Breathing and Behaviour: Exploring Infant Temperament and Autism Risk in Infants Born to Mothers with Asthma

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Declarations

STATEMENT OF ORIGINALITY

I hereby certify that the work embodied in the thesis is my own work, conducted under normal supervision. The thesis contains no material which has been accepted, or is being examined, for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968 and any approved embargo.

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ACKNOWLEDGMENT OF AUTHORSHIP

I hereby certify that the work embodied in this thesis contains scholarly work of which I am a joint author. I have included as part of the thesis a written declaration endorsed in writing by my supervisor, attesting to my contribution to the joint scholarly work.

By signing below I confirm that Carly Mallise contributed substantially to the conception and design of the research, to the acquisition, analysis, and interpretation of data, and to the drafting and revising of important intellectual content pertaining to the scholarly work entitled "The Temperament Features Associated with Autism Spectrum Disorder in Childhood: A Systematic Review".

Dr Linda Campbell

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> There's always gonna be another mountain
> I'm always gonna wanna make it move
> Always gonna be an uphill battle
> Sometimes I'm gonna have to lose
> Ain't about how fast I get there
> Ain't about what's waiting on the other side
> It's the climb
> - The Climb by Miley Cyrus

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Table of Abbreviations

Abbreviation	Definition
ATP	Australian Temperament Project
ASD	Autism Spectrum Disorder
Bayley-III	Bayley Scales of Infant and Toddler Development, 3rd edition
BF	Bayes Factor
BLT	Breathing for Life Trial study
BLT-ID	Breathing for Life Trial – Infant Development study
BMs	BabyMinds study
BMI	Body Mass Index
CTS	Carey Temperament Scales
CFHN	Children and Family Health Nursing Service
EAS	Emotionality, Activity and Sociability framework
EITQ	Early Infancy Temperament Questionnaire
EPDS	Edinburgh Postnatal Depression Scale
FYI	First Year Inventory
IBQ	Infant Behavior Questionnaire
ICS	inhaled corticosteroids
ID	Intellectual disability
Infant-sibs	infant siblings of children diagnosed with autism
ISP2	Infant Sensory Profile 2
JBI-CA	Joanna Briggs Institute Critical Appraisal checklist
LABA	long-acting beta-antagonist
MIA	maternal immune activation
NYLS	New York Longitudinal Study
RCT	randomised controlled trial
RITQ	Revised Infant Temperament Questionnaire
SABA	short-acting beta agonists
SP2	Sensory Profile 2
SPSS	Statistical Package for the Social Sciences
TSP2	Toddler Sensory Profile 2
TTS	Toddler Temperament Scale
VIF	variance inflation factor

Abstract

Background: Temperament is defined as the early individual differences in behavioural style and plays an important role in developmental processes across the lifespan. Temperament differences have been identified in infants at-risk for ASD, specifically infant siblings of children with ASD. Exploring temperament in at-risk groups may help identify individual differences within ASD, which can subsequently be used to promote improved customisation of interventions. However, there have been no published studies examining the temperament of other at-risk groups in infancy, such as infants born to mothers with asthma. Asthma commonly complicates pregnancy, affecting the physical health of mother and child. Infants born to mothers with asthma are more likely to have poorer perinatal outcomes. These outcomes, such as premature birth and low birthweight, are known risk factors for poorer developmental outcomes in childhood. Further, emerging research suggests that these infants may be at an increased risk of ASD. Exploring temperament and ASD risk in infants born to mothers with asthma may allow for the early identification of those at-risk for poorer developmental outcomes in later childhood.

Aims: This thesis aimed to (1) characterise the temperament features of infants born to mothers with asthma at 6 weeks, 6 months and 12 months of age, comparing to normative data and community controls; (2) examine whether temperament features were associated with ASD symptoms at 12 months of age, in infants born to mothers with and without asthma; and (3) explore the temperament, sensory and global developmental features of infants born to mothers with asthma who were screened as ‘at-risk’ for ASD.

