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Early life events and motor development: A longitudinal study

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Early Life Events and Motor Development: A Longitudinal Study

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Declaration of Authorship

This thesis is my own work and contains no material which has been accepted for the award of any degree or diploma in any other institution.

To the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

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Tegan Jade Grace Date

Abstract

Longitudinal studies are important to fully understand the processes of neurological development during gestation and how risk factors present during this time impact motor development outcomes, yet few to date have focused on this critical time period.

The purpose of this study was to identify modifiable risk factors influencing motor development during the prenatal period. Of particular interest was finding out whether these risk factors differed between the sexes.

Participants (N=2900) were from the Western Australian Pregnancy Cohort (Raine) Study. The Raine Study began in May 1989 and women were recruited between 16-20 weeks gestation (m = 18 weeks) from the main obstetric hospital in Western Australia (W.A.), King Edward Memorial Hospital. Approximately 100 participants per month were recruited, with the process completed during November 1991. The women were primarily Caucasian, from European descent (88.2%), and included mothers who identified as Aboriginal (2.4%), Chinese (4.4%), Indian (2.6%), Polynesian (0.9%) and Vietnamese (0.3%). Recruitment criteria included adequate English language skills for the understanding of the study process and a desire to reside in W.A. to facilitate future follow up. There were 2868 live births and extensive obstetric, antenatal and sociodemographic data were recorded. Maternal and child health data were collected in a series of data collection phases at ages 1, 2, 3, 5, 8, 10, 14, 17, and 21 years. Motor coordination was measured at 10 (n = 1622), 14 (n = 1584) and 17 (n = 1221) years using the McCarron Assessment of Neuromuscular Development (MAND) (McCarron, 1997). The Neuromuscular

Development Index (NDI) of the MAND was used as a continuous outcome measure.

Potential risk factors for a poorer motor outcome, including maternal smoking, alcohol and drug consumption, maternal age, parental handedness, maternal health (illness and infection), delivery mode, gestational hypertensive status, stress, socioeconomic status, percentage of optimal birth weight (a measure of whether growth potential has been met), child's sex, gestational age, parity and breastfeeding were examined. Cross sectional analyses comprising chi-square tests, t-tests and univariate ANOVA models (general linear model - GLM) with Bonferroni post hoc correction were used to identify variables that contributed to motor development outcomes. The effect of these variables on motor development were further examined using linear mixed models accounting for the unbalanced nature of longitudinal data with repeated measures. A series of studies were conducted to analyse the impact of these factors on long term motor development outcomes.

The first study found that maternal hypertensive disease, in particular preeclampsia, had negative long term effects on motor development outcomes. The second study examined the number, timing and type of stressful events mothers experienced during pregnancy. A significant relationship between number of stressful events and motor development outcomes was revealed, suggesting increased stress led to suboptimal neurological development. Stress later in pregnancy was found to have a greater effect than earlier stress. The impact of breastfeeding duration was investigated in the third study and a protective effect was found for those who were breastfed for six months or longer compared to those who were breastfed for less than six months.

When males and females were examined separately in the fourth study there were some differences in the type of factors that affected motor development outcomes. Maternal preeclampsia, mode of delivery and income affected both male and female motor outcomes. Lower percentage of optimal birth weight was related to a lower male NDI. Younger maternal age, smoking during early pregnancy and stress during later pregnancy were related to lower NDI in females.

Other factors considered in the analyses, including lower family income, male sex, maternal alcohol consumption, smoking and caesarean section delivery were also found to negatively impact motor development outcomes. This information can be utilized to help identify potentially at risk infants and ensure optimal future neurological development. Early detection and intervention strategies may help to increase motor development outcomes in those who are exposed to the identified risks.

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Publications

Full manuscripts are in Appendices

Grace, T., Bulsara, M., Pennell, C. & Hands, B. (2014). Maternal hypertensive diseases negatively affect offspring motor development. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 4*(3) 209-214. doi: 10.1016/j.preghy.2014.04.003

Grace, T., Bulsara, M., Robinson, M. & Hands, B. (2015). Maternal stress during pregnancy affects long term offspring motor development. *Child Development, 87* (1) 211-220 doi: 10.1111/cdev.12449

Grace, T., Bulsara, M., Robinson, M. & Hands, B. (2015). Early life events and motor development in childhood and adolescence: A longitudinal study. *Acta Paediatrica, (in press)* doi: 10.1111/apa.13302

Grace, T., Bulsara, M., Oddy, W. & Hands, B. (2016). Breastfeeding and motor development: A longitudinal cohort study. *Human Movement Science (under review*

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CHAPTER ONE

Introduction

"The brain is a subtle series of organ subsystems that are exquisitely integrated and mutually interdependent, especially during early development..."

(Morgane, Austin-LaFrance & Bronzino, 1992)

Individuals with low motor coordination (LMC) can be diagnosed as having Developmental Coordination Disorder (DCD), however this condition is currently under recognized and under diagnosed in the Australian population. Awareness of the consequences of poor motor development need to be increased in Australia in order to provide adequate support to those who need it. Children with LMC are at risk for developing low physical self-perceptions and withdrawing from social and physical activities during childhood and adolescence (Cantell, Smyth, & Ahonen, 1994; Fitzpatrick & Watkinson, 2003). They are often reported as having lower levels of fitness (Cantell, Crawford, & Doyle-Baker, 2008; Erwin & Castelli, 2004; Hands & Larkin, 2006), higher body fat percentage, decreased perceived physical ability and lower enjoyment of physical education classes (Cairney et al., 2007) compared to their more coordinated peers. LMC has also been linked to increased depressive symptomology (Lingam et al., 2012; Piek, Rigoli, et al., 2007) and peer victimization (Bejerot & Humble, 2013) and is a significant predictor of negative social behaviour (Cummins, Piek, & Dyck, 2005; Hands, Larkin, Kendall, Parker, & Sloan, 2007; Peters, Maathuis, & Hadders-Algra, 2010). Longitudinal studies indicate that many of these poor outcomes associated with LMC are likely to persist into adolescence (Cantell et al., 1994) and, for many, continue into adulthood (Cousins & Smyth, 2003; Rasmussen & Gillberg, 2000).

With poor health outcomes such as these it is imperative factors that impact motor coordination outcomes be identified as early as possible. A growing body of evidence suggests that events occurring during gestation and birth may have a lasting effect on fetal neurological systems and therefore on postnatal motor development (Pitcher, Henderson-Smart, & Robinson, 2006). Although the human brain and

nervous system have shown a capacity for adaptivity (often referred to as plasticity) there is some evidence that suggests insults to the developing central nervous system (CNS) in-utero can be long lasting and in some cases permanent (Pitcher et al., 2006). The development of the CNS is a complex process that begins at approximately three weeks gestation, however differentiation of embryo cells into specific tissues starts only a few days after fertilisation (Brodal, 2010). The CNS undergoes numerous changes throughout the antenatal, perinatal and neonatal periods, and development continues throughout infancy, childhood, adolescence and adulthood (de Graaf-Peter & Hadders-Algra, 2005; Pitcher et al., 2006). Developmental researchers have already identified a range of risk factors that can affect long term developmental outcomes during these early life stages. It is well established that fetal growth restriction (FGR), premature birth, small for gestational age (SGA) status, maternal stress, smoking and alcohol consumption are risk factors for compromised motor development in early (Goyen & Lui, 2002; Kalberg et al., 2006; Pitcher et al., 2006; Schmidhauser et al., 2006; Trasti, Vik, Jacobsen, & Bakketeig, 1999) and late (Hands, Kendall, Larkin, & Parker, 2009) childhood. However, although the antenatal period has been documented as a time of great importance for neurological development, there are few longitudinal studies that have sought to determine how exposure to known risk factors during this time effect motor development beyond childhood. Notable exceptions to this are longitudinal research undertaken by Gillberg and Rasmussen (1982), Cantell (1998), The Avon Longitudinal Study of Parents and Children (ALSPAC) (Boyd et al., 2013) and The Groningen Perinatal Project (Hadders-Algra, 2002). The findings from these studies highlight the need for further research with longitudinal cohort data that can shed more light on the early life factors that impact upon motor development. Researchers

in the area of motor development generally agree that, without intervention, the likelihood of any deficit in motor development simply disappearing with age is low however there is no definitive answer as to how many children enter adolescence and adulthood with a persistent motor coordination problem. Most longitudinal research into the area of motor development start by first categorizing the participants as high or low motor competent or as having either normal or dysfunctional motor development. The groups are usually then tracked and compared over time (Cantell, 1998; Gillberg & Rasmussen, 1982). This type of study design lacks the ability to pinpoint the predictive variables as motor development is generally the dependent not independent variable. Furthermore, there are very few longitudinal studies of motor development that can account for factors impacting development during the antenatal, perinatal and neonatal periods. If these factors are considered the data are usually collected retrospectively.

Research into the persistence of motor development issues has reported high numbers of children with an original diagnosis of motor dysfunction still having problems through childhood and into adolescence. Losse et al. (1991) reported that 87% of their original six-year-old cohort had motor competence difficulties that persisted into adolescence. Similarly Geuze and Borger (1993) found that, of their original group diagnosed with poor motor functioning at 6-12 years old, over 50% still had persistent motor problems when they were re-tested five years later at 11-17 years. Cantell and colleagues (2003) examined adolescents who were categorised at five years old into a control group, those with significant motor dysfunction and those with minor motor dysfunction. While the group with a milder form of motor impairment showed improvement during adolescence the majority originally diagnosed with significant motor dysfunction remained behind their peers. While

these studies contributed to understanding the importance of motor development and the negative effects of suboptimal development they did not always include factors that influenced the motor development process.

More recently the effects of various perinatal, antenatal and neonatal risk factors on motor development of 10 year olds were reported using the Western Australian Pregnancy (Raine) Cohort by Hands et al (Hands et al., 2009). The aim of the current series of studies was to expand these findings using additional data from the 14 and 17 year follow up phases. Early life factors were examined to determine the impact on longitudinal motor development outcomes during all three time periods.

Purpose.

The purpose of this study was to identify risk factors that influenced motor development during the antenatal, perinatal and neonatal periods. Of particular interest was identifying whether these risk factors differed between the sexes and whether critical time periods during gestation could be pinpointed as important to the development of competent movement. Examining the potential causes of compromised development will contribute to the volume of knowledge regarding developmental movement disorders such as Developmental Coordination Disorder (DCD).

Outline of Thesis

This thesis consists of four related papers (three published and one currently under review) that each focus on a specific area of antenatal, perinatal and infant health relating to long term motor development. The first paper in Chapter Three

‘Maternal hypertensive diseases negatively affect offspring motor development’ investigated the association of gestational hypertension and preeclampsia with motor outcomes. The second paper in Chapter Four ‘The impact of maternal gestational stress on motor development in late childhood and adolescence: a longitudinal study’ focused on the relationship between number and timing of stressful events during gestation and long term offspring motor development. Chapter Five contains the third paper, currently under review, 'Breastfeeding and motor development: a longitudinal cohort study’. This paper reviewed how breastfeeding practices in the Raine Study cohort were related to motor development at 10, 14 and 17 years of age. The final paper in Chapter Six ‘Early life events and motor development in childhood and adolescence: a longitudinal study’ examined sex differences in offspring motor development with a focus on how risk factors for motor outcomes differed between male and female offspring.

Significance of the study.

The integrity of an individual’s neuromuscular system is an important consideration for health and wellbeing over the life span. Longitudinal research so far has yielded few answers with regard to the contributing factors of motor development, although the negative outcomes of suboptimal motor development have often been cited. These are linked to negative psychological, cognitive and behavioral outcomes from infancy to adulthood (Cairney, Veldhuizen, & Szatmari, 2010; Cummins et al., 2005; Fitzpatrick & Watkinson, 2003; Hands et al., 2007; Rasmussen & Gillberg, 2000; Skinner & Piek, 2001). Longitudinal data from The Western Australian Pregnancy Cohort (Raine) Study, which commenced in 1989,

provided a unique source of antenatal, perinatal and neonatal data that covered a broad range of health, socioeconomic and environmental factors.

The current series of studies addressed several gaps where quality longitudinal research is lacking. These included a) identifying critical early life events that contribute to motor development outcomes, and b) examining gender differences in motor coordination development with particular emphasis on how events during the perinatal, antenatal and neonatal periods affected male and female motor development differently.

Definitions of Terms.

Human Development.

Development is the continuous process of change an individual undergoes throughout their lives (Haywood & Getchell, 2009; Payne & Isaacs, 1995). Although related to age development does not end with physical maturation or the cessation of growth; rather it is a lifelong process of sequential changes and includes cognitive, social, psychological and motor domains (Haywood & Getchell, 2009).

Motor Development.

Motor development is the term used to describe an individual's development of motor coordination i.e. their ability to move their body effectively and efficiently through space, to manipulate objects and to coordinate their movements within the requirements of the environment. Motor development is the process which underlies the observable outward changes in an individual's motor ability, while terms such as

motor skill and ability are often used to describe the end product of movement quality (Haywood & Getchell, 2009).

Unlike motor learning, which occurs when an individual learns a new movement or skill that is due to experience or practice, motor development is a lifelong process (Haywood & Getchell, 2009). As with all development motor development changes throughout the lifespan, depending upon the individual, environmental or task related factors (Haywood & Getchell, 2009).

Motor Coordination.

Motor coordination is the ability to undertake any physical task requiring competent and smooth movement, incorporating fine and/or gross motor control. Motor coordination is the result of a number of underlying processes and systems working together in order to create movement that is controlled and smooth (McCarron, 1997). Sugden and Keogh (1990) describe motor coordination as the co-ordination of muscle activity by the neuromuscular system. Motor coordination is the outward observable function of the interaction between the neuromotor system and the information processing systems that provide feedback regarding the changing demands on the environment and task (Sugden & Keogh, 1990).

Various terms can be used to describe movement quality such as motor competence, proficiency or skill however these tend to describe the movement itself as opposed to the underlying processes involved. Motor coordination, on the other hand, clearly refers to the fact that there are several systems involved in movement production and that it's the interaction of these systems that are paramount to the end result. Therefore motor coordination is the preferred terminology used in this paper.

Fine Motor Coordination.

Fine motor coordination describes the control of the small muscles in the body, usually referring to the hand and forearm in order to produce fine movement/s (McCarron, 1997). Generally fine motor coordination will be used in the context of grasping and manipulating objects such as pens, buttons or musical instruments. The underlying neuromuscular system must develop sufficiently to not only produce these fine movements but to ensure a controlled amount of force during the performance of them, as too much force is counterproductive to fine motor coordination (Sugden & Keogh, 1990).

Gross Motor Coordination.

Gross motor coordination refers to the use of large muscles to move the whole body or sections of the body in order to produce gross movement/s. Larger muscle groups are at play in gross motor coordination and often many joints and several body parts are involved, necessitating synergistic relationships between the muscles and joints in order to produce controlled smooth movements (Sugden & Keogh, 1990). Gross motor movement can involve the manipulation of larger objects such as a soccer or football, or the performance of whole body tasks such as walking, running or dancing.

Low Motor Coordination.

Individuals with motor coordination below what is expected for their age have been referred to by researchers as ‘clumsy’ (Cantell et al., 1994; Geuze & Borger, 1993), ‘awkward’ (Causgrove Dunn & Watkinson, 1994) or as having a ‘mild motor

disability' (Hands et al., 2009) 'delayed development' (Silva & Ross, 1980) and / or 'motor perception dysfunction' (Gillberg & Gillberg, 1989). Since 1994 Developmental Coordination Disorder (DCD) has been the preferred terminology for those with below average motor coordination. In order to fulfil the DSM-V (American Psychiatric Association, 2013) diagnosis for DCD four criteria have to be met including a) lowered ability to perform motor skills as would be expected for individual's age and skill learning opportunity; b) persistent interference with activities of daily living, school, work and/or leisure, from the motor skill deficit described in criteria a; c) symptoms are observed from the early period of development, and d) deficits in motor skills are not explained by intellectual disability, neurological condition or visual impairment. While DCD is used internationally in research the term LMC will be used in this paper as data addressing each criteria were not available, therefore a diagnosis of DCD could not be made. In this study LMC is operationally defined by scores 1SD below the mean (<85) of the Neuromuscular Development Index (NDI) of the McCarron Assessment of Neuromuscular Development (MAND) (McCarron, 1997).

Antenatal Period

The antenatal period refers to time during pregnancy, prior to birth. Also referred to as the prenatal period.

Perinatal Period

This time refers to the period around childbirth, usually given as either the 20th or 28th week of gestation until 4 weeks post-birth. This term is often used in relation to both mother and infant.

Infancy

The time period during the first year of an infant's life. Usually used in relation to the infant (e.g. neonatal care).

Sex and Gender

Although the terms sex and gender are often used interchangeably, sex generally refers to an individual's biological make up whilst gender is viewed as a sociological construct (Springer, Stellman, & Jordan-Young, 2011). In determining categories for the Raine Study participants biological guidelines were used, as the participants were enrolled from birth. For this reason we use the terminology sex for the categorization of males and females in this thesis.

CHAPTER TWO

Literature Review

In this review two main aspects of motor development were considered. Firstly, the contributing factors associated with motor development outcomes, with particular emphasis on early life factors during the antenatal, perinatal and infancy time periods were examined. Barker (1997) originally proposed that suboptimal conditions during pregnancy will lead to an increased chance of negative health outcomes in later life. While this theory has been tested with outcomes such as coronary heart disease, stroke, hypertension and diabetes there is little research that has applied the hypothesis to outcomes of motor coordination. An examination of longitudinal studies of motor development formed part of this review, with emphasis on study design and identifying gaps in knowledge.

Secondly, in order to highlight the importance of research on motor development the impact of low motor coordination was then examined, with reference to the psychological, social and physical burdens of living with LMC.

Early life factors impacting motor development.

Preterm birth and low birth weight.

Preterm birth and low birth weight have been recognised as risk factors for suboptimal motor development (Edwards et al., 2011; Foulder-Hughes & Cooke, 2003; Goyen & Lui, 2002; Jongmans, Mercuri, Dubowitz, & Henderson, 1998; Zwicker, 2014). Goyen and Lui (2002) found that motor development is more affected by premature birth than cognitive, psychological or social development, reporting a high proportion of preterm infants had persistently low fine motor coordination when tested at 18 months, three and five years. In addition the incidence of low gross motor coordination increased with age. Other researchers have identified a dose-response type of relationship between birth weight and gestational

age and motor development problems, as the more preterm and/or underweight an infant is born the higher the level of dysfunction (Foulder-Hughes & Cooke, 2003).

Schmidhauser and colleagues (2006) examined quality of movement in very low birth weight children and found that both speed and quality of movement were significantly impaired at six years of age. A longitudinal study of low birth weight infants followed up at five, 10, 18 months and 5.5 years found that 47% of infants born with very low birth weight had suboptimal motor development throughout infancy and early childhood (Erikson, Allert, Brogren Carlberg, & Katz-Salamon, 2003). More recently researchers investigating perinatal and neonatal risk factors for DCD in a very low birth weight cohort found male sex and low birth weight to be significant predictors of motor impairment in 4-5 year old children (Zwicker, Yoon, et al., 2013).

Sex.

Sex differences in developmental outcomes have been documented by researchers for several decades (Gualitieri & Hicks, 1985; Singer, Westphal, & Niswander, 1968).

A number of early researchers have hypothesized that the male foetus is more susceptible to in-utero insults. Nathaniesz (1999) concluded that the effects of the environment on a developing foetus are often different for males and females. A study into perinatal factors associated with motor development outcomes at 10 years of age, using Raine cohort data, yielded interesting results in relation to sex differences (Hands et al., 2009). Mothers of girls with low motor outcomes were more likely to have experienced either hypertension, anaemia, or a threatened preterm labour than girls who fell within the average range. In boys, however, the

factors associated with motor development outcomes were different. Mothers of boys with low motor outcomes were more likely to have experienced a caesarean section (either emergency or planned) and/or a stressful first year. The researchers hypothesized that the differences could have been due to sex specific developmental windows. Longitudinal analysis of the Raine cohort focusing on antenatal, perinatal and neonatal will allow a clearer picture on how the timing of potential risk factors affected male and female motor outcomes differently.

The overrepresentation of males with developmental disorders is well documented (Kadesjo & Gillberg, 1999; Kraemer, 2000). Kraemer (2000) concluded that "the male is more vulnerable from the beginning of life" (p.1611). This is supported by findings from the Dutch Groningen Perinatal Project which established that mild neurological dysfunction at age nine was related to sex (Hadders-Algra, 2002) and a more recent study which indicated male sex to be independently predictive of LMC in a low birth weight cohort (Zwicker, Yoon, et al., 2013).

While some studies report little or no differences in the incidence of LMC amongst boys and girls (Cairney et al., 2007; Rose, Larkin, & Berger, 1997) there are others (Kadesjo & Gillberg, 1999; Schoemaker & Kalverboer, 1994; Seelaender, Fidler, & Hadders-Algra, 2012) who report prevalence differences in both severe and moderate motor coordination problems between sexes. Kadesjo and Gillberg (1999) found a male-female ratio of 7.3:1 amongst children diagnosed as having severe LMC and 4:1 in those diagnosed as having moderate LMC. More recent findings reported boys assessed in Germany between 1990-1997 were three times more likely than girls to be diagnosed as having LMC (Seelaender et al., 2012). This sex disparity may be due to physiological differences in fetal development that have been estimated to disadvantage males by 4 to 6 weeks, meaning that males are born at a

less developed stage than females (Kraemer, 2000), however it is likely there are a number of factors that contribute to the reported differences. These will be examined in more detail in Chapters Six and Seven.

There are some researchers who theorise that sociological factors may play a role in the conflicted findings. Coakley (2007) argues that boys may be more readily recognised as having LMC because they are expected to be more physically skilled. Any lack of ability is therefore more readily noticed and referrals to remedial programs are higher. As research into LMC populations is often drawn from populations who are already enrolled in movement based remedial programs a gender bias that is not reflective of the general population may be found (Cairney, Hay, Faught, & Hawes, 2005). However, while there are several population based longitudinal studies that identify higher incidences of LMC in boys (Kadesjo & Gillberg, 1999; Seelaender et al., 2012) other recent population based studies reported ratios close to 1-1 (Missiuna et al., 2011). As the current study will be drawn from a general population cohort this possibility will be considered in the analysis.

Hypertension and preeclampsia.

Maternal hypertensive diseases, such as hypertension and preeclampsia have previously been linked to small for gestational age, fetal growth restriction, prematurity (Pitcher et al., 2006) and poorer cognitive development in early (Many et al., 2003) and late (Whitehouse, Robinson, Newnham, & Pennell, 2012) childhood. In some instances however researchers have reported differential effects. For example Robinson et al. (2009) found negative associations with behavioral outcomes in children born to hypertensive mothers, whilst the opposite was true for

those born to mothers with preeclampsia. Similarly other studies investigating serious mental health disorders reported hypertension was linked to a higher risk, while preeclampsia was associated with a lower risk among males (Tuovinen et al., 2012). Ogland and colleagues (Ogland, Nilsen, Forman, & Vatten, 2011) reported a possible reduction in the future risk of breast cancer in females born to mothers with preeclampsia. Together these findings suggest different pathways through which hypertension and preeclampsia may influence mental health development, behavioral outcomes and hormonal activity in the long term.

While preeclampsia may be associated with a positive effect on mental health and behavioral outcomes the impact is more likely to be negative for physical development, with reduced heart size and function (Fugelseth et al., 2011) and delays in mental and psychomotor development (Rep et al., 2008) reported in offspring from preeclampsia pregnancies.

One possible pathway of structural and functional change in the developing foetus may be a decrease in oxygen delivery via the placenta associated with preeclampsia (Matsuo, Malinow, Harman, & Baschat, 2009). Pitcher, Henderson-Smart, and Robinson (Pitcher et al., 2006), reported that during the third trimester, the most common time for preeclampsia to occur, the developing fetal brain may be more vulnerable to hypoxic and ischemic insults. During this time the cerebellum, an area responsible for some aspects of motor development such as coordination, precision and accuracy of movement is rapidly developing, and suboptimal maternal nutrition or deficits in the delivery of nutrients via the placenta at this time may cause developmental problems, particularly in the motor domain (Gramsbergen, 2003; Ivry, 2003). Therefore preeclampsia poses a greater concern for motor development outcomes.

Maternal stress.

Nathaniesz (1999) purports that stress during pregnancy can have specific negative effects on the developing foetus, particularly the development of the brain. This developmental interruption has implications for motor development and researchers have theorised the existence of underlying neurological impairments in children with LMC who present with 'soft neurological signs' (Gillberg, 1985). Stress experienced during pregnancy may be due to a number of reasons, for example relational stress, economic stress, physical health stress, lack of perceived or actual support and situational stress, such as moving house or the death of a relative. Many of these are often out of an expectant mother's control. In fact, the stress of pregnancy itself and the impending changes that accompany it can be a stressor for a number of women who discover they are pregnant.

Previous research has revealed maternal gestational stress negatively impacts a range of health and developmental outcomes in infancy and early childhood (Monk, 2001; Ruiz & Avant, 2005; Talge, Neal, & Glover, 2007; Tegethoff, Greene, Olsen, Schaffner, & Meinlschmidt, 2011). These include cognitive (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Huizink, Robles de Mina, Mulder, Visser, & Buitelaar, 2003; Laplante et al., 2004; Sandman, Davis, Buss, & Glynn, 2012), motor (Buitelaar et al., 2003; Huizink et al., 2003), language (Henrichs et al., 2011; Laplante et al., 2004), behavioral and emotional development (de Weerth, van Hees, & Buitelaar, 2003; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Robinson et al., 2008; Sandman et al., 2012) as well as physical and neuromuscular maturation (Ellman et al., 2008; Sandman et al., 2012). While longitudinal studies have shown that maternal pregnancy stress affects behavioral and mental development in middle childhood (Rodriguez & Bohlin, 2005; Van den Bergh &

Marcoen, 2004) and into adolescence (Robinson et al., 2011), few studies have investigated the long term consequences on motor development.

Sensitive periods during gestation when the foetus may be more vulnerable to prenatal stress have been identified across most aspects of development (Ellman et al., 2008; Laplante et al., 2004; Van den Bergh & Marcoen, 2004). While the majority of these findings indicate stress in early pregnancy is of particular importance to offspring development some researchers have reported stress in late pregnancy affects mental, emotional and behavioural development in infancy and early childhood (Huizink et al., 2003; O'Connor, Heron, Golding, & Glover, 2003). Prenatal stress could affect motor development outcomes through several pathways. The cerebellar cortex, which develops mainly during late pregnancy, is important for the development of postural control, coordination, and motor skill function (Gramsbergen, 2003). While work with animal models has supported this role it is not fully understood how pregnancy stress may affect the developing human cerebellar cortex and whether the timing of this stress has long term neurological consequences.

Long term functional deficits in motor development could also results from the increase in hormones such as cortisol (DiPietro, 2004), androgen (Kaiser & Sachser, 2009) or progestogen (Paris & Frye, 2011) which occur when the mother is stressed. Changes in these hormone levels are hypothesized to permanently affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (Lazinski, Shea, & Steiner, 2008; Paris & Frye, 2011), limbic system, prefrontal cortex (Van den Bergh, Mulder, Mennes, & Glover, 2005) and autonomic nervous system (ANS) (Lazinski et al., 2008) in offspring. Although not directly related to motor control, some of

these, for example the limbic system which controls spatial memory and motivation, may affect motor functioning.

Maternal alcohol consumption.

Evidence has emerged that children diagnosed with fetal alcohol spectrum disorder (FASD) present with delays in motor development (Kalberg et al., 2006). Excessive maternal alcohol intake can lead to damage of the developing child's central nervous system and children with FASD are characterized by the presence of physical abnormalities and growth retardation. This damage is likely to have effects on all developmental domains, including motor development.

The magnitude of any negative effects of maternal alcohol consumption is dependent on the amount, frequency and timing of alcohol exposure. According to Schiamberg (1985) there exists a time prenatally termed the epigenic period where a developing foetus is particularly sensitive to potentially harmful environmental factors. More recently developmental researchers have hypothesized the existence of 'critical windows' during development where the individual is particularly receptive to environmental factors impacting upon their development. Timing of alcohol exposure is therefore important when considering the impact it would have on a developing foetus.

Even without a diagnosis of FASD children who have been exposed to a significant amount of alcohol in-utero may have decreased neurological functioning (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000). Furthermore prenatal alcohol exposure has been linked to visuospatial learning and memory deficits (Willford, Richardson, Leech, & Day, 2004). Visuospatial deficits have been hypothesized by motor development researchers to be an underlying factor of motor

development problems such as DCD (Sigmundsson & Hopkins, 2005; Wilson & McKenzie, 1998) while other researchers (Piek, Dyck, & Francis, 2007) have identified that children with motor development dysfunction were slower in working memory and response inhibition, resulting in slower speed and greater variability in performance.

Maternal smoking

Maternal smoking during pregnancy has been found to affect motor development measures in middle (Trasti et al., 1999) and late childhood (Larsson & Montgomery, 2008), and processing speed, interhemispheric communication and visual-motor coordination in adolescence (Willforda, Chandlerb, Goldschmidt, & Daya, 2010). Children exposed to smoking during gestation had higher levels of externalizing behavioural problems and performed worse in academic tasks involving arithmetic and spelling (Batstra, Hadders-Algra, & Neeleman, 2003). Furthermore children exposed to prenatal smoking have reduced foetal head and body growth and have shown signs of altered brain structure and function (Ekblad, Korkeila, & Lehtonen, 2015).

Breastfeeding.

Previous research , including several international cohort studies from Ireland (McCroy & Murray, 2013), Britain (Sacker, Quigley, & Kelly, 2006), Denmark (Vestergaard et al., 1999), The United States (Dee, Li, Lee, & Grummer-Strawn, 2007), Honduras (Dewey, Cohen, Brown, & Rivera, 2001) and Iceland (Thorsdottir, Gunasdottir, Kvaran, & Gretarsson, 2005) have identified the benefits of breastfeeding on motor development. Breastfeeding may influence underlying

neurological systems and processes in numerous ways. Several studies have identified the role of long chain polyunsaturated fatty acids (LC-PUFAs) in human milk, such as docosahexaenoic acid (DHA) and arachidonic acid (AA) as an essential element of neural membranes and a potential mechanism for favorable neurological development (Guxens et al., 2011; Innis, 2000; Uauy & De Andraca, 1995). PUFAs also provide a neuroprotective effect (Lauritzen et al., 2000), with levels of prenatal DHA measured in umbilical veins found to influence motor development outcomes up until the age of nine in boys (de Jong et al., 2015). A longitudinal study of Australian children found that infants who were breastfed longer than four months had better fine motor development and communication at one and three years and higher adaptability scores at one, two and three years. (Oddy, Robinson, et al., 2011). Similar to the findings by de Jong et al. (2015), this relationship seemed to be mediated by sex, with breastfeeding having an effect on the gross motor development of boys but not girls. Differences in the timing of development between the sexes may be a possible cause of the reported differences. Kraemer (2000) found that at birth an infant boy is already developmentally some weeks behind a newborn girl. The difference in physiological maturity may be a confounding factor in the effect of breastfeeding on development.

Socioeconomic factors.

Gillberg (1985) and Hands, et al. (2009) found little evidence of socioeconomic status (SES) playing a significant role in the development of motor coordination in children. Cantell (1998) reported that the verbal IQ of Finnish children in a longitudinal study was related to SES at seven years however performance IQ and motor development were unrelated. Hadders-Algra (2002)

however found that infants born with neurological dysfunction into a family with low SES were four times more likely to develop a more pervasive form of motor development dysfunction at nine years of age than infants with a similar level of neurological dysfunction who were born into families with mid-high SES.

Studies in Brazil found SES to be an important contributing factor in motor development, with children entering private schools having an advantage over those beginning their first year in public schools (Bobbio, Gabbard, Goncalves, Filho, & Morcillo, 2010). Although improvements were gained by both groups of children the private school attendees still maintained an advantage at follow up testing 10 months later.

Longitudinal studies of motor development**.**

In 1982 Gillberg and Rasmussen began a study into the longitudinal nature of motor development, focusing on children with motor development dysfunction. The original cohort of 147 children, aged seven, were followed up at 10, 13 and 22 years old. The focus of this study was on comparison between typically and abnormally developing children over a range of neuromotor, behavioural, social and psychological outcomes. Gillberg did attempt to identify some factors that contributed to motor development through the collection of retrospective data on family history of developmental heredity and perinatal variables. In a three year follow up of the children, at 10 years old, a non-optimal perinatal period score, ranging from 0-29 was examined, with higher scores related to poorer outcomes. The 29 perinatal factors, included prematurity and postmaturity, infections during pregnancy, medications and high maternal age (Gillberg, 1985). Unfortunately these

were not analysed separately and therefore the significance of each factor was not reported.

Rasmussen and Gillberg (2000) followed up the original cohort, some of who were observed to have various diagnoses of Attention Deficit Disorder (ADD), Attention Deficit Hyperactivity Disorder (ADHD) and Developmental Coordination Disorder (DCD) at age 22, and administered neurological, neuropsychiatric and reading assessments. Those with DCD only had higher levels of poorer life outcomes, defined by reliance on a permanent sick pension, criminal offences with a conviction, alcohol and/or substance abuse disorders, psychiatric disorders, personality disorders and diagnosis of an autism spectrum disorder. Eighty percent of those with DCD only were reported to have poorer life outcomes compared to 13% of the control group. The authors suggested that a diagnosis of DCD either with or without co-morbid ADHD or ADD was "a strong marker for a poorer outcome" (p.1430), however it must be noted that the DCD group was very small and further longitudinal studies of this nature are necessary to support these findings. While not statistically significant, there were higher levels of poorer outcomes in the males (64%) compared to the females (38%) in the larger group defined as having one or more diagnosed attention or coordination disorders. Although the study did shed some light on what can contribute to motor development the focal point was on the outcomes of those with motor development dysfunction.

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a birth cohort study containing data from over 14000 infants born in the Bristol area of England (Boyd et al., 2013). Motor development in the ALSPAC cohort was measured at 7 and 8 years of age using a shortened version of the Movement Assessment Battery for Children (MABC) (Henderson & Sugden, 1992). Children

with severe LMC had greater difficulty with activities of everyday living, handwriting, reading, spelling, attention and social skills (Schoemaker, Lingam, Jongmans, van Heuvelen, & Emond, 2013). At 12 years of age male children with LMC showed reduced levels of physical activity compared to their more coordinated peers (Green et al., 2011). Studies using the ALSPAC cohort that focused on the influence of early events on motor development revealed preterm birth and female sex negatively impacted motor outcomes at 7 and 8 years of age (Golding et al., 2014; Odd, Lingam, Emond, & Whitelaw, 2013). These sex differences were in opposition to those who reported higher incidences of LMC in males (Hadders-Algra, 2002; Seelaender et al., 2012; Zwicker, Yoon, et al., 2013). This may be due to the use of less comprehensive testing, for example Golding and colleagues only reported on one throwing based test adapted from the MABC, whilst Odd et al. (2013) relied on only three of the eight subtests.

Maternal mental and social health during childhood were also linked to children's motor skill, however, as previously mentioned, the outcome measure in the study was restricted to throwing ability and not a full motor development assessment (Golding et al., 2014).

The Groningen Perinatal Project is a longitudinal research project undertaken in the Netherlands focusing on the prenatal and perinatal risk factors that contribute to neurological, behavioural, cognitive and motor development (Hadders-Algra, 2002). This project is possibly one of the most extensive in regards to collection of pre and perinatal data. Similar to Gillberg's study the original cohort were given diagnoses of neurologically 'normal', 'slightly abnormal' and 'definitely abnormal', although in the Groningen study this was done in the neonatal period. The infants with neurological abnormalities were age matched with controls. One of the main

findings of the study was the identification of two different types of motor development dysfunction. One group, comprising those with a more extensive motor dysfunction, were more heavily influenced by factors occurring during the perinatal period, while the other group, with less pervasive motor difficulties, was not as affected by perinatal factors (Hadders-Algra, 2002; Soorani-Lunsing, Hadders-Algra, Olinga, Huisjes, & Touwen, 1993). The authors suggested events during the antenatal and perinatal periods may contribute to a more complex form of neurological dysfunction, and that brain lesions occurring at an early age may be a contributing factor (Hadders-Algra, 2003).

Cantell (1998) examined the longitudinal nature of motor development problems in a cohort of Finnish children originally diagnosed at five years of age. One of the main objectives of the study was to observe the rates of persistence of motor development dysfunction by comparing participants with motor development problems against age and gender matched controls. At age seven there was a difference between the groups in 92% of recorded tasks. This trend continued at ages nine and 11, however the difference in task outcome reduced each follow up (81% and 76% respectively), indicating that there was a subgroup of children with motor development problems who 'outgrew' the dysfunction and improved enough to close the gap in performance between themselves and their peers. A further follow up of the same cohort at 17-18 years revealed similar results, with those who had mild motor development problems more likely to have shown improvement than those who had more severe levels of dysfunction (Cantell et al., 2003). While this cohort was originally recruited at age five and antenatal data were not reported the findings lend some support to those from the Groningen Perinatal Project, in that severity of

dysfunction at time of diagnosis may explain why some children seem to outgrow their movement problems.

The Western Australian Pregnancy Cohort (Raine) Study is a longitudinal research project originally designed to examine the effects of an intensive versus singular ultrasound imaging protocol on neonatal outcomes (Newnham, Evans, Michael, Stanley, & Landau, 1993). Pregnant women were recruited at a rate of approximately 100 per month between May 1989 and November 1991 from King Edward Memorial Hospital (KEMH) and surrounding private practices in Perth, Western Australia. Enrolment criteria included an expectation to deliver at KEMH, sufficient English speaking skills to understand the study requirements, and an intention to reside is Western Australia to facilitate further follow up. There were 2900 women enrolled in the study and 2868 live births were recorded. Extensive antenatal, perinatal and neonatal data were documented including maternal factors (smoking, alcohol intake, age, education, socioeconomic status, hypertensive status, stress, antepartum and postpartum hemorrhage, diabetes, general health, threatened abortion) and infant factors [sex, birthweight, parity, gestational age, time to spontaneous respiration, APGAR scores, mode of birth, percentage of optimal birth weight (a measure of whether fetal growth potential has been met) and breastfeeding]. Children were assessed at one, two, three, five, 10, 14, 17 and 21 years of age, with extensive health sociodemographic and physical data collected. The main care givers also completed physical assessments and questionnaires. Motor development was first comprehensively assessed in the Raine Study cohort at 10 years of age. An examination of early life factors revealed male sex, hypertensive disease, anaemia and threatened pre-term birth influenced later motor outcomes (Hands et al., 2009).

Overall findings from these longitudinal studies suggest that motor development dysfunction can continue well into life and perinatal factors influencing neuromotor outcomes may vary between males and females. Furthermore developmental pathways can differ according to the severity of the neurological impairment, with some milder cases of dysfunction improving with age while more severe cases seem to exhibit a more persistent form of impairment.

Psycho-social outcomes of low motor coordination.

A systematic review of literature regarding the impact of LMC on quality of life domains, including physical, psychological and social functioning, reported that the majority of articles found poorer results in LMC populations (Zwicker, Harris, & Klassen, 2013). Recent findings have indicated that level of motor competence explained 44% of psychosocial well-being in a cohort of adolescent females, with higher levels of conduct problems, hyperactivity and emotional problems recorded in those who had lower motor competence (Viholainen, Aro, Purtsi, Tolvanen, & Cantell, 2014). Children with LMC can become more introverted, have lower physical and social self-perceptions and higher rates of anxiety and depression than their more coordinated peers (Cantell et al., 1994; Missiuna et al., 2014; Pratt & Hill, 2011; Schoemaker & Kalverboer, 1994; Skinner & Piek, 2001). Longitudinal studies indicate that psycho-social problems associated with LMC can persist, with participants diagnosed as having LMC during childhood reporting social dysfunction during adolescence (Cantell et al., 1994) and adulthood (Rasmussen & Gillberg, 2000). Children with LMC are therefore at risk of not only poor motor performance and lowered levels of physical activity but also a variety of psychological and social setbacks. These children have been labeled ‘awkward’ (Causgrove Dunn &

Watkinson, 1994), ‘clumsy’ (Cantell et al., 1994; Geuze & Borger, 1993; Schoemaker & Kalverboer, 1994), ‘lazy’ or ‘accident prone’ and negative social experiences often result (Fitzpatrick & Watkinson, 2003).

An in depth qualitative study on the longitudinal effects of low motor competence undertaken by Canadian researchers (Fitzpatrick & Watkinson, 2003) revealed that the psychosocial implications for these individuals are indeed pervasive and can have lifelong implications. Four themes were deemed essential to capturing the experience of the individuals interviewed. These included ‘failing and falling’ a descriptive used to explain the frequent, continuing and publicly experienced inability of the person to complete required physical tasks. Secondly, the theme ‘hurt and humiliation’ stemmed from the public nature of the failure or fall. Thirdly, individuals with LMC experienced ‘worry and wonder’ which described how those who failed performing physical tasks would often dwell on past incidences, worry about future situations and wonder why they had lower physical abilities than their peers. The fourth and probably the most significant theme in relation to physical health implications was ‘avoiding awkwardness’ which described the participants’ development of avoidance behaviours regarding physical activity.

The ‘worry and wonder’ theme has been supported in other research where children with LMC were found to have a higher incidence of state and trait anxiety stemming from their inability to perform motor tasks (Schoemaker & Kalverboer, 1994). More recent research supports these findings of higher anxiety levels, with LMC children also reporting lower self-worth and perceived social support (Skinner & Piek, 2001). Gillberg and Gillberg (1983) noted that “depression in childhood is a disorder in which motor-perception dysfunction is likely to play an important role in a substantial amount of cases” (p.446). Research by Australian authors have also

linked LMC to increased depressive symptomology (Piek, Rigoli, et al., 2007). Coupled with research showing the increased levels of anxiety in those with LMC (Schoemaker & Kalverboer, 1994) this group presents as one at risk of poor emotional and mental health outcomes.

Researchers presenting at the American Academy of Child and Adolescent Psychiatry 56th Annual Meeting in 2009 reported significantly higher levels of depression and anxiety in children with LMC when compared to typically developing peers (MacDonald, Missiuna, Cairney, & Pollock, 2009). Furthermore, while parental reports of depressive symptoms were similar to the children's self-reported levels, anxiety was less likely to be recognised. Of particular concern was the severity of depression and anxiety within the LMC group "…we picked up several kids who had suicidal thoughts, but no one had ever asked them [about that], so it can be potentially life-threatening if these symptoms are not recognized" (MacDonald et al., 2009).

A follow up of Gillberg and Gillberg's original cohort found that 80% of those with motor development problems had poorer life outcomes including psychiatric disorders, personality disorders, alcohol or substance abuse and criminal offences at age 22 years compared with 13% in a comparison group (Rasmussen & Gillberg, 2000). Parental reports in a 5 year follow up study focusing on a group of children originally diagnosed as having LMC indicated that the group did not seem to advance their social network as much as their more coordinated peers (Geuze & Borger, 1993).

