1.24)
Separation Anxiety	**1.19 (1.00, 1.42)**	1.15 (0.96, 1.37)	1.18 (0.99, 1.40)
Physical Injury fears	1.21 (0.99, 1.48)	1.14 (0.93, 1.39)	1.15 (0.94, 1.41)
Social Phobia	1.17 (0.97, 1.41)	1.13 (0.93, 1.36)	1.14 (0.94, 1.38)
Obsessive Compulsive behaviour	1.16 (0.99, 1.36)	1.13 (0.96, 1.32)	1.14 (0.97, 1.33)
Generalised Anxiety	1.09 (0.92, 1.28)	1.06 (0.90, 1.25)	1.06 (0.83, 1.25)
CALIS			
Total	**1.61 (1.42, 1.83)**	**1.57 (1.39, 1.79)**	**1.58 (1.39, 1.80)**
At home	**1.25 (1.04, 1.49)**	**1.21 (1.01, 1.46)**	**1.21 (1.01, 1.45)**
Outside home	**2.10 (1.76, 2.51)**	**2.05 (1.72, 2.45)**	**2.10 (1.75, 2.51)**

*aRR: For those exposed to PE in utero (n=38); Reference category is controls (n=166).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale.
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's anxiety at 15 weeks' gestation and current mother's anxiety.

7.4.4 *Children born small for gestational age have increased anxiety interference*

There was no difference in risk of anxiety symptoms in children born SGA compared to controls in any of the models. However, in the final model (Model 3), the SGA group had a 33% increased risk of anxiety interference (total), and increased likelihood of outside the home anxiety compared to controls (Table 7.4).

Table 7.4 Adjusted relative risks (aRR) of child self-reported anxiety symptoms following being born small for gestational age compared to controls

	Child report (aRR*; 95% CI)		
	Model 1	Model 2	Model 3
SCAS			
Total	1.07 (0.99, 1.15)	1.03 (0.96, 1.11)	1.04 (0.96, 1.11)
Panic/Agoraphobia	1.03 (0.84, 1.26)	0.98 (0.80, 1.20)	0.98 (0.80, 1.20)
Separation Anxiety	1.16 (0.98, 1.37)	1.11 (0.93, 1.32)	1.12 (0.94, 1.34)
Physical Injury fears	1.05 (0.85, 1.29)	0.99 (0.80, 1.21)	0.99 (0.80, 1.21)
Social Phobia	1.17 (0.98, 1.39)	1.14 (0.95, 1.36)	1.14 (0.95, 1.36)
Obsessive Compulsive behaviour	1.02 (0.87, 1.20)	0.96 (0.85, 1.17)	1.00 (0.85, 1.18)
Generalised Anxiety	0.98 (0.82, 1.16)	0.95 (0.81, 1.13)	0.95 (0.80, 1.13)
CALIS			
Total	**1.36 (1.19, 1.55)**	**1.34 (1.17, 1.52)**	**1.33 (1.16, 1.52)**
At home	1.03 (0.85, 1.26)	1.01 (0.83, 1.23)	1.00 (0.82, 1.22)
Outside home	**1.75 (1.47, 2.09)**	**1.72 (1.44, 2.06)**	**1.73 (1.44, 2.07)**

*aRR: For those born SGA (n=34); Reference category is controls (n=166).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale.
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's anxiety at 15 weeks' gestation and current mother's anxiety.

7.4.5 *Preterm born children have decreased self-reported anxiety symptoms compared to controls*

In the final model (Model 3), preterm born children had a 10% decreased risk of anxiety symptoms (total) compared to controls (Table 7.5). There were no significant differences in risk in anxiety subscales or in anxiety interference.

Table 7.5 Adjusted relative risks (aRR) of child self-reported anxiety symptoms following preterm birth compared to controls

	Child report (aRR*; 95% CI)		
	Model 1	Model 2	Model 3
SCAS			
Total	**0.91 (0.84, 0.98)**	**0.90 (0.83, 0.98)**	**0.90 (0.83, 0.98)**
Panic/Agoraphobia	0.84 (0.67, 1.04)	0.83 (0.67, 1.04)	0.83 (0.66, 1.03)
Separation Anxiety	0.85 (0.70, 1.03)	0.85 (0.69, 1.03)	0.85 (0.70, 1.04)
Physical Injury	1.00 (0.81, 1.24)	1.00 (0.80, 1.23)	1.00 (0.81, 1.24)
Social Phobia	1.01 (0.84, 1.22)	1.01 (0.84, 1.22)	1.01 (0.84, 1.22)
Obsessive Compulsive behaviour	0.87 (0.73, 1.04)	0.87 (0.73, 1.04)	0.87 (0.72, 1.04)
Generalised Anxiety	0.88 (0.73, 1.05)	0.88 (0.73, 1.05)	0.87 (0.73, 1.05)
CALIS			
Total	0.94 (0.81, 1.08)	0.93 (0.81, 1.08)	0.92 (0.80, 1.07)
At home	0.86 (0.71, 1.06)	0.86 (0.70, 1.06)	0.85 (0.69, 1.05)
Outside home	1.02 (0.83, 1.25)	1.02 (0.83, 1.25)	1.01 (0.82, 1.24)

*aRR: For those born preterm (n=26); Reference category is controls (n=166).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale.
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's anxiety at 15 weeks' gestation and current mother's anxiety.
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7.4.6 *Children born after gestational diabetes mellitus have less self-reported anxiety interference*

Children born following GDM had no differences in risk of anxiety symptoms compared to controls in any of the models. However, they had significantly decreased likelihood of anxiety interference (total score), as well as decreased likelihood of anxiety interference on the 'outside home' subscale compared to controls (Table 7.6).

Table 7.6 Adjusted relative risks (aRR) of child self-reported anxiety symptoms following exposure to gestational diabetes mellitus in utero compared to controls

	Child report (aRR*; 95% CI)		
	Model 1	Model 2	Model 3
SCAS			
Total	1.01 (0.93, 1.09)	1.03 (0.95, 1.12)	1.02 (0.94, 1.11)
Panic/Agoraphobia	1.01 (0.81, 1.26)	1.04 (0.83, 1.30)	1.04 (0.83, 1.30)
Separation Anxiety	0.91 (0.74, 1.12)	0.93 (0.76, 1.15)	0.94 (0.76, 1.15)
Physical Injury fears	1.03 (0.82, 1.30)	1.06 (0.84, 1.33)	1.05 (0.84, 1.32)
Social Phobia	1.15 (0.95, 1.39)	1.16 (0.96, 1.41)	1.15 (0.95, 1.40)
Obsessive Compulsive behaviour	0.95 (0.79, 1.14)	0.96 (0.80, 1.16)	0.96 (0.80, 1.15)
Generalised Anxiety	0.92 (0.76, 1.12)	0.93 (0.77, 1.13)	0.93 (0.77, 1.13)
CALIS			
Total	**0.80 (0.67, 0.95)**	**0.81 (0.68, 0.96)**	**0.80 (0.67, 0.95)**
At home	0.85 (0.68, 1.07)	0.86 (0.69, 1.08)	0.86 (0.69, 1.08)
Outside home	**0.73 (0.56, 0.95)**	**0.74 (0.56, 0.97)**	**0.73 (0.56, 0.95)**

*aRR: For those exposed to GDM in utero (n=22); Reference category is controls (n=166).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale.
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's anxiety at 15 weeks' gestation and current mother's anxiety.

7.4.7 *No associations between gestational hypertension and child anxiety*

Children born following GH had increased risk of total anxiety symptoms and physical injury fears in Model 1, but these differences disappeared after adding child sex (Model 2). In the final model (Model 3), children born after pregnancies complicated by GH demonstrated no differences in risk of anxiety symptoms or anxiety interference compared to controls (Table 7.7).