Methods: Data was collected as part of two longitudinal studies based in New South Wales, Australia; the Breathing for Life Trial – Infant Development study and the BabyMinds study. Participants were mothers with (*n* = 183) and without (*n* = 82) asthma, and their infants. Mothers with asthma had asthma severity and asthma control assessed using the Global

Initiative for Asthma guidelines during pregnancy. All mothers reported on their infants' temperament (measured by the Carey Temperament Scales) and sensory features (measured by the Sensory Profile 2) at 6 weeks, 6 months and 12 months of age. Infant risk of ASD (measured by the First Year Inventory) was assessed by parental report at 12 months of age. Infant cognitive, language and motor development (measured by the Bayley Scales of Infant and Toddler Development) was assessed at 6 and 12 months of age.

Results: Infants born to mothers with asthma differed in their temperament from normative samples, yet not community infants. Additionally, there were no significant differences in infant temperament, based on maternal asthma severity and asthma control during pregnancy. Many associations between temperament domains across the three time points and autism risk were observed in infants born to mothers with asthma, with fewer associations observed in infants born to mothers without asthma. Adaptability (6 months) and distractibility (6 and 12 months) were significant predictors of increased autism risk in infants born to mothers with asthma. Across the three timepoints, infants born to mothers with asthma screened as at-risk for ASD (6 out of 76 infants who were screened for ASD risk) presented with differences to the norm in their temperament, sensory processing and language development. These at-risk infants were more arrhythmic, fussier in mood, less persistent with challenging tasks, and more difficult to distract. Two distinct sensory processing subtypes - sensory adaptive and sensory reactive - were present at 12 months in the at-risk infants. Lastly, the at-risk infants had developmentally appropriate cognitive skills, less-developed language skills, and varied motor skills.

Conclusions: This thesis provides no evidence that infants born to mothers with asthma are at an increased risk for temperament difficulties, regardless of maternal asthma severity or asthma control status. This finding is significant as it sends a positive message to both pregnancy women with asthma and their health professionals. However, behavioural features,

particularly slow adaptability to change, low distractibility and high sensory reactivity, may be early indicators of higher autism risk in this cohort. Overall, these results support the further examinations of developmental outcomes in infants born to mothers with asthma, in order to understand links between early behavioural features and later childhood functioning.

Chapter One: Introduction

The Construct of Temperament, Asthma during Pregnancy, and the Emergence of Autism Spectrum Disorder

Temperament is arguably one of the most important psychological constructs to shape child development (Baer et al., 2015; Galéra, Côté, Bouvard, & et al., 2011; Gartstein, Putnam, & Kliewer, 2016; Johnson, Gliga, Jones, & Charman, 2015; Studer-Luethi, Bauer, & Perrig, 2016). Temperament refers to the early individual differences in behavioural style (Thomas, Chess, Birch, Hertzig, & Korn, 1963). Previous work has identified that temperament in the first year of life is salient to the development of the infant, as it influences the mother-infant bonding experience, early cognition, and the emergence of behavioural problems in later childhood (Gueron-Sela, Atzaba-Poria, Meiri, & Marks, 2016; Miller, Degnan, Hane, Fox, & Chronis-Tuscano, 2019; Nolvi et al., 2016). In particular, infant temperament has been associated with Autism Spectrum Disorder (ASD) and may provide a unique contribution to the heterogeneity of the disorder (See systematic review in Chapter Two). Recently, there have been links observed between maternal asthma and ASD, with a child more likely to develop autism if their mother had asthma during pregnancy (e.g., Gong et al., 2019). To date, however, there is no study investigating early temperament in infants born to mothers with asthma and its links to ASD risk.

This thesis focuses on the characterisation and relationship of temperament and autism risk in infants born to mothers with asthma, during the first year of life. In this chapter, the construct of temperament will be described and an account of its relationship to development across childhood provided. I will then discuss maternal asthma during pregnancy and evidence for its links to developmental vulnerabilities in offspring, such as ASD. Subsequently, I will provide an overview of ASD and its associated developmental features in infancy. I will conclude with a summary of the gaps in the literature pertaining to temperament and ASD risk in infants born to mothers with asthma, linking to the research questions of this thesis.