Little is understood regarding why there are such poor mental health and social outcomes in those with LMC. Recent research by Australian psychologists (Cummins, Piek, & Dyck, 2007) sought to shed some light in this area by examining

the emotional recognition skills of children with LMC. Results indicated children with LMC performed worse on tests measuring static and changing facial expression. The authors hypothesised that the problems children with LMC had recognizing emotional expression may be linked to poor visuo-spacial processing, however even when this was controlled for the LMC group still displayed lower emotional recognition ability. More recent research has provided limited support suggesting a deficit in the mirror neuron system may be present in those with LMC (Reynolds et al., 2014). As mirror neurons activate when a person observes another's movement/s and expressions they may play an important role in establishing empathy and understanding others emotions (Iacoboni & Mazziotta, 2007). A deficit in this area of the neurological system could therefore contribute to poor social and behavioural outcomes. In any case it is clear that LMC is a significant predictor of poorer psycho-social outcomes, and these can persist long term for some.

Low motor coordination and learning difficulties.

Recently the importance of motor skills in relation to cognitive and educational outcomes has been identified (Hill, 2010; Hill & Barnett, 2011). Researchers using data from longitudinal studies have reported children with LMC were more likely to repeat a school grade in their primary schooling (Geuze & Borger, 1993), not progress as much in secondary education (Geuze & Borger, 1993; Rasmussen & Gillberg, 2000), have lower concentrations levels, more behavioural problems and be more easily distracted in class then their peers (Geuze & Borger, 1993). Similarly Kadesjo and Gillberg (1999) found children with DCD had higher levels of school dysfunction compared to typically developing peers, regardless of the severity of motor coordination problems. Rasmussen and Gillberg (2000)

revealed that, of the individuals originally diagnosed with attention or coordination disorders 80% had less than 12 years formal education and only 2% had a tertiary education at age 22. Furthermore the group in the study with movement difficulties showed problems with reading and writing similar to those who were diagnosed with both ADHD and DCD.

Children with LMC may experience problems with handwriting and other fine motor tasks required in the school environment however this relationship has not been clearly established. Smits-Engelsman et al. (2001) found that over half the children in their study who presented with poor handwriting had problems with fine motor coordination while Chang and Yu (2010) found that most of the children with poor writing ability in their study did not have associated fine motor control problems. This may be due to the numerous underlying factors that contribute to handwriting such as visual perceptual difficulties, fine motor control, orthographic coding, and language processing. More recent research, examining different types of neurological dysfunction, reported fine manipulative ability and coordination problems were associated with attention, memory, learning and language outcomes while others such as posture, muscle tone and reflexes were not (Kikkert, de Jong, & Hadders-Algra, 2013). Researchers have reported that the incidence of language difficulty in 10 year old Australian children with motor development problems was 20% (Larkin, Hands, Parker, Sloan, & Kendall, 2005). Reflective of the heterogeneous nature of LMC it was found that two out of six clusters displayed greater language difficulties.

Low motor coordination and level of physical activity.

Children with LMC participate in less physical activity than more coordinated children (Bouffard, Watkinson, Thompson, Causgrove Dunn, & Romanow, 1996; Smyth & Anderson, 2000; Watkinson, Dwyer, & Neilson, 2005). A qualitative study involving parents of children with LMC provided an in-depth picture of how these children are impacted by their inability to successfully interact within the physical domain, often resulting in lowered self-efficacy, participation and social isolation (Mandich, Polatajko, & Rodger, 2003).

A retrospective study of adults who had LMC in their school years (Fitzpatrick & Watkinson, 2003) showed that they deemed a physical education class a success if they effectively blended in to the background of the class, using avoidance techniques to lower their risk of public failure. Causgrove Dunn and Dunn (2006) identified other avoidance behaviours such as taking extended breaks or volunteering for non-participating duties such as umpiring in order to avoid physical activity.

Low motor coordination and overweight and obesity.

Withdrawal from physical activity opportunities is of major concern as it has far reaching consequences on both physical and mental health. A study that examined motor competence differences in overweight and non-overweight children found that the overweight children had lower levels of perceived and actual motor competence (Southall, Okely, & Steele, 2004). Low motor coordination has been linked to overweight and obesity in children (Cairney et al., 2005) and adults (Osika & Montgomery, 2008). Researchers comparing high and low motor competent children (Haga, 2007) and adolescents (Hands, Larkin, Parker, Straker, & Perry,

2008) reported significant correlations between motor competence and physical fitness. Cairney et al.(2005) found that children with LMC had higher body fat percentages and lower cardiorespiratory fitness than their better coordinated peers however this was mediated by sex, with LMC predicting overweight and obesity in boys aged 9-14 years, while similar rates of overweight and obesity were found in girls regardless of motor coordination ability. The authors postulated that this may be due to the overall lower levels of physical activity amongst the girls.

With outcomes such as increased anxiety and depression, lower self-esteem and self-efficacy, and higher rates of obesity and overweight it would seem obvious that LMC contributes significantly to health and wellbeing. It is therefore imperative that early life events related to motor development outcomes are identified, in order to formulate improved screening and intervention strategies. This is especially pertinent for those factors and events that may be modifiable, such as maternal smoking and alcohol intake, breastfeeding and, in some cases, stress. Whilst other events may not be modifiable, identifying potential risk factors may help health professionals to understand long term outcomes of these events and introduce better intervention and referral pathways.

CHAPTER THREE

Maternal Hypertensive Diseases Negatively Affect Offspring Motor Development

This chapter has been published and the full PDF is in the Appendices

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Original Article

Maternal hypertensive diseases negatively affect offspring motor development

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ABSTRACT

Objective: Hypertension in pregnancy and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. The purpose of this study was to determine if maternal hypertensive diseases during pregnancy are a risk factor for compromised motor development at 10, 14, and 17 years.

Study design: Longitudinal cohort study using data from the Western Australian Pregnancy Cohort Study (Raine).

Main outcome measure: Offspring ($n = 2868$) were classified by their maternal blood pressure profiles during pregnancy: normotension ($n = 2133$), hypertension ($n = 626$) and preeclampsia ($n = 109$). Offspring motor development, at 10, 14, and 17 years was measured by the Neuromuscular Developmental Index (NDI) of the McCarron Assessment of Motor Development (MAND).

Methods: Linear mixed models were used to compare outcomes between pregnancy groups.

Results: Offspring from pregnancies complicated by preeclampsia had poorer motor outcomes at all ages than offspring from either normotensive mothers ($p \leq 0.001$) or those with hypertension ($p = 0.002$).

Conclusion: Hypertensive diseases during pregnancy, in particular preeclampsia, have long term and possibly permanent consequences for motor development of offspring.

Introduction

Hypertension in pregnancy, and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. It is already well established that fetal growth restriction (FGR), premature birth, small for gestational age (SGA) status, maternal stress, smoking and alcohol consumption are risk factors for compromised motor development in early [1–5] and late [6] childhood. Maternal hypertensive diseases such as hypertension and preeclampsia have been linked to SGA, FGR, prematurity [2]

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Abstract

Objective: Hypertension in pregnancy and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. The purpose of this study was to determine if maternal hypertensive diseases during pregnancy are a risk factor for compromised motor development at 10, 14, and 17 years.

Study Design: Longitudinal cohort study using data from the Western Australian Pregnancy Cohort Study (Raine).

Main outcome measure: Offspring (*n*=2868) were classified by their maternal blood pressure profiles during pregnancy: normotension (*n*=2133), hypertension (n=626) and preeclampsia (n=109). Offspring motor development, at 10, 14, and 17 years was measured by the Neuromuscular Developmental Index (NDI) of the McCarron Assessment of Motor Development (MAND).

Methods: Linear mixed models were used to compare outcomes between pregnancy groups.

Results: Offspring from pregnancies complicated by preeclampsia had poorer motor outcomes at all ages than offspring from either normotensive mothers ($p \leq 0.001$) or those with hypertension ($p = 0.002$).

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Keywords: Hypertension, preeclampsia, motor development, Raine Study, adolescence

Introduction

Hypertension in pregnancy, and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. It is already well established that fetal growth restriction (FGR), premature birth, small for gestational age (SGA) status, maternal stress, smoking and alcohol consumption are risk factors for compromised motor development in early (Goyen & Lui, 2002; Kalberg et al., 2006; Pitcher et al., 2006; Schmidhauser et al., 2006; Trasti et al., 1999) and late (Hands et al., 2009) childhood. Maternal hypertensive diseases such as hypertension and preeclampsia have been linked to SGA, FGR, prematurity (Pitcher et al., 2006) and poorer cognitive development in early (Many et al., 2003) and late childhood (Whitehouse et al., 2012).

A differential effect of hypertension and preeclampsia has been reported in studies investigating mental health and behavior, with hypertension linked to a higher risk of negative outcomes, and preeclampsia associated with a lower risk in some cases (Robinson et al., 2009; Tuovinen et al., 2012). Other findings (Ogland et al., 2011) have indicated a possible reduction in the future risk of breast cancer in female offspring born to mothers with preeclampsia. Together these findings suggest different pathways through which hypertension and preeclampsia may influence mental health development, behavioral outcomes and hormonal activity in the long term.

While preeclampsia may be associated with a positive effect on mental health and behavioral outcomes, research indicates the impact is more likely to be negative

for physical development. Reduced heart size and heart function have been reported in five to eight year old children born to mothers with preeclampsia (Fugelseth et al., 2011) and delays in both mental and psychomotor development were found in up to 76% of one year old infants born to mothers with severe preeclampsia (Rep et al., 2008).

One possible mechanism that that may explain the association between maternal preeclampsia and offspring physical and motor outcomes may be a decrease in oxygen delivery to the developing foetus via the placenta that is seen in pregnancies complicated by preeclampsia (Matsuo et al., 2009). Pitcher, Henderson-Smart, and Robinson (2006) report that during the third trimester, the most common time for preeclampsia to occur, the developing fetal brain may be more vulnerable to hypoxic and ischemic insults. During this time, the cerebellum (an area responsible for some aspects of motor development such as coordination, precision and accuracy of movement) is rapidly developing and suboptimal maternal nutrition or deficits in the delivery of nutrients via the placenta at this time may result in developmental problems, particularly in the motor domain (Gramsbergen, 2003; Ivry, 2003). In order to examine the effect of hypertension and preeclampsia on motor development and explore the theory of restricted placental blood flow as a potential mechanism we used data from the Western Australian Pregnancy Cohort (the Raine Study). This large cohort has been followed longitudinally over twenty years and provided the opportunity to examine the longer term impact of hypertension and preeclampsia on motor development and the potential role played by restricted placental blood flow through use of Doppler flow velocity waveform data.

The effects of various perinatal risk factors on motor development have been previously reported in the Raine cohort by Hands et al. (Hands et al., 2009) who found that hypertensive diseases were linked to poorer outcomes in females at 10 years. The purpose of this study was to extend these findings by using both cross sectional and linear mixed models to identify the longer term consequences of maternal hypertensive diseases on the motor development of offspring as they matured from 10 to 14 and 17 years.

We predicted that the motor development of offspring at 10, 14 and 17 years would be negatively affected by the hypertensive status of the mother, with preeclampsia in particular contributing to a poorer motor outcome. Furthermore those mothers with preeclampsia were more likely to have experienced restricted placental blood flow, indicated by abnormal Doppler waveforms.

Method

Participants.

Participants (*n*=2900) were part of the Western Australian Pregnancy Cohort (Raine Study) and were recruited through the King Edward Memorial Hospital between 16 to 20 weeks gestation. The Raine Study is a randomized control study, with women being allocated to either an intensive ultrasound group or a regular ultrasound group (Newnham et al., 1993). Women in the intensive group had ultrasound and Doppler flow studies performed at approximately 18 weeks gestation, then again at 24, 28, 34 and 38 weeks gestation. Women in the control group had one ultrasound around 18 weeks and further scans only if requested by her physician. Full cohort details and enrolment criteria have previously been reported (Newnham et al., 1993). From the 2900 pregnancies, 2868 children were recruited for long-term

follow-up. Ultrasound and Doppler data were available for 1429 children born to mothers in the intensive ultrasound group and 1428 children born to those in the regular ultrasound (control) group.

Original data collection was by questionnaire, undertaken at enrolment with data obtained regarding maternal health, SES and psychosocial characteristics. The second data collection was administered at 34 weeks gestation. Obstetric data were obtained from antenatal, postnatal, and neonatal periods. Follow up data pertaining to motor development reported in this paper were obtained from the participants' offspring at 10, 14, and 17 years.

Ethics clearance was obtained by the Human Research Ethics Committee at King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained at enrolment and at each follow up from parents and/or guardians.

Measures.

Hypertension and preeclampsia.

Maternal blood pressure and other physiological data were recorded during antenatal visits in the first phase of the study (Newnham et al., 1993). Hypertension and preeclampsia diagnoses were confirmed by obstetricians and midwives after reviewing medical records. Essential hypertension was defined by a history of hypertension prior to pregnancy. Gestational hypertension was defined as an increase in systolic blood pressure ≥ 140mmHg and/or an increase in diastolic blood pressure ≥90mmHg in women who were normotensive previous to 24 weeks gestation (Newnham et al., 1993). Women with both essential (n=72) and gestational (n=554) hypertension were included in the hypertension group. Preeclampsia was defined as

gestational hypertension with the addition of proteinuria (300mg/24hrs). Women who had preeclampsia and gestational hypertension (n=68) and preeclampsia superimposed on essential hypertension (n=41) were included in the preeclampsia group. Three pregnancy groups were formed, indicating whether the offspring was from a mother that had normotension (N; *n*=2132), hypertension (HT; *n*=627), or preeclampsia (PE; *n*=109) based on the diagnostic criteria. The highest level of diagnoses was used to determine groups, ensuring no data duplication.

Placental blood flow.

Doppler flow velocity waveform study data were collected using a spectrum analyser and a D10 bi-directional continuous wave Doppler system (Newnham et al., 2004). Using ultrasound imaging and audible signals an umbilical artery and arcuate artery within the placenta were located and waveforms were obtained. A categorical variable was created to reflect if the offspring were from pregnancies that had any abnormal Doppler waveform (*n*=205), no abnormal Doppler waveform (*n*=1223) or had no Doppler study completed (*n*=1428).

Child motor development.

Motor development was assessed using the McCarron Assessment of Neuromuscular Development (MAND) [19] at 10 (*n*=1622), 14 (*n*=1584) and 17 (*n*=1221) years. The 10 item test comprises tasks designed to measure fine and gross motor skills, and derive a composite score of motor development, the Neuromuscular Development Index (NDI). To calculate the NDI the score for each task is converted to a scaled score (*M*=10, *SD*=3) using the age appropriate table of norms. The total of the scaled scores is then summed and converted to the NDI (*M*=100, *SD*=15). A score of ≤85 is used to indicate the presence of a minor motor disability (Hands et al., 2009; McCarron, 1997). McCarron (McCarron, 1997) states that the NDI can be

thought of as a 'motor quotient' giving the researcher an indication of where the child lies developmentally compared to their same age peers.

The test-retest reliability coefficient of the MAND is reported by McCarron (McCarron, 1997) as 0.99 overall and is a reliable measure of motor coordination in the Australian population (Hoare & Larkin, 1990). Further, a comparison of the MAND to two other highly utilized motor coordination tests revealed it to be superior in detecting motor development problems (Tan, Parker, & Larkin, 2001).

Control variables.

Other variables known to influence motor development (Goyen & Lui, 2002; Hands et al., 2009; Kalberg et al., 2006; Pitcher et al., 2006; Schmidhauser et al., 2006; Trasti et al., 1999) were included in all statistical models. These variables were gestational age, parity, percentage of expected birth weight (a measure of whether growth potential has been met), child's sex, maternal age, maternal smoking status, maternal alcohol intake, maternal stress and socio-economic status as measured by the relative rating of advantage and disadvantage (Australian Bureau of Statistics, 2006).

Statistical analyses.

Cross sectional analyses were accomplished using chi-square tests, t-tests and univariate ANOVA models (generalised linear model - GLM) with Bonferroni post hoc correction to identify the maternal and child variables that were related to motor development at 10, 14 and 17 years. No interactions were found between child's sex and hypertensive status or any of the control variables, so results were not stratified by sex. The NDI scores at each data collection for the offspring of mothers with

normotension, hypertension, and preeclampsia were then compared using linear mixed models which account for changes in motor development over time.

Results

Longitudinal motor development.

Linear Mixed Models, adjusting for maternal age, maternal stress, parity, gestational age, percentage of expected birth weight, child's sex, maternal alcohol and smoking and SES revealed a group difference between offspring of mothers with preeclampsia, hypertension and normotension (p=<0.001) over time. The mean NDI of offspring in the preeclampsia group was lower than those in the hypertension (p=0.002) and normotension (p=<0.001) groups (**Error! Reference source not ound.**) While the mean NDI of each group were within the range considered to be indicative of normal motor development (McCarron, 1997) the preeclampsia group contained a higher percentage of individuals (46.8%) who fell below the cutoff (≤85) used to determine motor disability (Hands et al., 2009; McCarron, 1997) compared to the hypertension (27.9%) and normotension (24.6%) groups (p = <0.001).

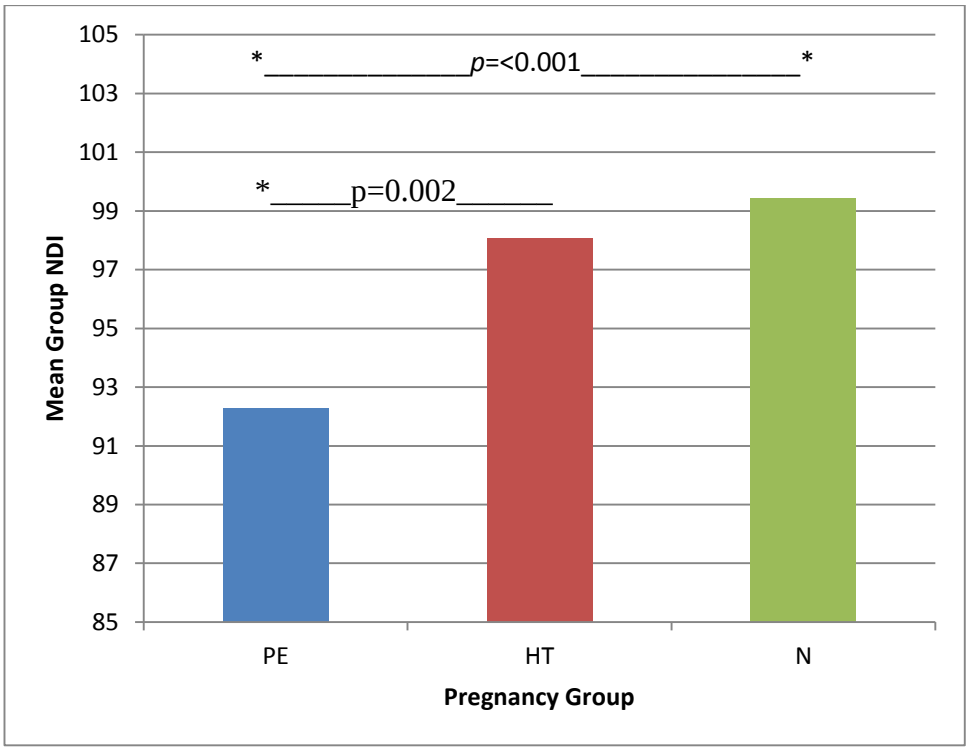

Figure 1 Mean NDI of pregnancy groups adjusted for maternal age, smoking and alcohol intake, income, anti-hypertensive medication, parity, gestational age, percentage of expected birth weight and sex

Doppler waveforms.

Doppler waveform data were not significantly different between pregnancy groups; however, those with preeclampsia did have a larger percentage of abnormal Doppler waveforms (21.1%) than the hypertension (15.9%) or normotension (13.5%) groups. Within the preeclampsia group, those with abnormal Doppler waveforms (*n*=12) were found to have lower NDIs at all years than those with hypertension, normotension or those with preeclampsia with no abnormal placental blood flow (*n*=45). Early onset preeclampsia may be indicative of a more severe type of preeclampsia, posing a greater health risk to mother and offspring (Leeson, 2013). Previous findings reported differences in placental morphology between early (≤34 weeks gestation) and late (>34 weeks gestation) onset preeclampsia (Egbor, Ansari, Morris, Green, & Sibbons, 2006) therefore we further examined the preeclampsia group for restricted placental function. Of those with preeclampsia and abnormal

Doppler waveform (*n*=12), 91% had early onset preeclampsia. Of those with preeclampsia and normal Doppler waveform (*n*=41) only 41% had early onset preeclampsia. Unfortunately the small numbers in these groups did not support further statistical analyses.

Motor development at 10, 14 and 17 years.

To examine the effect of hypertension and preeclampsia on motor outcomes at 10, 14 and 17 years general linear models were developed (Table 1). No significant interactions between hypertensive status and any of the control variables were found and were not included in the final models. Offspring born to mothers with preeclampsia had a significantly lower NDI at 10 (p = 0.041) and 14 years (p = 0.002) than the other two groups. Although not significant, a lower NDI score was also evident at 17 years for the preeclampsia group. Post hoc analyses at 10 years revealed the differences were between the preeclampsia group and the hypertension (p=0.031) and normotension (p = 0.012) groups. At 14 years the groups differences were between the preeclampsia group and the normotension group (p = 0.007) and between the hypertension and normotension groups (p = 0.006). In these cross sectional analyses the presence of abnormal Doppler waveform did not impact on motor development at any age.

The mean standard scores for the 10 individual tasks of the MAND were lower in the preeclampsia group for all tasks across the three follow up years, except the rod slide at 17 years. These differences were significant for the jump and beads on a rod tasks at 10, 14 and 17 years and for the finger tapping, finger-nose-finger, and balancing on one foot tasks in at least 2 of the 3 survey years.

Table 1 *Mean NDI of offspring at 10 14 and 17 years according to pregnancy group*

NDI	**Normotension**		**Hypertension**		**Preeclampsia**		**p value**
	M	(sd)	M	(sd)	M	(sd)	
10yrs	98.40	(4.72)[a]	97.66	(4.69)[b]	92.32	(6.17)[ab]	0.041
14yrs	102.37	(6.42)[ac]	98.41	(6.38)[c]	92.90	(8.71)[a]	0.002
17yrs	97.28	(6.68)	98.22	(6.70)	92.19	(9.12)	0.268

Adjusted for maternal age at conception, SES, maternal stress, maternal smoking and alcohol intake, use of anti-hypertensive medication, gestation age, parity, percentage of expected birth weight and child's sex.
[a] = difference between N and PE
[b] = difference between HT and PE
[c] = difference between N and HT

Mothers with preeclampsia had a significantly lower socioeconomic status as measured by the relative rating of advantage and disadvantage (p = 0.001) than either hypertensive or normotensive mothers (Table 2). These pregnancies also had significantly shorter gestational periods (p = <0.001) than those with hypertension and normal maternal blood pressure during pregnancy. Not surprisingly, higher numbers of stressful events in later pregnancy were reported in the preeclampsia group (p=0.003). A higher proportion of mothers with preeclampsia were more likely to have previously given birth (p=0.001) than those with hypertension or normotension.

Table 2 *Descriptive statistics according to pregnancy group*

	Normotension			Hypertension			Preeclampsia			p value
Continuous Variables	N	M	(sd)	N	M	(sd)	N	M	(sd)	
Maternal Age (yrs)	2133	27.57	(5.8)	626	27.62	(6.19)	109	27.30	(6.66)	0.872
Expected Birth Wt (%)	2111	97.44	(13.9)	623	97.40	(13.72)	109	96.45	(18.17)	0.775
Gest Age (wks)	2121	38.8	(2.30)[a]	623	38.53	(2.10)[b]	109	36.30	(3.46)[ab]	<0.001
Rating of Adv Dis	1448	1017	(90.5)[a]	421	1019	(85.8)[b]	70	978	(82.3)[ab]	0.001
Maternal Stress										
18 weeks	2132	1.19	(1.24)	626	1.28	(1.28)	109	1.02	(1.00)	0.088
34 weeks	1889	1.01	(1.18)[a]	572	1.12	(1.16)	92	1.39	(1.39)[a]	0.003
Categorical Variables	N	n	(%)	N	n	%	N	n	(%)	
Smoking	2127			626			109			0.001
None		1511	(71)		487	(77.8)		89	(81.7)	
≤10/day		344	(16.2)		87	(13.9)		14	(12.8)	
>10/day		272	(12.8)		52	(8.3)		6	(5.5)	
Alcohol	2125			625			109			0.562
None		1146	(53.9)		351	(56.2)		62	(56.9)	
1/wk or less		845	(39.8)		246	(39.4)		41	(37.6)	
Several times/ wk		118	(5.6)		23	(3.7)		6	(5.5)	
Daily		16	(0.8)		5	(0.8)		0	(0.0)	
Sex	2133			626			109			0.331
Males		1067	(50.0)		292	(46.6)		54	(49.5)	
Females		1066	(50.0)		334	(53.4)		55	(50.5)	
Parity	2116			623			109			<0.001
0		962	(45.5)		342	(54.9)		64	(58.7)	
1+		1154	(54.5)		281	(45.1)		45	(41.3)	

p values are for comparison between three groups according to ANOVA (continuous variables) and chi-squared analyses (categorical variables).

[a] = difference between Normotension and Preeclampsia

[b] = difference between Hypertension and Preeclampsia

[c] = difference between Normotension and Hypertension

Discussion

Results supported our hypothesis, with offspring of mothers who were diagnosed with preeclampsia during pregnancy having lower motor competence at 10, 14, and 17 years than those from mothers who had either hypertension or normal blood pressure during pregnancy. Furthermore there were a significantly higher number of individuals who fell below the recommended NDI cutoff score for motor dysfunction in the preeclampsia group. When examined longitudinally, preeclampsia was a greater risk factor than hypertension for persistent and potentially permanent lower motor competence into late adolescence. The findings of this paper also support and extend those of Hands et al. (2009) who found hypertensive diseases impacted on motor development at 10 years, and Rep et al. (Rep et al., 2008) who reported psychomotor delay in one year old infants born to mothers with severe preeclampsia.

The MAND tasks that were performed significantly worse by the preeclampsia group required underlying elements of postural control, proprioception and rhythm. For example, the broad jump necessitates the timing and synchronization of the leg and core muscles, the dynamic extension of the leg muscles and the orientation of the whole body in space. The finger-nose-finger and standing on one foot tasks required a sound sense of the positioning of relative body parts and balance, particularly when the eyes were closed and proprioceptive feedback became more important. Finger tapping required rhythm and control of small muscle groups, as well as postural control. It is possible poorer performance in these tasks may be due to an interruption in the development and functioning of the cerebellum and associated neurological pathways caused by placental dysfunction. While the presence of an abnormal Doppler waveform did not directly influence

motor outcome Egbor et al. (2006) suggest that preeclampsia is a heterogeneous condition, with reduced placental function being reported primarily in those diagnosed with early onset (≤34 weeks gestation) preeclampsia. Exploration of the pregnancies complicated by early and late onset preeclampsia provided limited support for this theory, with a trend towards those with early onset preeclampsia having a higher percentage of abnormal Doppler waveforms and lower NDIs than the late onset preeclampsia group. Mothers with abnormal Doppler waveforms and preeclampsia had a higher incidence of early-onset preeclampsia. While the numbers in these groups were small the trend suggests this may be indicative of a more severe form of the disease (Leeson, 2013; Lindheimer, Taler, & Cunningham, 2008) associated with restricted uteroplacental blood flow (Ghidini, Salafia, Pezzullo, & Minior, 1997). Abnormal placental morphology including significantly reduced intervillous space and terminal villi volume (Egbor et al., 2006) may play a role in the long term deficit of motor development seen in offspring with preeclampsia. Future research comparing the impact of early and late onset preeclampsia on motor development and the role of reduced placental function will require a larger sample size to support these findings.

Mothers with preeclampsia had higher incidences of other known risk factors that can effect development such as a lower socioeconomic status, higher stress levels in later pregnancy (Huizink et al., 2003; O'Connor et al., 2003) and shorter gestational length (Goyen & Lui, 2002). As no interactions were present in the models between any of these previously identified risk factors and the hypertensive status of the mothers preeclampsia emerged as a risk factor for impaired motor development independent of these factors.

Strengths.

This study had several strengths. Firstly, the longitudinal nature of the data and the large cohort allowed for a robust statistical analysis of the impact of maternal hypertension and preeclampsia on motor development using linear mixed models. Such data are rare. Secondly, while there is a growing body of evidence (Tranquilli, Landi, & Sibai, 2012) indicating preeclampsia may be responsible for long term health consequences in both mother and offspring there remains a paucity of research into the long term effects of hypertensive diseases on offspring motor development. Furthermore while motor development has been studied in infants, early, and late childhood, few studies have sought to identify the early determinants of motor development into adolescence. Finally, the measure of motor development used in the current study, the MAND is a reliable and accurate measure of motor development in an Australian population and was administered by trained personnel.

Limitations.

A challenge in using longitudinal data from the Raine Cohort was the lack of motor development data collected prior to the 10-year cohort review. This was unfortunate as tracking of motor development in younger years may have provided a picture of the changes in motor development throughout early childhood as well as late childhood and adolescence. While this was a limitation the high quality longitudinal data from late childhood to adolescence provided a unique profile of motor development throughout this often under researched time period.

Conclusion

Our findings indicate that hypertensive diseases during pregnancy, in particular preeclampsia, have long term and possibly permanent consequences that

compromise motor development of offspring into late adolescence. These findings are unique as no previous studies have investigated the effect of hypertensive diseases during pregnancy on motor development over such a long period of time. While there are reports of the negative effects of hypertension and preeclampsia on a range of developmental areas (Ogland et al., 2011; Rep et al., 2008; Robinson et al., 2009; Whitehouse et al., 2012) longitudinal motor outcomes have thus far remained under researched. Health professionals should be alerted to the risks for long term, possibly permanent motor dysfunction in offspring born to mothers diagnosed with preeclampsia, as early intervention may minimize poorer long term motor outcomes.

Acknowledgments

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CHAPTER FOUR

The Impact of Maternal Gestational Stress on Motor Development: A Longitudinal Study

This chapter has been published and the full PDF is in the Appendices

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The Impact of Maternal Gestational Stress on Motor Development in Late Childhood and Adolescence: A Longitudinal Study

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The number and timing of stressors experienced during pregnancy were investigated using longitudinal data from the Western Australian Pregnancy (Raine) Study cohort (N = 2,900). Motor development data were collected at 10 (n = 1,622), 14 (n = 1,584), and 17 (n = 1,222) years using the McCarron Assessment of Neuromuscular Development. Linear mixed models were used to examine the effect of stress on motor development, accounting for repeated measures. Number of stressful events and mean Neuromuscular Development Index were negatively related ($\beta = -1.197$, $p = .001$). Stressful events experienced in late pregnancy were negatively related with offspring motor development ($\beta = -0.0541$, $p = .050$), while earlier stressful events had no significant impact.

Although the human brain and nervous system have shown a capacity for adaptivity, often referred to as plasticity, there is evidence that suggests insults to the developing central nervous system (CNS) in utero can be long lasting and in some cases permanent (Pitcher, Henderson-Smart, & Robinson, 2006). Evidence of the impact the in utero environment has on short- and long-term health outcomes are growing, evidenced by the rapidly growing field of research, the Developmental Origins of Health and Disease (Barker, 2007). The development of the CNS is a complex process that begins at approximately 3 weeks of gestation, however differentiation of embryo cells into specific tissues starts only a few days after fertilization (Brodal, 2010). Prenatally the process includes neural induction, proliferation, migration, and differentiation. Pioneering work by Barker (2007) hypothesized that nutritional deficits in utero led to structural and functional changes in the developing fetus, termed "fetal programming," and coincided with an increased risk of disease in adult life. While this theory has been tested with outcomes such as coronary heart disease, stroke, hypertension, and diabetes, there is little research that has applied the hypothesis to outcomes of motor coordination.

Periods of critical importance during fetal development, have been previously reported (Barker, 1997; Nathanielsz, 1999). These windows of opportunity occur at times when cell proliferation and division in tissues, organs, and systems occur at a rapid rate; therefore, different critical periods occur for different tissues. The timing of events that can influence fetal development are an important consideration in the study of in utero environments; however, there have been few longitudinal studies that have sought to pinpoint these critical windows of development in relation to motor development. Sensitive periods during gestation when the fetus may be more vulnerable to prenatal stress have been identified across most aspects of development (Ellman et al., 2008; Laplante et al., 2004; Van den Bergh & Marcoen, 2004). While the majority of these findings indicate stress in early pregnancy is of particular importance to offspring development, some researchers (Huizink, Robles de Mina, Mulder, Visser, & Buitelaar, 2003; O'Con-

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Abstract

The number and timing of stressors experienced during pregnancy were investigated using longitudinal data from the Western Australian Pregnancy (Raine) Study cohort (*N*=2900). Motor development data were collected at 10 (*n* = 1622), 14 (*n* = 1584) and 17 (*n* = 1222) years using the McCarron Assessment of Neuromuscular Development (MAND). Linear mixed models were used to examine the effect of stress on motor development, accounting for repeated measures. Number of stressful events and mean Neuromuscular Development Index (NDI) were negatively related (β = -.1.197, p = 0.001). Stressful events experienced in late pregnancy were negatively related with offspring motor development (β = -.0541, p = 0.050) while earlier stressful events had no significant impact.

Introduction

Although the human brain and nervous system have shown a capacity for adaptivity, often referred to as plasticity, there is evidence that suggests insults to the developing central nervous system (CNS) in-utero can be long lasting and in some cases permanent (Pitcher et al., 2006). Evidence of the impact the in-utero environment has on short and long term health outcomes are growing, evidenced by the rapidly growing field of research, the Developmental Origins of Health and Disease (DoHAD) (Barker, 2007). The development of the CNS is a complex process that begins at approximately 3 weeks gestation, however differentiation of embryo cells into specific tissues starts only a few days after fertilization (Brodal, 2010). Prenatally the process includes neural induction, proliferation, migration and differentiation. Pioneering work by Barker and colleagues (Barker, 2007) hypothesized that nutritional deficits in-utero led to structural and functional changes in the developing foetus, termed 'fetal programming', and coincide with an increased risk of disease in adult life. While this theory has been tested with outcomes such as coronary heart disease, stroke, hypertension and diabetes there is little research that has applied the hypothesis to outcomes of motor coordination.

Periods of critical importance during fetal development, have been previously reported (Barker, 1997; Nathanielsz, 1999). These windows of opportunity occur at times when cell proliferation and division in tissues, organs and systems occur at a rapid rate, therefore different critical periods occur for different tissues. The timing of events which can influence fetal development are an important consideration in the study of in-utero environments, however there have been few longitudinal studies that have sought to pinpoint these critical windows of development in relation to motor development. Sensitive periods during gestation when the foetus may be more

vulnerable to prenatal stress have been identified across most aspects of development (Ellman et al., 2008; Laplante et al., 2004; Van den Bergh & Marcoen, 2004). While the majority of these findings indicate stress in early pregnancy is of particular importance to offspring development some researchers (Huizink et al., 2003; O'Connor et al., 2003) have reported that stress in late pregnancy affects mental, emotional and behavioral development in infancy and early childhood. Pitcher, Henderson-Smart, and Robinson (Pitcher et al., 2006), reported that during the third trimester, the developing fetal brain may be more vulnerable to hypoxic and ischemic affronts. The cerebellar cortex, which develops mainly during late pregnancy, is important for the development of postural control, coordination, and motor skill function (Gramsbergen, 2003). While work with animal models has supported this role it is not fully understood how pregnancy stress may affect the developing human cerebellar cortex and whether the timing of this stress has long term neurological consequences. Long term functional deficits in motor development could also results from the increase in hormones such as cortisol (DiPietro, 2004), androgen (Kaiser & Sachser, 2009) or progestogen (Paris & Frye, 2011) which occur when the mother is stressed. Changes in these hormone levels are hypothesized to permanently affect the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (Lazinski et al., 2008; Paris & Frye, 2011), limbic system, prefrontal cortex (Van den Bergh et al., 2005) and Autonomic Nervous System (ANS) (Lazinski et al., 2008) in offspring. Although not directly related to motor control, some of these, for example the limbic system which controls spatial memory and motivation, may affect motor functioning.

Changes in the structure and function of the developing fetal neurological system, due to maternal stress have been hypothesized to cause long term deficits in several developmental domains (Glover & O'Connor, 2006; 2003; Ruiz & Avant,

2005; Van den Bergh et al., 2005). Birth outcomes reportedly effected by maternal gestational stress include lower birth weight and gestational age, smaller head circumference and poorer neurological scores at birth (Glover & O'Connor, 2006). Previous research has revealed maternal gestation stress can also negatively impacts a range of health and developmental outcomes in infancy and early childhood (Monk, 2001; Ruiz & Avant, 2005; Talge et al., 2007; Tegethoff et al., 2011). These include cognitive (Buitelaar et al., 2003; Glover & O'Connor, 2006; Huizink et al., 2003; Laplante et al., 2004; Sandman et al., 2012), motor (Buitelaar et al., 2003; Huizink et al., 2003), language (Henrichs et al., 2011; Laplante et al., 2004), behavioral and emotional development (de Weerth et al., 2003; Glover & O'Connor, 2006; O'Connor et al., 2002; Robinson et al., 2008; Sandman et al., 2012) as well as physical and neuromuscular maturation (Ellman et al., 2008; Sandman et al., 2012). For example Buitelaar (2003) reported gestational stress to be predictive of lower motor development outcomes at 8 months and Huizink (2003) reported an average decline of 8 points on mental and motor development scales in infants born to mothers who recorded higher levels of the stress hormone cortisol.

While longitudinal studies have shown that maternal pregnancy stress affects behavioral, mental and cognitive development in middle childhood (Rodriguez & Bohlin, 2005; Van den Bergh & Marcoen, 2004) and into adolescence (Mennes, Van den Bergh, Lagae, & Stiers, 2009; Robinson et al., 2011) few studies have investigated the consequences on motor development. Earlier work using animal models revealed reduced motor skills and balance in infant monkeys after repeated maternal stress (Schneider & Coe, 1993). Hands and colleagues (Hands et al., 2009) examined whether a range of perinatal factors influenced human motor development and found that a high level of postnatal maternal stress was related to the presence of

mild motor delay in males at 10 years. Gestational stress was not reported as a contributing factor, however the variables were dichotomized, with a stressful pregnancy defined by the presence of 3 or more stressful events. In light of other findings regarding timing and number of stressors being pertinent to the effect on developmental outcomes (Davis & Sandman, 2010; Ellman et al., 2008; Robinson et al., 2011) further investigation of the available gestational stress data is warranted. The current study will examine how stressful events during early and late gestation, as well as total number of stressful events throughout pregnancy affect motor development outcomes at 10, 14 and 17 years.

Low motor competence has previously been linked to decreased short and long term mental and physical health outcomes (Cantell et al., 1994; Fitzpatrick & Watkinson, 2003; Schoemaker & Kalverboer, 1994; Skinner & Piek, 2001). While the body of evidence regarding the negative effects of lowered motor competence is growing there remains a paucity of research involving early risk factors for suboptimal neurological development during the antenatal, perinatal and neonatal stages.

Events which are believed to cause stress such as marital problems, financial issues, loss of a close family member or the accumulation of smaller daily hassles are most often used as stress markers (Huizink et al., 2003; Robinson et al., 2011; Whitehouse, Robinson, Zubrick, et al., 2010). The purpose of this paper is to investigate whether the number and timing of stressors experienced during pregnancy impacted long term motor development at 10, 14 and 17 years. We hypothesize that the experience of stressful events during pregnancy would negatively impact offspring motor development, with later pregnancy stress playing a more important role in motor outcomes than earlier stress.

Methods

Participants.

Participants (*N*=2900) were from the Western Australian Pregnancy Cohort (Raine) Study. The cohort were primarily Caucasian, from European descent (88.2%), and included mothers who identified as Aboriginal (2.4%), Chinese (4.4%), Indian (2.6%), Polynesian (0.9%) and Vietnamese (0.3%). Recruitment criteria included gestational age between 16-18 weeks, adequate English language skills to comprehend the study requirements, expected delivery at King Edward Memorial Hospital and for ease of future follow up of children, the desire to remain living in Western Australia. Mothers were recruited between 16-20 weeks gestation (*M*=18 weeks) from May 1989 to November 1991 at a rate of approximately 100 per month. Full cohort details and enrolment criteria have been published previously (Newnham et al., 1993). In total 2868 live births were recorded (Table 3) and questionnaire data including socioeconomic status and maternal health and psychosocial characteristics were collected from the mothers at 18 and 34 weeks gestation, with obstetric data collected throughout the antenatal, perinatal and neonatal periods. Physical data were collected at 10 (*M* = 10.54, *SD* = 2.27), 14 (*M = 14.02, SD = 2.33)* and 17 (*M = 16.99, SD = 2.97)* years from the offspring. A total of 989 children completed motor development testing at all three data collection phases, while 395 completed one data collection phase and 533 participated in two of the three follow ups. The participation rates for the active cohort (Table 3) were good at each follow up phase; 10 (*n* = 1622, 79%), 14 (*n* = 1584, 85%), 17 (*n* = 1221, 69%). There were no statistical differences in motor development outcome between those participants who

were assessed at 10 years only (*M* = 94.72, *SD* = 14.38) and those who participated in all three data collection phases (*M* = 94.35, *SD* = 14.12).

Ethics clearances were obtained from the Human Research Ethics Committee at King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained at enrolment and at each follow up from parents and/or guardians.

Table 3 *Available data from each follow up of the Raine Study*

Year	Active	MAND	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2868						2868
10	2047	1622	281	162	348	30	2868
14	1860	1584	357	207	412	32	2868
17	1754	1221	414	184	480	36	2868

Predictor variable.

Maternal stress data were collected at 18 and 34 weeks gestation from the mothers using a 10-item questionnaire based on the Tennant and Andrews (1977) Life Stress Inventory. A yes/no format was used to ask if the mothers had experienced any of the listed stressful events, such as pregnancy problems, death of a close relative, death of a close friend, separation or divorce, marital problems, problems with children, involuntary job loss, partner's job loss (involuntary), money problems and residential move (Table 4) Another item labeled 'other' was available if the mother had experienced stress from an unlisted event or circumstance. The first questionnaire at 18 weeks asked if the mothers had experienced any of the listed stressors since becoming pregnant, while the questionnaire at 34 weeks asked if they had experienced the listed stressors in the last four months. This ensured stressors that occurred during the first questionnaire were not counted in the second questionnaire unless they were still occurring. For example moving house which is a

one off event would only need to be included in one questionnaire while marital or financial problems which can be ongoing may have been included in both. To explore the impact of early and late stress two continuous variables were created to reflect the number of stressors experienced at both time points. Three groups were then created which categorized stress severity. This allowed for comparison to other published works which used similar methodology (O'Connor et al., 2003), including previous research using the Raine Study cohort (Robinson et al., 2011; Whitehouse, Robinson, Zubrick, et al., 2010). Each stressful event was weighted equally and mothers were categorized as experiencing either no stress (NS), low stress (LS; <3 stressors) or high stress (HS; ≥3 stressors) throughout pregnancy.