Table 7.7 Adjusted relative risks (aRR) of child self-reported anxiety symptoms following exposure to gestational hypertension in utero compared to controls

	Child report (aRR*; 95% CI)		
	Model 1	Model 2	Model 3
SCAS			
Total	**1.11 (1.02, 1.20)**	1.06 (0.98, 1.15)	1.06 (0.98, 1.15)
Panic/Agoraphobia	1.05 (0.85, 1.31)	0.99 (0.80, 1.24)	1.00 (0.80, 1.24)
Separation Anxiety	1.09 (0.89, 1.32)	1.04 (0.85, 1.26)	1.04 (0.85, 1.26)
Physical Injury fears	**1.28 (1.03, 1.58)**	1.19 (0.96, 1.48)	1.20 (0.96, 1.49)
Social Phobia	1.00 (0.81, 1.23)	0.97 (0.79, 1.20)	0.97 (0.79, 1.20)
Obsessive Compulsive behaviour	1.05 (0.87, 1.26)	1.01 (0.84, 1.21)	1.02 (0.85, 1.22)
Generalised Anxiety	1.18 (0.99, 1.41)	1.15 (0.96, 1.37)	1.15 (0.96, 1.37)
CALIS			
Total	0.99 (0.85, 1.16)	0.96 (0.82, 1.12)	0.97 (0.82, 1.13)
At home	0.96 (0.77, 1.19)	0.93 (0.75, 1.15)	0.94 (0.75, 1.16)
Outside home	1.03 (0.82, 1.30)	0.99 (0.79, 1.26)	1.00 (0.79, 1.27)

*aRR: For those exposed to GH in utero (n=20); Reference category is controls (n=166).
SCAS Spence Children's Anxiety Scale; *CALIS* Child Anxiety Life Interference Scale.
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's anxiety at 15 weeks' gestation and current mother's anxiety.

7.4.8 *No association between pregnancy complications and child depressive symptoms at 8-10 years old*

There were no differences in risk of depressive symptoms following any pregnancy complication when compared to the control group in any of the three models (Table 7.8).

Table 7.8 Adjusted relative risks (aRR) of child self-reported depressive symptoms following exposure to pregnancy complications compared to controls

	Depressive symptoms [a] aRR* (95% CI)		
	Model 1	Model 2	Model 3
PE (n=38)	1.03 (0.92, 1.14)	1.02 (0.91, 1.13)	1.01 (0.91, 1.13)
SGA (n=34)	0.96 (0.86, 1.07)	0.95 (0.85, 1.06)	0.95 (0.85, 1.06)
PTB (n=26)	0.90 (0.81, 1.01)	0.90 (0.81, 1.01)	0.90 (0.80, 1.01)
GDM (n=22)	0.98 (0.87, 1.10)	0.98 (0.87, 1.10)	0.98 (0.87, 1.10)
GH (n=20)	0.94 (0.83, 1.06)	0.94 (0.83, 1.06)	0.94 (0.84, 1.07)

*aRR: Reference category is controls (n=166).
[a]depressive symptoms scored on the Child Epidemiological Studies Depression Scale for Children (CES-DC).
Model 1 adjusted for smoking at 15 weeks' gestation (no versus yes), mother's age at recruitment, mother's years of education and child age;
Model 2 = Model 1 plus child sex;
Model 3 = Model 2 plus mother's depression at 15 weeks' gestation and current mother's depression.

7.5 Discussion

This study demonstrates that pregnancy complications are associated with child-reported anxiety and anxiety interference, but not depression, when compared to the control group. Specifically, children born after PE or born SGA were at the greatest risk of anxiety and anxiety interference, respectively, when compared to controls. Children born preterm and children born following GDM showed a decreased risk of anxiety and level of anxiety interference, respectively. For children born following

GH, there was no difference in risk of any anxiety compared to controls. This provides further information on early life adverse factors that may place children most at risk for future mental health problems, and hence allows for early identification of those who could benefit most from early interventions.

Pregnancy complications affect a large number of pregnancies, and these complications have been linked to long-term health outcomes by other studies. The DOHaD hypothesis has established links between early life adversity and long-term health outcomes [361, 362], and those from low SES appear to suffer the greatest impacts [22, 23]. Identification of associations between pregnancy complications and long-term outcomes could lead to early identification of those most at risk of poor outcomes, and hence enable early intervention.

Previous studies have found that PE was associated with reduced internalising behaviours, including anxious and depressed behaviours at ages five and eight years [138], while another study [139] also demonstrated that PE was not associated with anxiety disorder and/or depression in 20-30 year olds. Interestingly, GH alone has been associated with higher internalising behaviours at 14 years old [138], and data from the Helsinki birth cohort suggested that adults born after GH were at increased risk of anxiety disorders requiring hospitalisation [140]. In the current study, PE was associated with an increased risk of anxiety in children, while GH was not. Our findings suggest there are different impacts for PE and GH, and therefore PE confers some added risk to the child's mental health over GH alone. In this study, PE was diagnosed as GH with proteinuria and/or the presence of intrauterine growth restriction (ie. SGA) or other maternal organ involvement. This is a newer definition compared to previous studies which only include hypertension and proteinuria in the diagnosis, and hence could explain differences in findings between the present study and previous

studies. This suggests that the pathogenesis of PE is likely to lead to worse long-term outcomes for the child.

Children born preterm have greater emotional and/or mental health issues compared to their term born counterparts in early [209, 359] and late childhood [173, 210, 356, 357]. However, these studies assess child outcomes using parental report on their child's behaviour and/or symptoms. Previous research has suggested that parents own mental health may impact the perceptions of their child, and hence result in an over or under estimation of their child's symptoms [217, 285]. In addition, a recent study investigating anxiety symptoms of preterm and term born adolescents found no difference in self-reported anxiety symptoms between the two groups [218]. This suggests that while mothers may perceive their children as being more anxious, the children do not feel this themselves. Interestingly, the present study found a link between PTB and decreased likelihood of self-reported anxiety. The discrepancy in findings of previous work and the present study could be due to the fact that the present study utilised child-report to assess mental health symptoms rather than parent-report, or they may also be due to differences in definition of preterm birth used. Generally findings suggest poorer outcomes for those born preterm, with those born extremely preterm at largest risk of neurodevelopmental impairment [363]. Previous studies often only include early preterm born children (<32 weeks) to investigate these differences. In the present study, there were very few early preterm born children, and most were late term born children (SCOPE follow-up PTB group: median gestational age of 34 weeks). This suggests that those from our low SES cohort have lower self-reported anxiety when late preterm born. Future research would benefit from increasing the sample in order to stratify into different levels of preterm birth in order to further investigate differences.

While GDM is not uncommon and currently affects 12% of Australian pregnancies [230], studies investigating the implications of GDM on child mental health are scarce. Child neurodevelopmental outcomes following GDM have reported child deficits in cognitive function [236, 237, 240, 324, 364] and motor development [325], indicating an impact of GDM on brain development. One recent study demonstrated that children born after GDM had increased internalising and externalising behaviours at two years of age compared to control children, but these differences disappeared after adjustment for SES, maternal smoking, antenatal maternal diet, maternal postpartum depression and breastfeeding [245]. This suggests these other factors may be more important contributors to mental health status. However, GDM has been associated with an increased risk of schizophrenia in adulthood [136, 244]. Interestingly, the present study did not find differences in risk of child reported anxiety symptoms after GDM pregnancies, but found decreased risk of child reported anxiety interference. This discrepant finding may be because all participants who attended the follow-up had well controlled GDM, and there were no participants who had severe, uncontrolled diabetes. Differences in brain functioning between children born after GDM and those not exposed to GDM have also previously been suggested [247], but well controlled diabetes may alleviate this risk and constitute an important early intervention for exposed children. Further studies utilising larger cohorts investigating those with and without well-controlled diabetes would be necessary to investigate these differences.

SGA generally refers to a baby smaller than the 10^{th} percentile for the gestational age. On a population level, SGA impacts roughly 10% of pregnancies within Australia. The present study found an increased risk in anxiety interference compared to controls in children born SGA. Our definition of SGA utilised customised centiles that were

corrected for maternal height, weight, ethnicity, baby sex and gestational age. These results agree with Yi et al. [161], who found that SGA children had higher anxiety and depressive symptoms aged 8-16 years compared to AGA children. However, another study found that being born SGA was not associated with significantly increased psychiatric symptoms (including anxiety symptoms) at age 14 compared to controls [175]. Differences in findings between these studies could be due to comparator group being either "controls", which include children born large for gestational age (LGA), or only those born AGA. These differences suggest the importance of investigating SGA, AGA and LGA as separate groups to investigate long-term impacts. Many previous studies have also focused on the association between two or more complications, such as SGA and prematurity. For example, Hall and Wolke [173] demonstrated high levels of emotional problems in children born SGA who were very preterm, but not those who were born SGA at term. In the present study, pregnancy complications were not mutually exclusive, and hence some participants appeared in two or more pregnancy complication groups. Given that previous studies have shown the presence of two or more complications can increase the risk of neurodevelopmental impairment above one complication alone [125], this may suggest multiple pregnancy complications increase the severity of outcomes. Further analysis of a larger cohort could help elucidate differences from individual versus multiple pregnancy complications.