1.1 The Construct of Infant Temperament and its Influence on Child Development

Temperament was first defined by Gordon Allport as "…the characteristic phenomena of an individual's emotional nature, including his susceptibility to emotional stimulation, his customary strength and speed of response, the quality of his prevailing mood, and all peculiarities of fluctuation and intensity of mood…" (p.g. 91, 1937 in Goldsmith & Gottesman, 1981). This definition suggests that temperament is emotion-based, primarily involving mood. Key researchers in the field of temperament have since built upon this definition, in order to characterise the behavioural features linked to child development. The following two sections will firstly (a) review and contrast the four main conceptual frameworks of temperament in the field, and subsequently (b) explore the literature that examined temperamental features associated with psychosocial development, behavioural problems, and learning in childhood.

1.1.1 The Conceptual Frameworks of Temperament

There are four conceptual frameworks of temperament commonly discussed in the literature: (a) Thomas, Chess and Colleague's (1963) Child Psychiatric approach (b) Buss and Plomin's (1975) Emotionality, Activity and Sociability Criterion approach (c) Rothbart's (1981) Psychobiological approach and d) Goldsmith's (1981) Emotion Systems approach. I discuss them below in chronological order.

1.1.1.1 The New York Longitudinal Study: Child Psychiatric Framework of Alexander Thomas and Stella Chess

The New York Longitudinal Study (NYLS) conducted by Thomas et al. (1963) represents an early landmark in temperament research. In this study, temperament was defined as the early individual differences in behavioural style. While temperament was theorised to be stable over time, the expression of temperament was stated to be modifiable (Goldsmith et al., 1987). Further, the NYLS framework conceptualises temperament as different from personality, in that it is independent of motivations, abilities, values, and defence mechanisms.

The NYLS framework was developed using middle- and upper-class families, from urban and suburban areas in the state of New York. Parents were homogenous: they were predominately Caucasian, well-educated, professionals (i.e., non-manual workers) and from religious backgrounds. A parental interview was used to gather information about the infant's behaviour related to aspects of daily living, which included the following: sleep, feeding, bowel movements and wetting, bathing, nail-cutting and hair-brushing, doctor visits, dressing, sensory processing, motor movements, responses to people and illness, and crying. The questions that were asked specifically pertained to an objective description of how the infants behaved, rather than parental interpretation of their child's behaviour. For example, if the interviewer asked a question related to the infant's acceptance of a new food, and the parent stated that their infant did not like it, the interviewer would then ask the parent to say why they thought their infant did not like the food. The interviewer would ask this in order to extract how the infant reacted to the new food, rather than an interpretation of why (e.g., pushed spoon away, spat food out, grimaced etc). This interview process took approximately two hours, depending on the age of the infant.

Retrospectively to the interviews, the researchers identified related aspects of behaviour from parental responses. For instance, parental responses that pertained to the quality of their infant's mood were grouped together. This led to the conceptualisation of nine key behavioural domains that can be used to describe an infant's temperament: Activity, Rhythmicity, Approach, Adaptability, Mood, Intensity, Persistence, Distractibility and Threshold (Table 1.1 in Appendix A). Infants were rated on each domain as high, variable or low within each specific dimension. For example, an infant who was reported by their parents to cry extremely loud during nail cutting, whilst lying still, could be scored as high in mood, high in intensity, and low in activity. Whilst the NYLS framework was shown to produce a reliable and valid measure of infant temperament, the process in which it was carried out was lengthy and time-consuming making it challenging to use in clinical practice and research settings.