Table 4 *Type and frequency of stressful events*

Stressor	**18 Weeks** (N = 2804)		**34 Weeks** (N = 2580)	
	n	%	n	%
Money problems	789	28.1	665	25.7
Pregnancy problems	733	26.1	511	19.8
Residential move	455	16.2	466	18
Marital Problems	247	8.8	184	7.1
Problems with your children	177	6.3	164	6.3
Relationship problems	151	5.4	140	5.4
Death of a relative	149	5.3	138	5.3
Your partners job loss (not voluntary)	136	4.8	136	5.3
Separation or divorce	114	4	77	2.9
Your own job loss (not voluntary)	85	3	36	1.4
Death of a close friend	56	1.9	43	1.6

Outcome measure.

At 10, 14, and 17 years, offspring motor outcome was measured by the McCarron Assessment of Neuromuscular Development (MAND) (McCarron, 1997). The MAND comprises a battery of 10 items including a) hand strength b) finger-nose-finger placement c) jumping d) heel-toe walk e) standing on one foot f) beads in

a box g) beads on a rod h) finger tapping i) nut and bolt j) rod slide. Raw scores are converted to scaled scores (*M* = 10, *SD* = 3). The scaled cores are summed and the total normalized to form a composite score, the Neuromuscular Development Index (NDI) (*M*=100, *SD*=15). The NDI can be used as a continuous outcome measure (Table 5), or a cutoff of <85 can be used to determine the presence of mild motor delay (Table 6) (Hands et al., 2009; McCarron, 1997). Test-retest reliability coefficients of the MAND tasks are reported by McCarron (McCarron, 1997) at 0.99 overall. A comparison of the MAND to two other highly utilized motor coordination tests revealed the MAND to be superior in detecting motor development problems in Australian children (Tan et al., 2001).

Table 5 *Motor development scores according to pregnancy stress groups*

NDI	**N**	**No Stress 0 Stressors**		**N**	**Low Stress <3 Stressors**		**N**	**High Stress ≥3 Stressors**		**p value**
		M	SD		M	SD		M	SD	
10yrs	352	95.36[a]	13.55	616	94.74	14.21	542	93.09[a]	13.81	0.034*
14yrs	336	101.19[a]	18.32	612	99.48	17.62	524	97.54[a]	17.21	0.011*
17yrs	260	98.60[a]	17.51	466	97.53[b]	17.36	423	94.13[ab]	16.52	0.001*

* = significant group difference at the p = 0.05 level

Table 6 *Prevalence of mild motor delay within pregnancy stress groups*

NDI	**No Stress 0 Stressors**		**Low Stress <3 Stressors**		**High Stress ≥3 Stressors**		**p value**
	<85	≥85	<85	≥85	<85	≥85	
10yrs	272 (77.3%)	80 (22.7%)	467 (75.8%)	149 (24.2%)	286 (71.2%)	156 (28.8%)	0.082
14yrs	265 (78.9%)	71 (21.1%)	474 (77.5%)	138 (22.5%)	391 (74.6%)	133 (25.4%)	0.314
17yrs	192 (73.8%)	68 (26.2%)	341 (73.2%)	125 (26.8%)	279 (66.0%)	144 (34.0%)	0.029*

* = significant group difference at the *p* = 0.05 level

Covariates.

The statistical models controlled for other variables known to influence motor development. These included maternal age, maternal smoking and alcohol consumption, percentage of expected birth weight, parity, child's sex, gestational age and family income. A categorical variable for maternal smoking was created with three groups; non-smokers, ≤ 10 cigarettes a day, and > 10 cigarettes a day. Maternal alcohol intake was classified as daily, several times a week, once a week or less, or never. Family income was dichotomised to reflect a minimum income level (<$24000p.a. or ≥$24000p.a.) according to Australian Government guidelines at the time.

Statistical Analyses.

Maternal and child variables that were related to motor development at 10, 14 and 17 years were identified using cross sectional analyses including chi-square tests, t-tests and univariate ANOVA models (general linear model - GLM) with Bonferroni post hoc correction. No interactions were found between child's sex and maternal stress group or any of the control variables, so results were not stratified by sex.

Linear mixed models were used to examine the effect of stress on motor development, accounting for the unbalanced nature of longitudinal data with repeated measures. The first model examined the severity of pregnancy stress on offspring motor development throughout the entire pregnancy, using the categorical variables of no stress, low stress (<3 stressful events) and high stress (≥3 stressful events). The second model explored the difference in early and late pregnancy stress on motor development using continuous variables of stress calculated at 18 and 34 weeks

gestation. Covariates that were not significantly related to motor development were not included in the final models.

Results

Group characteristics are reported in (Table 7). Mothers who experienced high stress throughout pregnancy (≥3 stressful events) were younger than those in either the low stress (<3 stressful events) or no stress groups (p = <0.001). More women in the high stress group were classified as having a low income (p = <0.001) and they were more likely to smoke (p = <0.001). Infants born to mothers in the high stress group had a lower gestation age (p = <0.001). Money problems were the most commonly reported stressor with 28.1% of participants at 18 weeks and 26.1% at 34 weeks stating they had experienced financial stress (*Table 4*). Pregnancy problems were the next most common stressor, followed by residential moves and marital issues. Problems with children were the fifth most common stressor, while other stressors were reported by between 1.7 – 5.4% of participants.

Table 7 *Cohort characteristics according to pregnancy stress group*

	No Stress 0 Stress Events			**Low Stress <3 Stress Events**			**High Stress ≥3 Stress Events**			**p value**
Continuous Variables	N	M	(sd)	N	M	(sd)	N	M	(sd)	
Maternal Age (yrs)	567	28.67	(5.80)	1035	28.27	(5.82)	1014	26.48	(5.90)	<0.001
% Expected Birth Wt	567	97.48	(12.33)	1032	97.63	(12.44)	1007	96.63	(13.24)	0.173
Gestational Age (wks)	567	39.06	(1.70)	1034	38.91	(1.78)	1010	38.66	(2.21)	<0.001
Categorical Variables	N	n	(%)	N	n	%	N	N	(%)	
Smoking	567			1035			1014			<0.001
None		456	(80.4)		795	(76.8)		671	(66.2)	
≤10/day		67	(11.8)		156	(15.1)		172	(17.0)	
>10/day		44	(7.8)		84	(8.1)		171	(16.9)	
Alcohol	567			1034			1012			.661
None		309	(54.5)		576	(55.7)		533	(52.7)	
Once a wk or less		217	(38.3)		402	(38.9)		414	(40.9)	
Several times wk		36	(6.3)		48	(4.6)		58	(5.7)	
Daily		5	(0.9)		8	(0.8)		7	(0.7)	
Sex	567			1035			1014			0.792
Males		295	(52.0)		520	(50.2)		520	(50.8)	
Females		272	(48.0)		515	(49.8)		499	(49.2)	
Low Income	528			976			947			<0.001
No		414	(78.4)		710	(72.7)		551	(58.2)	
Yes		114	(21.6)		266	(27.3)		396	(41.8)	
Parity	567			1033			1008			0.686
0		266	(46.9)		505	(48.9)		477	(47.3)	
1+		301	(53.1)		528	(51.1)		531	(52.7)	

Note. *p* values are for comparison between three groups according to ANOVA (continuous variables) and chi-squared analyses (categorical variables).

The first linear mixed model, adjusting for sex, gestation age, percentage of expected birth weight, maternal age, parity, maternal alcohol and smoking and family income revealed that number of stressful events and mean NDI were negatively related ($\beta = -1.197$, $p = 0.001$). The overall adjusted mean NDI for the no stress groups was significantly larger than the high stress group. Pairwise comparison revealed a significant difference between the no stress (98.91) and high stress (97.16) ($p = 0.017$) groups.

Of the potential confounding factors included in the analyses sex ($p = <0.001$), gestational age ($p = 0.001$), parity ($p = 0.040$), family income ($p = <0.001$)

and maternal alcohol consumption (p = 0.003) were related to motor development. Males overall had higher NDI scores, while offspring with lower gestational ages had poorer NDI scores compared to their peers. First born children and those from families with incomes under the Australian Government threshold had lower motor development scores. Alcohol intake for those who were grouped as daily drinkers was negatively related to motor development.

The second model, investigating early and late pregnancy stress revealed that stressful events experienced in late pregnancy were negatively related with offspring motor development (β = -0.541, p = 0.050) while earlier stressful events had no significant impact. Covariates related to motor development scores in the second model included sex (p = <0.001), gestation age (p = 0.001), percentage of expected birth weight (p = 0.042), parity (p = 0.020), family income (p = <0.001) and maternal alcohol consumption (p = 0.042).

Cross sectional analyses revealed there were group differences in mean NDI at 10 years (p = 0.034), with Bonferroni post hoc results showing difference between the no stress and high stress groups (p = 0.050). At 14 years there was also a group difference (p = 0.011), with post hoc analyses showing difference between the no stress and high stress groups (p = 0.009). The highest group difference was seen at 17 years (p = 0.001) with post hoc results revealing differences between no stress and high stress (p = 0.003) and also low stress and high stress (p = 0.010) groups. The high stress group comprised more individuals whose NDI fell under the cutoff for mild motor delay at each year (Table 6). This difference was significant at 17 years (p = 0.029).

Discussion

The first linear mixed model, examining the impact of stressful events throughout pregnancy revealed support for the hypothesis that pregnancy stress would result in lower motor development scores in offspring. This was shown at ages 10, 14 and 17. The greatest difference in mean NDI was found between the no stress and high stress groups. Mothers who experienced three or more stressful events throughout their pregnancy had offspring with a lower motor competence than those who experienced none or less than three events. This may suggest an accumulative effect of stress on the developing fetal motor system, with small amounts of stress having a negligible effect and greater amounts having a negative effect. In contrast to our findings DiPietro and colleagues (DiPietro, Novak, Costigan, Atella, & Reusing, 2006) reported that non-specific maternal stress did not have a negative relation with overall child development at the age of two and motor development at this age was found to be positively impacted by higher levels of maternal stress. The smaller sample size (185) and restriction to low-risk, nonsmoking women over the age of 20 years may explain the difference in findings. Further to this the children measured in the previous study were much younger than the current study. Gramsbergen (2003) suggests that the underlying neurobiological processes that contribute to motor development, including neurophysiological factors such as motor programming and sensory processing, continue to develop during a child's first 10 years. It is possible that the effects of maternal gestational stress on these processes may not be fully manifested until after these systems have fully developed.

The second linear mixed model, investigating the impact of early versus late stressful events confirmed that late pregnancy stress had a greater influence on motor development during late childhood and into adolescence than early pregnancy stress.

The human neural system is one of the first systems to develop in utero, however disturbances of the developing cerebellar cortex, which occurs late in neuro-ontogeny, may be the key etiological factor for motor programming (Gramsbergen, 2003; Ivry, 2003). Growth of the cerebellar cortex occurs during the third trimester and includes a rapid increase in granule cells and the creation of neural pathways, which will eventually assist in adjustments to muscle tone, control of movement and posture and the learning of physical tasks and motor skills (Gramsbergen, 2003). While several previous studies highlight the importance of early pregnancy stress on cognitive, (Davis & Sandman, 2010; Laplante et al., 2004; Sandman et al., 2012) language (Laplante et al., 2004) and mental and behavioural (Van den Bergh & Marcoen, 2004) development, other researchers have found mid to late pregnancy stress affected early motor development (Huizink et al., 2003) and behavioral / emotional problems (O'Connor et al., 2003). Our findings support the theory of later pregnancy stress having a greater influence specifically on long term motor development and further research into the impact of this on the developing cerebellar cortex may help to further our understanding of how this occurs.

Alternatively the effect of maternal gestational stress on other areas of neurological development may account for the lower motor development scores. Changes in levels of hormones such as cortisol (DiPietro, 2004), androgen (Kaiser & Sachser, 2009) or progestogen (Paris & Frye, 2011) are hypothesized to permanently affect the functioning of the limbic system (Murmu et al., 2006). Changes in neuron development within the limbic system due to maternal gestational stress have been observed in rat models (Murmu et al., 2006) however whether these changes affect motor development in humans is unknown.

Cross sectional analyses showed group differences at 10 (p = 0.034), 14 (p = 0.011) and 17 (p = 0.001) years. This finding was unexpected as no previous research has reported that the negative relationship between maternal gestational stress and offspring motor development becomes stronger with age, however the continued growth of the neurological systems throughout the first decade (Gramsbergen, 2003) may explain why the full impact on these systems is not evident until after puberty.

Strengths.

A large population based sample and the collection of various potential confounders allowed for a stringent and robust analysis of the effect of pregnancy stress on motor development in late childhood and adolescence. As previously reported (Robinson et al., 2011), the inclusion of pregnancy concerns in the questionnaire allowed the mothers to include stressors that may have otherwise been overlooked, as pregnancy and impending birth, as well as related health problems, can be a cause of stress themselves. The use of two questionnaires to collect stress data allowed earlier and later stressors to be compared and the impact of timing to be analyzed. The MAND (McCarron, 1997) is a reliable and accurate measure of motor development among Australian children (Tan et al., 2001).

Limitations

While stressful events are commonly used as a measure of stress we acknowledge that this does not consider an individual's resilience which can ameliorate the level at which stressful events may impact them psychologically. The longitudinal nature of the study did not allow for further measures regarding maternal resilience or perceived severity of stress. Other environmental and lifestyle factors have previously been linked to motor development throughout infancy and

childhood however controlling for these factors was not within the scope of this study. The extensive and high quality antenatal data available allowed thorough and robust analyses of the factors contributing to motor development from this time period.

Conclusion

We found support for the hypothesis that stress during pregnancy contributed to a poorer motor development outcome in the long term. Glover (2014) has recently stated the emotional care of pregnant women is an often overlooked aspect of obstetric practice. With evidence for the importance of maternal emotional and mental health on a wide range of developmental and health outcomes for both mother and child, future programs aimed at early detection and reduction of maternal stress, may help improve offspring outcomes. Currently screening for postnatal depression with user-friendly questionnaires occurs in most antenatal clinics in Australia. This cost effective model could be used to screen for maternal stress throughout pregnancy as part of regular clinic visits. Previous research has highlighted the importance of exercise in the reduction of stress, improvement of mood and enhanced mental health outcomes (Fox, Boutcher, Faulkner, & Biddle, 2000). Da Costa and colleagues (2003) reported women who exercised during pregnancy had significantly better mental health markers, including less state anxiety and less pregnancy-specific stress. Exercise presents a low-cost yet effective method of ensuring healthy women experience optimal mental health during pregnancy. Antenatal clinics provide an ideal arena for pregnant women to be informed of the benefits of exercise, in particular if they are experiencing a stressful pregnancy.

CHAPTER FIVE

Breastfeeding and Motor Development: A Longitudinal Cohort Study

Abstract

Objective: The relationship between duration of breastfeeding and motor development outcomes at 10, 14, and 17 years were examined. We hypothesized that offspring who were breastfed for 6 months or longer would have better outcomes.

Methods: Data were obtained from the Western Australian Pregnancy (Raine) Study. There were 2868 live births recorded and children were examined for motor proficiency at 10 (*M* = 10.54, *SD* = 2.27), 14 (*M = 14.02, SD = 2.33)* and 17 (*M = 16.99, SD = 2.97)* years using the McCarron Assessment of Neuromuscular Development (MAND). Using linear mixed models, adjusted for covariates known to affect motor development, the influence of breastfeeding for <6 months and ≥6 months on motor development outcomes was examined.

Results: Breastfeeding for ≥6 months was positively associated with improved motor development outcomes at 10, 14 and 17 years of age (p = 0.019, β 1.38) when adjusted for child's sex, maternal age, alcohol intake, family income, hypertensive status, gestational stress and mode of delivery.

Conclusions: Early life feeding practices have an influence on motor development outcomes into late childhood and adolescence, independent of sociodemographic factors.

Key Words: Breastfeeding, motor development, child development, Raine Study

Abbreviations

MAND: McCarron Assessment of Neuromuscular Development
NDI: Neuromuscular Developmental Index
SRM: Spontaneous rupture of membranes
APGAR: Appearance, Pulse, Grimace, Activity, Respiration
TSR: Time to spontaneous respiration
BP: Blood Pressure

Introduction

Breastfeeding has been linked to a number of positive developmental outcomes including optimal neural (McCroy & Murray, 2013) and early brain development (Herba et al., 2013), improved immunity (Oddy & Rosales, 2010), mental health (Oddy et al., 2010), language ability (Dee et al., 2007; Whitehouse, Robinson, Li, & Oddy, 2010), cognitive function (Anderson, Johnstone, & Remley, 1999; Oddy et al., 2003) and academic achievement (Oddy, Li, Whitehouse, Zubrick, & Malacova, 2011). In addition breastfeeding has been reported to decrease the risk of asthma (Scholtens et al., 2009) and obesity (Chivers et al., 2010; Oddy et al., 2014). While there is a large body of work that has reported outcomes of breastfeeding in these domains, fewer have focused on motor development. Previous research, including several international cohort studies (Dee et al., 2007; McCroy & Murray, 2013; Oddy, Robinson, et al., 2011; Sacker et al., 2006; Thorsdottir et al., 2005; Vestergaard et al., 1999) have reported benefits of breastfeeding on motor development however there remains a paucity of research reporting outcomes beyond early childhood and into adolescence.

Current recommendations for breastfeeding according to the World Health Organization (WHO, 2003) and the National Health and Medical Research Council (National et al., 2012) in Australia are for exclusive breastfeeding until 6 months of age and beyond. Some socio-demographic factors can affect the decision to breastfeed and the duration of breastfeeding, including maternal age, education and socioeconomic status (Scott, Binns, Oddy, & Graham, 2006). Breastfeeding in western populations is reportedly higher in older mothers who have a greater level of education and socioeconomic status (Scott et al., 2006). Researchers who have previously focused on cognitive development suggested improved outcomes among breastfed children may be due to the benefits of having a more favorable home environment and socioeconomic

status rather than the breast milk itself (Zhou, Baghurst, Gibson, & Makrides, 2007). In contrast other researchers have reported developmental outcomes to be significantly better in breastfed infants after controlling for confounders such as income, maternal age and sociodemographic information (Oddy et al., 2003; Oddy, Li, et al., 2011; Oddy, Robinson, et al., 2011; Vestergaard et al., 1999). What still remains to be explored is whether predominant breastfeeding for at least six months has a long term effect on motor development and how these socio-demographic confounders influence that relationship.

Methods

Participants

Participants (N=2900) were from the Western Australian Pregnancy Cohort (Raine) Study. Pregnant women were recruited through the main obstetric hospital in Perth, Western Australia, King Edward Memorial Hospital (KEMH) from May 1989 to November 1991 at a rate of approximately 100 per month. Study requirements included a gestation between 16-20 weeks (M=18 weeks), sufficient English speaking skills to understand what the study entailed, expectation to deliver at KEMH and an intention to reside in Perth to facilitate future data collection. There were 2868 live births, with extensive obstetric, health, socioeconomic, demographic and medical data collected during gestation and subsequent follow up phases (Newnham et al., 1993).

Ethics clearances were obtained from the Human Research Ethics Committee at King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained at enrolment and at each follow up from parents and/or guardians.

Predictor Measure

Duration of breastfeeding was recorded in months and included any breastfeeding, regardless of the introduction of solid food or other milk sources. Breastfeeding data were collected retrospectively during the follow up phases at 1, 2, and 3 years, with each follow up interview within a year of the child's birth date. A binary variable of <6months or ≥6 months was created. In addition a categorical variable for breastfeeding, including <3months, 3-5months, 6-11months and ≥12months was created to investigate the effect of breastfeeding over time.

Outcome Measure

Motor development was measured at 10 (*M* = 10.54, *SD* = 2.27), 14 (*M = 14.02, SD = 2.33)* and 17 (*M = 16.99, SD = 2.97)* years of age using the McCarron Assessment of Neuromuscular Development (MAND) (McCarron, 1997). Participation in motor development testing at 10 (*n* = 1622), 14 (*n* = 1584) and 17 years (*n* = 1221) showed participation rates of 79%, 85% and 69% of the active cohort for each year. Nine hundred and eighty nine children completed all three data collection phases, while 533 participated in two of the three phases and 395 completed motor development testing once.

The MAND is a ten item battery of tests including fine and gross motor items including a) hand strength b) finger-nose-finger placement c) jumping d) heel-toe walk e) standing on one foot f) beads in a box g) beads on a rod h) finger tapping i) nut and bolt j) rod slide. The Neuromuscular Developmental Index (NDI) was calculated by converting each items' raw score to a scaled score (M=10, SD=3) which was summed and normalized according to age and sex appropriate norms. The NDI (M=100, SD=15) was used as a continuous outcome measure, with a higher score indicating better motor development. A cut-off score of 1SD below the mean (≤85) was used to indicate mild motor delay (McCarron, 1997). Test-retest reliability coefficients of the MAND are

reported at 0.99 overall (McCarron, 1997) and it has been compared favorably to two other motor development tests in detecting motor disability within an Australian population (Tan et al., 2001).

Covariates

Potential confounding risk factors experienced during pregnancy, including maternal age (years), smoking, drug and alcohol consumption, maternal stress, hypertensive status and low income were adjusted for in statistical modelling. Maternal smoking was recorded as a categorical variable, with none, <10/day and ≥10/day. Alcohol consumption was recorded as never, once a week or less, several times a week or daily. Due to the small number of individual recreational drugs used by the cohort a binary variable was recorded, reflecting whether or not any recreational drug/s during pregnancy were consumed. Hypertensive status was categorized as normal BP, hypertension (systolic BP >140mmHg and/or diastolic >90mmHg) or preeclampsia (hypertension with the addition of proteinurea >300mg/24hr). Stress was recorded as the total number of stressful events experienced during pregnancy, while low income was categorized as <$24000/p.a. according to the Australian government minimum threshold at the time of data collection.

Infant variables included percentage of optimal birth weight (a measure of whether growth potential has been met) (Pereira, Blair, & Lawrence, 2012), mode of delivery, sex, parity, APGAR scores at 1 minute and time to spontaneous respiration. Mode of delivery was recorded as spontaneous vaginal delivery, assisted vaginal delivery, elective caesarean section (decision made prior to spontaneous rupture of membranes, SRM) and non-elective caesarean section (decision made after SRM).

Data Analysis

Chi square, t-tests and univariate analyses of variance models with Bonferroni post hoc analyses were used to identify the maternal and child variables related to motor development outcomes at 10, 14 and 17 years, as measured by the NDI. Maternal and child factors that did not impact on NDI were excluded from the final analyses. No interactions were found between breastfeeding and any of the covariates. To examine the relationship between breastfeeding duration and motor development over time a linear mixed model was created, controlling for covariates related to motor outcome including sex, maternal age, alcohol, socioeconomic status, mode of delivery, gestational stress and hypertensive status.

Results

Available data and attrition for the cohort are reported in Table 8. Attrition for the cohort who participated in all three follow up phases was 34.9%, with an additional 18.8% completing two of the three MAND tests, and 13.9% completing one. There were differences found in a number of characteristics between breastfeeding groups (Table 9). Mothers who breastfed for ≥6 months were less likely to have been diagnosed with hypertension or preeclampsia during their pregnancy (p = 0.038), experienced less stressful events (p = <0.001) and were older (p = <0.001) than those who breastfed for <6 months. Similar to previous findings (Scott et al., 2006) there were more mothers who breastfed for <6 months that fell under the Australian government threshold for low income (p = <0.001). Maternal risk factors also differed between the groups, with a higher number of mothers in the breastfed ≥6 month group reporting drinking several times a week (6.6% vs 3.9%), while a higher number in the breastfed <6 months group reported drinking on a daily basis (0.6% vs 0.9%). These numbers were small (Table 9)

and the majority of women in the cohort reported never drinking (52%) or drinking less than once a day (42%) during their pregnancy. There was a greater percentage of non-smokers in the breastfed ≥6 month group (83.6%) compared to the breastfed <6 month group (67.6%). Infants born to mothers who reported breastfeeding for <6 months had a smaller percentage of optimal birth weight (p = 0.004) and a larger percent were firstborns (p = <0.001). Mode of delivery, infant sex and time to spontaneous respiration did not differ between the groups.

Table 8 *Available data from the Raine Study Cohort at 10, 14 and 17 years*

Year	Active	MAND	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2868						2868
10	2047	1622	281	162	348	30	2868
14	1860	1584	357	207	412	32	2868
17	1754	1221	414	184	480	36	2868

Table 9 *Cohort characteristics according to breastfeeding group*

Variables	Breastfed <6months		Breastfed ≥6months		Group Difference (p value)
Categorical Variables	N	%	N	%	
Maternal Gest. Hypertension	908		1151		p = 0.038*
Normal BP	651	71.7	873	75.8	
Hypertension	219	24.10	248	21.5	
Preeclampsia	38	4.2	30	2.6	
Maternal Gest. Smoking	907		1149		p = <0.001*
None	613	67.6	960	83.6	
<10/day	164	18.1	116	10.1	
≥10/day	130	14.3	73	6.4	
Maternal Gest. Drinking	905		1148		p = 0.038*
Never	474	52.4	589	51.3	
Once / week or less	391	43.2	473	41.2	
Several times / week	35	3.9	76	6.6	
Daily	5	0.6	10	0.9	
Family Income	843		1107		p = <0.001*
<$24000 p.a.	574	68.1	836	75.5	
≥$24000 p.a.	269	31.9	271	24.5	
Infant Sex	908		1151		p = 0.965
Male	472	52	597	51.9	
Female	436	48	554	48.1	
Parity	905		1146		p = <0.001*
Firstborn	480	53	509	44.4	
Siblings	425	47	637	55.6	
Mode of Delivery	904		1151		p = 0.505
Spontaneous Vaginal	541	59.8	712	61.9	
Assisted Vaginal	175	19.4	214	18.6	
Elective Caesarean	113	12.5	122	10.6	
Non-elective caesarean	75	8.3	103	8.9	
Continuous variables	M	SD	M	SD	
Maternal Age (years)	26.52	5.7	29.46	5.33	p = <0.001*
Percentage Optimal Birth Weight	96.59	15.78	98.36	12.27	p = 0.004*
Time to Spontaneous Respiration	1.88	8.61	1.71	7.83	p = 0.636
Stressful Events During Pregnancy	2.32	2.1	1.92	1.81	p = <0.001*

Cross sectional univariate analyses investigating the incidence of mild motor delay in the cohort revealed that a higher number of those who were breastfed for <6months fell below the recommended cut off score (Table 10). This trend was significant at 10 (p = 0.009), 14 years (p = 0.01) and 17 years (p = 0.05). In addition mean NDI was also lower at 10 (p = 0.008), 14 (p = <0.001) and 17 (p = 0.035) years in children from mothers who breastfed <6 months (Table 11).

Table 10 *Incidence of mild motor delay according to breastfeeding group*

	Breastfed <6 months				Breastfed ≥6 months				Group
	<85 NDI		≥85 NDI		<85 NDI		≥85 NDI		Difference
10 yrs	149	(27.1%)	401	(72.9%)	164	(20.9%)	621	(79.1%)	p = 0.009
14 yrs	138	(25.7%)	400	(74.3%)	150	(19.6%)	616	(80.4%)	p = 0.010
17 yrs	126	(31.2%)	278	(68.8%)	159	(25.6%)	463	(74.4%)	p = 0.054

Table 11 *Mean Neuromuscular Development Index according to breastfeeding group*

	Breastfed <6 months	Breastfed ≥6 months	Group Difference
10 years	92.96 (13.26)	95.03 (14.41)	p = 0.008
14 years	96.98 (17.18)	100.84 (18.12)	p = <0.001
17 years	95.06 (17.14)	97.42 (17.26)	p = 0.035

The linear mixed models, adjusted for sex, maternal age, alcohol, socioeconomic status, mode of delivery, gestational stress and hypertensive status revealed breastfeeding ≥ 6 months remained significantly protective (p = 0.019) over time (Table 12).

Table 12 *Linear mixed model results*

Variable	NDI*	CI 95%		Group Difference
Breastfed ≥6 months	95.01	92.96	97.06	p = 0.019
Breastfed <6months	93.62	91.55	95.70	
Delivery Mode				
Spontaneous Vaginal Delivery	96.11	94.10	98.12	p = <0.001
Assisted SVD	94.69	92.49	96.89	
Elective Caesarean	92.01	89.56	94.46	
Non-elective Caesarean	94.46	91.89	97.04	
Maternal Alcohol Intake				
Never	96.65	90.59	102.71	p = 0.027
Once per week or less	93.07	91.68	94.45	
Several times per week	95.39	92.80	97.98	
Daily	92.17	90.86	93.49	
Blood Pressure				
Normal BP	96.76	94.98	98.53	p = <0.001
Hypertension	95.18	93.83	97.80	
Preeclampsia	90.38	86.86	93.90	
Family Income				
Above $24,000p.a	95.84	93.87	97.81	p = <0.001
Below $24,000p.a	92.8	90.60	94.99	
Sex				
Male	96.3	94.28	98.32	p = <0.001
Female	93.92	91.89	95.94	

* Adjusted mean NDIs

Those who breastfed for <6 months had a lower average NDI (β -1.38) than the ≥6 months group. Males had a higher mean NDI than females (p = <0.001, β-2.38). Increased maternal age (p = 0.013, β 0.13) related to a higher NDI, while increased incidences of gestational stress were negatively related to motor outcome (p = 0.002, β-0.45). Children born from mothers who were diagnosed with preeclampsia (β-6.38) or hypertension (β-0.95) reported lower NDIs than the normal BP groups (p = <0.001).

Those who were delivered via elective caesarean section (β-4.10), emergency caesarean (β-1.65) and assisted vaginal birth (β-1.42) had a lower NDI compared to those who had spontaneous vaginal deliveries (p = <0.001).

When breastfeeding was categorized into <3 months, 3-5 months, 6-11 months and ≥12 months results revealed a positive linear trend (p = 0.012, β = 0.61), indicating that increased breastfeeding duration corresponded to improved motor development scores. Post hoc analysis showed an increase in mean adjusted NDI in the 6-11 month group (p = 0.039, β-1.55) compared to the <3 month group. Higher mean NDIs were also revealed in both the 6-11 month (p = 0.013, β-1.97) and ≥12 month (p = 0.021, β-1.85) groups compared to the 3-5 month group.

Discussion

Breastfeeding for ≥6 months was related to better motor development outcomes at 10, 14 and 17 years of age. Furthermore, when adjusted for maternal age, smoking, stress, delivery mode, hypertensive disease, percentage of optimal birth weight and socioeconomic status a longer duration of breastfeeding remained significantly related to long term motor development. While this is an important finding, it is pertinent to note that overall the group who were breastfed for less than six months had a mean motor development score that still fell within the normal range. However cross sectional univariate analyses investigating the incidence of mild motor delay revealed a higher number of those who were breastfed <6months fell below the recommended cut off score of the MAND compared to those who were breastfed for more than 6 months (Table 10). This was found at each year, with more cases of mild motor delay at 10 years (27.1% vs 20.9%), 14 years (25.7% vs 19.6%) and 17 years (31.2% vs 25.6%) in those breastfed for <6 months. These outcomes support previous research findings from other countries such

as Ireland (McCroy & Murray, 2013), Britain (Sacker et al., 2006), Denmark (Vestergaard et al., 1999), The United States (Dee et al., 2007), Honduras (Dewey et al., 2001) and Iceland (Thorsdottir et al., 2005) that identified the long term benefits of breastfeeding on the neurological system.

There are biologically plausible mechanisms that could be responsible for these findings. Underlying processes responsible for motor development, such as motor programming and sensory processing continue to progress well into the first decade of life (Gramsbergen, 2003). Specifically the cerebellar cortex, the layer of neural tissue that comprises the cerebellum, develops later in neural-ontogeny and is likely to be a key etiological factor in motor programming (Gramsbergen, 2003; Ivry, 2003; Zwicker, Missiuna, & Boyd, 2009). Several studies have acknowledged the role of long chain polyunsaturated fatty acids (LC-PUFAs) in human milk, such as docosahexaenoic acid (DHA) and arachidonic acid (AA) as an essential element of neural membranes and a potential mechanism for favorable neurological development (Guxens et al., 2011; Innis, 2000; Uauy & De Andraca, 1995). PUFAs are also noted to provide a neuroprotective effect (Lauritzen et al., 2000). While breast milk contains all the polyunsaturated fatty acids (PUFAs), formulae milk contains only precursors, which could be why the level of DHA in infant brain and erythrocytes is reportedly higher in breastfed infants (Makrides, Neumann, Byard, Simmer, & Gibson, 1994). Research into the levels of DHA in cerebellum gray and white matter of infants reported significantly higher levels in breastfed compared to formulae fed infants (Jamieson et al., 1999). This finding in particular could contribute to the better motor outcomes seen in breastfed infants, as the cerebellum, while not responsible for initiating movement is involved in adjustments to muscle tone, control of movement and posture and the learning of physical tasks and motor skills (Gramsbergen, 2003; Ivry, 2003).

Although no interactions were found between breastfeeding and other covariates mothers who breastfed ≥6 month had less incidence of hypertension or preeclampsia in pregnancy, experienced less stress during pregnancy, were older, more financially stable and less likely to be smokers. It has been previously reported that children from pregnancies involving hypertensive disease (Grace, Bulsara, Pennell, & Hands, 2014), maternal stress (Grace, Robinson, Bulsara, & Hands, 2015; Huizink et al., 2003), smoking (Larsson & Montgomery, 2008; Trasti et al., 1999) and lower socioeconomic situations (Bobbio et al., 2010) have poorer motor outcomes. While there were no interactions between these variables in the model they may have exerted an accumulative negative effect on motor development. Those in the breastfed for <6 month group may have therefore been disadvantaged through various other lifestyle factors, in addition to a shorter duration of breastfeeding.

Strengths

The strengths of our study include a large longitudinal cohort and extensive data that enabled a robust statistical analysis of the effects of breastfeeding on children over time. We controlled for factors known to influence breastfeeding duration such as family income and maternal age and known risk factors of compromised motor development. In addition the MAND provides a reliable and accurate measure of motor development within an Australian population (Tan et al., 2001).

Limitations

We acknowledge that there are potential limitations to the study. Retrospective data collection may have led to some inaccuracies in reporting of exact breastfeeding duration, however there has been support for the validity and reliability of maternal recall in breastfeeding data collection (Leeson, 2013). This is particularly evident when the recall is less than 3 years post-breastfeeding and recall in this study was within one year.

While there were extensive socio-demographic, obstetric and medical data available in the cohort controlling for every potential cofounder was not possible. The attrition rate for the cohort who participated in all three data collection phases was 34.9%, with an additional 18.8% completing two phases and 13.9% participating in one test. Those participants who did not complete any motor development testing were from pregnancies with younger mothers, who experienced greater numbers of stressful events and were more likely to fall below the threshold for low income and smoke cigarettes. As the original cohort slightly over represented socially disadvantaged women (Li et al., 2008), this drop out pattern may have increased the generalizability of the study. The amount of women breastfeeding for 6 months or longer was also lower in the drop out group, however numbers were still sufficient for a robust analysis between groups.

Conclusion

Our results revealed that early feeding practices have a long term influence on motor development. In particular we showed that breastfeeding for 6 months or longer enhances optimal neuromotor outcome. We found support for breastfeeding initiatives that focus on increasing the proportion of women breastfeeding for 6 months or longer.

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CHAPTER SIX

Early Life Events and Motor Development in Childhood and Adolescence: A Longitudinal Study

This chapter has been published and the full PDF is in the Appendices

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REGULAR ARTICLE

Early life events and motor development in childhood and adolescence: a longitudinal study

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Keywords
Antenatal, Motor development, Risk factors, Sex differences

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ABSTRACT

Aim: Few studies have reported on early life risk factors for motor development outcomes past childhood. Antenatal, perinatal and neonatal factors affecting motor development from late childhood to adolescence were explored. As sex differences in motor development have been previously reported, males and females were examined separately.

Methods: Participants (n = 2868) were from the Western Australian Pregnancy Cohort Study. Obstetric and neonatal data were examined to determine factors related to motor development at 10 (n = 1622), 14 (n = 1584) and 17 (n = 1221) years. The Neuromuscular Development Index (NDI) of the McCarron Assessment of Motor Development determined offspring motor proficiency. Linear mixed models were developed to allow for changes in motor development over time.

Results: Maternal pre-edampsia, Caesarean section and low income were negatively related to male and female motor outcomes. Lower percentage of optimal birthweight was related to a lower male NDI. Younger maternal age, smoking during early pregnancy and stress during later pregnancy were related to lower female NDIs.

Condusion: Events experienced during pregnancy were related to motor development into late adolescence. Males and females were influenced differently by antenatal and perinatal risk factors; this may be due to sex-specific developmental pathways.

INTRODUCTION

Short- and long-term physical and mental health consequences of poor motor development have been well documented. Past research has reported that children with low motor competence (LMC) are often more introverted, have lower physical and social self-perceptions and higher rates of anxiety than their more coordinated peers (1). In some cases, LMC has been linked to increased depressive symptomology, (2) peer victimisation (3) and antisocial behaviour (4). For those with more severe issues, the psycho-social problems associated with LMC may continue into adulthood (5).

With poor health outcomes such as these, it is imperative that contributing factors be identified as early as possible. A growing body of evidence suggests that events occurring during gestation and birth may have a lasting effect on foetal neurological systems and therefore on postnatal motor development (6). Interruptions to the developing central nervous system during neurogenesis, cell migration, proliferation, differentiation and myelination *in utero* may be potential causes for long-term neurological deficits (6). Foetal and birth-related factors such as sex (7–9), preterm birth (10), low birthweight, (11) intrauterine growth restriction (6), small for gestational age (6,12), as well as maternal factors including smoking (13), alcohol (14), illicit drug use (15), hypertensive disease (16) and maternal stress (17) are recognised risk factors for suboptimal neurophysiological development. Recent findings regarding perinatal risk factors for poor motor development at 10 years in an Australian birth cohort indicated differences in the risk factors impacting males and females (7). The long-term effects of adverse events during gestation and birth seem to have a more lasting effect on health and developmental

Abbreviations
BP, Blood pressure; LMC, Low motor coordination; MAND, McCarron assessment of neuromuscular development; NDI, Neuromuscular development index; SVD, Spontaneous vaginal delivery.

Key notes
- Events during the antenatal period impact motor development during childhood and into adolescence.
- For females, maternal hypertensive status, stress, smoking, family income and delivery mode were related to motor outcomes.
- For males, maternal hypertensive status, percentage of optimal birthweight, family income and delivery mode were related to motor outcomes.

Abstract

Aim; Compromised motor development affects a range of health outcomes, however few studies have reported on early life risk factors for outcomes past childhood. Antenatal, perinatal and neonatal factors affecting motor development from late childhood to adolescence were explored. As sex differences in motor development have been previously reported males and females were examined separately.

Methods; Participants (N = 2868) were from the Western Australian Pregnancy Cohort (Raine) Study. Obstetric and neonatal data were examined to determine which factors were related to motor development outcomes at 10 (n = 1622), 14 (n = 1584) and 17 (n = 1221) years. The Neuromuscular Development Index of the McCarron Assessment of Motor Development determined offspring motor proficiency. Linear Mixed Models were developed to allow for changes in motor development over time.

Results; Maternal preeclampsia, mode of delivery and income affected both male and female outcomes. Lower percentage of optimal birth weight was related to a lower male NDI. Younger maternal age, smoking during early pregnancy and stress during later pregnancy were related to lower female NDIs.

Conclusion; There were some differences in the variables that affected male and female outcomes. Events experienced during pregnancy were related to motor development into late adolescence.

Keywords; Motor Development, Antenatal, Sex Differences, Risk Factors

Key Notes:

- Events during the antenatal period impact motor development during childhood and into adolescence
- There are differences in the risk factors that affected males and females

Introduction

Short and long term physical and mental health consequences of poor motor development have been well documented. Past research has reported that children with low motor competence (LMC) are often more introverted; have lower physical and social self-perceptions and higher rates of anxiety than their more coordinated peers (Skinner & Piek, 2001). In some cases LMC has been linked to increased depressive symptomology, (Piek, Rigoli, et al., 2007) peer victimization (Bejerot & Humble, 2013) and anti-social behaviour (Gillberg & Gillberg, 1983). For those with more severe issues the psycho-social problems associated with LMC may continue into adulthood (Rasmussen & Gillberg, 2000).

With poor health outcomes such as these it is imperative that contributing factors be identified as early as possible. A growing body of evidence suggests that events occurring during gestation and birth may have a lasting effect on fetal neurological systems and therefore on post-natal motor development (Pitcher et al., 2006). Interruptions to the developing central nervous system during neurogenesis, cell migration, proliferation, differentiation and myelination in-utero may be potential causes for long term neurological deficits (Pitcher et al., 2006). Fetal and birth related factors such as sex (Cho, Holditch-Davis, & Miles, 2010; Hands et al., 2009; Kraemer, 2000), preterm birth (Pitcher et al., 2012), low birth weight, (Schmidhauser et al., 2006) intra-uterine growth restriction (Pitcher et al., 2006) small-for-gestational-age (Pitcher et al., 2006; Savchev et al., 2013), as well as maternal factors including smoking (Ekblad et al., 2015) alcohol (Simmons, Thomas, Levy, & Riley, 2010), illicit drug use (Willforda et al., 2010), hypertensive disease (Grace et al., 2014) and maternal stress (Sandman, Davis, Buss, & Glynn, 2011) are recognised risk factors for suboptimal neurophysiological development. Recent

findings regarding perinatal risk factors for poor motor development at 10 years in an Australian birth cohort indicated differences in the risk factors impacting males and females (Hands et al., 2009). The long term effects of adverse events during gestation and birth seem to have a more lasting effect on health and developmental outcomes in males compared to females (Cho et al., 2010; Hintz, Kendrick, Vohr, Poole, & Higgins, 2006). The higher incidence of mortality and morbidity in newborn males has been well documented (Cho et al., 2010; Hintz et al., 2006). The effects of these early in-utero insults on motor development have not, however, been widely reported past infancy and early childhood. The purpose of this study is to identify the long term consequences of antenatal, perinatal and neonatal factors on motor development during late childhood and adolescence. Of particular interest will be examining whether these risk factors differ between males and females.

Methods

Participants.

Participants were part of the Western Australian Pregnancy Cohort (Raine) Study. Women were recruited into the study from May 1989 to November 1991 from King Edward Memorial Hospital (KEMH), Perth, Western Australia. A total of 2868 live births were recorded. Enrolment criteria included a gestation between 16-18 weeks (M = 18), an expectation to deliver at KEMH, an intention to reside within the Perth area to facilitate future follow up, and a sufficient level of English speaking to ensure the parameters of the research were understood. Detailed enrolment criteria and cohort details have been previously published (Newnham et al., 1993). Original questionnaire data pertaining to socioeconomic status, maternal psychosocial characteristics and maternal health were obtained at enrolment. A second

questionnaire was administered at 34 weeks gestation, and obstetric data were collected during the antenatal, postnatal and neonatal periods. Motor development data were collected during the 10 (n=1622), 14 (n=1584) and 17 (n=1221) year follow up assessments (Table 13). At 10 years 779 female and 843 males participated in the physical assessment at 14 years 769 females and 815 males completed testing and at 17 years 607 females and 614 males were assessed. A total of 989 (34.9%) children completed motor development testing at all three stages, with 533 (18.8%) completing two out of the three phases and 395 (13.9%) completed testing at one stage.