Despite previous studies finding associations between pregnancy complications and child depressive symptoms, this study did not find any associations between pregnancy complications and child depression scores in 8-10 year old children. There is little evidence about depression following pregnancy complications and depressive symptoms in children. Previous research mostly focuses on adulthood, where findings

suggest that adults born after pregnancies complicated by hypertensive disorders are at increased risk of depression [137, 140], but those born preterm and/or SGA are not [176]. If children born after hypertensive disorders are at increased risk of depression, but do not have an increased risk at age 8-10 years, this may suggest these symptoms develop at older ages. The risk for depressive disorders increases greatly in adolescence [365], and mental health problems in adolescence often continue into adulthood [366]. These findings therefore suggest a unique opportunity to intervene with children at younger ages in order to prevent the development of depression later in life.

This study has some limitations. Firstly, participants were grouped according to the presence of a pregnancy complication, which therefore resulted in some participants being included in two or more pregnancy complication groups. Previous findings have suggested that exposure to multiple pregnancy complications may increase the risk of poor outcomes further than exposure to only one [125]. The possibility cannot be ruled out therefore that the impact of one or more complications being present may impact the overall effect of one complication alone. Further research would be needed to disentangle the individual contributions of each of these complications. Secondly, many women did not take part in the follow-up study, with some citing difficulties with their children as a reason for non-attendance. Further, several children could not answer the questionnaires due to autism. If only children without severe problems were included in the follow-up, this could potentially lead to a distorted estimation of overall effects. This also limits the generalisability of the study findings. However, we attempted to include all women and children who could be contacted and, if they did not want to attend, participants were offered the opportunity to complete hard copy questionnaires and return them via post. Finally,

this follow-up occurred 8-10 years after the initial pregnancy study, and there is limited data available about the mother's or child's mental health status and life events in between the two study time points. Previous findings suggest that pregnancy complications are associated with an increased risk of postnatal depression [367], which has also been associated with mental health outcomes in offspring [297]. However, the final analysis of this study did control for maternal mental health during pregnancy, as well as controlling for their current mental health. Adding maternal health to the regression models attenuated the association between pregnancy complications and child anxiety scores, but did not eliminate them.

This study found *in utero* exposure to PE or SGA increased the risk of self-reported anxiety, while exposure to PTB and GDM decreased the risk of self-reported anxiety compared to controls. Exposure to GH did not alter the risk of anxiety. There was no relationship between any of the pregnancy complications and risk of depressive symptoms in 8-10 year old children compared to the control group. These results provide information on early life factors that are most relevant to predict future mental health problems in a low SES cohort. Given that poor mental health in childhood and adolescence has been shown to precede the development of future mental health issues, this study highlights the importance of early intervention to reduce risk of anxiety disorders.

Chapter 8:

General Discussion

8.1 Summary of findings

The main aim of this thesis was to investigate early life adverse events, specifically antenatal depression and pregnancy complications, and their association with child cognitive and mental health outcomes at 8-10 years old within a low socioeconomic status (SES) cohort.

In chapters 3 and 4, we investigated the association between antenatal depression, and cognitive and mental health outcomes in 8-10 year old children. The results presented in this thesis indicate that within a low SES cohort, high maternal antenatal depression is associated with child anxiety at 8-10 years. More specifically, high maternal antenatal depression was associated with increased risk of parent-reported child anxiety symptoms, and also anxiety interference, compared to the low antenatal depression group, after adjustment for factors such as current maternal mental health. This difference was demonstrated in all subscales of the parent reported child anxiety, including separation anxiety, social phobia, obsessive/compulsive behaviours, panic/agoraphobia, physical injury fears and generalised anxiety, and also anxiety interference inside and outside the home, as well as parent life. High antenatal depression was also associated with increased risk in the child reported anxiety symptoms, and risk of anxiety interference, compared to those exposed to low antenatal depression. However, in the child-reported subscales, children exposed to high maternal depression had significantly increased risk on only the panic/agoraphobia and social phobia subscales. We found no association between antenatal depression and child self-reported depression scores at 8-10 years old. In relation to cognitive function, we found children exposed to high antenatal depression had increased likelihood of more errors in the 6-box new learning and spatial working memory tasks, but not in the more difficult 8-box tasks, compared to children exposed

to low maternal antenatal depression. Children exposed to maternal antenatal depression also had small, but significant, increases in motor movement time compared to those not exposed to maternal antenatal depression. There were no differences in delayed memory or executive functioning between those children exposed to high or low antenatal depression.

In chapters 6 and 7, we investigated the association of major pregnancy complications PE, SGA, PTB, GDM and GH with cognitive and mental health outcomes in 8 – 10 year old children. We found different complications were associated with varying degrees of risk for positive or negative outcomes in both cognitive and mental health outcomes. Out of the five major complications, SGA was associated with the most cognitive deficits, with deficits seen across executive function, memory and reaction time tasks. PE, SGA and PTB were all associated with increased risk of poorer executive function compared to controls. Children born following PE and/or SGA also had increased risk of poorer new learning memory compared to controls. There was a small, but significant difference in reaction times, whereby children born SGA or after GH had significantly longer movement and reaction times, respectively, compared to controls. In relation to child anxiety and depression, PE was associated with an increased risk of anxiety symptoms and total anxiety interference, including anxiety interference both at home and outside the home, compared to controls. Children born SGA had no significant difference in likelihood of anxiety symptoms, but were more likely to report higher total anxiety interference and interference outside the home compared to controls. Interestingly, children born preterm (PTB group) were less likely to report anxiety symptoms, and children born after GDM were less likely to report anxiety interference, including anxiety interference outside the home, than their control counterparts. There were no

significant differences in any anxiety measures between controls and children born after GH. There was also no difference between any pregnancy complication groups and controls on child self-reported depressive symptoms on the depression scale.

8.2 Disadvantage within the sample population

The sample of participants within the SCOPE study were from low SES backgrounds. Previous findings have also demonstrated that those who do not participate in follow-up studies are more likely to be of low SES [368, 369], more likely to use tobacco and alcohol [370], have lower academic ability [368], have lower educational attainment [371], and are less likely to be married and younger at time of initial recruitment [369]. These factors may all contribute to the difficulties in recruiting participants of low SES. Our findings also demonstrated similar attrition bias, where those who were "*Contacted but did not attend*" or who were "*Uncontactable*" had significantly lower SES, were more likely to be smoking at 15 weeks' gestation and were less likely to be married when pregnant, compared to the "*Attended*" group (Chapter 3, Table 3.3). However, the participants who did attend the SCOPE follow-up presented in this thesis were still of relatively low SES status (median socioeconomic index 27; scale 10-90, with 10 indicating most disadvantage). Since SES has been demonstrated an independent predictor of poor outcomes in children [304], this highlights the importance of investigating outcomes within cohorts of low SES participants, such as those from the SCOPE cohort, to investigate outcomes in those who are already at an increased risk of poor outcomes.

Interestingly, one study demonstrated that participation in follow-up studies was less likely if no contact had been made since original participation as occurred in this study, there was also evidence to suggest that too much contact (e.g. more than four

telephone calls about participating) also reduced the likelihood of participation in follow-up studies [372]. This study therefore only attempted to call participants three times, before sending a single text message, to ensure maximum participation rates.