1.1.1.1.1 The Development of the Carey Temperament Scales

Subsequent to the work of Thomas and Chess, Carey and colleagues (1970; Carey & McDevitt, 1978a; Fullard, McDevitt, & Carey, 1984; Medoff-Cooper, Carey, & McDevitt, 1993) developed parent-report forms to measure infant temperament, based on the original NYLS framework. The Carey Temperament Scales (CTS), include nine domain scores, each corresponding to one of the original NYLS domains. Each domain is bidirectional in nature, ranging from more manageable (scores more than one standard deviation below the normative mean) to more challenging behaviours (scores more than one standard deviation above the normative mean). The CTS domains included items that were based directly upon the NYLS interview content and confirmed through factor analysis (Carey, 1970; Carey & McDevitt, 1978a). The measure was standardised using infants, recruited between the late 1970's to early 1990's, from private paediatric practices in north-eastern United States. Most infants were from middle to upper class families, and had parents who were well educated (i.e., >40% were university graduates). Consequently, the devised norms may not be suitable for use with infants from other socioeconomic backgrounds. The CTS has acceptable test-retest reliability, however, internal consistency is poor for most of the domains, across each age version (Behavioral-Developmental Initiatives, 2007). This suggests that some items, in any given domain, may not be assessing the same aspect of behaviour. After the development of the initial form, for use with infants aged four to eight months (Carey, 1970; Carey &

McDevitt, 1978a), additional forms were development for use with other age groups (i.e., 1-4 months, 1-2 years, 3-7 years, & 8-12 years). The CTS has been one of the few measures used consistently in the field.

On the basis of the work by Thomas et al. (1963), Carey and colleagues proposed that infants could be categorised into one of four overarching temperament types, or “clinical diagnoses”: easy, difficult, slow-to-warm-up or intermediate. An easy temperament is characterised by positive mood, high approach, quick adaptability, regularity of biological responses, and low distractibility (Carey, 1970). In comparison, a difficult temperament refers to one that is characterised by withdrawal, unpredictability in sleep, hunger, and elimination patterns, being harder to sooth, negativity in mood and slow adaptability to change. A slow-to-warm-up temperament is characterised by inactivity, initial negative mood, and slow approach and adaptability, yet is less fussy and demanding than the difficult infant temperament. Lastly, all children who could not be categorised into one of the first three temperament types were argued to fall into either the intermediate low (more ‘easy’) or the intermediate high (more ‘difficult’) temperament categories.

The CTS is unique in its clinical utility, as it provides clinicians and parents with information on a child’s behavioural tendencies (Carey, 1972, 1985). Understanding the way their child behaves can help parents provide support for their child during situations that are anticipated to be demanding or stressful. It is argued that the temperament categories provide researchers with a ‘complete picture’ of an infant’s temperament profile, which in turn enables a better understanding of early individual differences in behaviour (Carey & McDevitt, 1978b). This enables researchers to explore whether specific temperament profiles make children more vulnerable to atypical developmental outcomes.

1.1.1.2 Emotionality, Activity and Sociability Criterion Framework of Arnold Buss and Robert Plomin

Subsequent to the research of Thomas et al. (1963), Buss and Plomin (1975) constructed a new temperament framework called the Emotionality, Activity and Sociability (EAS) framework (Table 1.1). It defined temperament as the inherited personality traits that appear early in life, thus temperament was thought to be genetic in origin and relatively stable over time. The EAS framework was derived from twin studies, which suggested that emotionality, activity and sociability were heritable in nature (Buss & Plomin, 1975). The research conducted under the EAS framework has helped explain the underlying biological features of temperament. The EAS Temperament Survey was then developed, for use with children aged 1 to 9 years (Buss & Plomin, 1984). As the EAS framework proposed that temperament appears in the first year of life, it was distinguishable from other personality traits which appear in later life, such as tolerance and selflessness (Buss & Plomin, 1975). The EAS framework excluded individual differences that are not personality traits (e.g., intelligence). As mentioned in section 1.1.1.1, the NYLS framework (Thomas et al., 1963) includes domains that are not personality traits, such as rhythmicity of biological functions. Thus, the EAS framework differs from the NYLS framework because the NYLS framework proposes that temperament is a separate construct related to personality, rather than a precursor for it. Furthermore, the EAS framework appears to be less frequently used in the literature, but has previously been reported to have good internal consistency (Bould, Joinson, Sterne, & Araya, 2013).