Ethics clearances were obtained from the Human Research Ethics Committee at the King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth Western Australia. Informed consent was obtained at the time of enrolment and each subsequent data collection period.

Table 13 *Available data from each follow up of the Raine Study*

Year	Active	MAND	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2868						2868
10	2047	1622	281	162	348	30	2868
14	1860	1584	357	207	412	32	2868
17	1754	1221	414	184	480	36	2868

Measures.

Outcome measure.

Motor development was assessed using the McCarron Assessment of Neuromuscular Development (MAND) (McCarron, 1997), a 10 item assessment in which individuals were scored on five fine motor and five gross motor tasks including a) hand strength b) finger-nose-finger placement c) jumping d) heel-toe walk e) standing on one foot f) beads in a box g) beads on a rod h) finger tapping

i) nut and bolt j) rod slide. Raw scores were converted to scaled scores (M=10, SD=3) using age appropriate tables of norms and the total of the scaled scores was used to calculate the Neuromuscular Development Index (NDI) (M=100, SD=15). Scores falling below one standard deviation of the mean are considered to indicate impaired motor ability (McCarron, 1997).

Infant Risk Factors.

Infant risk factors explored in the analyses were APGAR scores at 1 minute, parity, gestational age, percentage of optimal birth weight (a calculated measure of the appropriateness of fetal growth relying on non-clinical contributors to fetal size, including gestational duration, sex, maternal height and age and parity, rather than relying on specified percentile position) (Blair, Yingxin, de Klerk, & Lawrence, 2005), sex, time to spontaneous respiration and whether the child was a twin or triplet. Using ultrasound imaging and audible signals an umbilical artery and arcuate artery within the placenta were located and Doppler flow velocity waveforms were obtained in half of the women enrolled in the study, who were randomly selected (Newnham et al., 1993). Doppler flow was considered abnormal if one of the arteries had reduced blood flow detected. A categorical variable was created to reflect if the offspring were from pregnancies that had any abnormal Doppler waveform (*n*=205, 7%), no abnormal Doppler waveform (*n*=1223, 43%) or had no Doppler study completed (*n*=1428, 50%).

Maternal Risk Factors.

Maternal data were collected at enrolment and updated at 34 weeks gestation. Wording of the updated questionnaire ensured there were no duplications of data. Potential risk factors that were explored included maternal age and hypertensive status. Hypertension was defined as a systolic blood pressure above ≥ 140mmHg

and/or an increase in diastolic blood pressure ≥90mmHg. Preeclampsia was diagnosed if mothers had hypertension with the addition of proteinuria (300mg/24hrs). The number of stressful events experienced during pregnancy were recorded on a ten item questionnaire based on Tennant and Andrews Life Stress Inventory (Tennant & Andrews, 1977). The first questionnaire, completed at enrolment asked if any of the events had happened since becoming pregnant, while the second questionnaire at 34 weeks asked if any had happened in the last four months. The total number of stressful events were recorded as a continuous variable. Low family income was determined according to the Australian government minimum threshold for low income of $24,000/p.a. and a dichotomised variable was created. Breast feeding was recorded as a dichotomised variable reflecting those who breastfed for six months or more or less than six months. Maternal smoking, alcohol and drug consumption were recorded at 18 and 34 weeks gestation. Mothers were classed as either drinking never, once a week or less, several times a week or daily. Cigarettes were recorded as none, less than 10 a day or 10 or more a day. Mothers were asked if they took any recreational drugs during pregnancy and this was recorded as a binary variable, as individual numbers of each recreational drug were very low. Mode of birth was recorded as spontaneous vaginal delivery, assisted spontaneous vaginal delivery (use of forceps, vacuum etc), elective caesarean section (decision made prior to spontaneous rupture of membranes) and non-elective caesarean section (decision made after SRM). Maternal and pregnancy related factors such as whether the mother experienced antepartum haemorrhage, threatened abortion or diabetes were also included in the analyses.

Statistical Analyses.

Cross sectional analyses using chi-square and t-tests were used to identify the variables that impacted motor development at 10, 14 and 17 years. Linear mixed models with Bonferroni post-hocs were used to calculate the impact of the identified risk factors on motor development over the three time points. All variables in the models were analysed for interactions. Separate analyses were performed for males and females to explore how the risk factors differed between them.

Results

Available data for each year of assessment are reported in Table 13. Cohort characteristics (Table 14) were similar between sexes. Participants who did not record any motor development data tended to be from pregnancies where the mother was younger, experienced higher numbers of stressful events, were more likely to smoke cigarettes and fall below the threshold for low income. In addition there were higher numbers of antepartum haemorrhages and a longer average time to spontaneous respiration in the drop out group. The amount of women breastfeeding for 6 months or more was also lower in this group.

Table 14 *Characteristics of males and females*

Continuous Variables	Total			Females			Males			p value
	N	M	SD	N	M	SD	N	M	SD	
Maternal age (yrs)	2868	27.58	5.92	1413	27.50	5.95	1455	27.65	5.89	0.49
Percentage of expected birth weight	2843	97.40	14.12	1400	97.44	15.28	1443	97.35	12.88	0.87
Gestational age (wks)	2853	38.65	2.37	1409	38.62	2.45	1444	38.68	2.28	0.53
Time to spontaneous respiration (min)	2845	2.87	22.03	1402	3.53	29.56	1443	2.23	10.34	0.12
Number stressful events 18 weeks	2867	1.21	1.25	1413	1.23	1.27	1454	1.19	1.22	0.38
Number stressful events 34 weeks	2553	1.05	1.18	1248	1.04	1.18	1305	1.06	1.19	0.68
Categorical Variables	N	n	%		n	%		n	%	
Parity	2868									0.65
Singelton birth		2742	95.60		1342	46.80		1399	48.80	
Twin or triplet		127	4.40		71	2.50		56	2.00	
Threatened abortion	2803									0.60
Yes		193	6.70		91	3.20		102	3.60	
No		2803	91.00		1286	45.90		1324	47.20	
Antepartum haemorrhage	2803									0.45
Yes		235	8.20		121	4.30		114	4.10	
No		2568	89.50		1256	44.80		1312	46.80	
Breastfed	2057			988			1069			1.00
<6 months		908	44.10		436	44.10		472	44.20	
≥6 months		1149	55.90		552	55.90		597	55.80	
Family Income	2679			1298			1381			0.53
< $24000 p.a		842	31.40		400	30.80		442	32.00	
≥$24000 p.a		1837	68.60		898	69.20		939	68.00	
Alcohol consumption at 18 weeks	2859									0.25
Never		1559	54.40		787	27.50		772	27.00	
Once a week or less		1132	39.50		531	18.60		601	21.00	
Several time a week		147	5.10		77	2.70		70	2.40	
Daily		21	0.70		11	0.40		10	0.30	
Alcohol consumption at 34 weeks	2570									0.06
Never		1596	55.60		797	31.00		799	31.10	
Once a week or less		837	29.20		385	15.00		452	17.60	
Several time a week		124	4.30		60	2.30		64	2.50	
Daily		13	0.50		10	0.40		3	0.10	
Smoking at 18 weeks	2862									0.16
None		2087	72.80		1007	35.20		1080	37.70	
Less than 10 cigarettes a day		445	15.50		225	7.90		220	7.70	
More than 10 cigarettes a day		330	11.50		177	6.20		153	5.30	
Smoking at 34 weeks	2549									0.14
None		1905	66.40		906	35.50		999	39.20	
Less than 10 cigarettes a day		325	11.30		165	6.50		160	6.30	
More than 10 cigarettes a day		319	11.10		169	6.60		150	5.90	
Blood Pressure Status	2868									0.36
Normal blood pressure		2132	74.30		1066	37.20		1066	37.20	
Hypertension		627	21.90		293	10.20		334	11.60	
Preeclampsia		109	3.80		54	1.90		55	1.90	
Diabetes	2868									0.66
No		2715	94.70		1338	46.70		1377	48.00	
Yes		109	3.80		56	2.00		53	1.80	
Maybe		44	1.50		19	0.70		25	0.90	
Doppler waveform	2857									0.19
Normal		1223	42.60		585	20.50		638	22.30	
Abnormal		206	7.20		112	3.90		94	3.30	
No Doppler performed		1428	49.80		712	24.90		716	25.10	

Categorical Variables	N	n	%	n	%	n	%	
Mode of Delivery	2855			1408		1447		0.79
Spontaneous vaginal delivery		1725	60.40	864	50.10	861	59.50	
Assisted vaginal delivery		525	18.40	254	18.00	271	18.70	
Elective Caesarean section		346	12.10	166	11.80	180	12.40	
Non-elective Caesarean section		259	9.10	124	8.80	135	9.30	

During each year there were more males that fell below the cut off score on the MAND used to indicate mild motor delay (Table 15), and this reached significance at 10 (p = <0.001) and 17 (p = <0.001) years. Mean NDIs (Table 16) were also lower in males at 10 (p = <0.001), however this trend reversed at 17 years (p = <0.001).

Table 15 *Incidence of mild motor delay in males and females*

	Males				Females				Group Difference
Binary NDI	≥85		<85		≥85		<85		
	N	%	N	%	N	%	N	%	
10years	603	71.5	240	28.5	627	80.5	152	19.5	p = <0.001
14years	632	77.5	183	22.5	601	78.2	168	21.8	p = 0.81
17years	496	80.8	118	19.2	385	63.4	222	36.6	p = <0.001

NDI = Neuromuscular Development Index

Table 16 *Mean Neuromuscular Development Index for males and females*

	Male Neuromuscular Development Index		Female Neuromuscular Development Index		Group Difference
	M	SD	M	SD	
10 years	92.7	14.5	95.5	13.3	p = <0.001
14 years	99.5	18.5	98.3	16.7	p = 0.168
17 years	101.2	18.0	91.2	14.5	p = <0.001

In the female linear mixed model hypertensive status, family income, delivery mode, maternal smoking at 18 weeks and maternal stress at 34 weeks were related to motor development outcome. The model for males revealed hypertensive status, percentage of optimal birth weight, family income and delivery mode were related to the outcome measure.

Mode of delivery was related to motor development outcomes in males, with an interaction found (Table 17) between type of delivery and family income ($p = 0.022$). Overall delivery via caesarean section was related to a lower NDI score, however income affected this relationship. Males born via caesarean section (either elective or non-elective) whose mothers fell below the income threshold had lower NDI scores than those born via caesarean whose mothers were above the threshold. Bonferroni post hocs revealed group differences between spontaneous vaginal delivery (SVD) and elective ($p = 0.043$) and non-elective caesarean ($p = 0.011$) and between assisted SVD and non-elective caesarean ($p = 0.023$). Males born via SVD regardless of whether assisted or not had higher motor development outcomes than if they were born either by elective or non-elective caesarean.

Table 17 *Interaction between mode of delivery and income in male linear mixed model*

	>$24000 p.a. Mean NDI	<$24000 p.a. Mean NDI
Spontaneous Vaginal Delivery	97.56	94.29
Assisted SVD	95.50	96.82
Elective Caesarean	92.78	93.85
Non-elective Caesarean	96.01	88.44

NDI = Neuromuscular Development Index

Among the males higher NDI was related to a higher percentage of optimal birth weight (p = 0.003) (β = 0.08). Maternal hypertensive status were negatively related to motor outcomes in males (p = 0.001) with preeclampsia in particular related to lowered NDI scores. Bonferroni post hocs revealed group differences in male motor development outcomes between the preeclampsia and normal BP (p = <0.001) and preeclampsia and hypertension groups (p = 0.001).

Similar to the results of the male model, the female model showed higher motor development outcomes with spontaneous vaginal deliveries, assisted or not than either elective or non-elective caesarean sections (p = 0.009). In the female model however no interactions were found. Group differences existed between spontaneous vaginal delivery and elective (p = 0.014) and non-elective caesarean section (p = 0.025). There was also a difference between assisted SVD and elective (p = 0.015) and non-elective (p = 0.023) caesarean.

Maternal hypertensive status were negatively related to motor outcomes in females (p = 0.001). Bonferroni post hocs revealed group differences between preeclampsia and hypertension (p = 0.001) and preeclampsia and normal BP groups (p = <0.001).

For the females maternal smoking during early pregnancy was negatively related to motor development outcome (p = 0.009) with a group difference between non-smokers and those who smoked more than 10 cigarettes per day (p = 0.004). The presence of stressful events during late pregnancy was related to lowered female motor development outcomes (p = <0.001) (β = -1.12). An interaction was found in the female model between income and maternal age (p = 0.044). If the mothers were above the threshold for low income the decrease in average NDI scores were minimal as maternal age increased past 35 years, only dropping by one point on the

MAND from 85 to 84. In mothers below the threshold this decrease was markedly sharper, with MAND outcomes decreasing well below the recommended cut off for impaired motor development.

Discussion

Several early events were identified as potential risk factors for both male and female motor development outcomes. These included maternal hypertensive status, income and mode of delivery. In addition to this male motor development outcomes were related to percentage of optimal birth weight, whilst female outcomes related to maternal smoking at 18 weeks and the experience of stressful events at 34 weeks.

The influence of caesarean section on motor development outcome has previously been reported in the Raine cohort (Hands et al., 2009) however the effect was only identified in the males at 10 years and the differences between elective and non-elective caesarean were not explored. The impact of caesarean birth on both sexes in this study may be due to several factors; a difference in methodology, as the previous study focused on mild motor delay and used a binary outcome variable based on a cut-off score of <85 in the MAND (McCarron, 1997), the inclusion in the current study of data from the 14 and 17 year surveys, and the separation of caesarean into elective and non-elective. There are few studies that report on motor development outcomes in children born from caesarean section birth. As previously identified by Hands and colleagues there is some evidence of lower intellectual outcomes and more recent research has reported higher levels of adiposity in children born via caesarean from infancy to adolescence (Salehi-Abargouei, Shiranian, Ehsani, Surkan, & Asmaillzadeh, 2014). The incidence of asthma and allergies in children born via caesarean has been scrutinised by several international studies with

varying results (Almquist & Oberg, 2014). The explanation for the link between caesarean section and motor development outcomes is still unclear, however several recent studies have provided support for the theory that interruptions to normal colonisation of gut microbiota in infants may impact the central nervous system (Clarke, O'Mahony, Dinan, & Cryan, 2014). Mode of delivery can influence the composition of micro-organisms which colonise the newborn gut, with bifidobacteria (probiotics) more common in vaginal deliveries (Musilova, Rada, Vlkova, Bunesova, & Nevoral, 2015). It is theorised that gut microbiome can influence the synaptogenesis, stress response, neural growth and neurotransmission of the developing central nervous system (Clarke et al., 2014), although the end result of this relationship on motor development outcomes has not been widely researched. The impact of delivery mode however can also be related to other obstetric complications and this should be taken into account when examining delivery mode as a possible risk factor for any area of development.

Previous research has found that factors such as weight and gestational age may have more of an impact on male infant morbidity and mortality rates (Elsmen, Pupp, & Hellstrom-Westas, 2004; Mansson, Fellman, & Stjernqvist, 2015) and cognitive and motor outcomes during early childhood (Cho et al., 2010; Hintz et al., 2006) than females. This sex disparity may be due to physiological differences in fetal development that have been estimated to disadvantage males by 4 to 6 weeks, meaning that even premature female infants are still at an advantage compared to their male counterparts (Kraemer, 2000). Findings from the current study provide support for this sex difference, with percentage of optimal birth weight (a measure of fetal growth potential using both birth weight and gestational age) affecting male motor outcomes more than females.

Previous research into the effect of maternal hypertension and preeclampsia on motor development using data from the Raine cohort have found a relationship between maternal hypertensive status and motor outcomes at 10 years (Hands et al., 2009) and at 10, 14 and 17 years (Grace et al., 2014). The long term effect on motor development was theorised to be caused by a potential reduction in placental function due to abnormal placental morphology and restricted uteroplacental blood flow (Egbor et al., 2006; Matsuo et al., 2009), most often found in early-onset preeclampsia. Other recent findings, however indicate no difference in motor outcomes between infants of women with typical umbilical artery waveforms and those with absent end-diastolic flow (Kirsten, van Zyl, van Zijl, Maritz, & Odendaal, 2000). The effect of hypertensive disease on motor outcomes may indicate a permanent dysfunction or interruption during gestation of the developing neurological system. The role of restricted placental blood flow, as measured by Doppler flow velocities needs to be investigated further as a potential mechanism.

In the female model maternal smoking during early pregnancy, stressful events during late pregnancy and younger maternal age were all related to a decrease in motor development outcomes. Maternal smoking during pregnancy has been previously reported to affect motor development measures in middle (Trasti et al., 1999) and late childhood (Larsson & Montgomery, 2008), and processing speed, interhemispheric communication and visual-motor coordination in adolescents (Willforda et al., 2010). Furthermore recent findings indicate children exposed to prenatal smoking have reduced foetal head and body growth and have shown signs of altered brain structure and function (Ekblad et al., 2015). Previous studies reported males born to mothers who smoked were more susceptible to adverse motor development outcomes (Larsson & Montgomery, 2008). Furthermore preterm male

infants, when compared to preterm females reportedly needed more circulatory and respiratory support (Elsmen et al., 2004). These findings suggest male infants may have more vulnerable respiratory and neurological systems, whereas findings from the current study indicate female motor outcomes were more affected by maternal smoking. Measures of smoking used in the previous studies (Larsson & Montgomery, 2008) were similar, non-smokers, <10/day and >10/day, however the collection of smoking data at two time points in the current study allowed for changes in smoking status and comparison between early and late gestational intake to be analysed. Lung development occurs throughout the embryonic, fetal and neonatal period. It may be that critical windows of development occur at different times during male and female fetal development and the inclusion of two time frames of maternal smoking allowed this difference to be identified.

Gestational stress impacts motor development in infancy and early childhood (Ellman et al., 2008; Sandman et al., 2011) however sex differences in the outcomes have not often been reported. In the current study female motor development outcomes were affected by late gestational stress. The development of the cerebellar cortex, principally responsible for postural control and motor coordination occurs late in gestation (Gramsbergen, 2003). Disturbances in the formation of neural pathways, which occur during this time, may contribute to the lowered outcomes. Hands and colleagues (Hands et al., 2009) found males with mild motor disability at 10 years were more affected by birth and post-natal events (including a stressful first year), while females were more influenced by risk factors occurring during gestation. It was postulated that timing of developmental windows during gestation and post-natal life differed between males and females.

In the female model of motor development an interaction was revealed between maternal income and maternal age. As maternal age increased NDI decreased. This is in contrast to several previous studies that have found lowered levels of health, development, mortality, education and workplace outcomes in children born to 'young' mothers, those who were under 25 years of age (Bradbury, 2011; Myrskyla & Fenelon, 2011). These reports however were not conclusive and other underlying reasons, such as socioeconomic disadvantage were suggested as contributing factors. The current findings provide support for this, with income having a marked impact on whether maternal age affected motor development outcome. The effect of income on motor development outcome has not been extensively reported previously, however some international studies have indicated a difference in motor development between children from lower socioeconomic situations compared to their economically advantaged peers (Bobbio et al., 2010; de Barros, Fragoso, de Oliveira, Filho, & de Castro, 2003). These studies reported both gross (Bobbio et al., 2010) and fine (de Barros et al., 2003) motor outcomes were negatively affected by socioeconomic factors, however no studies have thus far reported the effect of socioeconomic status on motor development past early childhood. Furthermore studies that have reported income as a risk factor for lowered motor development outcomes have been undertaken in less affluent countries than Australia, and therefore the results may not be comparable to an Australian population. Further analyses using additional Raine Study socioeconomic data throughout childhood may help to evaluate the potential effect of changing economic circumstance on longitudinal motor development outcomes.

Strengths.

A large population based sample and in depth obstetric records, questionnaire and physical data allowed for a stringent and robust analysis of the effect of antenatal factors on motor development. The longitudinal nature of the study allowed the impact of early life risk factors on motor development outcomes to be measured throughout childhood and into adolescence, which has not been previously addressed adequately. The MAND (McCarron, 1997) is a reliable and accurate measure of motor development among Australian children (Tan et al., 2001).

Limitations.

While extensive obstetric and maternal health data were available a measure of parental motor development was not conducted. Analyses of the influence of parental motor development was therefore not possible. Retention of participants for all three phases of the study was 34.9% of the original cohort, however a further 18.8% completed two of the testing phases and 13.9% completed one testing phase. Younger mothers who experienced higher numbers of stressful events, were more likely to smoke cigarettes and fell below the threshold for low income were more likely to drop out of the study. However, as the original cohort slightly overrepresented socially disadvantaged women (Li et al., 2008) this attrition pattern may have increased the generalisability of the study.

Conclusion

A growing body of evidence is revealing the importance of early life factors on the development and functioning of the neurological and neuromuscular systems, however few studies can comprehensively report on the effects of these potential risk factors into adolescence. Results of this study indicate events experienced in the antenatal, perinatal and neonatal periods can impact long term motor development

outcomes. Maternal hypertensive status, socioeconomic status, and mode of delivery were related to motor development during late childhood and adolescence. The variance between males and females in other risk factors, such as maternal stress, smoking and percentage of optimal birth weight suggests that the underlying neurological systems of males and females may develop differently.

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CHAPTER SEVEN

Discussion and Conclusion

According to available literature the prevalence of low motor coordination, usually diagnosed in childhood, can range from as low as 1.7% (Lingam, Hunt, Golding, Jongmans, & Emond, 2009) up to 19% (Tsiotra et al., 2006) with the majority of studies reporting rates between 5-15% (Kadesjo & Gillberg, 1999; Santos & Vieira, 2013). Differences in assessment criteria, terminology, age and culture of the population studied probably affect these reported rates of LMC. In the Raine Study cohort prevalence of LMC was relatively stable, occurring in 13.7% of the cohort at 10 years, 12.2% at 14 years and 11.9% at 17 years of age. In this study a less stringent criteria for evaluating low motor coordination was used than studies that used the Diagnostics and Statistics Manual of Mental Disorders (DSM-V) diagnostic criteria for Developmental Coordination Disorder. In order to fulfil the DSM-V diagnosis for DCD four criteria have to be met including a) lowered ability to perform motor skills as would be expected for individual's age and skill learning opportunity b) persistent interference with activities of daily living from the motor skill deficit described in criterion a, c) symptoms are observed from the early period of development d) deficits in motor skills are not explained by intellectual disability, neurological condition or visual impairment. The scores from the MAND and other information available enabled us to identify criteria a and d, however the impact of LMC on activities of daily living and identifying the age at which motor difficulty started could not be fully explored due to the limitation of the study design. Therefore a diagnosis of DCD was not determined and the term LMC was used.

Original data analyses included a wide range of factors that were not included in the final analyses for each manuscript. For example data pertaining to parental handedness and preferential kicking foot, APGAR scores at 1 and 5 minutes, parity,

maternal diabetes, maternal illness, time to spontaneous respiration, highest level of maternal education, multiple birth (twin or triplet), antepartum hemorrhage and threatened abortion revealed no relationship to NDI scores at 10, 14 and 17 years of age in the Raine Study cohort. Although these factors were not found to impact motor development in this cohort, some have been reported previously as contributing to less optimal neurological outcomes (Gillberg, 1985). Several methodological differences exist which may account for these discrepancies. For example, whereas linear mixed models were used to examine the influence of each factor on the NDI scores of participants, Gillberg scored a cluster of hereditary factors such as left handedness, language delay and gross motor problems in first degree relatives using a scoring system of 0-6. Perinatal factors, including prematurity, high maternal age and infection during pregnancy were scored similarly with a range of 0-29. These end scores were then entered into a stepwise regression. An examination of the individual factors that influenced motor development outcomes was not undertaken. The results from our studies therefore provide much greater detail regarding the specific factors of importance to motor development.

Key Findings

In this thesis a series of studies revealed several unique findings which provide a significant contribution to identifying and understanding the impact of early life risk factors on motor development outcomes.

In the first study, investigating maternal hypertensive diseases, the negative impact of gestational hypertensive disease, in particular preeclampsia, on long term motor outcomes was discovered. This has not previously been investigated. Early onset preeclampsia (≤34 weeks gestation) was of particular interest as this was

indicative of a more severe form of the disease (Leeson, 2013; Lindheimer et al., 2008) which could result in abnormal placental morphology (Egbor et al., 2006) and restricted blood flow to the developing foetus (Ghidini et al., 1997).

The findings from the second paper, investigating the impact of maternal gestational stress on motor development in late childhood and adolescence revealed higher numbers of stressful events in pregnancy were related to lower motor development, and that stress during later pregnancy had a greater influence on motor outcomes compared to earlier pregnancy stress.

Taken together the findings from these two studies indicate late pregnancy to be of particular importance to the developing neuromotor system. This may be due to late gestation being an important time of growth for the cerebellar cortex, the layer of neural tissue that comprises the cerebellum, an area of the brain responsible for postural control, coordination and motor skill function (Gramsbergen, 2003). Development of the cerebellar cortex includes a rapid increase in granule cells and the creation of neural pathways, which will eventually assist in adjustments to muscle tone, control of movement and posture and the learning of physical tasks and motor skills (Gramsbergen, 2003).

The study examining motor outcomes in those who were breastfed for <6 months compared to those who were breastfed for more than 6 months revealed the <6 month group recorded a lower average NDI. There were also higher numbers of children at all three data collection phases who fell below the cutoff for motor disability in the group who were breastfed for <6 months. Furthermore there was a positive linear trend reported, with increased duration of breastfeeding up until one year corresponding to improved motor development scores. Whilst previous studies have suggested improved developmental outcomes found in breastfed children may

be a function of a favourable socioeconomic status and home environment we found breastfeeding to be linked to improved motor outcomes independent of these factors. Underlying neurological processes that support motor functioning continue to develop past the perinatal and neonatal periods and well into the first decade of life (Gramsbergen, 2003). Although a prime in-utero environment is critical to the development of an optimal neurological system (Pitcher et al., 2006) there is an amount of plasticity that can allow for postnatal events to influence this development. The long chain polyunsaturated fatty acids (LC-PUFAs) in human breastmilk can provide a neuroprotective effect (Lauritzen et al., 2000), as well as being essential elements of neural membranes and a potential mechanism for favourable neural development (Guxens et al., 2011; Innis, 2000; Uauy & De Andraca, 1995). One of the LC-PUFAs, docosahexaenoic acid (DA) has been found in higher levels in the grey and white matter of the cerebellum of infants who were breastfed, indicating an optimal neurological situation compared to formulae fed infants who recorded lower levels of cerebellar DA.

In examining how the impact of early life events on motor development differed between males and females we found that maternal hypertension and preeclampsia, low income and delivery via caesarean were related to poorer motor development in both males and females. The differences occurred when examining the impact of percentage of optimal birth weight, which was related to male outcomes, and maternal smoking during early pregnancy and stress during later pregnancy, which were related to female outcomes. Previous research suggests that males may be born developmentally behind their female counterparts by approximately 4-6 weeks (Kraemer, 2000) which is potentially why male infant

morbidity and mortality rates are more influenced by birth weight and gestational age (Elsmen et al., 2004; Mansson et al., 2015)

If the reported discrepancy is accurate, then windows of development occurring during the antenatal, perinatal periods and infancy would take place at different times for males and females. Hands and colleagues (2009) found males with motor difficulties at 10 years of age were more influenced by events around birth and during the first year, whilst females were more influenced by events during the antenatal period. For the females in this study maternal smoking at 18 weeks pregnant was related to decreased motor outcomes whilst it was not found to affect the male outcomes at all. This finding was surprising, considering previous research indicates males have a more susceptible respiratory system (Elsmen et al., 2004; Larsson & Montgomery, 2008). Maternal stress in later pregnancy was also more influential on female motor outcomes. Variation in neurological developmental windows may explain this discrepancy, however further research is needed to clarify how early life events affect male and female motor development differently.

The differences reported between male and female motor competence showed males had higher average NDIs than females at all years, however both sexes fell within the average range of the NDI. When investigating incidences of mild motor delay however there was an interesting trend. At 10 years of age there was a higher percentage of boys (28.5%) than girls (19.5%) who fell below 1SD of the NDI, classifying them as having mild motor delay. During the 14 year follow up this discrepancy disappeared and both sexes displayed similar rates of motor dysfunction. During the 17 year follow up girls were recorded as having a higher rate of motor delay (36.6%) when compared to boys (19.2%).

The findings from this thesis have added to the growing body of evidence that suggest early life factors are also an important consideration for both short and long term motor development outcomes. Furthermore the differences between how these factors affected males and females has allowed insight into the variance in development between the sexes.

Future Research

These findings indicate several important factors that need to be considered in future research. Firstly, the timing of risk factors during the antenatal, perinatal and neonatal periods should be included in future research pertaining to early life events associated with motor development outcomes. Late maternal gestational stress, preeclampsia and breastfeeding were all found to impact motor development outcomes, indicating that the later part of pregnancy and the neonatal period may be times of particular importance for neuromuscular development. Previous researchers have reported the third trimester may be when the developing foetal brain is more vulnerable to hypoxic and ischemic indults (Pitcher et al., 2006) and hypothesised that any damage to the developing cerebellum during this time may cause problems with aspects of motor development such as coordination, timing, precision and accuracy of movement (Gramsbergen, 2003; Ivry, 2003). The human neural system during development undergoes a "..protracted, neatly orchestrated chain of ontogenic events." (de Graaf-Peter & Hadders-Algra, 2005, p.263). Ensuring timing of events is taken into account is crucial to understanding how these incidences impact neurodevelopmental outcomes. As previously mentioned there are some children who present with motor development dysfunction in their early years who may later 'out grow' their movement problems, while others seem to have more persistent

issues (M. Cantell et al., 1994; Hadders-Algra, 2002). Due to the fact that the human neurological system continues developing throughout childhood and adolescence longitudinal studies are needed to determine changes in the presence of developmental disorders. The findings from this study provides a solid foundation for future research focusing on longitudinal motor outcomes of participants in the Raine Study cohort.

Differences in neuromuscular development between sexes must also be taken into consideration. Although several antenatal factors were found to impact motor development outcomes in both sexes, including hypertensive status, caesarean section mode of delivery and gestational stress, some sex differences were revealed. These included maternal smoking and stress, which surprisingly only impacted female motor development outcomes, while percentage of optimal birth weight was more influential on motor outcomes in males. In light of the impact of timing on development we hypothesise these differences to be due to sex specific developmental differences that have estimated male infants to be developmentally six to eight weeks behind females (Kraemer, 2000).

Past research has indicated that motor and cognitive development are closely related, and therefore maternal intelligence may play a role in motor competency. Highest level of maternal education, a potential surrogate measure of cognition, was examined in initial analyses however no significant relationship to NDI was found. A more specific measure of maternal IQ may be useful in further explorations of early life events related to motor outcomes.

Strengths

The Raine Study provided a large population based sample with extensive obstetric records, questionnaire and physical data allowing for a stringent and robust analysis of antenatal factors relating to motor development. The in depth series of studies conducted revealed several early life factors to be of importance to motor development outcomes in late childhood and adolescence. The impact of several of these factors have not been previously addressed adequately. For example maternal hypertensive disease, stress and breastfeeding duration, while previously reported to be linked to developmental outcomes in childhood, have not been clearly associated with motor development into adolescence. The outcome measure used, the MAND (McCarron, 1997) is a reliable and accurate measure of motor development among Australian children (Tan et al., 2001). The use of the Neuromuscular Developmental Index as a continuous independent variable allowed us to explore the impact of early life events on motor development in a way that has not previously been addressed. Furthermore the three time points of assessment allowed for late changes in motor development to be controlled for in the statistical models.

The use of linear mixed models (LMM) was also an advantage in the research papers, as LMMs explicitly model individual change across time, and provide more flexibility in dealing with repeated measure. LMMs are designed to maximise the use of all observed data despite study participants not having the same number of repeated observations. This type of modelling also provides generalisations for non-normal data and can be extended to higher level models providing robust parameter estimates.

Limitations

While the data selected from the Raine cohort during the prenatal, perinatal, infancy, childhood and adolescent years are extensive and inclusive of biological, social, and psychological factors the study was not originally intended to be a longitudinal study of motor development and therefore assessment of motor development was not undertaken on the children prior to the 10 year data collection phase, nor on the Raine Study parents. Consequently an examination of familial patterning was not possible.

With all longitudinal studies there was a limitation concerning those lost to follow up. Comparing those who were available for motor development testing at 10, 14 and 17 years to those who dropped out of the study, there were some differences in recorded variables. The original cohort was slightly over represented with socially disadvantaged women, however the pattern of drop out over time favoured women who were younger, less educated and more likely to fall below the Australian Government threshold for low income, possibly increasing the generalisability of the findings. Mothers who experienced higher levels of stress, and less time breastfeeding tended to record higher rates of drop out, however there were still sufficient numbers to allow for a robust analyses between stress groups and those who breastfed for less than or more than 6 months. Overall the cohort is generally representative of the general Western Australian population (Li et al., 2008) however conclusions drawn from this study may not be reflective of other populations

Recommendations

Results from this study have provided clear evidence of the relationship between the early life environment and long term neuromotor functioning. By

extending the findings from Hands et al. (2009) it was determined that a number of early life factors had a long term effect on neuromotor outcomes. Furthermore several of these were revealed to be dependent on sex.

Future research on motor development should focus on detection of early risk factors, in particular those that are modifiable. Health promotion policies that may help to minimise the identified risk factors can be implemented within existing health care services. Maternal stress, for example, can be monitored through antenatal clinics with the administration of screening questionnaires in the same relatively cost effective and time efficient process that is currently used to screen for maternal depression. The promotion of breastfeeding practices is a health strategy currently employed throughout Australian hospitals and birthing centres, however the effectiveness of these strategies on long term motor development outcomes is under researched. Future research into breastfeeding needs to provide focus on motor development in addition to behavioural, cognitive and mental outcomes.

International collaboration using data from several longitudinal studies may help to solidify the identification of early life factors that influence motor development outcomes across different cultures.

References

Almquist, C., & Oberg, A. S. (2014). The association between caesarean section and asthma or allergic disease continues to challenge. *Acta Paediatrica, 103*(4), 349-351. doi: 10.1111/apa.12562

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5 ed.). Arlington, VA: American Psychiatric Association.

Anderson, J. W., Johnstone, B. M., & Remley, D. T. (1999). Breast-feeding and cognitive development: a meta-analysis. *The American Journal of Clinical Nutrition, 70*(4), 525-535.

Australian Bureau of Statistics. (2006). Index of Relative Socio-economic Advantage and Disadvantage. from http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/2033.0.55.001Main+Features12006?OpenDocument

Barker, D. J. P. (1997). Maternal nutrition, fetal nutrition and disease in later life. *Nutrition, 13*, 807. doi: 10.1016/S0899-9007(97)00193-7

Barker, D. J. P. (2007). The origins of the develpmental origins theory. *Journal of Internal Medicine, 261*, 412-417. doi: 10.1111/j.1365-2796-2007.0189.x

Batstra, L., Hadders-Algra, M., & Neeleman, J. (2003). Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in children: prospective evidence from a Dutch birth cohort. *Early Human Development, 75*(1), 21-33. doi: 10.1016/j.earlhumdev.2003.09.001

Bejerot, S., & Humble, M. B. (2013). Childhood clumsiness and peer victimization: A case control study of psychiatric patients. *BioMed Central Psychology, 13*(1), 68-79. doi: 10.1186/1471-244X-13-68

Blair, E., Yingxin, L., de Klerk, N. H., & Lawrence, D. M. (2005). Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: An analysis of a total population perinatal database. *BMC Pediatrics, 5*(13). doi: doi:10.1186/1471-2431-5-13

Bobbio, T. G., Gabbard, C., Goncalves, V. G., Filho, A. A. B., & Morcillo, A. M. (2010). Interlimb coordination differentiates Brazilian children from two socioeconomic settings. *Pediatics International, 52*, 353-357. doi: 10.1111/j.1442-200X.2009.02960.x

Bouffard, M., Watkinson, E. J., Thompson, L. P., Causgrove Dunn, J. L., & Romanow, S. K. E. (1996). A test of the activity deficit hypothesis with children with movement difficulties. *Adapted Physical Activity Quarterly, 113*, 61-73.

Boyd, A., Golding, J., Macleod, J., Lawlor, D. A., Fraser, A., Henderson, J., . . . Davey Smith, G. (2013). Cohort profile: The children of the 90s' - the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of Epidemiology, 42*(1), 111-127. doi: 10.1093/ije/dys064

Bradbury, B. (2011). Young motherhood and child outcomes, SPRC Report 1/11 , prepared for the Australian Government Department of Families, Housing, Community Services and Indigenous Affairs.

Brodal, P. (2010). *The central nervous system structure and function (4th Ed)*. New York: Oxford University Press.

Buitelaar, J. K., Huizink, A. C., Mulder, E. J., de Medina, P. G. R., & Visser, G. H. A. (2003). Prenatal stress and cognitive development and temperament in infants. *Neurobiology of Ageing, 24*(1), S53-S60. doi: 10.1016/S0197-4580(03)00050-2

Cairney, J., Hay, J., Mandigo, J., Wade, T., Faught, B. E., & Flouris, A. (2007). Developmental coordination disorder and reported enjoyment of physical education in children. *European Physical Education Review, 13*(1), 81-98.

Cairney, J., Hay, J. A., Faught, B. E., & Hawes, R. (2005). Developmental coordination disorder and overweight and obesity in children aged 9-14y. *International Journal of Obesity, 29*, 369-372.

Cairney, J., Veldhuizen, S., & Szatmari, P. (2010). Motor coordination and emotional-behavioural problems in children. *Current Opinion in Psychiatry, 23*, 324-329.

Cantell, M. (1998). Develomental Coordination Disorder in adolescence: Perceptual, motor, academic and social outcomes of early motor delay. *Research reports on sports and health, 112*(LIKES - Research Centre for Sport and Health Science, Jyvaskyla, Finland).

Cantell, M., Crawford, S. G., & Doyle-Baker, P. K. (2008). Physical fitness and health indices in children, adolescents and adults with high and low motor competence. *Human Movement Science, 27*, 344-362. doi: 10.1016/j.humov.2008.02.007

Cantell, M., Smyth, M. M., & Ahonen, T. P. (1994). Clumsiness in adolescence: Educational, motor, and social outcomes of motor delay detected at 5 years *Adapted Physical Activity Quarterly, 11*, 115-129.

Cantell, M., Smyth, M. M., & Ahonen, T. P. (2003). Two distinct pathways for developmental coordination disorder: Persistence and resolution *Human Movement Science, 22*, 413-431. doi: 10.1016/j.humov.2003.09.002

Causgrove Dunn, J., & Dunn, J. G. H. (2006). Psychosocial determinents of physical education behavior in children with movement difficulties. *Adapted Physical Activity Quarterly, 23*, 293-309.

Causgrove Dunn, J., & Watkinson, E. J. (1994). A study of the relationship between physical awkwardness and children's perceptions of physical competence *Adapted Physical Activity Quarterly, 11*, 275-283.

Chang, S., & Yu, N. (2010). Characterization of motor control in handwriting difficulties in children with or without developmental coordination disorder. *Developmental Medicine & Child Neurology, 52*(3), 244-250. doi: 10.1111/j.4169-8749.2009.03478.x

Chivers, P., Hands, B., Parker, H., Bulsara, M., Beilin, L. J., Kendall, G. E., & Oddy, W. (2010). Body mass index, adiposity rebound and early feeding in a longitudinal cohort (Raine Study). *International Journal of Obesity, 34*, 1169-1176. doi: 10.1038/ijo.2010.61

Cho, J., Holditch-Davis, D., & Miles, M. S. (2010). Effects of gender on the health and development of medically at-risk infants. *Journal of Obstetric, Gynecologic and Neonatal Nursing, 39*(5), 536-549. doi: 10.1111/j.1552-6909.2010.01171.x

Clarke, G., O'Mahony, S. M., Dinan, T. G., & Cryan, J. F. (2014). Priming for health: gut microbiota aquired in early life regulates physiology, brain and behaviour. *Acta Paediatrica, 103*(8), 812-819. doi: 10.1111/apa.12674

Coakley, J. J. (2007). *Sports in Society: Issues and controversies (9th Ed.)*. Boston: Mcgraw-Hill.

Connor, P. D., Sampson, P. D., Bookstein, F. L., Barr, H. M., & Streissguth, A. P. (2000). Direct and indirect effects of prenatal alcohol damage on executive function. *Developmental Neuropsychology, 18*(3), 331-354.

Cousins, M., & Smyth, M. M. (2003). Develomental coordination impairments in adults. *Human Movement Science, 22*(4), 433-459. doi: 10.1016/j.humov.2003.09.003

Cummins, A., Piek, J., & Dyck, M. J. (2005). Motor coordination, empathy and social behaviour in school-aged children. *Developmental Medicine & Child Neurology, 47*(7), 437.

Cummins, A., Piek, J., & Dyck, M. J. (2007). Motor coordination, empathy and social behaviour in school-aged children. *Developmental Medicine & Child Neurology, 47*(7), 437.

Da Costa, D., Rippen, N., Drista, M., & Ring, A. (2003). Self-reported leisure time physical activity during pregnancy and relationship to psychological well-being. *Journal of Psychosomatic Obstetrics and Gynecology, 24*, 111-119.

Davis, E. P., & Sandman, C. A. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development, 81*(1), 131-148. doi: 0009-3920/2010/8101-0009

de Barros, K. M. F. T., Fragoso, A. G. C., de Oliveira, A. L. B., Filho, J. E. C., & de Castro, R. M. (2003). Do environmental influences alter motor ability aquisition? A comparison among children from day-care centers and private schools. *Arquivos de Neuro-psiquiatria, 61*(2-A), 170-175. doi: 10.1590/S0004-282X2003000200002

de Graaf-Peter, V. B., & Hadders-Algra, M. (2005). Ontogeny of the human centrel nervous system: What is happening when? *Early Human Development, 82*, 257-266.

de Jong, C., Kikkert, H. K., Seggers, J., Boehm, G., Decsi, T., & Hadders-Algra, M. (2015). Neonatal fatty acids status and neurodevelopmental outcome at 9 years. *Early Human Development, 91*(10), 587-591. doi: 10.1016/j.earlhumdev.2015.07.007

de Weerth, C., van Hees, Y., & Buitelaar, J. K. (2003). Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Human Development, 74*, 139-151. doi: 10.1016/S0378-3782(03)00088-4

Dee, D. L., Li, R., Lee, L., & Grummer-Strawn, L. M. (2007). Associations between breastfeeding practices and young children's language and motor skills. *Pediatrics, 119*(S1), 92-98. doi: 10.1542/peds.2006-2089N

Dewey, K. G., Cohen, R. J., Brown, K. H., & Rivera, L. L. (2001). Effects of exclusive breastfeeding for four versus six months on maternal nutritional status and infant motor development: Results of two randomized trials in Honduras. *Journal of Nutrition, 131*, 262-267.