8.3 Antenatal depression

Maternal depression has previously been associated with poor cognitive and mental health outcomes. This is evidenced by increased behavioural issues in childhood [41, 74], and increased likelihood of diagnosis of mental health disorders such as depression in adolescence and adulthood [Reviewed in 284]. The findings of this thesis support the association between high maternal antenatal depression and increased risk of anxiety in offspring, and add to this by suggesting that these symptoms start early. This suggests early intervention before mid-childhood may be needed to address the impact this may have on the development of long-term mental health outcomes. These findings also demonstrate there are differences between mother and child-reported anxiety, which suggests the importance of investigating both mother and child reported symptoms to increase the accuracy of overall symptoms. Interestingly, however, antenatal depression was not associated with child reported depression score at 8-10 years old. Previous findings suggest antenatal depression is associated with diagnosis of depression in late adolescence and adulthood [79, 80]. Since rates of poor mental health rise rapidly among those in adolescence, this may suggest a window of opportunity in childhood to intervene for children who are already at increased risk of anxiety, to reduce the risk of development of depression in adolescence and adulthood.

There have been mixed findings in regard to antenatal depression and child intelligence quotient (IQ) score, with some studies suggesting lower IQ in those

children exposed to antenatal depression [50] or no association [51]. This thesis builds on these outcomes by investigating multiple domains of cognitive functioning, for which few studies have undertaken. Our findings contrast a previous study, which found antenatal depression was associated with better executive function [52]. However, Buss et al. [52] measured executive function using an inhibition task, while the current thesis investigated executive functioning using a cognitive flexibility task. These contrasting findings suggest that different areas of executive function may be differentially impacted by antenatal depression, and therefore this warrants further investigation. High antenatal depression symptoms have also previously been demonstrated to be associated with working memory [52]. This thesis also found children exposed to high antenatal depression had increased likelihood of more errors in the 6-box new learning and spatial working memory tasks, but not in the more difficult 8-box tasks, compared to children exposed to low antenatal depression. This may suggest children exposed to high antenatal depression have shorter memory spans, therefore "fatigue" quicker during the task, and then perform comparably on the more difficult task, or it may suggest an increase in impulsivity, whereby children exposed to high antenatal depression become more impulsive quickly and therefore make more errors on the 6-box trials. Our findings also support previous studies which suggest antenatal depression is associated with poorer motor functioning at 16 months [53], and these findings add to this by suggesting these deficits continue into childhood. Together, these findings provide greater insight into which cognitive domains may be most impacted within a low SES cohort following antenatal depression, and therefore can more specifically help to identify children who could benefit from interventions.

8.4 Pregnancy complications

Previous research has demonstrated associations between pregnancy complications and later child outcomes, with the majority of the research suggesting pregnancy complications are associated with poorer outcomes [e.g. 125, 130]. Previous findings, however, mostly focus on the impact that only one or two pregnancy complications have on child outcomes. This thesis expanded on this previous research by investigating associations of five of the major complications of pregnancy all within one cohort. This allowed for a direct comparison between each pregnancy complication group and controls, to investigate which complications are most relevant in predicting poor outcomes in children. Overall, this thesis suggests those children born SGA are most at risk of cognitive deficits that occur in multiple cognitive domains, while children exposed to PE are most at risk of anxiety symptoms, compared to their control counterparts. However, it is worth noting that some pregnancy complication groups had fewer participants than others. In contrast to previous findings, we found those children born preterm or following GDM had decreased risk of anxiety and anxiety life interference, respectively, compared to controls. Differences between the present and previous findings may be due to the fact that this research utilised child self-reported anxiety levels in chapter 7, whereas previous research in similar aged children utilises child symptoms based on parent report. These findings could also be explained by the fact that the majority of our participants in the PTB group were late preterm, and GDM mothers had well controlled diabetes, meaning the impacts of these diagnoses compared to previous research was reduced. Further research would benefit from investigating differences of varying definitions and severity of complications within different complication groups and in larger samples sizes to further elucidate differences.

8.5 Associations between antenatal depression and pregnancy complications

While we investigated associations between antenatal depression and pregnancy complications separately on child outcomes, previous studies have found that antenatal depression is associated with increased risk for pregnancy complications, such as PE and PTB [281, 373]. This research found that while there was no association between antenatal depression groups and frequency of complicated pregnancy (Chapter 4, Table 4.2), statistical tests of association were not conducted between antenatal depression groups and each specific complication. Given that both antenatal depression and pregnancy complications were associated with increased risk of deficits in certain cognitive domains and mental health, it could be hypothesised that exposure to both of these early life adverse events may increase risk of cognitive and mental health deficits even further than exposure to one event alone. Unfortunately, the sample size of participants in this thesis did not allow for investigation of this hypothesis. Future work could investigate multiple exposures to determine the full extent of additive risk to outcomes.

8.6 Association between child anxiety and cognitive performance

Associations between child anxiety and cognitive performance may have also impacted upon outcomes. Previous research has suggested that anxiety may negatively impact upon academic performance [374-377], with deficits shown more specifically in areas such as executive functioning [378, 379] and memory [380]. In the present thesis, child anxiety was not controlled for in the analyses which investigated cognitive outcomes. For example, children exposed to PE had increased risk of anxiety symptoms compared to controls, and also had poorer executive functioning and new learning memory compared to controls, suggesting anxiety may be linked to poorer

cognitive function. In contrast, children born preterm had decreased risk of anxiety symptoms but also had a deficits in executive functioning, suggesting that decreased anxiety may be associated with poorer executive function. This may reflect differential impacts of anxiety within different complication groups, or may suggest no association within this cohort between complication groups and anxiety. Additionally, we did not investigate school performance anxiety, only general anxiety. If we had assessed specifically test-related performance anxiety, we may have achieved greater accuracy for anxiety specifically related to test like situations. This would have allowed us to investigate the impact anxiety may have had on the child's cognitive performance. Future research would benefit from taking into account this potential association and using measures and analyses to interrogate potential interactions between child anxiety and thus cognitive function.

8.7 Strengths and limitations

This study had a number of strengths. Firstly, this study included a cohort from low SES background. SES is one of the most important contributing factors to poor neurodevelopment and mental health issues, and risk for poor outcomes is amplified by increasing levels of socioeconomic disadvantage [39]. This means cohorts such as the SCOPE cohort are incredibly valuable to providing insight into which other factors may be most relevant for predicting poor outcomes in an already at risk population. Secondly, this study investigated five of the most common pregnancy complications affecting women in Australia within the same cohort of women and children. This allowed for a direct comparison of each complication with the same control group, allowing for identification of those complications that may be most relevant to predict poor outcomes. Thirdly, we investigated cognitive functioning within multiple

cognitive domains. Investigating cognition in different domains (instead of generally as IQ) will allow for more specific interventions that are able to target certain cognitive domains that are most at risk of deficits. Finally, this follow-up was from a prospective, longitudinal cohort. All data was initially collected prospectively, in detail, and checked for accuracy. We also therefore had access to data on other pregnancy specific factors such as smoking during pregnancy, which were controlled for in the statistical analyses. This allowed for increased statistical robustness while also controlling for other factors known to influence child neurodevelopment.

There were a number of limitations for this study. Firstly, our follow-up cohort was subject to attrition bias. Although we did attempt to give each participant equal opportunity to participate via call and text to valid numbers, women who attended the follow-up were older at the time of child's birth, had higher SES and were less likely to have smoked during pregnancy compared to those who did not attend the follow-up (Chapter 3, Table 3.3). This could have led to an underestimation of the overall impact that disadvantage had on the child's neurodevelopment. Secondly, this thesis investigated child outcomes 8-10 years after the first pregnancy. The data available during pregnancy and at 8-10 years was very detailed, but there were no follow-ups between these two time points, and therefore we could not account for all other factors that may have influenced the child during this time. However, we did attempt to control for the factors for which we did have information that have been shown previously to influence cognitive and mental health outcomes in children, such as smoking during pregnancy. Thirdly, while mothers did complete cognitive tests at the same time as their children, it was outside the scope of this thesis to investigate how mother's current cognitive function influenced outcomes of the child. Mother's cognitive ability may be directly associated with child cognitive ability, and depression