DiPietro, J. A. (2004). The role of prenatal maternal stress in child development. *Current Directions in Psychological Science, 13*(2), 71-74.

DiPietro, J. A., Novak, M. F. S. X., Costigan, K. A., Atella, L. D., & Reusing, S. P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development, 77*(3), 573-587. doi: 0009-3920/2006/7703-006

Edwards, J., Berube, M., Erlandson, K., Haug, S., Johnstone, H., Meagher, M., . . . Zwicker, J. (2011). Developmental coordination disorder in school-aged children born very preterm and/or at very low birth weight: A systematic review. *Journal of Developmental and Behavioral Pediatrics, 32*(9), 678-687. doi: 10.1097/DBP.0b013e31822a396a

Egbor, M., Ansari, T., Morris, N., Green, C. J., & Sibbons, P. D. (2006). Morphometric placental villous and vascular abnormalities in early-and late-onset pre-eclampsia with and without fetal growth restriction. *British Journal of Obstetrics and Gynaecology, 113*(5), 580-589. doi: 10.111/j.1471-0528.2006.00882.x

Ekblad, M., Korkeila, J., & Lehtonen, L. (2015). Smoking during pregnancy affects foetal brain development. *Acta Paediatrica, 104*(1), 12-18. doi: 10.1111/apa.12791

Ellman, L. M., Dunkel-Schetter, C., Hobel, C. J., Chicz-DeMet, A., Glynn, L. M., & Sandman, C. A. (2008). Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Developmental Psychobiology, 50*, 232-241. doi: 10.1002/dev.20293

Elsmen, E., Pupp, I. H., & Hellstrom-Westas, L. (2004). Preterm male infants need more initial respiratory and circulatory support than female infants. *Acta Paediatrica, 93*, 529-533. doi: 10.1080/08035250410024998

Erikson, C., Allert, C., Brogren Carlberg, E., & Katz-Salamon, M. (2003). Stability of longitudinal motor development in very low birthweight infants from 5 months to 5.5 years. *Acta Paediatrica, 92*(2), 197-203. doi: 10.1111/j.1651-2227.2003.tb00526.x

Erwin, H. E., & Castelli, D. M. (2004). What do motor competent and noncompetent children look like? (Pedagogy) *Research Consortium Interdisciplinary Poster Session*: AAHPERD National Convention and Exposition 2005.

Fitzpatrick, D. A., & Watkinson, E. J. (2003). The lived experience of physical awkwardness: Adults' retrospective views. *Adapted Physical Activity Quarterly, 20*, 279-297.

Foulder-Hughes, L. A., & Cooke, R. W. I. (2003). Motor, cognitive, and behavioural disorders in childen born very preterm. *Developmental Medicine & Child Neurology, 45*(2), 97-103.

Fox, K. R., Boutcher, S. H., Faulkner, G. E., & Biddle, S. J. H. (2000). The case for exercise in the promotion of mental health and psychological well-being. In S. J. H. Biddle, K. R. Fox & S. H. Boutcher (Eds.), *Physical Activity and Psychological Well-Being*. London: Routledge.

Fugelseth, D., Ramstad, H. B., Kvehaugen, A. S., Nestaas, E., Stoylen, A., & Staff, A. C. (2011). Myocardial function in offpsring 5-8 years after pregnancy complicated by preeclampsia. *Early Human Development, 87*, 531-535. doi: 10.1016/j.earlhumdev.2011.04.006

Geuze, R., & Borger, H. (1993). Children who are clumsy: Five years later. *Adapted Physical Activity Quarterly, 10*, 10-21.

Ghidini, A., Salafia, C. M., Pezzullo, J. C., & Minior, V. K. (1997). Extent of placental vascular lesions and likelihood of diagnosis of preeclampsia. *American Journal of Obstetrics and Gynecology, 176*(6), 668.

Gillberg, C. (1985). Children with minor neurological developmental disorders. Neurological and neuro-developmental problems at age 10. *Developmental Medicine & Child Neurology, 27*, 3-16.

Gillberg, C., & Gillberg, C. (1983). Three-year follow up at age 10 of children with minor neurodevelopmental disorders. I: Behavioural problems. *Developmental Medicine & Child Neurology, 25*(4), 438-449.
Gillberg, C., & Gillberg, C. (1989). Children with preschool minor neurodevelopmental disorders. IV: Behaviour and school achievement at age 13. *Developmental Medicine & Child Neurology, 31*(1), 3-13.
Gillberg, C., & Rasmussen, P. (1982). Perceptual, motor and attention deficits in six-year-old children. Screening procedure in pre-school. *Acta Paediatrica Scandinavica, 71*, 121-129.
Glover, V. (2014). Maternal depression, anxiety and stress during pregnancy and child outcomes; what needs to be done. *Best Practice & Research Clinical Obstetrics and Gynaecology, 28*, 25-35. doi: 10.1016/jbpobgyn.2013.08.017
Glover, V., & O'Connor, T. (2006). Maternal anxiety: its effect on the fetus and the child. *British Journal of Midwifery, 14*(11), 663-667.
Golding, J., Gregory, S., Ils-Caven, Y., Lingam, R., Davis, J., Emmett, P., . . . Hibbeln, J. R. (2014). Parental, prenatal, and neonatal associations with ball skills at age 8 using an exposome approach. *Journal of Child Neurology, 29*(10), 1390-1398. doi: 10.1177/0883073814530501
Goyen, T., & Lui, K. (2002). Longitudinal motor development of "apparently normal" high-risk infants at 18 months, 3 and 5 years. *Early Human Development, 70*, 103-115.
Grace, T., Bulsara, M., Pennell, C., & Hands, B. (2014). Maternal hypertensive diseases negatively affect offspring motor development. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 4*(3), 209. doi: 10.1016/j.preghy.2014.04.003
Grace, T., Robinson, M., Bulsara, M., & Hands, B. (2015). Maternal stress during pregnancy affects long term motor development. *Child Development*.
Gramsbergen, A. (2003). Clumsiness and disturbed cerebellar development: Insights from animal experiments. *Neural Plasticity, 10*(1-2), 129-140. doi: 10.115/NP.2003.129
Green, D., Lingam, R., Mattocks, C., Riddoch, C., Ness, A., & Emond, A. (2011). The risk of reduced physical activity in children with probable Developmental Coordination Disorder: A prospective longitudinal study. *Research in Develomental Disabilities, 32*, 1332-1342. doi: 10.1016/j.ridd.2011.01.040
Gualitieri, T., & Hicks, R. E. (1985). An immunoreactive theory of selective male affliction. *Behavioral & Brain Sciences, 8*(3), 427-441. doi: 10.1017/s0140525x00001035
Guxens, M., Mendez, M. A., Molto-Puigmarti, C., Julvez, J., CGarcia-Esteban, R., Forns, J., . . . Sunyer, J. (2011). Breastfeeding, long-chain polyunsaturated fatty acids in colustrum, and infant mental development. *Pediatrics, 128*(4), e880-e889. doi: 10.1542/peds.2010-1633
Hadders-Algra, M. (2002). Two distinct forms of neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. *Developmental Medicine & Child Neurology, 44*, 561-571.
Hadders-Algra, M. (2003). Developmental coordination disorder: Is clumsy motor behavior caused by a lesion of the brain at early age? *Neural Plasticity, 10*(1), 39-50. doi: 10.1155/NP.2003.39

Haga, M. (2007). The relationship between physical fitness and motor competence in children. *Child: Care, Health & Development, 34*(3), 329-334. doi: 10.1111/j.1365-2214.2008.00814x

Hands, B., Kendall, G., Larkin, D., & Parker, H. (2009). Perinatal risk factors for mild motor disability. *International Journal of Disability, Development and Education, 56*(4), 317-331. doi: 10.1080/10349120903306533

Hands, B., & Larkin, D. (2006). Physical fitness of children with motor learning difficulties. *European Journal of Special Needs Education, 21*(4), 447-456.

Hands, B., Larkin, D., Kendall, G., Parker, H., & Sloan, N. (2007, July). *Behavioural and emotional problems in children with varying levels of motor learning difficulties.* Paper presented at the International Symposium of Adapted Physical Activity, Rio Claro, Brazil.

Hands, B., Larkin, D., Parker, H., Straker, L., & Perry, M. (2008). The relationship among physical activity, motor competence and health related fitness in 14-year-old adolescents. *Scandinavian Journal of Medicine & Science in Sports*, 1-9.

Haywood, K. M., & Getchell, N. (2009). *Life Span Motor Development 5th Ed.* (5th ed.). Champaign, IL: Human Kinetics.

Henderson, S. E., & Sugden, D. A. (1992). *Movement Assessment Battery for Children*. London: Psychological Corporation.

Henrichs, J., Schenk, J. J., Kok, R., Ftitache, B., Schmidt, H. G., Hofman, A., . . . Tiemeier, H. (2011). Parental family stress during pregnancy and cognitive functioning in early childhood: The Generation R Study. *Early Childhood Research Quarterly, 26*(3), 332-343. doi: 10.1016/j.ecresq.2011.01.003

Herba, C. M., Roza, S., Govaert, P., Hofman, A., Jaddoe, V. W. V., Verhulst, F. C., & Tiemeier, H. (2013). Breastfeeding and early brain development: the Generation R study. *Maternal and Child Nutrition, 9*, 332-349. doi: 10.1111/mcn.12015

Hill, E. L. (2010). The importance of motor skill in general development. *Developmental Medicine & Child Neurology, 52*(10), 888. doi: 10.1111/j.1469-8749.2010.03700.x

Hill, E. L., & Barnett, A. (2011). Movement difficulties in children. *Psychologist, 24*(1), 34-37.

Hintz, S. R., Kendrick, D. E., Vohr, B. R., Poole, W. K., & Higgins, R. D. (2006). Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birth-weight infants. *Acta Paediatrica, 95*, 1239-1248. doi: 10.1080/08035250600599727

Hoare, D., & Larkin, D. (1990). Assessment and classification using the MAND. *International Journal of Neuroscience, 51*, 114.

Huizink, A. C., Robles de Mina, P. G., Mulder, E. J. H., Visser, G. H. A., & Buitelaar, J. K. (2003). Stress during pregnancy is associated with developmental outcome in infancy. *Journal of Child Psychology and Psychiatry, 44*(6), 810-818. doi: 10.1111/1469-7610.00166

Iacoboni, M., & Mazziotta, J. C. (2007). Mirror nuron system: Basic fundings and clinical applications. *Annals of Neurology, 62*(3), 213-218. doi: 10.1002/ana.21198

Innis, S. M. (2000). The role of n-6 and n-3 fatty acids in the developing brain. *Developmental Neuroscience, 22*(474-480). doi: 10.1016/j.conb.2010.12.001

Ivry, R. B. (2003). Cerebellar Involvement in Clumsiness and Other Developmental Disorders. *Neural Plasticity, 10*(1-2), 141-153. doi: 10.1155/NP.2003.141

Jamieson, E. C., Farquharson, J., Logan, R. W., Howatson, A. G., Patrick, W. J., Weaver, L. T., & Cockburn, F. (1999). Infant cerebellar grey and white matter fatty acids in relation to age and diet. *Lipids, 34*(10), 1065-1071.

Jongmans, M. J., Mercuri, E., Dubowitz, L. M. S., & Henderson, S. E. (1998). Perceptual-motor difficulties and their concomitants in six-year-old children born prematurely. *Human Movement Science, 17*, 629-653.

Kadesjo, B., & Gillberg, C. (1999). Developmental Coordination Disorder in Swedish 7-year-old children. *Journal of the American Academy of Child & Adolescent Psychiatry, 38*(7), 820-828.

Kaiser, S., & Sachser, N. (2009). Effects of prenatal social stress on offspring development. *Current Directions in Psychological Science, 18*(2), 118-121. doi: 10.1111/j.1467-8721.2009.01620.x

Kalberg, W. O., Provost, B., Tollison, S. J., Tabachnick, B. G., Robinson, L. K., Hoyme, H. E., . . . May, P. A. (2006). Comparison of motor delays in young children with fetal alcohol syndrom to those with prenatal alcohol exposure and with no prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 30*(12), 2037-2045.

Kikkert, H. K., de Jong, C., & Hadders-Algra, M. (2013). Minor neurological dysfunction and cognition in 9-year-olds born at term. *Early Human Development, 89*(5), 263-270. doi: 10.1016/j.earlhumdev.2012.10.001

Kirsten, G. F., van Zyl, J. I., van Zijl, F., Maritz, J. S., & Odendaal, H. J. (2000). Infants of women with severe early pre-eclampsia: The effect of absent end-diastolic umbilical artery Doppler flow velocities on neurodevelopomental outcome. *Acta Paediatrica, 89*(5), 566-570.

Kraemer, S. (2000). The fragile male. *British Medical Journal, 321*, 1609-1612.

Laplante, D. P., Barr, R. G., Brunet, A., Du Fort, G., G,, Meaney, M. L., Saucier, J. F., . . . King, S. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research, 56*(3), 400-410. doi: 10.1203/01.PDR.0000136281.34035.44

Larsson, M., & Montgomery, S. M. (2008). Maternal smoking during pregnancy and physical control and coordination among offspring. *Journal of Epidemiology and Community Health, 65*(12), 1151-1158. doi: 10.1136/jech.2008.085241

Lauritzen, I., Blondeau, N., Heurteaux, C., Widman, C., Romey, G., & Lazunski, M. (2000). Polunsaturated fatty acids are potent neuroprotectors. *The European Molecular Biology Organization Journal, 19*(8), 1784-1793.

Lazinski, M. J., Shea, A. K., & Steiner, M. (2008). Effects of maternal prenatal stress on offspring development: A commentary. *Archives of Womens Mental Health, 11*, 363-375. doi: 10.1007/s00737-008-0035-4

Leeson, P. (2013). Invited Plenary Orals: Long term cardiovascular outcomes for mother and child. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 3*, 57-61. doi: 10.1016/j.preghy.2013.04.012

Li, C., Kendall, G. E., Henderson, S., Downie, J., Landsborough, L., & Oddy, W. H. (2008). Maternal psychosocial well-being in pregnancy and breastfeeding duration. *Acta Paediatrica, 97*(2), 221-225.

Lindheimer, M. D., Taler, S. J., & Cunningham, F. G. (2008). Hypertension in Pregnancy. *Journal of the American Society of Hypertension, 2*(6), 484-494. doi: 10.1016/j.jash.2008.10.1001

Lingam, R., Hunt, L., Golding, J., Jongmans, M., & Emond, A. (2009). Prevalence of developmental coordination disorder using the DSM-IV at 7 years of age: A

UK population-based study. *Pediatrics, 123*(4), e693-e700. doi: 10.1542/peds.2008-1770

Lingam, R., Jongmans, M., Ellis, M., Hunt, L., Golding, J., & Emond, A. (2012). Mental health difficulties in children with developmental coordination disorder. *Pediatrics, 129*(4), e882-e891. doi: DOI: 10.1542/peds.2011-1556

Losse, A., Henderson, S. E., Elliman, D., Hall, D., Knight, E., & Jongmas, M. (1991). Clumsiness in children: do they grow out of it? *Developmental Medicine & Child Neurology, 33*(1), 55-68.

MacDonald, K., Missiuna, C., Cairney, J., & Pollock, N. (2009). *Mood and Anxiety Symptoms in Children with Developmental Coordination Disorder*. Paper presented at the American Academy of Child & Adolescent Psychiatry 56th Annual Meeting, Hawaii.

Makrides, M., Neumann, M. A., Byard, R. W., Simmer, K., & Gibson, R. A. (1994). Fatty acid composition of brain, retina and erythrocytes in breastf and formula-fed infants. *American Journal of Clinical Nutrition, 60*(2), 189-194.

Mandich, A. D., Polatajko, H. J., & Rodger, S. (2003). Rites of passage: understanding participation of children with developmental coordination disorder. *Human Movement Science, 22*, 583-595.

Mansson, J., Fellman, V., & Stjernqvist, K. (2015). Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. *Acta Paediatrica, 104*(5), 514-521. doi: DOI:10.1111/apa.12937

Many, A., Fattal, A., Leitner, Y., Kupferminc, M. J., Harel, S., & Jaffa, A. (2003). Neurodevelopmental and cognitive assessment of children born growth restricted to mothers with and without preeclampsia. *Hypertension in Pregnancy, 22*(1), 25-29. doi: 10.1081/PRG-120016791

Matsuo, K., Malinow, A. M., Harman, C. R., & Baschat, A. A. (2009). Decreased placental oxygenation capacity in preeclampsia: Clinical application of a novel index of placental function performed at the time of delivery. *Journal of Perinatal Medicine, 37*(6), 657-661. doi: 10.1515/JPM.2009.121

McCarron, L. T. (1997). *MAND McCarron Assessment of Neuromuscular Development*. Dallas, TX: Common Market Press.

McCroy, C., & Murray, A. (2013). The effect of breastfeeding on neuro-development in infancy. *Maternal and Child Health Journal, 17*, 1680-1688. doi: 10.1007/s10995-012-1182-9

Mennes, M., Van den Bergh, B. R. H., Lagae, L., & Stiers, P. (2009). Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. *Clinical Neurophysiology, 120* 1116-1122. doi: 10.1016/j.clinph.2009.04.003

Missiuna, C., Cairney, J., Pollock, N., Campbell, W., Russel, D. J., Macdonald, K., . . . Cousins, M. (2014). Psychological distress in children with developmetnal coordination disorder and attention deficit hyperactivity disorder. *Research in Developmental Disabilities, 35*(5), 1198-1207. doi: 10.1016/j.ridd.2014.01.007

Missiuna, C., Cairney, J., Pollock, N., Russell, D., Macdonald, K., Cousins, M., . . . Schmidt, L. (2011). A staged approach for identifying children with develomental coordination disorder from the population. *Research in Develomental Disabilities, 32*(1), 549-559. doi: 10.1016/j.ridd.2010.12.025

Monk, C. (2001). Stress and mood disorders during pregnancy: Implications for child development. *Psychiatric Quarterly, 72* (4), 347-357. doi: 0033-2720/01/1200-0347

Murmu, M. S., Salomon, S., Biala, Y., Weinstock, M., Braun, K., & Bock, J. (2006). Changes in spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy. *European Journal of Neuroscience, 24*, 1477-1487. doi: 10.1111/j.1460-9568.2006.05024.x

Musilova, S., Rada, V., Vlkova, E., Bunesova, V., & Nevoral, J. (2015). Colonisation of the gut by bifidobacteria is much more common in vaginal deliveries than caesarean sections. *Acta Paediatrica, 104*, e184-e186. doi: 10.1111/apa.12931

Myrskyla, M., & Fenelon, A. (2011). Maternal age and offspring adult health: evidence from the health and retirement study. *Max Planck Institute for Demographic Research*.

Nathanielsz, P. W. (1999). *Life in the Womb: The Origin of Health and Disease*. NY: Promethean Press.

National, Health, and, Medical, Research, & Council. (2012). *Infant feeding guidelines*. Canberra: National Health and Medical Research Council.

Newnham, J. P., Doherty, D. A., Kendall, G. E., Zubrick, S. R., Landau, L. L., & Stanley, F. J. (2004). Effects of repeated prenatal ultrasound examintations on childhood outcome up to 8 years of age: follow up of a randomised controlled trial. *Lancet, 364*, 2038-2044.

Newnham, J. P., Evans, S. F., Michael, C. A., Stanley, F. J., & Landau, L. I. (1993). Effects of frequent ultrasound during pregnancy: A randomised controlled trial. *Lancet, 342*(8876), 887-891. doi: 10.1016/0140-6736(93)91944-H

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. *British Journal of Psychiatry, 180*, 502-508. doi: 10.1192/bjp.180.6.502

O'Connor, T. G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry, 44*(7), 1025-1036. doi: 10.1111/1469-7610.00187

Odd, D. E., Lingam, R., Emond, A., & Whitelaw, A. (2013). Movement outcomes of infants born moderate to late preterm. *Acta Paediatrica, 102*, 876-882. doi: 10.1111/apa.12320

Oddy, W. H., Kendall, G. E., Blair, E., De Klerk, N. H., Stanley, F. J., Landau, L. I., . . . Zubrick, S. R. (2003). Breast feeding and cognitive development in childhood: a prospective birth cohort study. *Paediatric and Perinatal Epidemiology, 17*, 81-90.

Oddy, W. H., Kendall, G. E., Li, J., Jacoby, P., Robinson, M., De Klerk, N. H., . . . Stanley, F. J. (2010). The long-term effects of breastfeeding on child and adolescent mental health: a pregnancy cohort study followed for 14 years. *The Journal of Pediatrics, 156*(4), 568-574. doi: 10.1016/j.jpeds.2009.10.020

Oddy, W. H., Li, J., Whitehouse, A. J. O., Zubrick, S. R., & Malacova, E. (2011). Breastfeeding duration and academic achievement at 10 years. *Pediatrics, 127*(1), 137-145. doi: 10.1542/peds.2009-3489

Oddy, W. H., Mori, T. A., Huang, R., Marsh, J. A., Pennell, C. E., Chivers, P. T., . . . Beilin, L. J. (2014). Early infant feeding and adiposity risk: from infancy to adulthood. *Nutrition and Metabolism, 64*, 262-270. doi: 10.1159/000365031

Oddy, W. H., Robinson, M., Kendall, G., Li, J., Zubrick, S. R., & Stanley, F. (2011). Breastfeeding and early child development: a prospective cohort study. *Acta Paediatrica, 100*(7), 992-999. doi: 10.1111/j.1651-2227.2011.02199.x

Oddy, W. H., & Rosales, F. (2010). A systematic review of the importance of milk TGF-beta on immunological outcomes in the infant and young child. *Pediatric Allergy and Immunology, 21*, 47-59.

Ogland, B., Nilsen, S. T., Forman, M. R., & Vatten, L. J. (2011). Pubertal development of daughters of women with pre-eclampsia. *Archives of Disease in Childhood, 96*, 740-743. doi: 10.1136/adc.2009.178434

Osika, W., & Montgomery, S. M. (2008). Physical control and coordination in childhood and adult obesity: longitudinal birth cohort study. *British Medical Journal, 337a699*.

Paris, J. J., & Frye, C. A. (2011). Juvenile offspring of rate exposed to restraint stress in late gestation have impaired cognitive performance and dysregulated progestogen formation. *Stress, 14*(1), 23-32. doi: 10.3109/10253890.2010.512375

Payne, V. G., & Isaacs, L. D. (1995). *Human Motor Development A Lifespan Approach*. Mountain View CA: Mayfield Publishing Company.

Pereira, G., Blair, E., & Lawrence, D. (2012). Validation of a model for optimal birth weight: a prospective study using serial ultrasounds. *BMC Pediatrics, 12*. doi: 10.1186/1471-2431-12-73

Peters, L. H. J., Maathuis, C. G. B., & Hadders-Algra, M. (2010). Minor neurological dysfunction and behavioural problems. *Developmental Medicine & Child Neurology; Abstracts of the European Academy of Childhood Disability 22nd Annual Meeting, 52*(5), 30.

Piek, J., Dyck, M. J., & Francis, M. (2007). Working memory, processing speed, and set-shifting in children with developmental coordination disorder and attention-deficit-hyperactivity disorder. *Developmental Medicine and Child Neurology, 49*(9), 678-683.

Piek, J., Rigoli, D., Pearsall-Jones, J. G., Martin, N. C., Hay, D. A., Bennett, K. S., & Levy, F. (2007). Depressive symptomatology in child and adolescent twins with Attention-Deficit Hyperactivity Disorder and/or Developmental Coordination Disorder. *Twin Research and Human Genetics, 10*(4), 587-596.

Pitcher, J. B., Henderson-Smart, D. J., & Robinson, J. S. (2006). Prenatal Programming of Human Motor Function. In E. M. Wintour & J. A. Owens (Eds.), *Early Life Origins of Health and Disease*. New York: Springer Science + Business Media.

Pitcher, J. B., Schneider, L. A., Burns, N. R., Drysdale, J. L., Higgins, R. D., Ridding, M. C., . . . Robinson, J. S. (2012). Reduced corticomotor excitability and motor skills development in children born preterm. *The Journal of Physiology, 590*(22), 5827-5844. doi: 10.1113/jphysiol.2012.239269

Pratt, M. L., & Hill, E. L. (2011). Anxiety profiles in children with and without developmental coordination disorder. *Research in Develomental Disabilities, 32*(4), 1253-1259. doi: doi:10.1016/j.ridd.2011.02.006

Rasmussen, P., & Gillberg, C. (2000). Natural outcome of ADHD with Developmental Coordination Disorder at age 22 years: A controlled, longitudinal, community-based study. *American Academy of of Child and Adolescent Psychiatry, 39*(11), 1425-1431.

Rep, A., Ganzevoort, W., Van Wassenaer, A. G., Bonsel, G. J., Wolf, H., & De Vries, J. I. P. (2008). One-year infant outcome in women with early onset hypertensive disorders of pregnancy. *British Journal of Obstetrics and Gynaecology, 115*, 290-298. doi: 10.1111/j.1471-0528.2007.01544.x

Reynolds, J. E., Thornton, A. L., Elliot, C., Williams, J., Lay, B. S., & Licari, M. K. (2014). A systematic review of mirror neuron system function in developmental coordination disorder: Imitation, motor imagery and neuroimaging. *Research in Develomental Disabilities, 47*, 234-283. doi: 10.1016/j.ridd.2015.09.015

Robinson, M., Mattes, E., Oddy, W. H., De Klerk, N. H., Li, J., Mclean, N. J., . . . Newnham, J. P. (2009). Hypertensive diseases of pregnancy and the development of behavioral problems in childhood and adolescence: The Western Australian Pregnancy Cohort Study. *Journal of Pedatrics, 154*, 218-224. doi: 10.1016/j.peds.2008.07.061

Robinson, M., Mattes, E., Oddy, W. H., Pennell, C., Van Eekelen, A., Mclean, N. J., . . . Newnham, J. P. (2011). Prenatal stress and risk of behavioral morbidity from age 2 to 14 years: The influence of the number, type, and timing of stressful life events. *Development and Psychopathology, 23*, 507-520. doi: 10.1017/s0954579411000241

Robinson, M., Oddy, W. H., Li, J., Kendall, G. E., De Klerk, N. H., Silburn, S. R., . . . Mettes, E. (2008). Pre- and postnatal influences on preschool mental health: A large scale cohort study. *Journal of Child Psychology and Psychiatry, 49*(10), 1118-1128. doi: 10.111/j.1469-7610.2008.01955.x

Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *Journal of Child Psychology and Psychiatry, 46*(3), 246-254. doi: 10.1111/j.1469-7610.2004.00359.x

Rose, B., Larkin, D., & Berger, B. G. (1997). Coordination and gender influences on the perceived competence of children. *Adapted Physical Activity Quarterly, 14*, 210-221.

Ruiz, R. J., & Avant, K. C. (2005). Effects of maternal prenatal stress on infant outcomes. *Advances in Nursing Science, 28*(4), 345-355.

Sacker, A., Quigley, M. A., & Kelly, Y. J. (2006). Breastfeeding and develomental delay: findings from the millenium cohort study. *Pediatrics, 118*, e682-e689.

Salehi-Abargouei, A., Shiranian, A., Ehsani, S., Surkan, P. J., & Asmaillzadeh, A. (2014). Caesarean delivery is associated with childhood general obesity but not abdominal obesity in Iranian elementary school children. *Acta Paediatrica, 103*(9), e383-e387. doi: DOI: 10.1111/apa.12711

Sandman, C. A., Davis, E. P., Buss, C., & Glynn, L. M. (2011). Prenatal programming of human neurological funtion. *International Journal of Peptides*, 1-9. doi: 10.115/2011/837596

Sandman, C. A., Davis, E. P., Buss, C., & Glynn, L. M. (2012). Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology, 95*(1), 8-21. doi: 10.1159/000327017

Santos, V. A. P., & Vieira, J. L. L. (2013). Prevalence of developmental coordination disorder in children aged 7 to 10 years. *Revista Brasiliera de Cineantropometria e Desempenho Humano, 15*(2), 233-242. doi: 10.5007/1980-0037.2013v15n2p233

Savchev, S., Sanz-Cortes, M., Cruz-Martinez, R., Arranz, A., Botet, F., Gratacos, E., & Figueras, F. (2013). Neurodevelopmental outcome of full term small for gestational age infants with normal placental function. *42*(2), 201-206. doi: DOI: 10.1002/uog.12391

Schiamberg, L. B. (1985). *Human Development* (Vol. 2nd Ed.). New York: Macmillan.

Schmidhauser, J., Caflisch, J., Rousson, V., Bucher, H. U., Largo, R. H., & Latal, B. (2006). Impaired motor performance and movement quality in very-low-birthweight children at 6 years of age. *Developmental Medicine & Child Neurology, 48*, 718-722.

Schneider, M. L., & Coe, C. L. (1993). Repeated social stress during pregnancy impairs neuromotor develpoment of the infant primate. *Journal of Developmental and Behavioral Pediatrics, 14*(2), 81-87. doi: 10.1097/00004703-199304000-00002

Schoemaker, M. M., & Kalverboer, A. F. (1994). Social and affective problems of children who are clumsy: How early do they begin? *Adapted Physical Activity Quarterly, 11*, 130-140.

Schoemaker, M. M., Lingam, R., Jongmans, M. J., van Heuvelen, M., & Emond, A. (2013). Is severity of motor coordination difficulties related to co-morbidity in children at risk for developmental coordination disorder? *Research in Developmental Disabilities, 34*, 3084-3091. doi: 10.1016/j.ridd.2013.06.028

Scholtens, S., Wijga, A. H., Brunekreef, B., Kerkhof, M., Hoestra, M. O., Gerritsen, J., . . . Smit, H. A. (2009). Breast feeding, parental allergy and asthma in children followed for 8 years. The PIAMA birth cohort study. *Thorax, 64*(7), 604-609.

Scott, J. A., Binns, C. W., Oddy, W. H., & Graham, K. I. (2006). Predictors of breastfeeding duration: evidence from a cohort study. *Pediatrics, 117*(4), e646.

Seelaender, J., Fidler, V., & Hadders-Algra, M. (2012). Increase in impaired motor development in six-year-old German children between 1990 and 2007. *Acta Paediatrica, 102*(1), e44-e48. doi: 10.1111/apa.12057

Sigmundsson, H., & Hopkins, B. (2005). Do 'clumsy' children have visual recognition problems? *Child: Care, Health & Development, 31*(2), 155-158.

Silva, P. A., & Ross, B. (1980). Gross motor development and delays in development in early childhood: assessment and significance. *Journal of Human Movement Studies, 6*, 211-226.

Simmons, R. W., Thomas, J. D., Levy, S. S., & Riley, E. P. (2010). Motor response programming and movement time in children with heavy prenatal alcohol exposure. *Alcohol, 44*(4), 371-378. doi: 10.1016/j.alcohol.2010.02.013

Singer, J. E., Westphal, M., & Niswander, K. R. (1968). Sex differences in the incidence of neonatal abnormalities and abnormal performance in early childhood. *Child Development, 39*(1), 103-113.

Skinner, R. A., & Piek, J. P. (2001). Psychosocial implications of poor motor coordination in children and adolescence. *Human Movement Science, 20*, 73-94. doi: 10.1016/S0167-9457(01)00029-X

Smits-Engelsman, B. C. M., Neimeijer, A. S., & Van Galen, G. P. (2001). Fine motor deficiencies in children diagnosed as DCD based on poor grapho-motor ability. *Human Movement Science, 20*, 161-182.

Smyth, M. M., & Anderson, H. I. (2000). Coping with clumsiness in the school playground: Social and physical play in children with coordination impairments. *British Journal of Developmental Psychology, 18*, 389-413.

Soorani-Lunsing, R. J., Hadders-Algra, M., Olinga, A. A., Huisjes, H. J., & Touwen, B. C. L. (1993). Minor neurological dysfunction after the onset of puberty: Association with perinatal events. *Early Human Development, 33*(1), 71-80. doi: 10.1016/0378-3782(93)90174-S

Southall, J., Okely, A. D., & Steele, J. R. (2004). Actual and perceived physical competence in overweight and non-overweight children. *Pediatric Exercise Science, 16*, 15-24.

Springer, K. W., Stellman, J. M., & Jordan-Young, R. M. (2011). Beyond a catalogue of differences: A theoretical frame and good practive guidelines for researching sex/gender in human health. *Social Science & Medicine, 74*, 1817-1824. doi: 10.1016/jsocscimed.2011.05.033

Sugden, D. A., & Keogh, J. F. (1990). *Problems in Movement Skill Development*. Columbia, SC: University of Columbia Press.

Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry, 48*, 245-261. doi: 10.1111/j.1469-7610.2006.01714.x

Tan, S. K., Parker, H., & Larkin, D. (2001). Concurrent validity of motor tests used to identify children with motor impairment. *Adapted Physical Activity Quarterly, 18*, 168-182.

Tegethoff, M., Greene, N., Olsen, J., Schaffner, E., & Meinlschmidt, G. (2011). Stress during pregnancy and offpsring pediatric disease: A national cohort study. *Environmental Health Perspectives, 119*(11), 1647-1652. doi: 10.1289/ehp.1003253

Tennant, C., & Andrews, G. (1977). A scale to measure the cause of life events. *Australian and New Zealand Journal of Psychiatry, 11*, 163-167. doi: 10.3109/00048677609159482

Thorsdottir, I., Gunasdottir, J., Kvaran, M. A., & Gretarsson, S. J. (2005). Maternal body mass index, duration of exclusive breastfeeding and children's developmental status at the age of 6 years. *European Journal of Clinical Nutrition, 59*, 426-431. doi: 10.1038/sj.ejcn.1602092

Tranquilli, A. L., Landi, B., S.R., G., & Sibai, B. H. (2012). Preeclampsia: No longer solely a pregnancy disease. *Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 2*, 350-357. doi: 10.1016/j.preghy.2012.05.006

Trasti, N., Vik, T., Jacobsen, G., & Bakketeig, L. S. (1999). Smoking in pregnancy and children's mental health and motor development at age 1 and 5 years. *Early Human Development, 55*, 137-147.

Tsiotra, G. D., Flouris, A. D., Koutedakis, Y., Faught, B. E., Nevill, A. M., Lane, A. M., & Skenteris, N. (2006). A comparison of developmental coordination disorder prevalence rates in Canadian and Greek children. *Journal of Adolescent Health, 39*, 125-127. doi: 10.1016/j.jadohealth.2005.07.011

Tuovinen, S., Raikkonen, K., Pesonen, A., Lahti, M., Heinonen, K., Wahlbeck, K., . . . Eriksson, J. G. (2012). Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring: The Helsinki Birth Cohort Study. *Journal of Psychiatric Research, 46*, 303-310. doi: 10.1016/j.jpsychires.2011.11.015

Uauy, R., & De Andraca, I. (1995). Human milk and breastfeeding for optimal mental development. *The Journal of Nutrition, 125*(8), 2278S-2280S.

Van den Bergh, B. R. H., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Development, 75*(4), 1085-1097. doi: 0009-3920/2004/7504-0008

Van den Bergh, B. R. H., Mulder, E. J. H., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neuroscience and Biobehavioral Reviews, 29*, 237-258. doi: 10.1016/j.neubiorev.2004.10.007

Vestergaard, M., Obel, C., Henriksen, T. B., Sorensen, H. T., Skajaa, E., & Ostergaards, J. (1999). Duration of breastfeeding and developmental milestones during the latter half of infancy. *Acta Paediatrica, 88*, 1327-1332.

Viholainen, H., Aro, T., Purtsi, J., Tolvanen, A., & Cantell, M. (2014). Adolescents' school-related self-concept mediates motor skills and psychological well-being. *British Journal of Educational Psychology, 84*, 268-280. doi: 10.1111/bjep.12023

Watkinson, E. J., Dwyer, S. A., & Neilson, A. B. (2005). Children theorize about reasons for recess engagement: Does expectancy-value theory apply? *Adapted Physical Activity Quarterly, 22*, 179-197.

Whitehouse, A. J. O., Robinson, M., Li, J., & Oddy, W. H. (2010). Duration of breastfeeding and language ability in middle childhood. *Paediatric and Perinatal Epidemiology, 25*, 44-52. doi: 10.1111/j.1365-3016.2010.01161.x

Whitehouse, A. J. O., Robinson, M., Newnham, J. P., & Pennell, C. (2012). Do hypertensive diseases of pregnancy disrupt neurocognitive development in offspring? . *Paediatric and Perinatal Epidemiology, 26*, 101-108. doi: 10.1111/j.1365-3016.2011.01257.x

Whitehouse, A. J. O., Robinson, M., Zubrick, S. R., Ang, Q. W., Stanley, F. J., & Pennell, C. (2010). Maternal life events during pregnancy and offspring language ability in middle childhood: The Western Australian Pregnancy Cohort Study. *Early Human Development, 86*, 487-492. doi: 10.1016/j.earlhumdev.2010.06.009

WHO. (2003). *Global Strategy for Infant and Young Child Feeding*. Geneva, Switzerland: World Health Organization.

Willford, J. A., Richardson, G. A., Leech, S. L., & Day, N. L. (2004). Verbal and visuospatial learning and memory function in children with moderate prenatal alcohol exposure. *Alcoholism, clinical and experimental research, 28*(3), 497-507.

Willforda, J. A., Chandlerb, L. S., Goldschmidt, L., & Daya, N. L. (2010). Effects of prenatal tobacco, alcohol and marijuana exposure on processing speed, visual-motor coordination, and interhemispheric transfer. *Neurotoxicology and Teratology, 32*(6), 580-588. doi: 10.1016/j.ntt.2010.06.004

Wilson, P. H., & McKenzie, B. E. (1998). Information processing deficits associated with developmental coordination disorder: a meta-analysis of research findings. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 39*(6), 829-840.

Zhou, S. J., Baghurst, P., Gibson, R. A., & Makrides, M. (2007). Home environment, not duration of breastfeeding, predicts intelligence quotient at children at four years. *Nutrition, 23*(3), 236-241.

Zwicker, J. G. (2014). Motor impairment in very preterm infants: Implications for clinical practice and research. *Developmental Medicine & Child Neurology, 56*(6), 509-514. doi: 10.1111/dmcn.12454

Zwicker, J. G., Harris, S. R., & Klassen, A. F. (2013). Quality of life domains affected in children with developmental coordination disorder: a systematic

review. *Child: Care, Health and Development, 39*(4), 562-580. doi: 10.1111/j.1365-2214.2012.013790.x

Zwicker, J. G., Missiuna, C., & Boyd, L. A. (2009). Neural correlated of develomental coordination disorder: A review of hypotheses. *Journal of Child Neurology, 24*(10), 1273-1281. doi: 10.1177/0883073809333537

Zwicker, J. G., Yoon, S. W., Mackay, M., Petrie-Thomas, J., Rogers, M., & Synnes, A. R. (2013). Perinatal and neonatal predictors of developmental coordination disorder in very low birth weight children. *Archives of Disease in Childhood, 98*(2), 118-122. doi: 10.1136/archdischild-2012-302268

Appendices

Appendix **A Hypertension Pregnancy Article and Associated Awards and Presentations**

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Original Article

Maternal hypertensive diseases negatively affect offspring motor development

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ABSTRACT

Objective: Hypertension in pregnancy and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. The purpose of this study was to determine if maternal hypertensive diseases during pregnancy are a risk factor for compromised motor development at 10, 14, and 17 years.

Study design: Longitudinal cohort study using data from the Western Australian Pregnancy Cohort Study (Raine).

Main outcome measure: Offspring ($n = 2868$) were classified by their maternal blood pressure profiles during pregnancy: normotension ($n = 2133$), hypertension ($n = 626$) and preeclampsia ($n = 109$). Offspring motor development, at 10, 14, and 17 years was measured by the Neuromuscular Developmental Index (NDI) of the McCarron Assessment of Motor Development (MAND).

Methods: Linear mixed models were used to compare outcomes between pregnancy groups.

Results: Offspring from pregnancies complicated by preeclampsia had poorer motor outcomes at all ages than offspring from either normotensive mothers ($p \leqslant 0.001$) or those with hypertension ($p = 0.002$).

Conclusion: Hypertensive diseases during pregnancy, in particular preeclampsia, have long term and possibly permanent consequences for motor development of offspring.

Introduction

Hypertension in pregnancy, and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence. It is already well established that fetal growth restriction (FGR), premature birth, small for gestational age (SGA) status, maternal stress, smoking and alcohol consumption are risk factors for compromised motor development in early [1–5] and late [6] childhood. Maternal hypertensive diseases such as hypertension and preeclampsia have been linked to SGA, FGR, prematurity [2]

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and poorer cognitive development in early [7] and late childhood [8].

A differential effect of hypertension and preeclampsia has been reported in studies investigating mental health and behavior, with hypertension linked to a higher risk of negative outcomes, and preeclampsia associated with a lower risk in some cases [9,10]. Other findings [11] have indicated a possible reduction in the future risk of breast cancer in female offspring born to mothers with preeclampsia. Together these findings suggest different pathways through which hypertension and preeclampsia may influence mental health development, behavioral outcomes and hormonal activity in the long term.

While preeclampsia may be associated with a positive effect on mental health and behavioral outcomes, research indicates that the impact is more likely to be negative for physical development. Reduced heart size and heart function have been reported in five to eight year old children born to mothers with preeclampsia [12] and delays in both mental and psychomotor development were found in up to 76% of one year old infants born to mothers with severe preeclampsia [13].

One possible mechanism that may explain the association between maternal preeclampsia and offspring physical and motor outcomes may be a decrease in oxygen delivery to the developing fetus via the placenta that is seen in pregnancies complicated by preeclampsia [14]. Pitcher et al. [2] report that during the third trimester, the most common time for preeclampsia to occur, the developing fetal brain may be more vulnerable to hypoxic and ischemic insults. During this time, the cerebellum (an area responsible for some aspects of motor development such as coordination, precision and accuracy of movement) is rapidly developing and suboptimal maternal nutrition or deficits in the delivery of nutrients via the placenta at this time may result in developmental problems, particularly in the motor domain [15,16]. In order to examine the effect of hypertension and preeclampsia on motor development and explore the theory of restricted placental blood flow as a potential mechanism we used data from the Western Australian Pregnancy Cohort (the Raine Study). This large cohort has been followed longitudinally over twenty years and provided the opportunity to examine the longer term impact of hypertension and preeclampsia on motor development and the potential role played by restricted placental blood flow through the use of Doppler flow velocity waveform data.

The effects of various perinatal risk factors on motor development have been previously reported in the Raine cohort by Hands et al. [6] who found that hypertensive diseases were linked to poorer outcomes in females at 10 years. The purpose of this study was to extend these findings by using both cross sectional and linear mixed models to identify the longer term consequences of maternal hypertensive diseases on the motor development of offspring as they matured from 10 to 14 and 17 years.

We predicted that the motor development of offspring at 10, 14 and 17 years would be negatively affected by the hypertensive status of the mother, with preeclampsia in particular contributing to a poorer motor outcome. Furthermore those mothers with preeclampsia were more likely to have experienced restricted placental blood flow, indicated by abnormal Doppler waveforms.

Method

Participants

Participants ($n = 2900$) were part of the Western Australian Pregnancy Cohort (Raine Study) and were recruited through the King Edward Memorial Hospital between 16 and 20 weeks gestation. The Raine Study is a randomized control study, with women being allocated to either an intensive ultrasound group or a regular ultrasound group [17]. Women in the intensive group had ultrasound and Doppler flow studies performed at approximately 18 weeks gestation, then again at 24, 28, 34 and 38 weeks gestation. Women in the control group had one ultrasound around 18 weeks and further scans only if requested by her physician. Full cohort details and enrollment criteria have previously been reported [17]. From the 2900 pregnancies, 2868 children were recruited for long-term follow-up. Ultrasound and Doppler data were available for 1429 children born to mothers in the intensive ultrasound group and 1428 children born to those in the regular ultrasound (control) group.

Original data collection was by questionnaire, undertaken at enrollment with data obtained regarding maternal health, SES and psychosocial characteristics. The second data collection was administered at 34 weeks gestation. Obstetric data were obtained from antenatal, postnatal, and neonatal periods. Follow up data pertaining to motor development reported in this paper were obtained from the participants' offspring at 10, 14, and 17 years.

Measures

Hypertension and preeclampsia

Maternal blood pressure and other physiological data were recorded during antenatal visits in the first phase of the study [17]. Hypertension and preeclampsia diagnoses were confirmed by obstetricians and midwives after reviewing medical records. Essential hypertension was defined by a history of hypertension prior to pregnancy. Gestational hypertension was defined as an increase in systolic blood pressure $\geqslant$140 mmHg and/or an increase in diastolic blood pressure $\geqslant$90 mmHg in women who were normotensive previous to 24 weeks gestation [17]. Women with both essential ($n = 72$) and gestational ($n = 554$) hypertension were included in the hypertension group. Preeclampsia was defined as gestational hypertension with the addition of proteinuria (300 mg/24 h). Women who had preeclampsia and gestational hypertension ($n = 68$) and preeclampsia superimposed on essential hypertension ($n = 41$) were included in the preeclampsia group. Three pregnancy groups were formed, indicating whether the offspring was from a mother who had normotension (N; $n = 2132$), hypertension (HT; $n = 627$), or preeclampsia (PE; $n = 109$) based on the diagnostic criteria.

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The highest level of diagnoses was used to determine groups, ensuring no data duplication.

Placental blood flow

Doppler flow velocity waveform study data were collected using a spectrum analyzer and a D10 bi-directional continuous wave Doppler system [18]. Using ultrasound imaging and audible signals an umbilical artery and arcuate artery within the placenta were located and waveforms were obtained. A categorical variable was created to reflect if the offspring were from pregnancies that had any abnormal Doppler waveform ($n = 205$), no abnormal Doppler waveform ($n = 1223$) or had no Doppler study completed ($n = 1428$).

Child motor development

Motor development was assessed using the McCarron Assessment of Neuromuscular Development (MAND) [19] at 10 ($n = 1622$), 14 ($n = 1584$) and 17 ($n = 1221$) years. The 10 item test comprises tasks designed to measure fine and gross motor skills, and derive a composite score of motor development, the Neuromuscular Development Index (NDI). To calculate the NDI the score for each task is converted to a scaled score ($M = 10$, SD = 3) using the age appropriate table of norms. The total of the scaled scores is then summed and converted to the NDI ($M = 100$, SD = 15). A score of $\leqslant 85$ is used to indicate the presence of a minor motor disability [6,19]. McCarron [19] states that the NDI can be thought of as a 'motor quotient' giving the researcher an indication of where the child lies developmentally compared to their peers of the same age.

The test–retest reliability coefficient of the MAND is reported by McCarron [19] as 0.99 overall and is a reliable measure of motor coordination in the Australian population [20]. Further, a comparison of the MAND to two other highly utilized motor coordination tests revealed it to be superior in detecting motor development problems [21].

Control variables

Other variables known to influence motor development [1–6] were included in all statistical models. These variables were gestational age, parity, percentage of expected birth weight (a measure of whether growth potential has been met), child's sex, maternal age, maternal smoking status, maternal alcohol intake, maternal stress and socioeconomic status as measured by the relative rating of advantage and disadvantage [22].

Statistical analyses

Cross sectional analyses were accomplished using chi-square tests, *t*-tests and univariate ANOVA models (generalized linear model – GLM) with Bonferroni post hoc correction to identify the maternal and child variables that were related to motor development at 10, 14 and 17 years. No interactions were found between child's sex and hypertensive status or any of the control variables, so results were not stratified by sex. The NDI scores at each data collection for the offspring of mothers with normotension, hypertension, and preeclampsia were then compared using linear mixed models which account for changes in motor development over time.

Results

Longitudinal motor development

Linear Mixed Models, adjusting for maternal age, maternal stress, parity, gestational age, percentage of expected birth weight, child's sex, maternal alcohol and smoking and SES revealed a group difference between offspring of mothers with preeclampsia, hypertension and normotension ($p \leqslant 0.001$) over time. The mean NDI of offspring in the preeclampsia group was lower than those in the hypertension ($p = 0.002$) and normotension ($p \leqslant 0.001$) groups (Fig. 1). While the mean NDI of each group was within the range considered to be indicative of normal motor development [19] the preeclampsia group contained a higher percentage of individuals (46.8%) who fell below the cutoff ($\leqslant 85$) used to determine motor disability [6,19] compared to the hypertension (27.9%) and normotension (24.6%) groups ($p \leqslant 0.001$).

Doppler waveforms

Doppler waveform data were not significantly different between pregnancy groups; however, those with preeclampsia did have a larger percentage of abnormal Doppler waveforms (21.1%) than the hypertension (15.9%) or normotension (13.5%) groups. Within the preeclampsia group, those with abnormal Doppler waveforms ($n = 12$) were found to have lower NDIs at all years than those with hypertension, normotension or those with preeclampsia with no abnormal placental blood flow ($n = 45$). Early onset preeclampsia may be indicative of a more severe type of preeclampsia, posing a greater health risk to mother and offspring [23]. Previous findings reported differences in

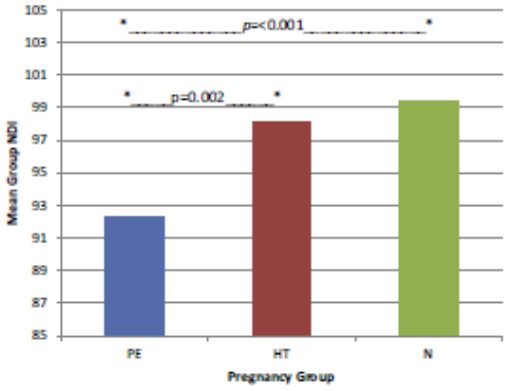

Fig. 1. Mean NDI of pregnancy groups based on Linear Mixed Model adjusted for maternal age at conception, SES, maternal smoking and alcohol intake, use of antihypertensive medication, parity, gestational age, percentage of expected birth weight and child's sex.

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placental morphology between early (⩽34 weeks gestation) and late (>34 weeks gestation) onset preeclampsia [24] therefore we further examined the preeclampsia group for restricted placental function. Of those with preeclampsia and abnormal Doppler waveform ($n = 12$), 91% had early onset preeclampsia. Of those with preeclampsia and normal Doppler waveform ($n = 41$) only 41% had early onset preeclampsia. Unfortunately the small numbers in these groups did not support further statistical analyses.

Motor development at 10, 14 and 17 years

To examine the effect of hypertension and preeclampsia on motor outcomes at 10, 14 and 17 years general linear models were developed (Table 2). No significant interactions between hypertensive status and any of the control variables were found and were not included in the final models. Offspring born to mothers with preeclampsia had a significantly lower NDI at 10 ($p = 0.041$) and 14 years ($p = 0.002$) than the other two groups. Although not significant, a lower NDI score was also evident at 17 years for the preeclampsia group. Post hoc analyses at 10 years revealed the differences between the preeclampsia group and the hypertension ($p = 0.031$) and normotension ($p = 0.012$) groups. At 14 years the group differences were found between the preeclampsia group and the normotension group ($p = 0.007$) and between the hypertension and normotension groups ($p = 0.006$). In these cross sectional analyses the presence of abnormal Doppler waveform did not impact on motor development at any age.

The mean standard scores for the 10 individual tasks of the MAND were lower in the preeclampsia group for all tasks across the three follow up years, except the rod slide at 17 years. These differences were significant for the jump and beads on a rod tasks at 10, 14 and 17 years and for the finger tapping, finger-nose-finger, and balancing on one foot tasks in at least 2 of the 3 survey years.

Population characteristics

Mothers with preeclampsia had a significantly lower socioeconomic status as measured by the relative rating of advantage and disadvantage ($p = 0.001$) than either hypertensive or normotensive mothers (Table 1). These pregnancies also had significantly shorter gestational periods ($p<0.001$) than those with hypertension and normal maternal blood pressure during pregnancy. Not surprisingly, higher numbers of stressful events in later pregnancy were reported in the preeclampsia group ($p = 0.003$). A higher proportion of mothers with preeclampsia were more likely to have previously given birth ($p = 0.001$) than those with hypertension or normotension.

Discussion

Results supported our hypothesis, with offspring of mothers who were diagnosed with preeclampsia during pregnancy having lower motor competence at 10, 14, and 17 years than those from mothers who had either hypertension or normal blood pressure during pregnancy (Table 2). Furthermore there were a significantly higher number of individuals who fell below the recommended NDI cutoff score for motor dysfunction in the preeclampsia group. When examined longitudinally, preeclampsia was a greater risk factor than hypertension for persistent and potentially permanent lower motor competence into late adolescence (Fig. 1). The findings of this paper also support and extend those of Hands et al. [6] who found that hypertensive diseases impacted on motor development at 10 years, and Rep et al. [13] who reported psychomotor delay in one year old infants born to mothers with severe preeclampsia.

The MAND tasks that were performed significantly worse by the preeclampsia group required underlying elements of postural control, proprioception and rhythm. For example, the broad jump necessitates the timing and synchronization of the leg and core muscles, the dynamic extension of the leg muscles and the orientation of the whole body in space. The finger-nose-finger and standing on one foot tasks required a sound sense of the positioning of relative body parts and balance, particularly when the eyes were closed and proprioceptive feedback became more important. Finger tapping required rhythm and control of small muscle groups, as well as postural control. It is possible that poorer performance in these tasks may be due to an interruption in the development and functioning of the cerebellum and associated neurological pathways caused by placental dysfunction. While the presence of an abnormal Doppler waveform did not directly influence motor outcome Egbor et al. [24] suggest that preeclampsia is a heterogeneous condition, with reduced placental function being reported primarily in those diagnosed with early onset (⩽34 weeks gestation) preeclampsia. Exploration of the pregnancies complicated by early and late onset preeclampsia provided limited support for this theory, with a trend toward those with early onset preeclampsia having a higher percentage of abnormal Doppler waveforms and lower NDIs than the late onset preeclampsia group. Mothers with abnormal Doppler waveforms and preeclampsia had a higher incidence of early-onset preeclampsia. While the numbers in these groups were small the trend suggests this may be indicative of a more severe form of the disease [23,25] associated with restricted uteroplacental blood flow [26]. Abnormal placental morphology including significantly reduced intervillous space and terminal villi volume [24] may play a role in the long term deficit of motor development seen in offspring with preeclampsia. Future research comparing the impact of early and late onset preeclampsia on motor development and the role of reduced placental function will require a larger sample size to support these findings.

Mothers with preeclampsia had higher incidences of other known risk factors that can effect development such as a lower socioeconomic status, higher stress levels in later pregnancy [27,28] and shorter gestational length [3]. As no interactions were present in the models between any of these previously identified risk factors and the hypertensive status of the mothers preeclampsia emerged as a risk factor for impaired motor development independent of these factors.

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Table 1
Descriptive statistics of cohort according to the pregnancy group.

Continuous variables	Normotension			Hypertension			Preeclampsia			Group Diff
	N	*M*	(sd)	*N*	*M*	(sd)	*N*	*M*	(sd)	
Maternal age (yrs)	2133	27.57	(5.8)	626	27.62	(6.19)	109	27.30	(6.66)	0.872
% Expected birth wt	2111	97.44	(13.9)	623	97.40	(13.72)	109	96.45	(18.17)	0.775
Gestational age (wks)	2121	38.8	(2.30)[a]	623	38.53	(2.10)[b]	109	36.30	(3.46)[a,b]	<0.001
Rating of adv dis	1448	1017	(90.5)[a]	421	1019	(85.8)[b]	70	978	(82.3)[a,b]	0.001
Maternal stress										
18 weeks	2132	1.19	(1.24)	626	1.28	(1.28)	109	1.02	(1.00)	0.088
34 weeks	1889	1.01	(1.18)[a]	572	1.12	(1.16)	92	1.39	(1.39)[a]	0.003
Categorical variables	*N*	*n*	(%)	*N*	*n*	%	*N*	*n*	(%)	
Smoking	2127			626	109		109			0.001
None		1511	(71)		487	(77.8)		89	(81.7)	
⩽10/day		344	(16.2)		87	(13.9)		14	(12.8)	
>10/day		272	(12.8)		52	(8.3)		6	(5.5)	
Alcohol	2125			625	109		109			0.562
None		1146	(53.9)		351	(56.2)		62	(56.9)	
Once a wk or less		845	(39.8)		246	(39.4)		41	(37.6)	
Several times a wk		118	(5.6)		23	(3.7)		6	(5.5)	
Daily		16	(0.8)		5	(0.8)		0	(0.0)	
Sex	2133			626	109		109			0.331
Males		1067	(50.0)		292	(46.6)		54	(49.5)	
Females		1066	(50.0)		334	(53.4)		55	(50.5)	
Parity	2116			623	109		109			<0.001
0		962	(45.5)		342	(54.9)		64	(58.7)	
1+		1154	(54.5)		281	(45.1)		45	(41.3)	

p values are for comparison between three groups according to ANOVA (continuous variables) and chi-squared analysis (categorical variables).
[a] Difference between Normotension and Preeclampsia.
[b] Difference between Hypertension and Preeclampsia.

Table 2
Mean NDI of offspring at 10, 14 and 17 years according to the pregnancy group.

NDI	Normotension		Hypertension		Preeclampsia		Group difference
	M	(sd)	*M*	(sd)	*M*	(sd)	
10 yrs	98.40	(4.72)[a]	97.66	(4.69)[b]	92.32	(6.17) [a,b]	0.041
14 yrs	102.37	(6.42)[a,c]	98.41	(6.38)[c]	92.90	(8.71)[a]	0.002
17 yrs	97.28	(6.68)	98.22	(6.70)	92.19	(9.12)	0.268

Adjusted for maternal age at conception, SES, maternal stress, maternal smoking and alcohol intake, use of anti-hypertensive medication, gestation age, parity, percentage of expected birth weight and child's sex.
[a] Difference between *N* and PE.
[b] Difference between HT and PE.
[c] Difference between *N* and HT.

This study had several strengths. Firstly, the longitudinal nature of the data and the large cohort allowed for a robust statistical analysis of the impact of maternal hypertension and preeclampsia on motor development using linear mixed models. Such data are rare. Secondly, while there is a growing body of evidence [29] indicating that preeclampsia may be responsible for long term health consequences in both mother and offspring there remains a paucity of research into the long term effects of hypertensive diseases on offspring motor development. Furthermore while motor development has been studied in infants, early, and late childhood, few studies have sought to identify the early determinants of motor development into adolescence. Finally, the measure of motor development used in the current study, the MAND is a reliable and accurate measure of motor development in an Australian population and was administered by trained personnel.

A challenge in using longitudinal data from the Raine Cohort was the lack of motor development data collected prior to the 10-year cohort review. This was unfortunate as tracking of motor development in younger years may have provided a picture of the changes in motor development throughout early childhood as well as late childhood and adolescence. While this was a limitation the high quality longitudinal data from late childhood to adolescence provided a unique profile of motor development throughout this often under researched time period.

Conclusion

Our findings indicate that hypertensive diseases during pregnancy, in particular preeclampsia, have long term and possibly permanent consequences that compromise motor development of offspring into late adolescence. These findings are unique as no previous studies have investigated

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the effect of hypertensive diseases during pregnancy on motor development over such a long period of time. While there are reports of the negative effects of hypertension and preeclampsia on a range of developmental areas [8,10,11,13] longitudinal motor outcomes have thus far remained under researched. Health professionals should be alerted to the risks for long term, possibly permanent motor dysfunction in offspring born to mothers diagnosed with preeclampsia, as early intervention may minimize poorer long term motor outcomes.

Ethics Statement

Ethics clearance was obtained by the Human Research Ethics Committee at the King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained at enrollment and at each follow up from parents and/or guardians.

Funding

The authors have no support or funding to report.

Competing interests

The authors have declared that no competing interests exist.

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References

[1] Trasti N, Vik T, Jacobsen G, Bakketeig LS. Smoking in pregnancy and children's mental health and motor development at age 1 and 5 years. Early Hum Dev 1999;55:137–47.
[2] Pitcher JB, Henderson-Smart DJ, Robinson JS. Prenatal pro… of human motor function. In: Wintour EM, Owens JA, edi… life origins of health and disease. New York: Springer Science + Business Media; 2006.
[3] Goyen T, Lui K. Longitudinal motor development of "apparently normal" high-risk infants at 18 months, 3 and 5 years. Early Hum Dev 2002;70:103–15.
[4] Kalberg WO, Provost B, Tollison SJ, Tabachnick BG, Robinson LK, Hoyme HE, et al. Comparison of motor delays in young children with fetal alcohol syndrome to those with prenatal alcohol exposure and with no prenatal alcohol exposure. Alcohol Clin Exp Res 2006;30(12):2037–45.
[5] Schmidhauser J, Caflisch J, Rousson V, Bucher HU, Largo RH, Latal B. Impaired motor performance and movement quality in very-low-birthweight children at 6 years of age. Dev Med Child Neurol 2006;48:718–22.
[6] Hands B, Kendall G, Larkin D, Parker H. Perinatal risk factors for mild motor disability. Int J Disabil Dev Educ 2009;56(4):317–31.
[7] Many A, Fattal A, Leitner Y, Kupferminc MJ, Harel S, Jaffa A. Neurodevelopmental and cognitive assessment of children born growth restricted to mothers with and without preeclampsia. Hypertens Pregnancy 2003;22(1):25–9.
[8] Whitehouse AJO, Robinson M, Newnham JP, Pennell C. Do hypertensive diseases of pregnancy disrupt neurocognitive development in offspring? Paediatr Perinat Epidemiol 2012;26:101–8.
[9] Tuovinen S, Raikkonen K, Pesonen A, Lahti M, Heinonen K, Wahlbeck K, et al. Hypertensive disorders in pregnancy and risk of severe mental disorders in the offspring: the Helsinki Birth Cohort Study. J Psychiatr Res 2012;46:303–10.
[10] Robinson M, Mattes E, Oddy WH, De Klerk NH, Li J, Mclean NJ, et al. Hypertensive diseases of pregnancy and the development of behavioral problems in childhood and adolescence: the Western Australian Pregnancy Cohort Study. J Pediatr 2009;154:218–24.
[11] Ogland B, Nilsen ST, Forman MR, Vatten LJ. Pubertal development of daughters of women with pre-eclampsia. Arch Dis Child 2011;96:740–3.
[12] Fugelseth D, Ramstad HB, Kvehaugen AS, Nestaas E, Stoylen A, Staff AC. Myocardial function in offspring 5–8 years after pregnancy complicated by preeclampsia. Early Hum Dev 2011;87:531–5.
[13] Rep A, Ganzevoort W, Van Wassenaer AG, Bonsel GJ, Wolf H, De Vries JIP. One-year infant outcome in women with early onset hypertensive disorders of pregnancy. Br J Obstet Gynaecol 2008;115:290–8.
[14] Matsuo K, Malinow AM, Harman CR, Baschat AA. Decreased placental oxygenation capacity in preeclampsia: clinical application of a novel index of placental function performed at the time of delivery. J Perinat Med 2009;37(6):657–61.
[15] Gramsbergen A. Clumsiness and disturbed cerebellar development: insights from animal experiments. Neural Plast 2003;10(1–2):129–40.
[16] Ivry RB. Cerebellar involvement in clumsiness and other developmental disorders. Neural Plast 2003;10(1–2):141–53.
[17] Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LL Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 1993;342(8876):887–91.
[18] Newnham JP, Doherty DA, Kendall GE, Zubrick SR, Landau LL, Stanley FJ. Effects of repeated prenatal ultrasound examinations on childhood outcome up to 8 years of age: follow up of a randomised controlled trial. Lancet 2004;364:2038–44.
[19] McCarron LT. MAND McCarron assessment of neuromuscular development. Dallas, TX: Common Market Press; 1997.
[20] Hoare D, Larkin D. Assessment and classification using the MAND. Int J Neurosci 1990;51:114.
[21] Tan SK, Parker H, Larkin D. Concurrent validity of motor tests used to identify children with motor impairment. Adapt Phys Activ Q 2001;18:168–82.
[22] Australian Bureau of Statistics. Index of relative socio-economic advantage and disadvantage; 2006. Available from: <http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/2033.0.55.001Main+Features12006?OpenDocument>.
[23] Leeson P. Invited plenary orals: long term cardiovascular outcomes for mother and child. Pregnancy Hypertens Int J Women's Cardiovasc Health 2013;3:57–61.
[24] Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Morphometric placental villous and vascular abnormalities in early-and late-onset pre-eclampsia with and without fetal growth restriction. Br J Obstet Gynaecol 2006;113:1–2.
[25] Lindheimer MD, Taler SJ, Cunningham FG. Hypertension in … http://refhub.elsevier.com/S2210-7789(14)00062-2/h0005 … of placental vascular lesions and likelihood of diagnosis of preeclampsia. Am J Obstet Gynecol 1997;176(6):668.
[27] Huizink AC, Robles de Mina PG, Mulder EJH, Visser GHA, Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry 2003;44(6):810–8.
[28] O'Connor TG, Heron J, Golding J, Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J Child Psychol Psychiatry 2003;44(7):1025–36.
[29] Tranquilli AL, Landi B, Giannubilo SR, Sibai BM. Preeclampsia: no longer solely a pregnancy disease. Pregnancy Hypertens Int J Women's Cardiovasc Health 2012;2:350–7.

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Best Poster Award, Science on the Swan, Perth, WA, April 2015

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Poster Presentation, Science on the Swan, Perth WA, April 2015

The Long Term Impact of Hypertensive Diseases on Motor Development

Tegan Grace, Prof. Beth Hands, Prof. Max Bulsara & Prof. Craig Pennell
The University Of Notre Dame,

BACKGROUND

Hypertension in pregnancy and preeclampsia have been linked to poor outcomes in cognitive, mental and psychomotor development; however, few longitudinal studies have researched their effect on offspring motor development, particularly in late childhood and adolescence.

During the third trimester, the most common time for preeclampsia to occur, the developing fetal brain may be more vulnerable to hypoxic and ischemic insults [1]. During this time the cerebellum, an area responsible for aspects of motor development such as coordination, precision and accuracy of movement is rapidly developing. Suboptimal maternal nutrition or deficits in the delivery of nutrients via the placenta at this time may result in developmental problems, particularly in the motor domain [2,3].

Eabor et al. [4] suggest that preeclampsia is a heterogeneous condition, with reduced placental function being reported primarily in those diagnosed with early onset (≤34 weeks gestation) preeclampsia.

Hypothesis

We predicted that the motor development of offspring at 10, 14 and 17 years would be negatively affected by the hypertensive status of the mother, with preeclampsia in particular contributing to a poorer motor outcome. Furthermore those mothers with preeclampsia were more likely to have experienced restricted placental blood flow, indicated by abnormal Doppler waveforms.

METHODS

Year	Active	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2868	-	-	-	-	2868
10	2047	281	162	348	30	2868
14	1860	357	207	412	32	2868
17	1754	414	184	480	36	2868

Participants (*n*=2900) were from the Western Australian Pregnancy (Raine) Study, and were recruited between 16-20wks gestation (*M*=18wks). There were 2868 live births and ultrasound and Doppler data were available for 2857 infants.

Maternal Hypertension was defined as an increase in systolic BP ≥140mmHg and/or an increase in diastolic BP ≥ 90mmHg

Maternal Preeclampsia was defined as hypertension in addition to proteinuria (≥ 300mg/24hr)

3 Pregnancy Groups were formed based on clinical diagnosis of hypertensive disease; Normotension (N, *n*=2133), Hypertension (HT, *n*=626) and Preeclampsia (PE, *n*=109)

Motor Development: Offspring motor development was measured by the Neuromuscular Developmental Index (NDI) (*M*=100, *SD*=15) of the McCarron Assessment of Motor Development (McCarron, 1997) at 10, 14, and 17 years.

Analysis

Cross Sectional: Chi Squared tests, t-tests, univariate ANOVAs with bonferroni post hocs

Longitudinal: Linear Mixed Models

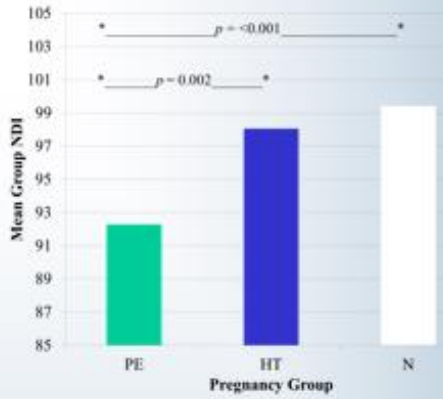
RESULTS

The MAND tasks that were performed significantly worse by the preeclampsia group required underlying elements of postural control, proprioception and rhythm. Performance in these tasks may be affected by an interruption in the development and functioning of the cerebellum and associated neurological pathways caused by reduced placental function, reported primarily in those diagnosed with early onset (≤34 weeks gestation) preeclampsia. Abnormal placental morphology including significantly reduced intervillous space and terminal villi volume may play a role in the long term deficit of motor development seen in offspring with preeclampsia.

Mean NDI of offspring at 10, 14 and 17 years according to pregnancy group

NDI	Normotension M (sd)	Hypertension M (sd)	Preeclampsia M (sd)	Group Difference
10yrs	98.40 (4.72)*	97.66 (4.69)*	92.32 (6.17)**	0.041
14yrs	102.37 (6.42)**	98.41 (6.38)*	92.90 (8.71)*	0.002
17yrs	97.28 (6.68)	98.22 (6.70)	92.19 (9.12)	0.268

Adjusted for maternal age at conception, SES, maternal stress, maternal smoking and alcohol intake, use of anti-hypertensive medication, gestation age, parity, percentage of expected birth weight and child's sex.
* – difference between N and PE
* – difference between HT and PE
* – difference between N and HT



Linear Mixed Model results for mean NDI over time

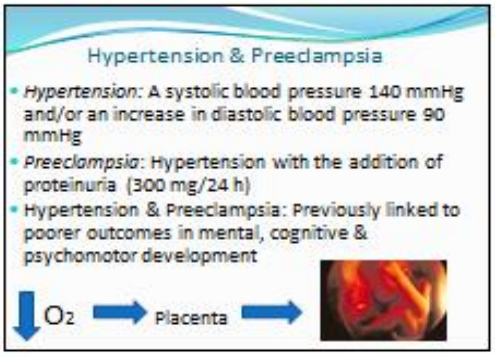
CONCLUSIONS

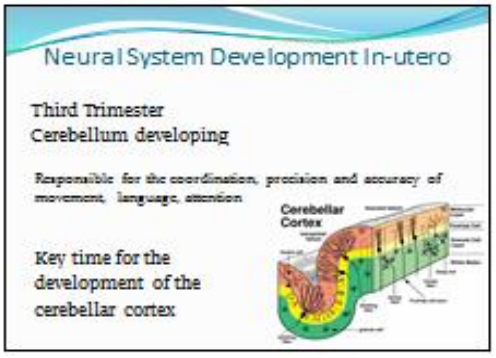
The effect of hypertensive diseases, in particular preeclampsia have long term and possibly permanent consequences to compromised motor development throughout late childhood and adolescence.

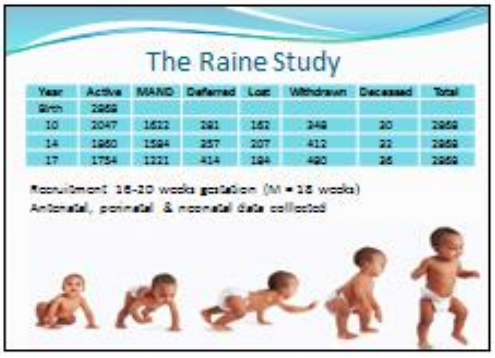
Acknowledgments

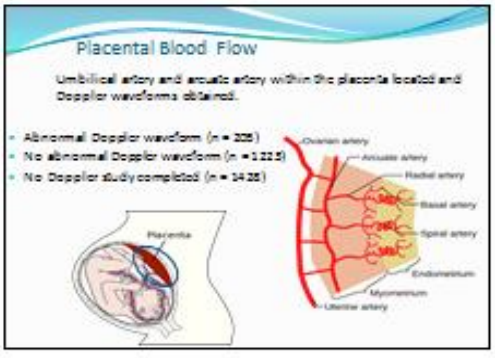
We would like to thank the Raine Study participants and families

Oral Presentation Slides: DCD 11 Conference, Toulouse, France, July 2015

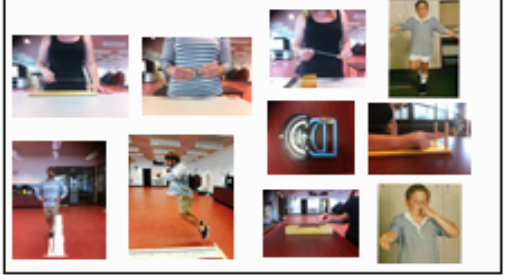








McCarron Assessment of Neuromuscular Development



Data Analyses

Maternal Variables

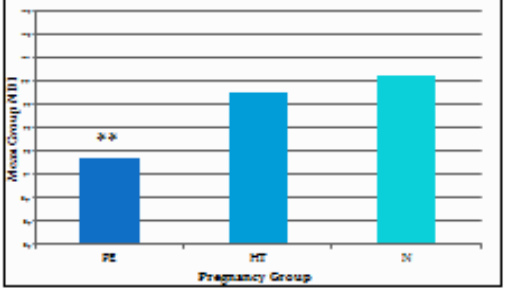
hypertensive status
age
socioeconomic status
drug use
alcohol consumption
cigarette smoking
stress
infection / illness
gestational diabetes
obstetric complications

NDI
10yrs
14yrs
17yrs

Child Variables

breast feeding
gestational age
birth weight
POBW
TSR
APGAR (1min)
Mode of delivery (SVD, CS)

Results: Linear Mixed Model



Results: Mild Motor Delay

	NDI	
	<85 (%)	≥85 (%)
Normal BP	24.6	75.4
Hypertension	27.9	72.1
Preeclampsia	46.8*	53.2

*p = 0.001

Neuromuscular Development Index of the MAND can be used as indicate the presence of a minor motor disability (NDI <85)

Results: Placental Blood Flow

	Doppler Waveforms	
	Normal (%)	Abnormal (%)
Normotension	86.5	13.5
Hypertension	84.1	15.9
Preeclampsia	78.9	21.1

Early Vs Late Onset Preeclampsia

Preeclampsia + Abnormal Doppler – 92% had early onset preeclampsia

Preeclampsia + Normal Doppler – 49% had early onset preeclampsia

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Professor Beth Hands
Professor Max Sulsers
Professor Wendy Oddy
Raine Study participants and their families
Raine Study Executive Committee & Management
Raine Study data collection team
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Appendix B Child Development Article and Associated Presentations and Awards

CHILD DEVELOPMENT

Child Development, xxxx 2015, Volume 00, Number 0, Pages 1–10

The Impact of Maternal Gestational Stress on Motor Development in Late Childhood and Adolescence: A Longitudinal Study

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The number and timing of stressors experienced during pregnancy were investigated using longitudinal data from the Western Australian Pregnancy (Raine) Study cohort (N = 2,900). Motor development data were collected at 10 (n = 1,622), 14 (n = 1,584), and 17 (n = 1,222) years using the McCarron Assessment of Neuromuscular Development. Linear mixed models were used to examine the effect of stress on motor development, accounting for repeated measures. Number of stressful events and mean Neuromuscular Development Index were negatively related ($\beta = -1.197$, $p = .001$). Stressful events experienced in late pregnancy were negatively related with offspring motor development ($\beta = -0.0541$, $p = .050$), while earlier stressful events had no significant impact.

Although the human brain and nervous system have shown a capacity for adaptivity, often referred to as plasticity, there is evidence that suggests insults to the developing central nervous system (CNS) in utero can be long lasting and in some cases permanent (Pitcher, Henderson-Smart, & Robinson, 2006). Evidence of the impact the in utero environment has on short- and long-term health outcomes are growing, evidenced by the rapidly growing field of research, the Developmental Origins of Health and Disease (Barker, 2007). The development of the CNS is a complex process that begins at approximately 3 weeks of gestation, however differentiation of embryo cells into specific tissues starts only a few days after fertilization (Brodal, 2010). Prenatally the process includes neural induction, proliferation, migration, and differentiation. Pioneering work by Barker (2007) hypothesized that nutritional deficits in utero led to structural and functional changes in the developing fetus, termed "fetal programming," and coincided with an increased risk of disease in adult life. While this theory has been tested with outcomes such as coronary heart disease, stroke, hypertension, and diabetes, there is little research that has applied the hypothesis to outcomes of motor coordination.

Periods of critical importance during fetal development, have been previously reported (Barker, 1997; Nathanielsz, 1999). These windows of opportunity occur at times when cell proliferation and division in tissues, organs, and systems occur at a rapid rate; therefore, different critical periods occur for different tissues. The timing of events that can influence fetal development are an important consideration in the study of in utero environments; however, there have been few longitudinal studies that have sought to pinpoint these critical windows of development in relation to motor development. Sensitive periods during gestation when the fetus may be more vulnerable to prenatal stress have been identified across most aspects of development (Ellman et al., 2008; Laplante et al., 2004; Van den Bergh & Marcoen, 2004). While the majority of these findings indicate stress in early pregnancy is of particular importance to offspring development, some researchers (Huizink, Robles de Mina, Mulder, Visser, & Buitelaar, 2003; O'Con-

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nor, Heron, Golding, & Glover, 2003) have reported that stress in late pregnancy affects mental, emotional, and behavioral development in infancy and early childhood. Pitcher et al. (2006) reported that during the third trimester, the developing fetal brain may be more vulnerable to hypoxic and ischemic affronts. The cerebellar cortex, which develops mainly during late pregnancy, is important for the development of postural control, coordination, and motor skill function (Gramsbergen, 2003). While work with animal models has supported this role, it is not fully understood how pregnancy stress may affect the developing human cerebellar cortex and whether the timing of this stress has long-term neurological consequences. Long-term functional deficits in motor development could also result from the increase in hormones such as cortisol (DiPietro, 2004), androgen (Kaiser & Sachser, 2009), or progestogen (Paris & Frye, 2011), which occur when the mother is stressed. Changes in these hormone levels are hypothesized to permanently affect the functioning of the hypothalamic–pituitary–adrenal axis (Lazinski, Shea, & Steiner, 2008; Paris & Frye, 2011), limbic system, prefrontal cortex (Van den Bergh, Mulder, Mennes, & Glover, 2005), and autonomic nervous system (Lazinski et al., 2008) in offspring. Although not directly related to motor control, some of these, for example, the limbic system that controls spatial memory and motivation, may affect motor functioning.

Changes in the structure and function of the developing fetal neurological system due to maternal stress have been hypothesized to cause long-term deficits in several developmental domains (Glover & O'Connor, 2006; O'Connor, Heron, Golding, & Glover, 2003; Ruiz & Avant, 2005; Van den Bergh et al., 2005). Birth outcomes reportedly affected by maternal gestational stress include lower birth weight and gestational age, smaller head circumference, and poorer neurological scores at birth (Glover & O'Connor, 2006). Previous research has revealed that maternal gestation stress can also negatively impact a range of health and developmental outcomes in infancy and early childhood (Monk, 2001; Ruiz & Avant, 2005; Talge, Neal, & Glover, 2007; Tegethoff, Greene, Olsen, Schaffner, & Meinlschmidt, 2011). These include cognitive (Buitelaar, Huizink, Mulder, de Medina, & Visser, 2003; Glover & O'Connor, 2006; Huizink et al., 2003; Laplante et al., 2004; Sandman, Davis, Buss, & Glynn, 2012), motor (Buitelaar et al., 2003; Huizink et al., 2003), language (Henrichs et al., 2011; Laplante et al., 2004), and behavioral and emotional development (de Weerth, van Hees, & Buitelaar, 2003; Glover & O'Connor, 2006; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; Robinson et al., 2008; Sandman et al., 2012) as well as physical and neuromuscular maturation (Ellman et al., 2008; Sandman et al., 2012). For example, Buitelaar et al. (2003) reported gestational stress to be predictive of lower motor development outcomes at 8 months and Huizink et al. (2003) reported an average decline of 8 points on mental and motor development scales in infants born to mothers who recorded higher levels of the stress hormone cortisol.

While longitudinal studies have shown that maternal pregnancy stress affects behavioral, mental, and cognitive development in middle childhood (Rodriguez & Bohlin, 2005; Van den Bergh & Marcoen, 2004), and into adolescence (Mennes, Van den Bergh, Lagae, & Stiers, 2009; Robinson et al., 2011), few studies have investigated the consequences on motor development. Earlier work using animal models revealed reduced motor skills and balance in infant monkeys after repeated maternal stress (Schneider & Coe, 1993). Hands, Kendall, Larkin, and Parker (2009) examined whether a range of perinatal factors influenced human motor development and found that a high level of postnatal maternal stress was related to the presence of mild motor delay in males at 10 years. Gestational stress was not reported as a contributing factor; however, the variables were dichotomized, with a stressful pregnancy defined by the presence of three or more stressful events. In light of other findings regarding timing and number of stressors being pertinent to the effect on developmental outcomes (Davis & Sandman, 2010; Ellman et al., 2008; Robinson et al., 2011), further investigation of the available gestational stress data is warranted. The current study will examine how stressful events during early and late gestation, as well as total number of stressful events throughout pregnancy affect motor development outcomes at 10, 14, and 17 years.

Low motor competence has previously been linked to decreased short- and long-term mental and physical health outcomes (Cantell, Smyth, & Ahonen, 1994; Fitzpatrick & Watkinson, 2003; Schoemaker & Kalverboer, 1994; Skinner & Piek, 2001). While the body of evidence regarding the negative effects of lowered motor competence is growing, there remains a paucity of research involving early risk factors for suboptimal neurological development during the antenatal, perinatal, and neonatal stages.

Events that are believed to cause stress such as marital problems, financial issues, loss of a close

family member, or the accumulation of smaller daily hassles are most often used as stress markers (Huizink et al., 2003; Robinson et al., 2011; Whitehouse et al., 2010). The purpose of this article is to investigate whether the number and timing of stressors experienced during pregnancy impacted long-term motor development at 10, 14, and 17 years. We hypothesized that the experience of stressful events during pregnancy would negatively impact offspring motor development, with later pregnancy stress playing a more important role in motor outcomes than earlier stress.

Method

Participants

Participants (N = 2,900) were from the Western Australian Pregnancy Cohort (Raine) Study. The cohort was primarily Caucasian, from European descent (88.2%), and included mothers who identified as Aboriginal (2.4%), Chinese (4.4%), Indian (2.6%), Polynesian (0.9%), and Vietnamese (0.3%). Recruitment criteria included gestational age between 16 and 18 weeks, adequate English language skills to comprehend the study requirements, expected delivery at King Edward Memorial Hospital and for ease of future follow-up of children, and the desire to remain living in Western Australia. Mothers were recruited between 16 and 20 weeks gestation (M = 18 weeks) from May 1989 to November 1991 at a rate of approximately 100 per month. Full cohort details and enrollment criteria have been published previously (Newnham, Evans, Michael, Stanley, & Landau, 1993). In total, 2,868 live births were recorded (Table 1) and questionnaire data including socioeconomic status and maternal health and psychosocial characteristics were collected from the mothers at 18 and 34 weeks gestation, with obstetric data collected throughout the antenatal, perinatal, and neonatal periods. Physical data were collected at 10 (M = 10.54, SD = 2.27), 14 (M = 14.02, SD = 2.33), and 17 (M = 16.99, SD = 2.97) years from the offspring. A total of 989 children completed motor development testing at all three data collection phases, while 395 completed one data collection phase and 533 participated in two of the three follow-ups. The participation rates for the active cohort (Table 1) were good at each follow-up phase: 10 (n = 1,622, 79%), 14 (n = 1,584, 85%), and 17 (n = 1,221, 69%). There were no statistical differences in motor development outcome between those participants who were assessed at only 10 years (M = 94.72, SD = 14.38) and those who participated in all three data collection phases (M = 94.35, SD = 14.12).

Ethics clearances were obtained from the Human Research Ethics Committee at King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth, Western Australia. Informed consent was obtained at enrollment and at each follow-up from parents and/or guardians.

Predictor Variable

Maternal stress data were collected at 18 and 34 weeks gestation from the mothers using a 10-item questionnaire based on the Tennant and Andrews (1977) Life Stress Inventory. A yes–no format was used to ask if the mothers had experienced any of the listed stressful events, such as pregnancy problems, death of a close relative, death of a close friend, separation or divorce, marital problems, problems with children, involuntary job loss, partner's job loss (involuntary), money problems, and residential move (Table 2). Another item labeled "other" was available if the mother had experienced stress from an unlisted event or circumstance. The first questionnaire at 18 weeks asked if the mothers had experienced any of the listed stressors since becoming pregnant, while the questionnaire at 34 weeks asked if they had experienced the listed stressors in the last 4 months. This ensured stressors that occurred during the first questionnaire were not counted in the second questionnaire unless they were still occurring. For example, moving house, which is a one-off event, would only need to be included in one questionnaire while marital or

Table 1
Available Data From Each Follow Up of the Raine Study

Year	Active	MAND	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2,868						2,868
10	2,047	1,622	281	162	348	30	2,868
14	1,860	1,584	357	207	412	32	2,868
16	1,754	1,221	414	184	480	36	2,868

Table 2
Type and Frequency of Stressful Events

	18 weeks (N = 2,804)		34 weeks (N = 2,580)	
Stressor	n	%	n	%
Money problems	789	28.1	665	25.7
Pregnancy problems	733	26.1	511	19.8
Residential move	455	16.2	466	18
Marital Problems	247	8.8	184	7.1
Problems with your children	177	6.3	164	6.3
Relationship problems	151	5.4	140	5.4
Death of a relative	149	5.3	138	5.3
Your partners job loss (not voluntary)	136	4.8	136	5.3
Separation or divorce	114	4	77	2.9
Your own job loss (not voluntary)	85	3	36	1.4
Death of a close friend	56	1.9	43	1.6

financial problems, which can be ongoing, may have been included in both. To explore the impact of early and late stress, two continuous variables were created to reflect the number of stressors experienced at both time points. Three groups were then created that categorized stress severity. This allowed for comparison to other published works that used similar methodology (O'Connor et al., 2003), including previous research using the Raine Study cohort (Robinson et al., 2011; Whitehouse et al., 2010). Each stressful event was weighted equally and mothers were categorized as experiencing either no stress (NS), low stress (LS; < 3 stressors), or high stress (HS; ≥ 3 stressors) during their pregnancy.