has also been associated with deficits in cognitive ability [311, 381]. Given that those mothers in the high antenatal depression group also had significantly higher current depression scores (Chapter 4, Table 4.2), this may suggest that those mothers were more susceptible to cognitive deficits, which may in turn directly or indirectly impact child cognitive outcomes. Therefore, we did attempt to control as best we could for differences in mother's cognitive ability by controlling for maternal education level at the birth of her child. Additionally, there were no statistically significant differences in univariate analyses of mother's cognition between the low and high antenatal depression groups, or the control and pregnancy complication groups (data not presented). This would suggest that our findings are not being driven by differences in the mothers' cognition. Fourthly, measuring cognitive ability is a large undertaking, and while cognitive tasks were chosen to reflect primary cognitive domains, the tasks chosen only tested very specific areas within these domains. For example, the executive functioning task in this thesis was primarily a measure of cognitive flexibility, however, executive function is also comprised of other factors such as inhibition, planning and organisation [382]. Similarly, the reaction time task in this study was a fine motor movement task, and did not investigate gross motor movement. Future work would benefit from investigating more detailed tests within these areas to further elucidate differences. Finally, pregnancy complication groups were not mutually exclusive. This means children who were exposed to PE and were born SGA for example, would have appeared in both PE and SGA complication groups for analysis. Previous research suggests multiple complications appear to have a cumulative effect, where more pregnancy complications increase the risk further of poor neurodevelopment [125], and therefore children exposed to two or more complications may at even further increased risk than those exposed to only one.

Unfortunately, in this study, we did not have a large enough sample to distinguish between exclusive pregnancy complication groups. Further research would benefit from investigating the impact of individual, but also multiple, complications within the same cohort to further elucidate the impact of complications on long-term outcomes.

8.8 Future directions/Implications

Firstly, this research should be replicated in larger cohorts. A larger sample would allow investigation of interaction effects of exposure to different early life adverse events. For example, being born SGA may predispose an individual to increased risk of poor cognitive function in the future. These cognitive deficits may be amplified by other factors such as antenatal depression or maternal smoking during pregnancy. Having a larger cohort would allow these different pathway trajectories for different early life events to be addressed and investigated to see which pathways are most relevant to predict poor outcomes, particularly in low SES cohorts. We also saw fewer significant differences in the pregnancy complication groups with smaller numbers of participants (e.g. GH, n=20), and more differences in those complication groups with more participants (e.g. PE, n=38). This may be a true effect, or potentially this difference may be due to reduced statistical power within the smaller complication groups. Increasing the sample size would help to further elucidate any differences. Additionally, as stated in the limitations, this study also investigated different pregnancy complication groups that were not mutually exclusive. Larger sample sizes would allow us to be able to separate out all complications exclusively to investigate cognitive and mental health differences between exclusive complications and controls. This may provide a more detailed picture of which complications are most relevant to predicting outcomes.

Once these findings had been replicated in larger samples and specific early life adverse events associated with long-term outcomes, specific interventions could be designed to address those who are most at risk of deficits in cognitive function and mental health issues. For example, an intervention study found that giving 5-6 year old children small group tasks that specifically involved executive functions significantly improved their executive function over a six week period [383]. This suggests tasks specifically focussing on the area of deficits may be most effective for increasing cognitive function in that domain. Additionally, a review of randomised controlled trials suggested cognitive behavioural therapy (CBT) is a successful treatment of child anxiety and post-treatment gains were generally maintained [384]. This suggests CBT is a viable option for decreasing child anxiety but future research would be needed to investigate how best this could be implemented, particularly in a low SES cohort.

Future work could also incorporate the use of genetics and investigate different gene-environment interactions. Genetic association studies have demonstrated that certain genetic variants are associated with the development of mental illnesses such as depression [385]. Further studies may incorporate these genetic factors that predispose individuals to poor outcomes and investigate the relationship with early life environmental influences that may predict development of the illness. This may allow for earlier interventions, or earlier diagnosis, for those at increased risk.

Ideally, antenatal depression should be treated as early as possible to reduce the likelihood of development of future depression. Currently, the Lyell McEwin Hospital refers all women who score above 18 on the EPDS, or who indicate intent to self-harm, to mental health services during pregnancy. However, women who are depressed are less likely to take up the offer of help. Recently, a pilot study investigated the use of a mobile app to reduce pregnancy related anxiety and

depressive symptoms in a cohort of women at the Lyell McEwin Hospital [386]. Findings demonstrated there was no significant difference between pre- and post-app anxiety and depression scores. However, there was also poor participation rate, and those who did not participate had increased levels of anxiety and depression compared to those who did participate. This highlights the need for further research into engagement of women within low SES cohorts, such as those attending the Lyell McEwin Hospital, to investigate how to improve engagement with health services for those who need it most.

8.9 Conclusion

Previous research has demonstrated links between early life adverse events and long-term outcomes in offspring. To date, the majority of research has focused on general cognitive outcomes, such as IQ, or mental health at older ages, and often in only one specific pregnancy complication. Also, given that SES has been demonstrated to be a strong, independent predictor of child outcomes, we conducted this research in a low SES cohort who are most at risk of neurodevelopmental disadvantage. Therefore, the research presented in this thesis aimed to investigate the impact of antenatal depression and pregnancy complications on child cognitive function and anxiety and depression in children aged 8-10 years old within one cohort of children in a disadvantaged population. We found that antenatal depression was associated with child anxiety, but not child depression. We also found that each complication was associated with different impacts on cognitive function and anxiety, but none were associated with child depressive symptoms. If differences in outcomes can be identified through different exposures to early life adverse events, this could lead to the development of targeted interventions to reduce the risk of neurodevelopmental

deficits in the future. This is particularly important in low SES cohorts, who are at the greatest risk of poor outcomes.

Chapter 9:

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Appendix A– Edinburgh Postnatal Depression Scale (EPDS)

Edinburgh Postnatal Depression Scale (EPDS)

Patient Label

Mother's OB or Doctor's Name:

Doctor's Phone #: _____

Since you are either pregnant or have recently had a baby, we want to know how you feel. Please place a **CHECK MARK** (✔) on the blank by the answer that comes closest to how you have felt **IN THE PAST 7 DAYS**—*not just how you feel today.* Complete all 10 items and find your score by adding each number that appears in parentheses (#) by your checked answer. This is a screening test; not a medical diagnosis. If something doesn't seem right, *call your health care provider regardless of your score.*

Below is an example already completed.

I have felt happy:
Yes, all of the time ____ (0)
Yes, most of the time ✔ (1)
No, not very often ____ (2)
No, not at all ____ (3)

This would mean: "I have felt happy most of the time" in the past week. Please complete the other questions in the same way.

1. I have been able to laugh and see the funny side of things:
   As much as I always could ____ (0)
   Not quite so much now ____ (1)
   Definitely not so much now ____ (2)
   Not at all ____ (3)

2. I have looked forward with enjoyment to things:
   As much as I ever did ____ (0)
   Rather less than I used to ____ (1)
   Definitely less than I used to ____ (2)
   Hardly at all ____ (3)

3. I have blamed myself unnecessarily when things went wrong:
   Yes, most of the time ____ (3)
   Yes, some of the time ____ (2)
   Not very often ____ (1)
   No, never ____ (0)

4. I have been anxious or worried for no good reason:
   No, not at all ____ (0)
   Hardly ever ____ (1)
   Yes, sometimes ____ (2)
   Yes, very often ____ (3)

5. I have felt scared or panicky for no good reason:
   Yes, quite a lot ____ (3)
   Yes, sometimes ____ (2)
   No, not much ____ (1)
   No, not at all ____ (0)

6. Things have been getting to me:
   Yes, most of the time I haven't been able to cope at all ____ (3)
   Yes, sometimes I haven't been coping as well as usual ____ (2)
   No, most of the time I have coped quite well ____ (1)
   No, I have been coping as well as ever ____ (0)

7. I have been so unhappy that I have had difficulty sleeping:
   Yes, most of the time ____ (3)
   Yes, sometimes ____ (2)
   No, not very often ____ (1)
   No, not at all ____ (0)

8. I have felt sad or miserable:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Not very often ____ (1)
   No, not at all ____ (0)

9. I have been so unhappy that I have been crying:
   Yes, most of the time ____ (3)
   Yes, quite often ____ (2)
   Only occasionally ____ (1)
   No, never ____ (0)

10. The thought of harming myself has occurred to me:*
    Yes, quite often ____ (3)
    Sometimes ____ (2)
    Hardly ever ____ (1)
    Never ____ (0)

TOTAL YOUR SCORE HERE ▶

Thank you for completing this survey. Your doctor will score this survey and discuss the results with you.