Outcome Measure

At 10, 14, and 17 years, offspring motor outcomes were measured by the McCarron Assessment of Neuromuscular Development (MAND; McCarron, 1997). The MAND comprises a battery of 10 items including (a) hand strength, (b) finger–nose–finger placement, (c) jumping, (d) heel–toe walk, (e) standing on one foot, (f) beads in a box, (g) beads on a rod, (h) finger tapping, (i) nut and bolt, and (j) rod slide. Raw scores were converted to scaled scores ($M = 10$, $SD = 3$). The scaled cores were summed and the total was normalized to form a composite score, the Neuromuscular Development Index (NDI; $M = 100$, $SD = 15$). The NDI can be used as a continuous outcome measure (Table 3), or a cutoff of < 85 can be used to determine the presence of mild motor delay (Table 4; Hands et al., 2009; McCarron, 1997). Test–retest reliability coefficients of the MAND tasks are reported by McCarron (1997) at 0.99 overall. A comparison of the MAND to two other highly utilized motor coordination tests revealed the MAND to be superior in detecting motor development problems in Australian children (Tan, Parker, & Larkin, 2001).

Covariates

The statistical models controlled for other variables known to influence motor development; these included maternal age, maternal smoking and alcohol consumption, percentage of expected birth weight, parity, child's sex, gestational age, and family income. A categorical variable for maternal smoking was created with three groups: nonsmokers, ≤ 10 cigarettes a day, and > 10 cigarettes a day. Maternal alcohol intake was classified as daily, several times a week, once a week or less, or never. Family income was dichotomized to reflect a minimum income level (< $24,000 p.a. or ≥ $24,000 p.a.) according to the Australian Government guidelines at the time.

Statistical Analyses

Maternal and child variables that were related to motor development at 10, 14, and 17 years were

Table 3
MAND Scores at 10, 14 and 17 Years According to Pregnancy Groups

	No stress 0 stressors			Low stress < 3 stressors			High stress ≥ 3 stressors			
NDI	N	M	SD	N	M	SD	N	M	SD	Group difference
10 years	352	95.36[a]	13.55	616	94.74	14.21	542	93.09[a]	13.81	0.034
14 years	336	101.19[a]	18.32	612	99.48	17.62	524	97.54[a]	17.21	0.011*
17 years	260	98.60[a]	17.51	466	97.53[b]	17.36	423	94.13[ab]	16.52	0.001*

*Significant group difference at the $p = .05$ level.

Table 4
Prevalence of Mild Motor Delay at 10, 14 and 17 Years According to Pregnancy Groups

	No stress		Low stress		High stress		
	0 stress events		< 3 stress events		≥ 3 stress events		
NDI	> 85	≤ 85	> 85	≤ 85	> 85	≤ 85	Group difference
10 years *N* (%)	272 (77.3)	80 (22.7)	467 (75.8)	149 (24.2)	386 (71.2)	156 (28.8)	0.082
14 years *N* (%)	265 (78.9)	71 (21.1)	474 (77.5)	138 (22.5)	391 (74.6)	133 (25.4)	0.314
17 years *N* (%)	192 (73.8)	68 (26.2)	341 (73.2)	125 (26.8)	279 (66.0)	144 (34.0)	0.029*

*Significant group difference at the $p = .05$ level.

identified using cross-sectional analyses including chi-square tests, *t* tests, and univariate analysis of variance models (generalized linear model) with Bonferroni post hoc correction. No interactions were found between child's sex and maternal stress group or any of the control variables, so results were not stratified by sex.

Linear mixed models were used to examine the effect of stress on motor development, accounting for the unbalanced nature of longitudinal data with repeated measures. The first model examined the severity of pregnancy stress on offspring motor development throughout the entire pregnancy, using the categorical variables of NS, LS (< 3 stressful events), and HS (≥ 3 stressful events). The second model explored the difference in early and late pregnancy stress on motor development using continuous variables of stress calculated at 18 and 34 weeks gestation. Covariates that were not significantly related to motor development were not included in the final models.

Results

Group characteristics are reported in Table 5. Mothers who experienced HS throughout pregnancy (≥ 3 stressful events) were younger than those in either the LS (< 3 stressful events) or NS groups ($p = < .001$). More women in the HS group were classified as having a low income ($p = < .001$) and they were more likely to smoke ($p = < .001$). Infants born to mothers in the HS group had a lower gestation age ($p = < .001$). Money problems were the most commonly reported stressor, with 28.1% of participants at 18 weeks and 26.1% at 34 weeks stating they had experienced financial stress (Table 2). Pregnancy problems were the next most common stressor, followed by residential moves and marital issues. Problems with children were the fifth most common stressor, while other stressors were reported by between 1.7% and 5.4% of participants.

The first linear mixed model, adjusting for sex, gestation age, percentage of expected birth weight, maternal age, parity, maternal alcohol consumption and smoking, and family income revealed that number of stressful events and mean NDI were negatively related ($\beta = -1.197$, $p = .001$). The overall adjusted mean NDI for the NS group was significantly larger than the HS group. Pairwise comparison revealed a significant difference between the NS (98.91) and HS (97.16; $p = .017$) groups.

Of the potential confounding factors included in the analyses, sex ($p = < .001$), gestational age ($p = .001$), parity ($p = .040$), family income ($p = < .001$), and maternal alcohol consumption ($p = .003$) were related to motor development. Males overall had higher NDI scores, while offspring with lower gestational ages had poorer NDI scores compared to their peers. Firstborn children and those from families with incomes under the Australian Government threshold had lower motor development scores. Alcohol intake for those who were grouped as daily drinkers was negatively related to motor development.

The second model, investigating early and late pregnancy stress revealed that stressful events experienced in late pregnancy were negatively related to offspring motor development ($\beta = -0.541$, $p = .050$), while earlier stressful events had no significant impact. Covariates related to motor development scores in the second model included sex ($p = < .001$), gestation age ($p = .001$), percentage of expected birth weight ($p = .042$), parity ($p = .020$), family income

Table 5
Descriptive Statistics of Cohort According to Pregnancy Groups

	No stress 0 stress events		Low stress < 3 stress events		High stress ≥ 3 stress events		Group difference
Continuous variables	*N*	*M* (*SD*)	*N*	*M* (*SD*)	*N*	*M* (*SD*)	
Maternal age (years)	567	28.67 (5.80)	1,035	28.27 (5.82)	1,014	26.48 (5.90)	< .001
% Expected birth weight	567	97.48 (12.33)	1,032	97.63 (12.44)	1,007	96.63 (13.24)	.173
Gestational age (weeks)	567	39.06 (1.70)	1,034	38.91 (1.78)	1,010	38.66 (2.21)	< .001
Categorical variables	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)	
Smoking	567		1,035		1,014		< .001
None		456 (80.4)		795 (76.8)		671 (66.2)	
≤ 10/day		67 (11.8)		156 (15.1)		172 (17.0)	
> 10/day		44 (7.8)		84 (8.1)		171 (16.9)	
Alcohol	567		1,034		1,012		.661
None		309 (54.5)		576 (55.7)		533 (52.7)	
Once a week or less		217 (38.3)		402 (38.9)		414 (40.9)	
Several times a week		36 (6.3)		48 (4.6)		58 (5.7)	
Daily		5 (0.9)		8 (0.8)		7 (0.7)	
Sex	567		1,035		1,014		.792
Males		295 (52.0)		520 (50.2)		520 (50.8)	
Females		272 (48.0)		515 (49.8)		499 (49.2)	
Low income	528		976		947		< .001
No		414 (78.4)		710 (72.7)		551 (58.2)	
Yes		114 (21.6)		266 (27.3)		396 (41.8)	
Parity	567		1,033		1,008		.686
0		266 (46.9)		505 (48.9)		477 (47.3)	
1+		301 (53.1)		528 (51.1)		531 (52.7)	

Note. *p* values are for comparison between three groups according to ANOVA (continuous variables) and chi-squared analyses (categorical variables).

($p = < .001$), and maternal alcohol consumption ($p = .042$).

Cross-sectional analyses revealed there were group differences in mean NDI at 10 years ($p = .034$), with Bonferroni post hoc results showing difference between the NS and HS groups ($p = .050$). At 14 years, there was also a group difference ($p = .011$), with post hoc analyses showing difference between the NS and HS groups ($p = .009$). The highest group difference was seen at 17 years ($p = .001$) with post hoc results revealing differences between NS and HS ($p = .003$) and also LS and HS ($p = .010$) groups. The HS group comprised more individuals whose NDI fell under the cutoff for mild motor delay at each year (Table 4). This difference was significant at 17 years ($p = .029$).

Discussion

The first linear mixed model, examining the impact of stressful events throughout pregnancy revealed support for the hypothesis that pregnancy stress would result in lower motor development scores in offspring. This was shown at ages 10, 14, and 17 years. The greatest difference in mean NDI was found between the NS and HS groups. Mothers who experienced three or more stressful events throughout their pregnancy had offspring with a lower motor competence than those who experienced between zero and two events. This may suggest an accumulative effect of stress on the developing fetal motor system, with small amounts of stress having a negligible effect and greater amounts having a negative effect. In contrast to our findings, DiPietro, Novak, Costigan, Atella, and Reusing (2006) reported that nonspecific maternal stress did not have a negative relation with overall child development at the age of 2 and motor development at this age was found to be positively impacted by higher levels of maternal stress. The smaller sample size (185) and restriction to low-risk, nonsmoking women over the age of 20 years may explain the difference in findings. Furthermore,

the children measured in the previous study were much younger than in the current study. Gramsbergen (2003) suggests that the underlying neurobiological processes that contribute to motor development, including neurophysiological factors such as motor programming and sensory processing, continue to develop during a child's first 10 years. It is possible that the effects of maternal gestational stress on these processes may not be fully manifested until after these systems have fully developed.

The second linear mixed model, investigating the impact of early versus late stressful events, confirmed that late pregnancy stress had a greater influence on motor development during late childhood and in adolescence than early pregnancy stress. Disturbances of the developing cerebellar cortex, which occurs late in neuro-ontogeny, may be the key etiological factor for motor programming (Gramsbergen, 2003; Ivry, 2003). Growth of the cerebellar cortex occurs during the third trimester and includes a rapid increase in granule cells and the creation of neural pathways, which will eventually assist in adjustments to muscle tone, control of movement and posture, and the learning of physical tasks and motor skills (Gramsbergen, 2003). While several previous studies highlight the importance of early pregnancy stress on cognitive (Davis & Sandman, 2010; Laplante et al., 2004; Sandman et al., 2012), language (Laplante et al., 2004), and mental and behavioral (Van den Bergh & Marcoen, 2004) development, other researchers have found mid to late pregnancy stress affected early motor development (Huizink et al., 2003) and behavioral/emotional problems (O'Connor et al., 2003). Our findings support the theory of later pregnancy stress having a greater influence specifically on long-term motor development, and further research into the impact of this on the developing cerebellar cortex may help to further our understanding of how this occurs.

Alternatively the effect of maternal gestational stress on other areas of neurological development may account for the lower motor development scores. Changes in levels of hormones such as cortisol (DiPietro, 2004), androgen (Kaiser & Sachser, 2009), or progestogen (Paris & Frye, 2011) are hypothesized to permanently affect the functioning of the limbic system (Murmu et al., 2006). Changes in neuron development within the limbic system due to maternal gestational stress have been observed in rat models (Murmu et al., 2006); however, whether these changes affect motor development in humans is unknown.

Cross-sectional analyses showed group differences at 10 ($p = .034$), 14 ($p = .011$), and 17 ($p = .001$) years. This finding was unexpected as no previous research has reported that the negative relation between maternal gestational stress and offspring motor development becomes stronger with age; however, the continued growth of the neurological systems throughout the first decade (Gramsbergen, 2003) may explain why the full impact on these systems is not evident until after puberty.

Strengths

A large population-based sample and the collection of various potential confounders allowed for a stringent and robust analysis of the effect of pregnancy stress on motor development in late childhood and adolescence. As previously reported (Robinson et al., 2011), the inclusion of pregnancy concerns in the questionnaire allowed the mothers to include stressors that may have otherwise been overlooked, as pregnancy and impending birth, as well as related health problems, can be a cause of stress themselves. The use of two questionnaires to collect stress data allowed earlier and later stressors to be compared and the impact of timing to be analyzed. The MAND (McCarron, 1997) is a reliable and accurate measure of motor development among Australian children (Tan et al., 2001).

Limitations

While stressful events are commonly used as a measure of stress, we acknowledge that this does not consider an individual's resilience that can ameliorate the level at which stressful events may impact them psychologically. The longitudinal nature of the study did not allow for further measures regarding maternal resilience or perceived severity of stress. Other environmental and lifestyle factors have previously been linked to motor development throughout infancy and childhood; however, controlling for these factors was not within the scope of this study. The extensive and high-quality antenatal data available allowed thorough and robust analyses of the factors contributing to motor development from this time period.

Conclusion

We found support for the hypothesis that stress during pregnancy contributed to a poorer motor development outcome in the long term. Glover (2014) has recently stated the emotional

care of pregnant women is an often overlooked aspect of obstetric practice. With evidence for the importance of maternal emotional and mental health on a wide range of developmental and health outcomes for both the mother and the child, future programs aimed at early detection and reduction of maternal stress may help improve offspring outcomes. Currently screening for postnatal depression with user-friendly questionnaires occurs in most antenatal clinics in Australia. This cost-effective model could be used to screen for maternal stress throughout pregnancy as part of regular clinic visits. Previous research has highlighted the importance of exercise in the reduction of stress, improvement of mood, and enhanced mental health outcomes (Fox, Boutcher, Faulkner, & Biddle, 2000). Da Costa, Rippen, Drista, and Ring (2003) reported women who exercised during pregnancy had significantly better mental health markers, including less state anxiety and less pregnancy-specific stress. Exercise presents a low-cost yet effective method of ensuring healthy women experience optimal mental health during pregnancy. Antenatal clinics provide an ideal arena for pregnant women to be informed of the benefits of exercise, in particular if they are experiencing a stressful pregnancy.

References

Barker, D. J. P. (1997). Maternal nutrition, fetal nutrition and disease in later life. *Nutrition, 13*, 807–813. doi:10.1016/S0899-9007(97)00193-7.

Barker, D. J. P. (2007). The origins of the develpmental origins theory. *Journal of Internal Medicine, 261*, 412–417. doi:10.1111/j.1365-2796-2007.0189.x

Brodal, P. (2010). *The central nervous system structure and function* (4th ed.). New York, NY: Oxford University Press.

Buitelaar, J. K., Huizink, A. C., Mulder, E. J., de Medina, P. G. R., & Visser, G. H. A. (2003). Prenatal stress and cognitive development and temperament in infants. *Neurobiology of Ageing, 24*(1), S53–S60. doi:10.1016/S0197-4580(03)00050-2

Cantell, M. H., Smyth, M. M., & Ahonen, T. P. (1994). Clumsiness in adolescence: Educational, motor, and social outcomes of motor delay detected at 5 years. *Adapted Physical Activity Quarterly, 11*, 115–129.

Da Costa, D., Rippen, N., Drista, M., & Ring, A. (2003). Self-reported leisure time physical activity during pregnancy and relationship to psychological well-being. *Journal of Psychosomatic Obstetrics and Gynecology, 24*, 111–119. doi:10.3109/01674820309042808

Davis, E. P., & Sandman, C. A. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development, 81*, 131–148. doi:10.1111/j.1467-8624.2009.01385.x

de Weerth, C., van Hees, Y., & Buitelaar, J. K. (2003). Prenatal maternal cortisol levels and infant behavior during the first 5 months. *Early Human Development, 74*, 139–151. doi:10.1016/S0378-3782(03)00088-4

DiPietro, J. A. (2004). The role of prenatal maternal stress in child development. *Current Directions in Psychological Science, 13*(2), 71–74.

DiPietro, J. A., Novak, M. F. S. X., Costigan, K. A., Atella, L. D., & Reusing, S. P. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development, 77*, 573–587. doi:10.1111/j.1467-8624.2006.00891.x

Ellman, L. M., Dunkel-Schetter, C., Hobel, C. J., Chicz-DeMet, A., Glynn, L. M., & Sandman, C. A. (2008). Timing of fetal exposure to stress hormones: Effects on newborn physical and neuromuscular maturation. *Developmental Psychobiology, 50*, 232–241. doi:10.1002/dev.20293

Fitzpatrick, D. A., & Watkinson, E. J. (2003). The lived experience of physical awkwardness: Adults' retrospective views. *Adapted Physical Activity Quarterly, 20*, 279–297.

Fox, K. R., Boutcher, S. H., Faulkner, G. E., & Biddle, S. J. H. (2000). The case for exercise in the promotion of mental health and psychological well-being. In S. J. H. Biddle, K. R. Fox, & S. H. Boutcher (Eds.), *Physical activity and psychological well-being*. London, UK: Routledge.

Glover, V. (2014). Maternal depression, anxiety and stress during pregnancy and child outcomes; what needs to be done. *Best Practice & Research Clinical Obstetrics and Gynaecology, 28*, 25–35. doi:10.1016/jbpobgyn.2013.08.017

Glover, V., & O'Connor, T. (2006). Maternal anxiety: Its effect on the fetus and the child. *British Journal of Midwifery, 14*, 663–667.

Gramsbergen, A. (2003). Clumsiness and disturbed cerebellar development: Insights from animal experiments. *Neural Plasticity, 10*, 129–140. doi:10.1155/NP.2003.129

Hands, B., Kendall, G., Larkin, D., & Parker, H. (2009). Perinatal risk factors for mild motor disability. *International Journal of Disability, Development and Education, 56*, 317–331. doi:10.1081/10349120903306533

Henrichs, J., Schenk, J. J., Kok, R., Ftitache, B., Schmidt, H. G., Hofman, A., . . . Tiemeier, H. (2011). Parental family stress during pregnancy and cognitive functioning in early childhood: The Generation R Study. *Early Childhood Research Quarterly, 26*, 332–343. doi:10.1016/j.ecresq.2011.01.003

Huizink, A. C., Robles de Mina, P. G., Mulder, E. J. H., Visser, G. H. A., & Buitelaar, J. K. (2003). Stress during pregnancy is associated with developmental outcome in infancy. *Journal of Child Psychology and Psychiatry, 44*, 810–818. doi:10.1111/1469-7610.00166

Ivry, R. B. (2003). Cerebellar involvement in clumsiness and other developmental disorders. *Neural Plasticity, 10*, 141–153. doi:10.1155/NP.2003.141

Kaiser, S., & Sachser, N. (2009). Effects of prenatal social stress on offspring development. *Current Directions in Psychological Science, 18,* 118–121. doi:10.1111/j.1467-8721.2009.01620.x

Laplante, D. P., Barr, R. G., Brunet, A., Du Fort, G., Meaney, M. L., Saucier, J. F., . . . King, S. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research, 56,* 400–410. doi:10.1203/01.PDR.0000136281.34035.44

Lazinski, M. J., Shea, A. K., & Steiner, M. (2008). Effects of maternal prenatal stress on offspring development: A commentary. *Archives of Womens Mental Health, 11,* 363–375. doi:10.1007/s00737-008-0035-4

McCarron, L. T. (1997). *MAND McCarron Assessment of Neuromuscular Development*. Dallas, TX: Common Market Press.

Mennes, M., Van den Bergh, B. R. H., Lagae, L., & Stiers, P. (2009). Developmental brain alterations in 17 year old boys are related to antenatal maternal anxiety. *Clinical Neurophysiology, 120,* 1116–1122. doi:10.1016/j.clinph.2009.04.003

Monk, C. (2001). Stress and mood disorders during pregnancy: Implications for child development. *Psychiatric Quarterly, 72,* 347–357. doi:0033-2720/01/1200-0347

Murmu, M. S., Salomon, S., Biala, Y., Weinstock, M., Braun, K., & Bock, J. (2006). Changes in spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy. *European Journal of Neuroscience, 24,* 1477–1487. doi:10.1111/j.1460-9568.2006.05024.x

Nathanielsz, P. W. (1999). *Life in the womb: The origin of health and disease*. Ithaca, NY: Promethean Press.

Newnham, J. P., Evans, S. F., Michael, C. A., Stanley, F. J., & Landau, L. I. (1993). Effects of frequent ultrasound during pregnancy: A randomised controlled trial. *Lancet, 342,* 887–891. doi:10.1016/1040-6736(93)91944-H

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. *British Journal of Psychiatry, 180,* 502–508. doi:10.1192/bjp.180.6.502

O'Connor, T. G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: A test of a programming hypothesis. *Journal of Child Psychology and Psychiatry, 44,* 1025–1036. doi:10.1111/1469-7610.00187

Paris, J. J., & Frye, C. A. (2011). Juvenile offspring of rate exposed to restraint stress in late gestation have impaired cognitive performance and dysregulated progestogen formation. *Stress, 14*(1), 23–32. doi:10.3109/10253890.2010.512375

Pitcher, J. B., Henderson-Smart, D. J., & Robinson, J. S. (2006). Prenatal programming of human motor function. In E. M. Wintour & J. A. Owens (Eds.), *Early life origins of health and disease*. New York, NY: Springer Science + Business Media.

Robinson, M., Mattes, E., Oddy, W. H., Pennell, C., Van Eekelen, A., Mclean, N. J., . . . Newnham, J. P. (2011). Prenatal stress and risk of behavioral morbidity from age 2 to 14 years: The influence of the number, type, and timing of stressful life events. *Development and Psychopathology, 23,* 507–520. doi:10.1017/s0954579411000241

Robinson, M., Oddy, W. H., Li, J., Kendall, G. E., De Klerk, N. H., Silburn, S. R., . . . Mettes, E. (2008). Pre- and postnatal influences on preschool mental health: A large scale cohort study. *Journal of Child Psychology and Psychiatry, 49,* 1118–1128. doi:10.1111/j.1469-7610.2008.01955.x

Rodriguez, A., & Bohlin, G. (2005). Are maternal smoking and stress during pregnancy related to ADHD symptoms in children? *Journal of Child Psychology and Psychiatry, 46,* 246–254. doi:10.1111/j.1469-7610.2004.00359.x

Ruiz, R. J., & Avant, K. C. (2005). Effects of maternal prenatal stress on infant outcomes. *Advances in Nursing Science, 28,* 345–355.

Sandman, C. A., Davis, E. P., Buss, C., & Glynn, L. M. (2012). Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology, 95*(1), 8–21. doi:10.1159/000327017

Schneider, M. L., & Coe, C. L. (1993). Repeated social stress during pregnancy impairs neuromotor develpoment of the infant primate. *Journal of Developmental and Behavioral Pediatrics, 14*(2), 81–87. doi:10.1097/00004703-199304000-00002

Schoemaker, M. M., & Kalverboer, A. F. (1994). Social and affective problems of children who are clumsy: How early do they begin? *Adapted Physical Activity Quarterly, 11,* 130–140.

Skinner, R. A., & Piek, J. P. (2001). Psychosocial implications of poor motor coordination in children and adolescence. *Human Movement Science, 20,* 73–94. doi:10.1016/S0167-9457(01)000029-X

Talge, N. M., Neal, C., & Glover, V. (2007). Antenatal maternal stress and long term effects on child neurodevelopment: How and why? *Journal of Child Psychology and Psychiatry, 48,* 245–261. doi:10.1111/j.1469-7610.2006.01714.x

Tan, S. K., Parker, H., & Larkin, D. (2001). Concurrent validity of motor tests used to identify children with motor impairment. *Adapted Physical Activity Quarterly, 18,* 168–182.

Tegethoff, M., Greene, N., Olsen, J., Schaffner, E., & Meinlschmidt, G. (2011). Stress during pregnancy and offpsring pediatric disease: A national cohort study. *Environmental Health Perspectives, 119,* 1647–1652. doi:10.1289/ehp.1003253

Tennant, C., & Andrews, G. (1977). A scale to measure the cause of life events. *Australian and New Zealand Journal of Psychiatry, 11,* 163–167. doi:10.3109/00048677609159482

Van den Bergh, B. R. H., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and

9-year-olds. *Child Development, 75,* 1085–1097. doi:10.1111/j.1467-8624.2004.00727.x

Van den Bergh, B. R. H., Mulder, E. J. H., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience and Biobehavioral Reviews, 29,* 237–258. doi:10.1016/j.neubiorev.2004.10.007

Whitehouse, A. J. O., Robinson, M., Zubrick, S. R., Ang, Q. W., Stanley, F. J., & Pennell, C. (2010). Maternal life events during pregnancy and offspring language ability in middle childhood: The Western Australian Pregnancy Cohort Study. *Early Human Development, 86,* 487–492. doi:10.1016/j.earlhumdev.2010.06.009

Society for Research in Child Development Press Release

Society for Research in Child Development

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PRESS RELEASE
Child Development

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Stress During Pregnancy Related to Children's Later Movement, Coordination

Stress experienced by mothers during pregnancy is related to their children's behavior, as well as mental and cognitive outcomes in middle childhood and into adolescence, but few studies have looked at the relationship between maternal pregnancy stress and children's motor development. Now a new longitudinal study has found that mothers who experienced more stressful events during their pregnancies had children who scored lower on a test of movement competence.

The study, by researchers at the University of Notre Dame Australia and the Telethon Kids Institute, appears in the journal *Child Development*.

To test the relationship between maternal stress and children's motor development, researchers followed 2,900 primarily Caucasian Australian mothers. When the women were 18 weeks pregnant, they were asked to complete a questionnaire about stressful events during their pregnancies. These events included financial hardship, losing a close relative or friend, separation or divorce, marital problems, problems with the pregnancy, losing a job, and moving residences. The moms completed the same questionnaire when they were 34 weeks pregnant.

When the children born of those pregnancies were 10, 14, and 17 years old, they were assessed on their overall motor development and coordination using a 10-item movement test. The test measured children's hand strength as well as their ability to touch a finger to one's nose and then back to the index finger, distance jump, walk along a line heel to toe, and stand on one foot. The test also measured their ability to move small beads from one box to another, thread beads onto a rod, tap a finger over 10 seconds, turn a nut onto a bolt, and slide a rod along a bar as slowly as possible. Children were grouped according to those born to mothers who experienced no stress during pregnancy, those born to moms who experienced fewer than three stressful events during their pregnancies, and those born to moms who experienced three or more stressful events during pregnancy.

The study found that children born to mothers who experienced more stressful events during pregnancy scored lower on motor development across all three survey years (ages 10, 14, and 17). This may suggest an accumulative effect of stress on the developing fetal motor system. The greatest differences in motor development outcomes were between individuals whose mothers experienced no stress and those who experienced high stress (i.e., more than three stressful events). Stressful events experienced in later pregnancy had more influence on children's motor development scores than those experienced earlier. According to the researchers, this may be related to the development of the cerebellar cortex, a part of the brain that develops later in pregnancy and that controls many motor outcomes.

Low motor development is defined by how children score on the test used in this study, with children who fall below a certain cutoff point having different manifestations of low motor development that involve poor fine motor skills or poor gross motor skills or both. Low motor development has been linked to poorer short- and long-term mental and physical health outcomes, so it is important to assess the early risk factors to provide early intervention and support. Children with low motor competence can have difficulty in everyday life with fine and gross motor tasks such as writing, throwing, and running. However, with intervention and support, this can be improved in a number of cases.

"Given our findings on the importance of mothers' emotional and mental health on a wide range of developmental and health outcomes, programs aimed at detecting and reducing maternal stress during pregnancy may alert parents and health professionals to potential difficulties and improve the long-term outcomes for these children," notes Beth Hands, professor of human movement at the University of Notre Dame Australia, who coauthored the study.

Adds Tegan Grace, a Ph.D. candidate at the University of Notre Dame Australia, another coauthor of the study: "Screening for postnatal depression occurs in most antenatal clinics in Australia. This cost-effective model could be used to screen for maternal stress throughout pregnancy as part of regular clinic visits." Pregnant women who are under stress could be counseled about cost-effective stress-reduction techniques such as gentle exercise, she suggests.

The study was funded by the National Health and Medical Research Council of Australia; the University of Western Australia (UWA); the Telethon Kids Institute; Edith Cowan University; Raine Medical Research Foundation; UWA Faculty of Medicine, Dentistry and Health Sciences; Women's and Infant's Research Foundation, and Curtin University.

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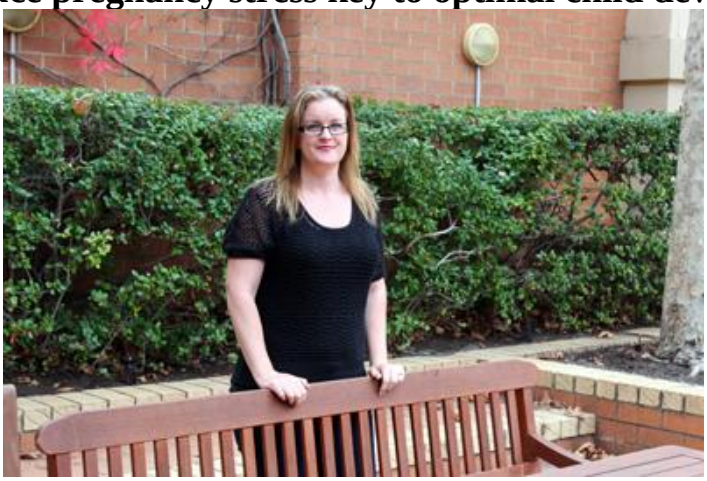
Notre Dame Press Release

Care to reduce pregnancy stress key to optimal child development



Research conducted by Tegan Grace (pictured) and Professor Beth Hands can lead to the development of programs to support pregnant mothers through any challenges they may experience.

29 October 2015

Improving access to care for expectant mothers experiencing a stressful pregnancy is one of many outcomes from a recent Western Australian study published in the international research journal, *Child Development*.

The study, conducted by researchers at The University of Notre Dame Australia and the Telethon Kids Institute, found that mothers who experienced more stressful events during their pregnancies had children who scored lower in motor coordination tests.

Professor Beth Hands, Senior Research Scholar in Notre Dame's Institute for Health Research and co-author of the study, says this research can lead to the development of programs to support pregnant mothers through any challenges they may experience.

"Given our findings on the importance of mothers' emotional and mental health on a wide range of child developmental and health outcomes, programs aimed at detecting and reducing maternal stress during pregnancy may alert parents and health professionals to potential difficulties and improve the long-term outcomes for these children," Professor Hands said.

When children born of stressful pregnancies were aged 10, 14 and 17-years-old, they were assessed on their overall motor development and coordination using a 10-point test. The test includes measures of a child's hand strength, hand-eye coordination in moving beads along a rod and turning a nut onto a bolt, balance and postural control.

The greatest differences in motor development outcomes were between individuals whose mothers experienced no stress and those who experienced high levels of stress due to a number of personal and socio-economic factors.

“Those expectant mothers who had been experiencing a stressful pregnancy identified financial hardship, losing a close friend or relative, separation or divorce, marital problems, pregnancy complications and job loss as contributing factors,” Tegan Grace, a PhD candidate and project researcher, said.

“Screening for post-natal depression already takes place in most Australian antenatal clinics. This cost-effective model could be used to screen for maternal stress throughout pregnancy.”

This research is based on the Raine Study, jointly conducted by the Telethon Kids Institute and the University of Western Australia. The study started in 1989, when 2900 pregnant women were recruited into a research study at King Edward Memorial Hospital to examine ultrasound imaging. The mothers were assessed during pregnancy and health and lifestyle information was collected on the mother and the father.

After the children were born, they were assessed at birth, at one year, then two, three and five years of age. Further follow-ups of the cohort have been conducted at eight, 10, 14, 17, 20 and now 23 years of age.

Find out more about the Raine Study at www.rainestudy.org.au.

As Notre Dame is a direct entry university, you can still apply for 2016. Apply direct – www.notredame.edu.au

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- See more at: http://www.nd.edu.au/news/media-releases/2015/131#sthash.vpKcOyUv.dpuf

IOL Lifestyle / Parenting Press Release

Stressed moms-to-be 'have clumsy children'
lifestyle/parenting /
23 October 2015 at 10:19am
By: **COLIN FERNANDEZ**
London - Mothers-to-be suffering stress in late pregnancy give birth to clumsier, more un-coordinated children, warned a study.

Their offspring's development can be affected by major events like divorce, moving home, losing a job or a relative's death.

Other major experiences which affect the last third of pregnancy can include financial hardship or marital problems.

Women who had to deal with three or more stressful events gave birth to the least co-ordinated children, said researchers.

They interviewed mothers-to-be when they were 18 weeks' pregnant and then at 34 weeks. The 2 900 children in the study were tested at the ages of ten, 14 and 17 using a ten-item movement test.

This tested abilities including hand strength, standing on one foot, turning a nut on a bolt, threading beads on to a rod and walking along a straight line.

Children born to mothers who suffered more stressful events in pregnancy recorded the worse scores on all three survey years.

Academics at the University of Notre Dame Australia suggested this is down to the accumulative effect of stress on the part of the child's brain called the cerebellar cortex which develops later in pregnancy.

Any resulting low motor development could be linked to ill-health and trouble with tasks like writing, throwing and running.

Money problems were the most common stress factor affecting just over a quarter of the pregnant women at 34 weeks, said the study in the journal Child Development.

The second was having a difficult pregnancy while the other most common reasons were moving home, marital concerns and problems with other children.

Study co-author Beth Hands, professor of human movement at the university, said it showed "the importance of mothers' emotional and mental health on a wide range of developmental and health outcomes".
Earlier work using animal models revealed reduced motor skills and balance in infant monkeys after repeated maternal stress. This research suggested the stress hormone cortisol may be causing the problems.

Pregnancy Health Press Release

PREGNANCY HEALTH

Stress in Pregnancy May Affect Child's Motor Skills
New research shows that experiencing high levels of stress during pregnancy may have a lasting impact on your child. So relax—here's what you need to know.

0

ByColleen Travers

It's the number one rule you hear when trying to conceive: Don't stress! (Because it's that easy, right?) And when you do get pregnant, those worries seem to multiply overnight, especially if you've taken to Dr. Google to analyze every twitch and pang you're feeling in those early weeks and months. But now is the time to really relax, according to new research published in the journal Child Development. Researchers at the University of Notre Dame Australia and the Telethon Kids Institute looked at the relationship between pregnancy stress in mothers and children's motor development to find that mothers who experienced stressful events during pregnancy had children who scored lower on a series of motor skill tests.

The effects of stress

Past research has provided evidence of a link between pregnancy stress and other developmental areas in children, such as mental, behavioral, and cognitive differences, but little has been done on the movement outcomes, say the co-authors of the study, Tegan Grace, a Ph.D. candidate and Beth Hands, Ph.D., professor of human movement, both at the University of Notre Dame Australia.

Using data from the West Australian Pregnancy Cohort (Raine) Study, which was established in 1989 to determine how events in pregnancy and childhood influence health later in life, Grace was able to examine the stress levels reported by mothers at different stages of their pregnancy and how they impacted their child during late childhood and adolescence. According to the study, the children were grouped into three categories: those born to mothers who experienced no stress during pregnancy, those born to mothers who experienced fewer than three stressful events during pregnancy, and those born to mothers who experienced three or more stressful events during pregnancy. The study found that children in the latter group scored lower on motor development tests out of all three groups, which included things like a distance jump, walking in a straight line heel to toe, and standing on one foot. While this may not seem like a huge issue at face value, the study adds that children with low motor competence can have difficulty with everyday tasks, such as writing, throwing, and running.

Not all stress is created equal

Before you start stressing out about, well, stressing out, it's important to remember that high-stress in this study was categorized as major life-changing events, such as financial hardship, losing a relative or friend, divorce, marital problems, losing a job,

moving, or problems with the pregnancy. The co-authors also found that these high-stress situations in pregnancy affected the child's motor development more the later in pregnancy they occurred. "Statistically, my models revealed that the mothers that experienced high-stress later in their pregnancy were more likely to have a child with poorer motor outcomes that persisted into adolescence," Grace says.

It may all start in the brain

The reason these levels of late pregnancy high-stress may have such an impact on the fetus might simply be an issue of timing. "We were surprised to find that later pregnancy stress was more strongly linked to movement outcomes," Grace says. "We think this might be because the part of the brain that is mainly concerned with movement—the cerebellum—is developing later in pregnancy." That doesn't mean all hope is lost if you have a stressful situation you just can't avoid. "The great thing about this part of the brain is that it continues to develop throughout the first decade of life, which means we have time to continue providing optimal growth for this area."

Permission to chill

Whether you're pregnant with your first or third child, pregnancy is always going to be a time of heightened stress, but Grace hopes that the findings from this study will serve as a little nudge that sometimes you've got to throw in the towel and give your brain and body a break. "Hopefully this increased awareness will lead to programs that will help mothers gain access to support both during and after their pregnancy," Grace says. "Women need to know it's OK to ask for help and put their own health and well-being—and consequently that of her child—first." So go ahead, put your feet up and watch that *Real Housewives of Orange County* marathon—doctor's orders.

List of Media Releases Internationally

October 14, 2015EurekAlert! (United States)

October 14, 2015Medical Xpress (United States)

October 14, 2015Mail Online UK (United Kingdom)

October 14, 2015University Herald (United States)

October 14, 2015NewsOnFeeds.com (Indonesia

October 14, 2015TV3 Ireland (Ireland)

October 14, 2015Medical News Today (United Kingdom)

October 14, 2015NewsReality.com (United States)

October 14, 2015DailyNews724.com (United States)

October 14, 2015Latest Nigerian News.com (Nigeria)

October 14, 2015Huffington Post (United States)

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October 14, 2015DailyNews724.com (United States)

October 14, 2015The World 247.com (United States)

October 15, 2015HealthMediciNet.com (United States)

October 15, 2015Medical Daily (United States)

October 15, 2015New Zealand Herald (New Zealand)

October 15, 2015DailyNews724.com (United States)

October 15, 2015International Business Times Australia (Australia)

October 15, 2015Hngn.com (United States)

October 15, 2015Newser (United States)

October 15, 2015The Utah People's Post (United States)

October 15, 2015MyInforms (United States)

October 16, 2015CBS News (United States)

October 16, 2015HealthMediciNet.com (United States)

October 16, 2015Fit Pregnancy (United States)

October 16, 2015Latinos Health (United States)

October 17, 2015Yahoo!Xtra (New Zealand)

October 19, 2015Science World Report (United States)

October 19, 2015Inquisitr (United States)

October 20, 2015Fit Pregnancy (United States)

October 23, 2015South Africa Star (South Africa)

October 23, 2015IOL (South Africa)

October 24, 2015IOL (South Africa)

October 28, 2015Noodls (Italy)

Appendix C Acta Paediatrica Article

ACTA PÆDIATRICA
NURTURING THE CHILD

Acta Paediatrica ISSN 0803-5253

REGULAR ARTICLE

Early life events and motor development in childhood and adolescence: a longitudinal study

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Keywords
Antenatal, Motor development, Risk factors, Sex differences

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ABSTRACT

Aim: Few studies have reported on early life risk factors for motor development outcomes past childhood. Antenatal, perinatal and neonatal factors affecting motor development from late childhood to adolescence were explored. As sex differences in motor development have been previously reported, males and females were examined separately.

Methods: Participants (n = 2868) were from the Western Australian Pregnancy Cohort Study. Obstetric and neonatal data were examined to determine factors related to motor development at 10 (n = 1622), 14 (n = 1584) and 17 (n = 1221) years. The Neuromuscular Development Index (NDI) of the McCarron Assessment of Motor Development determined offspring motor proficiency. Linear mixed models were developed to allow for changes in motor development over time.

Results: Maternal pre-eclampsia, Caesarean section and low income were negatively related to male and female motor outcomes. Lower percentage of optimal birthweight was related to a lower male NDI. Younger maternal age, smoking during early pregnancy and stress during later pregnancy were related to lower female NDIs.

Conclusion: Events experienced during pregnancy were related to motor development into late adolescence. Males and females were influenced differently by antenatal and perinatal risk factors; this may be due to sex-specific developmental pathways.

INTRODUCTION

Short- and long-term physical and mental health consequences of poor motor development have been well documented. Past research has reported that children with low motor competence (LMC) are often more introverted, have lower physical and social self-perceptions and higher rates of anxiety than their more coordinated peers (1). In some cases, LMC has been linked to increased depressive symptomology, (2) peer victimisation (3) and antisocial behaviour (4). For those with more severe issues, the psycho-social problems associated with LMC may continue into adulthood (5).

With poor health outcomes such as these, it is imperative that contributing factors be identified as early as possible. A growing body of evidence suggests that events occurring during gestation and birth may have a lasting effect on foetal neurological systems and therefore on postnatal motor development (6). Interruptions to the developing central nervous system during neurogenesis, cell migration, proliferation, differentiation and myelination *in utero* may be potential causes for long-term neurological deficits (6). Foetal and birth-related factors such as sex (7–9), preterm birth (10), low birthweight, (11) intrauterine growth restriction (6), small for gestational age (6,12), as well as maternal factors including smoking (13), alcohol (14), illicit drug use (15), hypertensive disease (16) and maternal stress (17) are recognised risk factors for suboptimal neurophysiological development. Recent findings regarding perinatal risk factors for poor motor development at 10 years in an Australian birth cohort indicated differences in the risk factors impacting males and females (7). The long-term effects of adverse events during gestation and birth seem to have a more lasting effect on health and developmental

Abbreviations
BP, Blood pressure; LMC, Low motor coordination; MAND, McCarron assessment of neuromuscular development; NDI, Neuromuscular development index; SVD, Spontaneous vaginal delivery.

Key notes

- Events during the antenatal period impact motor development during childhood and into adolescence.
- For females, maternal hypertensive status, stress, smoking, family income and delivery mode were related to motor outcomes.
- For males, maternal hypertensive status, percentage of optimal birthweight, family income and delivery mode were related to motor outcomes.

outcomes in males compared to females (9,18). The higher incidence of mortality and morbidity in newborn males has been well documented (9,18). The effects of these early *in utero* insults on motor development have not, however, been widely reported past infancy and early childhood. The purpose of this study was to identify the long-term consequences of antenatal, perinatal and neonatal factors on motor development during late childhood and adolescence. Of particular interest will be examining whether these risk factors differ between males and females.

METHODS

Participants

Participants were part of the Western Australian Pregnancy Cohort (Raine) Study. Women were recruited into the study from May 1989 to November 1991 from King Edward Memorial Hospital (KEMH), Perth, Western Australia. A total of 2868 live births were recorded. Enrolment criteria included a gestation between 16 and 18 weeks (M = 18), an expectation to deliver at KEMH, an intention to reside within the Perth area to facilitate future follow-up and a sufficient level of English speaking to ensure the parameters of the research were understood. Detailed enrolment criteria and cohort details have been previously published (19). Original questionnaire data pertaining to socio-economic status, maternal psychosocial characteristics and maternal health were obtained at enrolment. A second questionnaire was administered at 34 weeks gestation, and obstetric data were collected during the antenatal, postnatal and neonatal periods. Motor development data were collected during the 10 (n = 1622), 14 (n = 1584) and 17 (n = 1221) year follow-up assessments (Table 1). At 10 years, 779 female and 843 males participated in the physical assessment; at 14 years, 769 females and 815 males completed testing, and at 17 years, 607 females and 614 males were assessed. A total of 989 (34.9%) children completed motor development testing at all three stages, with 533 (18.8%) completing two of the three phases and 395 (13.9%) completed testing at one stage.