Verbal consent to contact above mentioned MD witnessed by:

_____

Edinburgh Postnatal Depression Scale (EPDS). Adapted from the *British Journal of Psychiatry*, June, 1987, vol. 150 by J.L. Cox, J.M. Holden, R. Segovsky.

Appendix B – Mother consent form

Robinson Research Institute
Healthy children for life.

Government of South Australia

I, _____ *(please print name)*

hereby consent to my child's involvement in the research project entitled:

Early Life Exposures and Child Development

1. The nature and purpose of the research project described on the attached Information Sheet has been explained to me. I understand it, and agree to my child taking part.
2. I understand that my child may not directly benefit by taking part in this study.
3. I acknowledge that the possible risks and/or side effects, discomforts and inconveniences, as outlined in the Information Sheet, have been explained to me.
4. I understand that while information gained in the study may be published, neither my child nor I will be identified, and information will be confidential.
5. I understand that I can withdraw my child from the study at any stage and that this will not affect medical care or any other aspects of either my or my child's relationship with this hospital.
6. I understand that there will be no payment to me or my child for taking part in this study.
7. I have had the opportunity to discuss taking part in this research project with a family member or friend and/or have had the opportunity to have a family member or friend present whilst the research project was being explained to me by the researcher.
8. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.
9. I consent to the biological samples being collected in this study being used for other similar research projects by the SCOPE research team that have received ethics approval.
   ☐ Yes ☐ No (please tick)
10. I consent to my child's GP being notified by the research team if the results on the questionnaires indicate a potential health problem. ☐ Yes ☐ No (please tick)

    GP Name: _____ GP address: _____

Signed: _____ Dated: _____

Relationship to Child: _____ Full Name of Child: _____

I, _____ (child's name) have had the study explained to me and I am happy to take part. I understand that I can change my mind and stop being involved whenever I want to.

Signature of Child: _____

Research team member: I certify that I have explained the study to the parent/legal guardian and consider that he/she understands what is involved.

Signed: _____ Title: _____ Date: _____

Version 1, August 5 2015

Appendix C – Child consent form

Robinson Research Institute
Healthy children for life.

Government of South Australia

I, _____ *(please print name)*

hereby consent to my child's involvement in the research project entitled:

Early Life Exposures and Child Development

1. The nature and purpose of the research project described on the attached Information Sheet has been explained to me. I understand it, and agree to my child taking part.
2. I understand that my child may not directly benefit by taking part in this study.
3. I acknowledge that the possible risks and/or side effects, discomforts and inconveniences, as outlined in the Information Sheet, have been explained to me.
4. I understand that while information gained in the study may be published, neither my child nor I will be identified, and information will be confidential.
5. I understand that I can withdraw my child from the study at any stage and that this will not affect medical care or any other aspects of either my or my child's relationship with this hospital.
6. I understand that there will be no payment to me or my child for taking part in this study.
7. I have had the opportunity to discuss taking part in this research project with a family member or friend and/or have had the opportunity to have a family member or friend present whilst the research project was being explained to me by the researcher.
8. I am aware that I should retain a copy of the Consent Form, when completed, and the Information Sheet.
9. I consent to the biological samples being collected in this study being used for other similar research projects by the SCOPE research team that have received ethics approval.
   ☐ Yes ☐ No (please tick)
10. I consent to my child's GP being notified by the research team if the results on the questionnaires indicate a potential health problem. ☐ Yes ☐ No (please tick)

    GP Name: _____ GP address: _____

Signed: _____ Dated: _____

Relationship to Child: _____ Full Name of Child: _____

I, _____ (child's name) have had the study explained to me and I am happy to take part. I understand that I can change my mind and stop being involved whenever I want to.

Signature of Child: _____

Research team member: I certify that I have explained the study to the parent/legal guardian and consider that he/she understands what is involved.

Signed: _____ Title: _____ Date: _____

Version 1, August 5 2015

Appendix D – Spence Children's Anxiety Scale (SCAS; Parent Report)

SPENCE CHILDREN'S ANXIETY SCALE
(Parent Report)

Your Name: _____ **Date:** _____

Your Child's Name: _____

BELOW IS A LIST OF ITEMS THAT DESCRIBE CHILDREN. FOR EACH ITEM PLEASE CIRCLE THE RESPONSE THAT BEST DESCRIBES YOUR CHILD. PLEASE ANSWER ALL THE ITEMS.

1.	My child worries about things.....	Never	Sometimes	Often	Always
2.	My child is scared of the dark.....	Never	Sometimes	Often	Always
3.	When my child has a problem, s(he) complains of having a funny feeling in his / her stomach	Never	Sometimes	Often	Always
4.	My child complains of feeling afraid.....	Never	Sometimes	Often	Always
5.	My child would feel afraid of being on his/her own at home.....	Never	Sometimes	Often	Always
6.	My child is scared when s(he) has to take a test.....	Never	Sometimes	Often	Always
7.	My child is afraid when (s)he has to use public toilets or bathrooms.....	Never	Sometimes	Often	Always
8.	My child worries about being away from us / me.....	Never	Sometimes	Often	Always
9.	My child feels afraid that (s)he will make a fool of him/herself in front of people.....	Never	Sometimes	Often	Always
10.	My child worries that (s)he will do badly at school.....	Never	Sometimes	Often	Always
11.	My child worries that something awful will happen to someone in our family.....	Never	Sometimes	Often	Always
12.	My child complains of suddenly feeling as if (s)he can't breathe when there is no reason for this.....	Never	Sometimes	Often	Always
13.	My child has to keep checking that (s)he has done things right (like the switch is off, or the door is locked)..	Never	Sometimes	Often	Always
14.	My child is scared if (s)he has to sleep on his/her own.....	Never	Sometimes	Often	Always
15.	My child has trouble going to school in the mornings because (s)he feels nervous or afraid.....	Never	Sometimes	Often	Always
16.	My child is scared of dogs	Never	Sometimes	Often	Always
17.	My child can't seem to get bad or silly thoughts out of his / her head.....	Never	Sometimes	Often	Always
18.	When my child has a problem, s(he) complains of his/her heart beating really fast.....	Never	Sometimes	Often	Always

19.	My child suddenly starts to tremble or shake when there is no reason for this.....	Never	Sometimes	Often	Always
20.	My child worries that something bad will happen to him/her.....	Never	Sometimes	Often	Always
21.	My child is scared of going to the doctor or dentist	Never	Sometimes	Often	Always
22.	When my child has a problem, (s)he feels shaky.....	Never	Sometimes	Often	Always
23.	My child is scared of heights (eg. being at the top of a cliff).....	Never	Sometimes	Often	Always
24.	My child has to think special thoughts (like numbers or words) to stop bad things from happening.....	Never	Sometimes	Often	Always
25.	My child feels scared if (s)he has to travel in the car, or on a bus or train	Never	Sometimes	Often	Always
26.	My child worries what other people think of him/her.....	Never	Sometimes	Often	Always
27.	My child is afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds).....	Never	Sometimes	Often	Always
28	All of a sudden my child feels really scared for no reason at all.....	Never	Sometimes	Often	Always
29.	My child is scared of insects or spiders.....	Never	Sometimes	Often	Always
30.	My child complains of suddenly becoming dizzy or faint when there is no reason for this.....	Never	Sometimes	Often	Always
31.	My child feels afraid when (s)he has to talk in front of the class.....	Never	Sometimes	Often	Always
32.	My child's complains of his / her heart suddenly starting to beat too quickly for no reason	Never	Sometimes	Often	Always
33.	My child worries that (s)he will suddenly get a scared feeling when there is nothing to be afraid of.....	Never	Sometimes	Often	Always
34.	My child is afraid of being in small closed places, like tunnels or small rooms.....	Never	Sometimes	Often	Always
35.	My child has to do some things over and over again (like washing his / her hands, cleaning or putting things in a certain order).....	Never	Sometimes	Often	Always
36.	My child gets bothered by bad or silly thoughts or pictures in his/her head	Never	Sometimes	Often	Always
37.	My child has to do certain things in just the right way to stop bad things from happening	Never	Sometimes	Often	Always
38.	My child would feel scared if (s)he had to stay away from home overnight.....	Never	Sometimes	Often	Always
39.	Is there anything else that your child is really afraid of?	YES	NO		
	Please write down what it is, and fill out how often (s)he is afraid of this thing: _____	Never	Sometimes	Often	Always
	_____	Never	Sometimes	Often	Always
	_____	Never	Sometimes	Often	Always

Appendix E – Spence Children's Anxiety Scale (SCAS; Child Report)

SPENCE CHILDREN'S ANXIETY SCALE

Your Name: _____ **Date:** _____

PLEASE PUT A CIRCLE AROUND THE WORD THAT SHOWS HOW OFTEN EACH OF THESE THINGS HAPPEN TO YOU. THERE ARE NO RIGHT OR WRONG ANSWERS.

1.	I worry about things	Never	Sometimes	Often	Always
2.	I am scared of the dark	Never	Sometimes	Often	Always
3.	When I have a problem, I get a funny feeling in my stomach	Never	Sometimes	Often	Always
4.	I feel afraid	Never	Sometimes	Often	Always
5.	I would feel afraid of being on my own at home	Never	Sometimes	Often	Always
6.	I feel scared when I have to take a test	Never	Sometimes	Often	Always
7.	I feel afraid if I have to use public toilets or bathrooms	Never	Sometimes	Often	Always
8.	I worry about being away from my parents	Never	Sometimes	Often	Always
9.	I feel afraid that I will make a fool of myself in front of people	Never	Sometimes	Often	Always
10.	I worry that I will do badly at my school work	Never	Sometimes	Often	Always
11.	I am popular amongst other kids my own age	Never	Sometimes	Often	Always
12.	I worry that something awful will happen to someone in my family	Never	Sometimes	Often	Always
13.	I suddenly feel as if I can't breathe when there is no reason for this	Never	Sometimes	Often	Always
14.	I have to keep checking that I have done things right (like the switch is off, or the door is locked)	Never	Sometimes	Often	Always
15.	I feel scared if I have to sleep on my own	Never	Sometimes	Often	Always
16.	I have trouble going to school in the mornings because I feel nervous or afraid	Never	Sometimes	Often	Always
17.	I am good at sports	Never	Sometimes	Often	Always
18.	I am scared of dogs	Never	Sometimes	Often	Always
19.	I can't seem to get bad or silly thoughts out of my head	Never	Sometimes	Often	Always
20.	When I have a problem, my heart beats really fast	Never	Sometimes	Often	Always
21.	I suddenly start to tremble or shake when there is no reason for this	Never	Sometimes	Often	Always
22.	I worry that something bad will happen to me	Never	Sometimes	Often	Always
23.	I am scared of going to the doctors or dentists	Never	Sometimes	Often	Always
24.	When I have a problem, I feel shaky	Never	Sometimes	Often	Always
25.	I am scared of being in high places or lifts (elevators)	Never	Sometimes	Often	Always

26.	I am a good person.....	Never	Sometimes	Often	Always
27.	I have to think of special thoughts to stop bad things from happening (like numbers or words).....	Never	Sometimes	Often	Always
28	I feel scared if I have to travel in the car, or on a Bus or a train.....	Never	Sometimes	Often	Always
29.	I worry what other people think of me.....	Never	Sometimes	Often	Always
30.	I am afraid of being in crowded places (like shopping centres, the movies, buses, busy playgrounds).....	Never	Sometimes	Often	Always
31.	I feel happy.....	Never	Sometimes	Often	Always
32.	All of a sudden I feel really scared for no reason at all.....	Never	Sometimes	Often	Always
33.	I am scared of insects or spiders.....	Never	Sometimes	Often	Always
34.	I suddenly become dizzy or faint when there is no reason for this.....	Never	Sometimes	Often	Always
35.	I feel afraid if I have to talk in front of my class.....	Never	Sometimes	Often	Always
36.	My heart suddenly starts to beat too quickly for no reason.....	Never	Sometimes	Often	Always
37.	I worry that I will suddenly get a scared feeling when there is nothing to be afraid of.....	Never	Sometimes	Often	Always
38.	I like myself.....	Never	Sometimes	Often	Always
39.	I am afraid of being in small closed places, like tunnels or small rooms.	Never	Sometimes	Often	Always
40.	I have to do some things over and over again (like washing my hands, cleaning or putting things in a certain order).....	Never	Sometimes	Often	Always
41.	I get bothered by bad or silly thoughts or pictures in my mind.....	Never	Sometimes	Often	Always
42.	I have to do some things in just the right way to stop bad things happening.....	Never	Sometimes	Often	Always
43.	I am proud of my school work.....	Never	Sometimes	Often	Always
44.	I would feel scared if I had to stay away from home overnight.....	Never	Sometimes	Often	Always
45.	Is there something else that you are really afraid of?.....	YES	NO		
	Please write down what it is_____				
	_____				
	_____				
	How often are you afraid of this thing?.....	Never	Sometimes	Often	Always

Appendix F – Child Anxiety Life Interference Scale (CALIS; Parent Report)

Child Anxiety Life Interference Scale (Parent Version)

1. Do fears and worries upset or distress your child?

Not at all ⓪ Only a little ① Sometimes ② Quite a lot ③ A great deal ④

2.	**How much do fears and worries interfere with your child's everyday life in the following areas?**	**Not at all**	**Only a little**	**Some**	**Quite a lot**	**A great deal**
a.	Getting on with parents	⓪	①	②	③	④
b.	Getting on with siblings (Answer 'Not at All' if you have only one child)	⓪	①	②	③	④
c.	Being with friends outside of school	⓪	①	②	③	④
d.	Performance in the classroom	⓪	①	②	③	④
e.	Interacting with peers at recess and lunch	⓪	①	②	③	④
f.	Playing sport	⓪	①	②	③	④
g.	Doing enjoyable activities like going to parties, movies or holidays	⓪	①	②	③	④
h.	Daily activities (eg sleeping, going to school, homework, playing)	⓪	①	②	③	④

3.	**How much do your child's fears and worries interfere with your everyday life in the following areas**	**Not at all**	**Only a little**	**Some**	**Quite a lot**	**A great deal**
a.	Your relationship with your partner or a potential partner	⓪	①	②	③	④
b.	Your relationship with extended family	⓪	①	②	③	④
c.	Your relationship with friends	⓪	①	②	③	④
d.	Your career (choice to work, how many hours you do or how often you miss work)	⓪	①	②	③	④
e.	Your ability to go out to activities/events without your child	⓪	①	②	③	④
f.	Your ability to go out to activities/events with your child	⓪	①	②	③	④
g.	Your level of stress	⓪	①	②	③	④

Appendix G – Child Anxiety Life Interference Scale (CALIS; Child Report)

Child Anxiety Life Interference Scale – Child Report

1. Do fears and worries upset you?

Not at all	Only a little	Sometimes	Quite a lot	A great deal
⓪	①	②	③	④

2. How much do fears and worries make it difficult for you to do the following things?

		Not at all	Only a little	Some	Quite a lot	A great deal
a.	Getting on with parents ……..	⓪	①	②	③	④
b.	Getting on with brothers and sisters … (answer not at all if you are an only child)	⓪	①	②	③	④
c.	Being with friends outside of school …	⓪	①	②	③	④
d.	Getting your schoolwork done ……	⓪	①	②	③	④
e.	Being with class mates at recess and lunch ……	⓪	①	②	③	④
f.	Playing sport ……	⓪	①	②	③	④
g.	Doing enjoyable activities like going to parties, movies or holidays ……	⓪	①	②	③	④
h.	Daily activities such as getting ready for school, going to sleep and homework …	⓪	①	②	③	④

Appendix H – Center for Epidemiological Studies Depression Scale for Children (CES-DC)

BRIGHT FUTURES TOOL FOR PROFESSIONALS

Center for Epidemiological Studies Depression Scale for Children (CES-DC)

Number _____

Score _____

INSTRUCTIONS

Below is a list of the ways you might have felt or acted. Please check how *much* you have felt this way during the *past week*.