Ethics clearances were obtained from the Human Research Ethics Committee at the King Edward Memorial Hospital and the Princess Margaret Hospital for Children, Perth Western Australia. Informed consent was obtained at the time of enrolment and each subsequent data collection period.

Table 1 Available data from each follow-up of the raine study

Year	Active	MAND	Deferred	Lost	Withdrawn	Deceased	Total
Birth	2868		–	–	–	–	2868
10	2047	1622	281	162	348	30	2868
14	1860	1584	357	207	412	32	2868
16	1754	1221	414	184	480	36	2868

MEASURES

Outcome measure

Motor development was assessed using the McCarron Assessment of Neuromuscular Development (MAND) (20), a 10-item assessment in which individuals were scored on five fine motor and five gross motor tasks including (i) hand strength, (ii) finger–nose–finger placement, (iii) jumping, (iv) heel-toe walk, (v) standing on one foot, (vi) beads in a box, (vii) beads on a rod, (viii) finger tapping, (ix) nut and bolt and (x) rod slide. Raw scores were converted to scaled scores (M = 10, SD = 3) using age appropriate tables of norms, and the total of the scaled scores was used to calculate the Neuromuscular Development Index (NDI) (M = 100, SD = 15). Scores falling below one standard deviation of the mean are considered to indicate impaired motor ability (20).

Infant risk factors

Infant risk factors explored in the analyses were APGAR scores at 1 minute, parity, gestational age, percentage of optimal birthweight (a calculated measure of the appropriateness of foetal growth relying on nonclinical contributors to foetal size, including gestational duration, sex, maternal height and age and parity, rather than relying on specified percentile position) (21), sex, time to spontaneous respiration and whether the child was a twin or triplet. Using ultrasound imaging and audible signals, an umbilical artery and arcuate artery within the placenta were located and Doppler flow velocity waveforms were obtained in half of the women enrolled in the study, who were randomly selected (19). Doppler flow was considered abnormal if one of the arteries had reduced blood flow detected. A categorical variable was created to reflect whether the offspring were from pregnancies that had any abnormal Doppler waveform (n = 205, 7%), no abnormal Doppler waveform (n = 1223, 43%) or had no Doppler study completed (n = 1428, 50%).

Maternal risk factors

Maternal data were collected at enrolment and updated at 34 weeks gestation. Wording of the updated questionnaire ensured there were no duplications of data. Potential risk factors that were explored included maternal age and hypertensive status. Hypertension was defined as a systolic blood pressure above ≥ 140 mmHg and/or an increase in diastolic blood pressure ≥90 mmHg. Pre-eclampsia was diagnosed if mothers had hypertension with the addition of proteinuria (300 mg/24 hours). The number of stressful events experienced during pregnancy was recorded on a ten-item questionnaire based on Tennant and Andrews Life Stress Inventory (22). The first questionnaire completed at enrolment asked if any of the events had happened since becoming pregnant, while the second questionnaire at 34 weeks asked if any had happened in the last 4 months. The total number of stressful events was recorded as a continuous variable. Low family income was determined according to the Australian government minimum

threshold for low income of $24 000/p.a., and a dichotomised variable was created. Breastfeeding was recorded as a dichotomised variable reflecting those who breastfed for 6 months or more or >6 months. Maternal smoking, alcohol and drug consumption were recorded at 18 and 34 weeks gestation. Mothers were classed as either drinking never, once a week or less, several times a week or daily. Cigarettes were recorded as none, >10 a day or 10 or more a day. Mothers were asked if they took any recreational drugs during pregnancy and this was recorded as a binary variable, as individual numbers of each recreational drug were very low. Mode of birth was recorded as spontaneous vaginal delivery, assisted spontaneous vaginal delivery (use of forceps, vacuum, etc.), elective Caesarean section (decision made prior to spontaneous rupture of membranes) and nonelective Caesarean section (decision made after SRM). Maternal and pregnancy-related factors such as whether the mother experienced antepartum haemorrhage, threatened abortion or diabetes were also included in the analyses.

STATISTICAL ANALYSES

Cross-sectional analyses using chi-square and *t*-tests were used to identify the variables that impacted motor development at 10, 14 and 17 years. Linear mixed models with Bonferroni post hocs were used to calculate the impact of the identified risk factors on motor development over the three time points. All variables in the models were analysed for interactions. Separate analyses were performed for males and females to explore how the risk factors differed between them.

RESULTS

Available data for each year of assessment are reported in Table 1. Cohort characteristics (Table 2) were similar between sexes. Participants who did not record any motor development data tended to be from pregnancies where the mother was younger, experienced higher numbers of stressful events, were more likely to smoke cigarettes and fall below the threshold for low income (Table 3). In addition, there were higher numbers of antepartum haemorrhages and a longer average time to spontaneous respiration in the dropout group. The amount of women breastfeeding for 6 months or more was also lower in this group.

During each year, there were more males that fell below the cut-off score on the MAND used to indicate mild motor delay (Table 4), and this reached significance at 10 ($p = <0.001$) and 17 ($p = <0.001$) years. Mean NDIs (Table 5) were also lower in males at 10 ($p = <0.001$) and 17 years ($p = <0.001$).

In the female linear mixed model, hypertensive status, family income, delivery mode, maternal smoking at 18 weeks and maternal stress at 34 weeks were related to motor development outcome. The model for males revealed hypertensive status, percentage of optimal birthweight, family income and delivery mode was related to the outcome measure.

Mode of delivery was related to motor development outcomes in males, with an interaction found (Table 6) between type of delivery and family income ($p = 0.022$). Overall delivery via Caesarean section was related to a lower NDI score; however, income affected this relationship. Males born via Caesarean section (either elective or nonelective) whose mothers fell below the income threshold had lower NDI scores than those born via Caesarean whose mothers were above the threshold (Table 2). Bonferroni post hocs revealed group differences between spontaneous vaginal delivery (SVD) and elective ($p = 0.043$) and nonelective Caesarean ($p = 0.011$) and between assisted SVD and nonelective Caesarean ($p = 0.023$). Males born via SVD regardless of whether assisted or not had higher motor development outcomes than if they were born either by elective or nonelective Caesarean.

Among the males, higher NDI was related to a higher percentage of optimal birthweight ($p = 0.003$) ($\beta = 0.08$). Maternal hypertensive status was negatively related to motor outcomes in males ($p = 0.001$) with pre-eclampsia in particular related to lowered NDI scores. Bonferroni post hocs revealed group differences in male motor development outcomes between the pre-eclampsia and normal BP ($p = <0.001$) and pre-eclampsia and hypertension groups ($p = 0.001$).

Similar to the results of the male model, the female model showed higher motor development outcomes with spontaneous vaginal deliveries, assisted or not than either elective or nonelective Caesarean sections ($p = 0.009$). In the female model, however, no interactions were found. Group differences existed between spontaneous vaginal delivery and elective ($p = 0.014$) and nonelective Caesarean section ($p = 0.025$). There was also a difference between assisted SVD and elective ($p = 0.015$) and nonelective ($p = 0.023$) Caesarean.

Maternal hypertensive status was negatively related to motor outcomes in females ($p = 0.001$). Bonferroni post hocs revealed group differences between pre-eclampsia and hypertension ($p = 0.001$) and pre-eclampsia and normal BP groups ($p = <0.001$).

For the females, maternal smoking during early pregnancy was negatively related to motor development outcome ($p = 0.009$) with a group difference between nonsmokers and those who smoked more than 10 cigarettes per day ($p = 0.004$). The presence of stressful events during late pregnancy was related to lowered female motor development outcomes ($p = <0.001$) ($\beta = -1.12$). An interaction was found in the female model between income and maternal age ($p = 0.044$). If the mothers were above the threshold for low income, the decrease in average NDI scores was minimal as maternal age increased past 35 years, only dropping by one point on the MAND from 85 to 84. In mothers below the threshold, this decrease was markedly sharper, with MAND outcomes decreasing well below the recommended cut-off for impaired motor development.

Table 2 Characteristics of cohort

	Total			Females			Males			
Continuous variables	N	M	SD	N	M	SD	N	M	SD	p Value
Maternal age (years)	2868	27.58	5.92	1413	27.50	5.95	1455	27.65	5.89	0.49
Percentage of expected birthweight	2843	97.40	14.12	1400	97.44	15.28	1443	97.35	12.88	0.87
Gestational age (weeks)	2853	38.65	2.37	1409	38.62	2.45	1444	38.68	2.28	0.53
Time to spontaneous respiration (minutes)	2845	2.87	22.03	1402	3.53	29.56	1443	2.23	10.34	0.12
Number stressful events 18 weeks	2867	1.21	1.25	1413	1.23	1.27	1454	1.19	1.22	0.38
Number stressful events 34 weeks	2553	1.05	1.18	1248	1.04	1.18	1305	1.06	1.19	0.68
	Total			Females			Males			
Categorical variables	N	n	%	N	n	%	N	n	%	p Value
Parity	2868									0.65
Singleton birth		2742	95.60		1342	46.80		1399	48.80	
Twin or triplet		127	4.40		71	2.50		56	2.00	
Threatened abortion	2803									0.60
Yes		193	6.70		91	3.20		102	3.60	
No		2803	91.00		1286	45.90		1324	47.20	
Antepartum haemorrhage	2803									0.45
Yes		235	8.20		121	4.30		114	4.10	
No		2568	89.50		1256	44.80		1312	46.80	
Breastfed	2057			988			1069			1.00
<6 months		908	44.10		436	44.10		472	44.20	
≥6 months		1149	55.90		552	55.90		597	55.80	
Family Income	2679			1298			1381			0.53
<$24 000 p.a		842	31.40		400	30.80		442	32.00	
≥$24 000 p.a		1837	68.60		898	69.20		939	68.00	
Alcohol consumption at 18 weeks	2859									0.25
Never		1559	54.40		787	27.50		772	27.00	
Once a week or less		1132	39.50		531	18.60		601	21.00	
Several time a week		147	5.10		77	2.70		70	2.40	
Daily		21	0.70		11	0.40		10	0.30	
Alcohol consumption at 34 weeks	2570									0.05
Never		1596	55.60		797	31.00		799	31.10	
Once a week or less		837	29.20		385	15.00		452	17.60	
Several time a week		124	4.30		60	2.30		64	2.50	
Daily		13	0.50		10	0.40		3	0.10	
Smoking at 18 weeks	2862									0.16
None		2087	72.80		1007	35.20		1080	37.70	
10 cigarettes a day		445	15.50		225	7.90		220	7.70	
More than 10 cigarettes a day		330	11.50		177	6.20		153	5.30	
Smoking at 34 weeks	2549									0.14
None		1905	66.40		906	35.50		999	39.20	
>10 cigarettes a day		325	11.30		165	6.50		160	6.30	
More than 10 cigarettes a day		319	11.10		169	6.60		150	5.90	
Blood Pressure Status	2868									0.36
Normal blood pressure		2132	74.30		1066	37.20		1066	37.20	
Hypertension		627	21.90		293	10.20		334	11.60	
Pre-eclampsia		109	3.80		54	1.90		55	1.90	
Diabetes	2868									0.66
No		2715	94.70		1338	46.70		1377	48.00	
Yes		109	3.80		56	2.00		53	1.80	
Maybe		44	1.50		19	0.70		25	0.90	
Doppler waveform	2857									0.19
Normal		1223	42.60		585	20.50		638	22.30	
Abnormal		206	7.20		112	3.90		94	3.30	
No Doppler performed		1428	49.80		712	24.90		716	25.10	

Table 2 (Continued)

Categorical variables	Total			Females			Males			p Value
	N	n	%	N	n	%	N	n	%	
Mode of Delivery	2855			1408			1447			0.79
Spontaneous vaginal delivery		1725	60.40		864	50.10		861	59.50	
Assisted vaginal delivery		525	18.40		254	18.00		271	18.70	
Elective Caesarean section		346	12.10		166	11.80		180	12.40	
Nonelective Caesarean section		259	9.10		124	8.80		135	9.30	

DISCUSSION

Several early events were identified as potential risk factors for both male and female motor development outcomes. These included maternal hypertensive status, income and mode of delivery. In addition to this male motor development outcomes were related to percentage of optimal birthweight, while female outcomes related to maternal smoking at 18 weeks and the experience of stressful events at 34 weeks.

The influence of Caesarean section on motor development outcome has previously been reported in the Raine cohort (7); however, the effect was only identified in the males at 10 years, and the differences between elective and nonelective Caesarean were not explored. The impact of Caesarean birth on both sexes in this study may be due to several factors; a difference in methodology, as the previous study, focused on mild motor delay and used a binary outcome variable based on a cut-off score of <85 in the MAND (20), the inclusion in the current study of data from the 14- and 17-year surveys and the separation of Caesarean into elective and nonelective. There are few studies that report on motor development outcomes in children born from Caesarean section birth. As previously identified by Hands and colleagues, there is some evidence of lower intellectual outcomes and more recent research has reported higher levels of adiposity in children born via Caesarean from infancy to adolescence (23). The incidence of asthma and allergies in children born via Caesarean has been scrutinised by several international studies with varying results (24). The explanation for the link between Caesarean section and motor development outcomes is still unclear; however, several recent studies have provided support for the theory that interruptions to normal colonisation of gut microbiota in infants may impact the central nervous system (25). Mode of delivery can influence the composition of microorganisms which colonise the newborn gut, with bifidobacteria (probiotics) more common in vaginal deliveries (26). It is theorised that gut microbiome can influence the synaptogenesis, stress response, neural growth and neurotransmission of the developing central nervous system (25), although the end result of this relationship on motor development outcomes has not been widely researched. The impact of delivery mode however can also be related to other obstetric complications, and this should be taken into account when examining delivery mode as a possible risk factor for any area of development.

Previous research has found that factors such as weight and gestational age may have more of an impact on male infant morbidity and mortality rates (27,28) and cognitive and motor outcomes during early childhood (9,18) than females. This sex disparity may be due to physiological differences in foetal development that have been estimated to disadvantage males by 4–6 weeks, meaning that even premature female infants are still at an advantage compared to their male counterparts (8). Findings from the current study provide support for this sex difference, with percentage of optimal birthweight (a measure of foetal growth potential using both birthweight and gestational age) affecting male motor outcomes more than females.

Previous research into the effect of maternal hypertension and pre-eclampsia on motor development using data from the Raine cohort has found a relationship between maternal hypertensive status and motor outcomes at 10 years (7) and at 10, 14 and 17 years (16). The long-term effect on motor development was theorised to be caused by a potential reduction in placental function due to abnormal placental morphology and restricted uteroplacental blood flow (29,30), most often found in early-onset pre-eclampsia. Other recent findings, however, indicate no difference in motor outcomes between infants of women with typical umbilical artery waveforms and those with absent end-diastolic flow (31). The effect of hypertensive disease on motor outcomes may indicate a permanent dysfunction or interruption during gestation of the developing neurological system. The role of restricted placental blood flow, as measured by Doppler flow velocities, needs to be investigated further as a potential mechanism.

In the female model maternal smoking during early pregnancy, stressful events during late pregnancy and younger maternal age were all related to a decrease in motor development outcomes. Maternal smoking during pregnancy has been previously reported to affect motor development measures in middle (32) and late childhood (33), and processing speed, interhemispheric communication and visual-motor coordination in adolescents (15). Furthermore, recent findings indicate children exposed to prenatal smoking have reduced foetal head and body growth and have shown signs of altered brain structure

Table 3 Group difference according to attrition rates

	Total			MAND* completed			No MAND* completed			
Continuous variables	N	M	SD	N	M	SD	N	M	SD	p Value
Maternal age (years)	2868	27.57	5.92	1917	28.3	5.79	951	26.1	5.91	<0.001
Percentage of expected birthweight	2843	97.4	14.11	1906	97.68	14.14	937	96.81	14.05	0.122
Time to spontaneous respiration (minutes)	2845	2.87	22.03	1907	1.18	8.47	938	5.01	36.33	<0.001
Number stressful events 18 weeks	2867	1.21	1.24	1917	1.17	1.21	951	1.28	1.31	0.017
Number stressful events 34 weeks	2553	1.05	1.18	1752	1.01	1.15	801	1.13	1.25	0.016
	Total			MAND* completed			No MAND* completed			
Categorical variables	N	n	%	N	n	%	N	n	%	p Value
Sex	2868			1917			951			0.81
Male		1455	50.7		995	51.9		460	48.4	
Female		1413	49.3		922	48.1		491	51.6	
Multiple Birth	2868			1917			951			0.772
Singleton birth		2741	95.6		1834	95.7		907	95.4	
Twin or triplet		127	4.4		83	4.3		44	4.6	
Parity	2848			1911			937			0.102
First born		1368	48		897	46.9		471	50.3	
Has older siblings		1480	52		1014	53.1		466	49.7	
Threatened abortion	2803			1875			928			0.268
No		2610	93.1		1753	93.5		857	92.3	
Yes		193	6.9		122	6.5		71	7.7	
Antepartum haemorrhage	2803			1784			928			0.004
No		2568	91.6		1738	92.7		830	89.4	
Yes		235	8.4		137	7.3		98	10.6	
Breastfed	2057			1568			489			0.003
<6 months		907	44.1		664	42.3		244	49.9	
≥6 months		1149	55.9		904	57.7		245	50.1	
Family Income	2679			1819			860			<0.001
<$24 000 p.a		842	31.4		487	26.8		355	41.3	
≥$24 000 p.a		1837	68.6		1332	73.2		505	58.7	
Alcohol consumption at 18 weeks	2859			1910			949			0.039
Never		1559	54.5		1013	53		546	57.5	
Once a week or less		1132	39.6		791	41.4		341	35.9	
Several time a week		147	5.1		92	4.8		55	5.8	
Daily		21	0.7		14	0.7		7	0.7	
Alcohol consumption at 34 weeks	2570			1765			805			0.023
Never		1596	62.1		1063	60.2		533	66.2	
Once a week or less		837	32.6		604	34.2		233	28.9	
Several time a week		124	4.8		87	4.9		37	4.6	
Daily		13	0.5		11	0.6		2	0.2	
Smoking at 18 weeks	2862			1913			949			<0.001
None		2087	72.9		1477	77.2		610	64.3	
>10 cigarettes a day		445	15.5		257	13.4		188	19.8	
More than 10 cigarettes a day		330	11.5		179	9.4		151	15.9	
Smoking at 34 weeks	2549			1751			798			<0.001
None		1905	74.7		1381	78.9		524	65.7	
>10 cigarettes a day		325	12.8		196	11.2		129	16.2	
More than 10 cigarettes a day		319	12.5		174	9.9		145	18.2	
Blood Pressure Status	2868			1917			951			0.085
Normal blood pressure		2132	74.3		1404	73.2		728	76.6	
Hypertension		627	21.9		442	23.1		185	19.5	
Pre-eclampsia		109	3.8		71	3.7		38	4	
Diabetes	2868			1917			951			0.872
No		2715	94.7		1813	94.6		902	94.8	
Yes		109	3.8		73	3.8		36	3.8	
Maybe		44	1.5		31	1.6		13	1.4	

Table 3 (Continued)

Categorical variables	Total N	Total n	Total %	MAND* completed N	MAND* completed n	MAND* completed %	No MAND* completed N	No MAND* completed n	No MAND* completed %	p Value
Doppler waveform	2857			1914			943			0.281
Normal		1223	42.8		838	43.8		385	40.8	
Abnormal		206	7.2		139	7.3		67	7.1	
No Doppler performed		1428	50		937	49		491	52.1	
Mode of Delivery	2855			1913			942			0.831
Spontaneous vaginal delivery		1725	60.4		1150	60.1		575	61	
Assisted vaginal delivery		525	18.4		353	18.5		172	18.3	
Elective Caesarean section		346	12.1		230	12		116	12.3	
Nonelective Caesarean section		259			180	9.4		79	8.4	

*MAND – McCarron Assessment of Neuromuscular Development.

Table 4 Number of males and females who scored below the recommended cut-off for mild motor delay

	Males				Females				
	≥85		<85		≥85		<85		
Binary NDI*	N	%	N	%	N	%	N	%	Group difference
10 years	603	71.5	240	28.5	627	80.5	152	19.5	p = <0.001
14 years	632	77.5	183	22.5	601	78.2	168	21.8	p = 0.81
17 years	496	80.8	118	19.2	385	63.4	222	36.6	p = <0.001

*NDI – Neuromuscular Development Index.

Table 5 Mean scores of the NDI for males and females

	Males NDI*		Females NDI*		
	M	SD	M	SD	Group difference
10 years	92.7	14.5	95.5	13.3	p = <0.001
14 years	99.5	18.5	98.3	16.7	p = 0.168
17 years	101.2	18.0	91.2	14.5	p = <0.001

*NDI – Neuromuscular Development Index.

Table 6 Delivery mode and income interaction, male linear mixed model

	>$24 000 p.a. Mean NDI*	<$24 000 p.a. Mean NDI*
Spontaneous Vaginal Delivery	97.56	94.29
Assisted SVD	95.50	96.82
Elective Caesarean	92.78	93.85
Nonelective Caesarean	96.01	88.44

*NDI – Neuromuscular Development Index.

and function (13). Previous studies reported males born to mothers who smoked were more susceptible to adverse motor development outcomes (33). Furthermore, preterm male infants, when compared to preterm females, reportedly needed more circulatory and respiratory support (28). These findings suggest male infants may have more vulnerable respiratory and neurological systems, whereas findings from the current study indicate female motor outcomes were more affected by maternal smoking. Measures of smoking used in the previous studies (33) were similar, nonsmokers, <10/day and >10/day; however, the collection of smoking data at two time points in the current study allowed for changes in smoking status and comparison between early and late gestational intake to be analysed. Lung development occurs throughout the embryonic, foetal and neonatal period. It may be that critical windows of development occur at different times during male and female foetal development and the inclusion of two time frames of maternal smoking allowed this difference to be identified.

Gestational stress impacts motor development in infancy and early childhood (17,34); however, sex differences in the outcomes have not often been reported. In the current study, female motor development outcomes were affected by late gestational stress. The development of the cerebellar cortex, principally responsible for postural control and motor coordination occurs late in gestation (35). Disturbances in the formation of neural pathways, which occur during this time, may contribute to the lowered outcomes. Hands and colleagues (7) found males with mild motor disability at 10 years were more affected by birth and postnatal events (including a stressful first year), while females were more influenced by risk factors occurring

during gestation. It was postulated that timing of developmental windows during gestation and postnatal life differed between males and females.

In the female model of motor development, an interaction was revealed between maternal income and maternal age. As maternal age increased NDI decreased. This is in contrast to several previous studies that have found lowered levels of health, development, mortality, education and workplace outcomes in children born to 'young' mothers, those who were under 25 years of age (36,37). These reports, however, were not conclusive and other underlying reasons, such as socio-economic disadvantage were suggested as contributing factors. The current findings provide support for this, with income having a marked impact on whether maternal age affected motor development outcome. The effect of income on motor development outcome has not been extensively reported previously; however, some international studies have indicated a difference in motor development between children from lower socio-economic situations compared to their economically advantaged peers (38,39). These studies reported both gross (38) and fine (39) motor outcomes were negatively affected by socio-economic factors; however, no studies have thus far reported the effect of socio-economic status on motor development past early childhood. Furthermore, studies that have reported income as a risk factor for lowered motor development outcomes have been undertaken in less affluent countries than Australia, and therefore, the results may not be comparable to an Australian population. Further analyses using additional Raine Study socio-economic data throughout childhood may help to evaluate the potential effect of changing economic circumstance on longitudinal motor development outcomes.

STRENGTHS

A large population-based sample and in-depth obstetric records, questionnaire and physical data allowed for a stringent and robust analysis of the effect of antenatal factors on motor development. The longitudinal nature of the study allowed the impact of early life risk factors on motor development outcomes to be measured throughout childhood and into adolescence, which has not been previously addressed adequately. The MAND (20) is a reliable and accurate measure of motor development among Australian children (40).

LIMITATIONS

While extensive obstetric and maternal health data were available, a measure of parental motor development was not conducted. Analyses of the influence of parental motor development were therefore not possible. Retention of participants for all three phases of the study was 34.9% of the original cohort; however, a further 18.8% completed two of the testing phases and 13.9% completed one testing phase. Younger mothers who experienced higher numbers of stressful events were more likely to smoke cigarettes and fell below the threshold for low income were more likely to drop out of the study. However, as the original cohort slightly overrepresented socially disadvantaged women (41), this attrition pattern may have increased the generalisability of the study.

CONCLUSION

A growing body of evidence is revealing the importance of early life factors on the development and functioning of the neurological and neuromuscular systems; however, few studies can comprehensively report on the effects of these potential risk factors into adolescence. Results of this study indicate events experienced in the antenatal, perinatal and neonatal periods can impact long-term motor development outcomes. Maternal hypertensive status, socio-economic status and mode of delivery were related to motor development during late childhood and adolescence. The variance between males and females in other risk factors, such as maternal stress, smoking and percentage of optimal birthweight suggests that the underlying neurological systems of males and females may develop differently.

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CONFLICT OF INTEREST

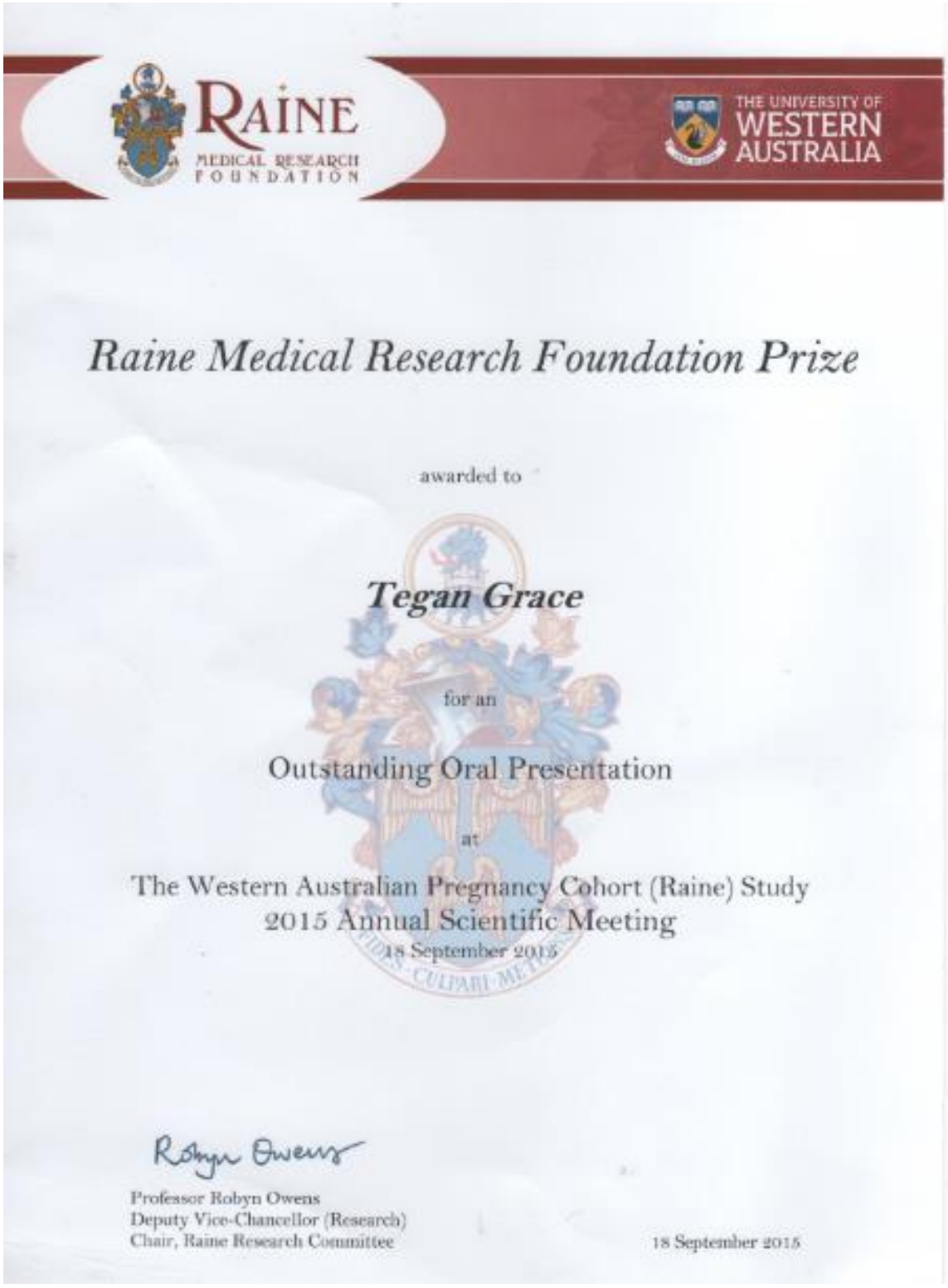
The authors have no conflict of interest to disclose. There are no financial relationships relevant to this article to disclose.

References

1. Skinner RA, Piek JP. Psychosocial implications of poor motor coordination in children and adolescence. *Hum Mov Sci* 2001; 20: 73–94.
2. Piek JP, Rigoli D, Pearsall-Jones JG, Martin NC, Hay DA, Bennett KS, et al. Depressive symptomatology in child and adolescent twins with Attention-Deficit Hyperactivity Disorder and/or Developmental Coordination Disorder. *Twin Res Hum Gen* 2007; 10: 587–96.
3. Bejerot S, Humble MB. Childhood clumsiness and peer victimization: a case-control study of psychiatric patients. *BioMed Central Psych* 2013; 13: 68–79.

4. Gillberg C, Gillberg C. Three-year follow up at age 10 of children with minor neurodevelopmental disorders. I: behavioural problems. *Dev Med Child Neurol* 1983; 25: 438–49.
5. Rasmussen P, Gillberg C. Natural outcome of ADHD with Developmental Coordination Disorder at age 22 years: a controlled, longitudinal, community-based study. *Am Academy Child Adol Psych* 2000; 39: 1425–31.
6. Pitcher JB, Henderson-Smart DJ, Robinson JS. Prenatal Programming of Human Motor Function. In: EM Wintour, JA Owens, editors. *Early Life Origins of Health and Disease*. New York: Springer Science + Business Media, 2006.
7. Hands B, Kendall G, Larkin D, Parker H. Perinatal risk factors for mild motor disability. *Int J Dis Dev Ed* 2009; 56: 317–31.
8. Kraemer S. The fragile male. *British Med J* 2000; 321: 1609–12.
9. Cho J, Holditch-Davis D, Miles MS. Effects of gender on the health and development of medically at-risk infants. *J Obstet Gynecol Neonatal Nurs* 2010; 39: 536–49.
10. Pitcher JB, Schneider LA, Burns NR, Drysdale JL, Higgins RD, Ridding MC, et al. Reduced corticomotor excitability and motor skills development in children born preterm. *J Physiol* 2012; 590: 5827–44.
11. Schmidhauser J, Caflisch J, Rousson V, Bucher HU, Largo RH, Latal B. Impaired motor performance and movement quality in very-low-birthweight children at 6 years of age. *Dev Med Child Neurol* 2006; 48: 718–22.
12. Savchev S, Sanz-Cortes M, Cruz-Martinez R, Arranz A, Botet F, Gratacos E, et al. Neurodevelopmental outcome of full term small-for-gestational-age infants with normal placental function. *Ultrasound Obstet Gynecol* 2013; 42: 201–6.
13. Ekblad M, Korkeila J, Lehtonen L. Smoking during pregnancy affects foetal brain development. *Acta Paediatr* 2015; 104: 12–8.
14. Simmons RW, Thomas JD, Levy SS, Riley EP. Motor response programming and movement time in children with heavy prenatal alcohol exposure. *Alcohol* 2010; 44: 371–78.
15. Willforda JA, Chandler LS, Goldschmidt L, Daya NL. Effects of prenatal tobacco, alcohol and marijuana exposure on processing speed, visual-motor coordination and interhemispheric transfer. *Neurotoxicol Teratol* 2010; 32: 580–8.
16. Grace T, Bulsara M, Pennell C, Hands B. Maternal hypertensive diseases negatively affect offspring motor development. *Preg Hyp* 2014; 4: 209.
17. Sandman CA, Davis EP, Buss C, Glynn LM. Prenatal programming of human neurological function. *Int J Peptides* 2011. doi:10.1155/2011/837596.
18. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birth-weight infants. *Acta Paediatr* 2006; 95: 1239–48.
19. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. *Lancet* 1993; 342: 887–91.
20. McCarron LT. *MAND McCarron Assessment of Neuromuscular Development*. Dallas, TX: Common Market Press, 1997.
21. Blair E, Yingxin L, de Klerk NH, Lawrence DM. Optimal fetal growth for the Caucasian singleton and assessment of appropriateness of fetal growth: an analysis of a total population perinatal database. *BMC Pediatr* 2005; 5: 1–12.
22. Tennant C, Andrews G. A scale to measure the cause of life events. *Aust N Z J Psych* 1977; 11: 163–7.
23. Salehi-Abargouei A, Shiranian A, Ehsani S, Surkan PJ, Asmaillzadeh A. Caesarean delivery is associated with childhood general obesity but not abdominal obesity in Iranian elementary school children. *Acta Paediatr* 2014; 103: e383–7.
24. Almquist C, Oberg AS. The association between caesarean section and asthma or allergic disease continues to challenge. *Acta Paediatr* 2014; 103: 349–51.
25. Clarke G, O'Mahony SM, Dinan TG, Cryan JF. Priming for health: gut microbiota aquired in early life regulates physiology, brain and behaviour. *Acta Paediatr* 2014; 103: 812–9.
26. Musilova S, Rada V, Vlkova E, Bunesova V, Nevoral J. Colonisation of the gut by bifidobacteria is much more common in vaginal deliveries than caesarean sections. *Acta Paediatr* 2015; 104: e184–6.
27. Mansson J, Fellman V, Stjernqvist K. Extremely preterm birth affects boys more and socio-economic and neonatal variables pose sex-specific risks. *Acta Paediatr* 2015; 104: 514–21.
28. Elsmen E, Pupp IH, Hellstrom-Westas L. Preterm male infants need more initial respiratory and circulatory support than female infants. *Acta Paediatr* 2004; 93: 529–33.
29. Egbor M, Ansari T, Morris N, Green CJ, Sibbons PD. Morphometric placental villous and vascular abnormalities in early-and late-onset pre-eclampsia with and without fetal growth restriction. *Bri J Obstet Gynaecol* 2006; 113: 580–9.
30. Matsuo K, Malinow AM, Harman CR, Baschat AA. Decreased placental oxygenation capacity in preeclampsia: clinical application of a novel index of placental function performed at the time of delivery. *J Perinat Med* 2009; 37: 657–61.
31. Kirsten GF, van Zyl JI, van Zijl F, Maritz JS, Odendaal HJ. Infants of women with severe early pre-eclampsia: the effect of absent end-diastolic umbilical artery Doppler flow velocities on neurodevelopomental outcome. *Acta Paediatr* 2000; 89: 566–70.
32. Trasti N, Vik T, Jacobsen G, Bakketeig LS. Smoking in pregnancy and children's mental health and motor development at age 1 and 5 years. *Early Hum Dev* 1999; 55: 137–47.
33. Larsson M, Montgomery SM. Maternal smoking during pregnancy and physical control and coordination among offspring. *J Epidemiol Community Health* 2008; 65: 1151–8.
34. Ellman LM, Dunkel-Schetter C, Hobel CJ, Chicz-DeMet A, Glynn LM, Sandman CA. Timing of fetal exposure to stress hormones: effects on newborn physical and neuromuscular maturation. *Dev Psychobiol* 2008; 50: 232–41.
35. Gramsbergen A. Clumsiness and disturbed cerebellar development: insights from animal experiments. *Neural Plastic* 2003; 10: 129–40.
36. Bradbury B. *Young motherhood and child outcomes, SPRC Report 1/11, prepared for the Australian Government Department of Families*. Community Services and Indigenous Affairs: Housing, 2011.
37. Myrskyla M, Fenelon A. *Maternal age and offspring adult health: evidence from the health and retirement study*. USA: Max Planck Institute for Demographic Research, 2011: 1–46.
38. Bobbio TG, Gabbard C, Goncalves VG, Filho AAB, Morcillo AM. Interlimb coordination differentiates Brazilian children from two socioeconomic settings. *Pediatics Int* 2010; 52: 353–7.
39. de Barros KMFT, Fragoso AGC, de Oliveira ALB, Filho JEC, de Castro RM. Do environmental influences alter motor ability acquisition? A comparison among children from day-care centers and private schools. *Arq Neuropsiquiatr* 2003; 61: 170–5.
40. Tan SK, Parker H, Larkin D. Concurrent validity of motor tests used to identify children with motor impairment. *Adapt Phys Act Quart* 2001; 18: 168–82.
41. Li C, Kendall GE, Henderson S, Downie J, Landsborough L, Oddy WH. Maternal psychosocial well-being in pregnancy and breastfeeding duration. *Acta Paediatr* 2008; 97: 221–5.

Appendix D Breastfeeding Manuscript Award and Presentation



RAINE MEDICAL RESEARCH FOUNDATION

THE UNIVERSITY OF WESTERN AUSTRALIA

Raine Medical Research Foundation Prize

awarded to

Tegan Grace

for an

Outstanding Oral Presentation

at

The Western Australian Pregnancy Cohort (Raine) Study
2015 Annual Scientific Meeting
18 September 2015

Robyn Owens

Professor Robyn Owens
Deputy Vice-Chancellor (Research)
Chair, Raine Research Committee

18 September 2015

Raine Study Scientific Day Oral Presentation, Perth, WA, Nov 2015

Duration of Breastfeeding and Motor Development Outcomes at 10, 14 and 17 years: A Longitudinal Study

Tegan Grace
Professor Beth Hands
Professor Wendy Oddy
Professor Max Bulsara

The Raine Study

Year	Active	MAND	% Active	Deferred	Lost	Withdrawn	Deceased	Total
Birth	1868							
10	2047	1622	79%	191	162	349	20	1868
14	1960	1594	85%	257	207	412	22	1868
17	1754	1221	69%	414	184	480	26	1868

Importance of Motor Competence

Current rate for low motor competence in Australian school children reported at 15-18%

Mental Health

- Depression
- Lower Global Self Worth
- Higher Incidence of Behavioural Problems
- Learning Difficulties

Physical Health

- Lower level of physical activity
- Increased obesity

Early Determinants of Motor Competence

- Breastfeeding
- Sex (Holdrich-Davis & Miles, 2010; Hands et al., 2009; Kraemer, 2000)
- Low Birth Weight (Schmidhauser et al., 2008)
- Pre-term birth (Pitcher et al, 2006 Foulder-Hughes & Cooke, 2003)
- Intrauterine Growth Restriction (Pitcher et al, 2006)
- Small for Gestational Age (Pitcher et al., 2006; Sanchez et al., 2013)
- Smoking (Bisgaard, Kotelchuck, & Lehmann, 2010)
- Maternal Stress (Grace, Hands, Bulsara & Robinson, 2013)
- Maternal Alcohol Intake (Simmons, Thomas, Levy, & Riley, 2010)
- Maternal Drug Use (Williams, Chandler, Goldschmidt, & Day, 2010)
- Maternal Hyp. Disease (Grace, Bulsara, Pennell, & Hands, 2014)

Breast feeding & Motor Development

Current recommendations include exclusive breastfeeding for at least 6 months (WHO, 2008; NHMRC, 2012)

Sociodemographic Factors – known to influence decision to BF and duration of BF

Confounding factors

- Favourable home environment
- Higher socioeconomic status
- Older mothers

(Scott, Binns, Oddy, & Graham, 2006; Zhou, Baghurst, Gibson, & Makrides, 2007; Oddy et al., 2011; Oddy et al., 2003; Oddy et al., 2011; Vanegaard et al., 1999)

Method – Predictor Variable

- Breastfeeding - measured as duration of breastfeeding in months
- Data collected retrospectively during follow up phases at 1, 2 and 3 years.
- Binary variable
  - Breastfed <6 months
  - Breastfed ≥6 months

McCarron Assessment of Neuromuscular Development

Data Analyses

Maternal Variables

hypertensive status
age
socioeconomic status
drug use
alcohol consumption
cigarette smoking
stress
infection / illness
gestational diabetes
obstetric complications

NDI
10yrs
14yrs
17yrs

Child Variables

breast feeding
gestational age
girth weight
POBW
TSR
APGAR (1min)
Mode of delivery (SVD, CS)

Table 1. Average NDI of Breastfeeding Groups

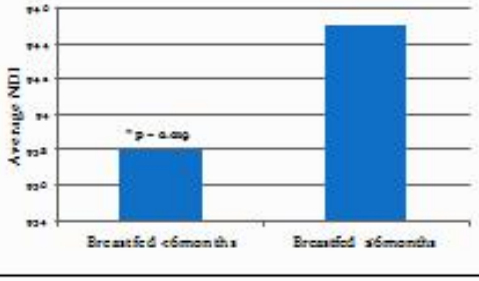
	Breastfed <6 months	Breastfed ≥6 months	Group Difference
10	92.96 (13.26)	95.03 (14.41)	p = 0.008
14	96.98 (17.18)	100.84 (18.12)	p = <0.001
17	95.06 (17.14)	97.42 (17.26)	p = 0.035

Table 1. Incidences of mild motor disability in breastfeeding groups

	Breastfed <6 months		Breastfed ≥6 months		Group Difference
	<85 NDI	≥85 NDI	<85 NDI	≥85 NDI	
Yr 10	149 27.1%	401 72.9%	164 20.9%	621 79.1%	p=0.003
Yr 14	158 25.7%	400 74.3%	150 19.6%	616 80.4%	p=0.010
Yr 17	126 31.2%	278 68.8%	159 25.6%	463 74.4%	p=0.054

* An NDI of ≤85 can indicate a mild motor disability

Linear Mixed Model Results

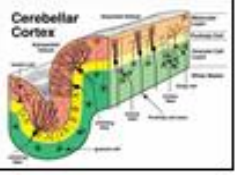


Neural System Development

Third trimester & well into first decade of life
Cerebellum developing

Responsible for the coordination, precision and accuracy of movement, language, attention

Key time for the development of the cerebellar cortex



Breast Milk Components

Long Chain Polyunsaturated Fatty Acids (LC-PUFAs)
- docosahexaenoic acid (DHA)
- arachidonic acid (AA)

Essential element of neural membranes & potential mechanism for favourable neurological development

Provide a neuroprotective effect

DHA levels in cerebellum grey matter higher in BF infants

(Clowes et al., 2001; Innis, 2000; Uauy & DeAndraca, 1995; Lauritzen et al., 2000; Malcolm, Neumann, Eyland, Simmer, & Gibson, 1994; Jamieson et al., 1999)

Conclusion...

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