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
1. I was bothered by things that usually don't bother me.	____	____	____	____
2. I did not feel like eating, I wasn't very hungry.	____	____	____	____
3. I wasn't able to feel happy, even when my family or friends tried to help me feel better.	____	____	____	____
4. I felt like I was just as good as other kids.	____	____	____	____
5. I felt like I couldn't pay attention to what I was doing.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
6. I felt down and unhappy.	____	____	____	____
7. I felt like I was too tired to do things.	____	____	____	____
8. I felt like something good was going to happen.	____	____	____	____
9. I felt like things I did before didn't work out right.	____	____	____	____
10. I felt scared.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
11. I didn't sleep as well as I usually sleep.	____	____	____	____
12. I was happy.	____	____	____	____
13. I was more quiet than usual.	____	____	____	____
14. I felt lonely, like I didn't have any friends.	____	____	____	____
15. I felt like kids I know were not friendly or that they didn't want to be with me.	____	____	____	____

DURING THE PAST WEEK	Not At All	A Little	Some	A Lot
16. I had a good time.	____	____	____	____
17. I felt like crying.	____	____	____	____
18. I felt sad.	____	____	____	____
19. I felt people didn't like me.	____	____	____	____
20. It was hard to get started doing things.	____	____	____	____

www.brightfutures.org

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Appendix I – GP letter for child

DATE

Dear [DOCTOR NAME],

Your patient, [CHILD NAME], was recently involved in a study with the University of Adelaide at the Lyell McEwin Hospital.

This study included a measure of depression on the Centre for Epidemiological Studies Depression Scale for Children (CES-DC), which was used for research purposes. Before commencing the study, [CHILD NAME]'s mother, [MOTHER NAME], was asked whether she consented to her GP to be contacted if scores on questionnaires indicated her child might need or benefit from professional help. She provided your name and address to us for this purpose.

Scores on the CES-DC range from 0-60, with cut-off scores that may indicate depressive symptoms outlined below. Results from [CHILD NAME] are also outlined in the table below.

Scores indicating depressive symptoms	Participant's Score
15 - 60	XX

While the CES-DC has been validated for research purposes, it is a screening measure and is not a clinical diagnosis. Scores on questionnaires can also be susceptible to other factors, such as recent events, current mood, etc.

At the time of participation, we gave [MOTHER NAME] and [CHILD NAME] details of helplines (attached for your reference). Nevertheless, it is an ethical requirement that we notify you of your patient's scores should you wish to pursue this further.

Kind Regards,

Nicolette Hodyl, PhD

Coordinating Principal Investigator

SCOPE follow up study

Phone: 8313 1303

Email: nicolette.hodyl@adelaide.edu.au

Appendix J – Depression Anxiety Stress Scale (DASS-42)

DASS

Name: *Date:*

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you *over the past week*. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

1	I found myself getting upset by quite trivial things	0	1	2	3
2	I was aware of dryness of my mouth	0	1	2	3
3	I couldn't seem to experience any positive feeling at all	0	1	2	3
4	I experienced breathing difficulty (eg, excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5	I just couldn't seem to get going	0	1	2	3
6	I tended to over-react to situations	0	1	2	3
7	I had a feeling of shakiness (eg, legs going to give way)	0	1	2	3
8	I found it difficult to relax	0	1	2	3
9	I found myself in situations that made me so anxious I was most relieved when they ended	0	1	2	3
10	I felt that I had nothing to look forward to	0	1	2	3
11	I found myself getting upset rather easily	0	1	2	3
12	I felt that I was using a lot of nervous energy	0	1	2	3
13	I felt sad and depressed	0	1	2	3
14	I found myself getting impatient when I was delayed in any way (eg, lifts, traffic lights, being kept waiting)	0	1	2	3
15	I had a feeling of faintness	0	1	2	3
16	I felt that I had lost interest in just about everything	0	1	2	3
17	I felt I wasn't worth much as a person	0	1	2	3
18	I felt that I was rather touchy	0	1	2	3
19	I perspired noticeably (eg, hands sweaty) in the absence of high temperatures or physical exertion	0	1	2	3
20	I felt scared without any good reason	0	1	2	3
21	I felt that life wasn't worthwhile	0	1	2	3

Please turn the page ☞

Lovibond, S.H. & Lovibond, P.F. (1995). Manual for the Depression Anxiety Stress Scales (2nd. Ed.). Sydney: Psychology Foundation.

Reminder of rating scale:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree, or a good part of time
3 Applied to me very much, or most of the time

22	I found it hard to wind down	0	1	2	3
23	I had difficulty in swallowing	0	1	2	3
24	I couldn't seem to get any enjoyment out of the things I did	0	1	2	3
25	I was aware of the action of my heart in the absence of physical exertion (eg, sense of heart rate increase, heart missing a beat)	0	1	2	3
26	I felt down-hearted and blue	0	1	2	3
27	I found that I was very irritable	0	1	2	3
28	I felt I was close to panic	0	1	2	3
29	I found it hard to calm down after something upset me	0	1	2	3
30	I feared that I would be "thrown" by some trivial but unfamiliar task	0	1	2	3
31	I was unable to become enthusiastic about anything	0	1	2	3
32	I found it difficult to tolerate interruptions to what I was doing	0	1	2	3
33	I was in a state of nervous tension	0	1	2	3
34	I felt I was pretty worthless	0	1	2	3
35	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
36	I felt terrified	0	1	2	3
37	I could see nothing in the future to be hopeful about	0	1	2	3
38	I felt that life was meaningless	0	1	2	3
39	I found myself getting agitated	0	1	2	3
40	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
41	I experienced trembling (eg, in the hands)	0	1	2	3
42	I found it difficult to work up the initiative to do things	0	1	2	3

Lovibond, S.H. & Lovibond, P.F. (1995). Manual for the Depression Anxiety Stress Scales (2nd. Ed.). Sydney: Psychology Foundation.

Appendix K – GP letter for mother

DATE

Dear [DOCTOR NAME],

Your patient, [MOTHER NAME], was recently involved in a study conducted by the University of Adelaide at the Lyell McEwin Hospital.

This study included measures of depression, anxiety and stress on the DASS-42, which was used for research purposes. Before commencing the study, [MOTHER NAME] was asked whether she consented to her GP to be contacted if scores on questionnaires indicated they might need or benefit from professional help. She provided your name and address to us for this purpose.

Scores on the DASS-42 range from 0-42 on three domains: depression, anxiety, stress. Cut-off scores that indicate severe or extreme scores on each domain are outlined below. Results from [MOTHER NAME] are also outlined in the table below.

	Range of scores indicating severe or extreme rating for each domain	Participant's Score
Depression	21 - 42	XX
Anxiety	15 - 42	XX
Stress	26 - 42	XX

While the DASS-42 questionnaire has been validated for research purposes, it is a screening measure and is not a clinical diagnosis. Scores on questionnaires can also be susceptible to other factors, such as recent events, current mood, etc.

At the time of participation, we gave [MOTHER NAME] details of helplines (attached for your reference). Nevertheless, it is an ethical requirement that we notify you of your patient's scores should you wish to pursue this further.

Kind Regards,

Nicolette Hodyl, PhD

Coordinating Principal Investigator

SCOPE follow-up study

Phone: 8313 1303

Email: nicolette.hodyl@adelaide.edu.au

Appendix L – National Helplines

National help lines and websites for parents and children

Parentline

Parentline is a confidential telephone counselling service providing professional counselling and support for parents and those who care for children.
The aim of Parentline is to nurture and support positive, caring relationships between parents, children, teenagers and significant other people who are important to the wellbeing of families.

1300 364 100 (cost of a local call)
24 hours a day, 7 days a week

Raising children

This website contains information, discussion forums, videos, articles and resources for helping parents raise their children.
http://raisingchildren.net.au/pre-teens/pre-teens.html

eheadspace

Eheadspace is a confidential, free and secure space where young people or their family can chat, email or speak on the phone with a qualified youth mental health professional.

1800 650 890 (free call)
24 hours a day, 7 days a week
www.eheadspace.org.au