1.1.1.3 Psychobiological Framework of Mary Rothbart

Another widely held framework of infant temperament is the psychobiological approach, constructed by Mary Rothbart. In her initial paper (1981), she defined infant temperament as the early individual differences in reactivity and self-regulation (Table 1.1 in

Appendix A). Reactivity refers to motor activity, smiling and laughing, fear, vocal activity and frustration. In comparison, self-regulation relates to the processes that enhance or inhibit reactivity, including behavioural approach and avoidance, self-soothing and attentional regulation. The psychobiological framework led to the development of three overarching temperament factors: negative affectivity (concerned with negative emotions), surgency (concerned with extraversion and positive emotions) and effortful control (concerned with attention, inhibition and sensory perception). The factors of negative affectivity, surgency and effortful control have since been incorporated into parent-report measures of temperament, such as the Infant Behavior Questionnaire (IBQ; Rothbart, 1986). The IBQ and associated measures were standardised using American infants recruited within the Eugene-Springfield area of Oregon. The infants were from a range of socioeconomic backgrounds but were primarily Caucasian. The psychometric properties of the IBQ and associated measures are comparable to that of the CTS. Rothbart (1982) has argued against the categorisation of infants based on their temperament features, as labels such as 'difficult' have negative connotations. One limitation of the IBQ and associated measures, thus, is that they can only be used to compare the temperament of groups and are not appropriate to use with individual assessment (Putnam, 2006). The IBQ and associated measures were designed for use with large samples to investigate trends in the temperament of a group over time, so there are no published norms that can be used to assess a single child's temperament (Putnam, 2006). Therefore, they cannot be used to profile an infant's temperament, limiting the study of individual differences.

In line with the EAS model (Buss, 1991), an underlying assumption of the psychobiological framework is that temperament is genetically based, and thus, relatively stable over time. Rothbart's (1981, 1986) model extends the concept of infant temperament, by including motor activity and orientation, and a range of emotions, rather than just negative affect. In this sense, the psychobiological framework differs from the previous theories proposed by Thomas et al. (1963), and Buss and Plomin (1975). Furthermore, Rothbart's theory goes beyond the concept of temperament as the behavioural style of the infant, put forth by Thomas et al. (1963), to specify it as the predisposition to certain reactions (Goldsmith et al., 1987). Thus, infant temperament in this model overlaps with the construct of personality and is seen as the basis for its development.

1.1.1.4 Emotion Systems Framework of H. Hill Goldsmith

At the same time as Rothbart (1981), Goldsmith and colleagues (1982; 1981) were also constructing a theory of infant temperament (Table 1.1 in Appendix A). Goldsmith defined temperament to be the individual differences in "the probability of experiencing and expressing the primary emotions" (p.g. 510; Goldsmith et al., 1987). Hence, unlike Rothbart, Goldsmith believed infant temperament to be primarily emotion-based. It was proposed that infant temperament forms the emotional substrate of later personality, and as a result, does not include aspects of cognition or perception (Goldsmith et al., 1987). Therefore, the Emotion Systems framework is similar to Buss and Plomin's (Goldsmith et al., 1987) theory, in that it excludes individual differences not related to personality factors (e.g., intelligence). Out of the four frameworks, the approach by Goldsmith is the only one to include a researcher-administered measure of temperament, the Laboratory Temperament Assessment Battery. This measure focuses on primary emotions, including anger, fear, sadness and positive affect. While this measure has good psychometric properties, it does not correlate with parent-report equivalents (Planalp, Van Hulle, Gagne, & Goldsmith, 2017).

1.1.1.5 Summary of the Conceptual Frameworks of Temperament

In summary, there are key similarities and differences regarding the definition and composition of temperament, leading to the development of several conceptual frameworks (Goldsmith et al., 1987; Zentner & Bates, 2008). While the main conceptual frameworks differ on the definition of infant temperament, they collectively suggest that it involves early individual differences in behaviour (Figure 1.1; Buss & Plomin, 1975; Goldsmith & Gottesman, 1981; Rothbart, 1981; Thomas et al., 1963). The conceptual frameworks differ on their extent of involving personality and genetics. However, overall, the frameworks suggest that temperament is the result of complex, bidirectional processes between biological tendencies and the environment.

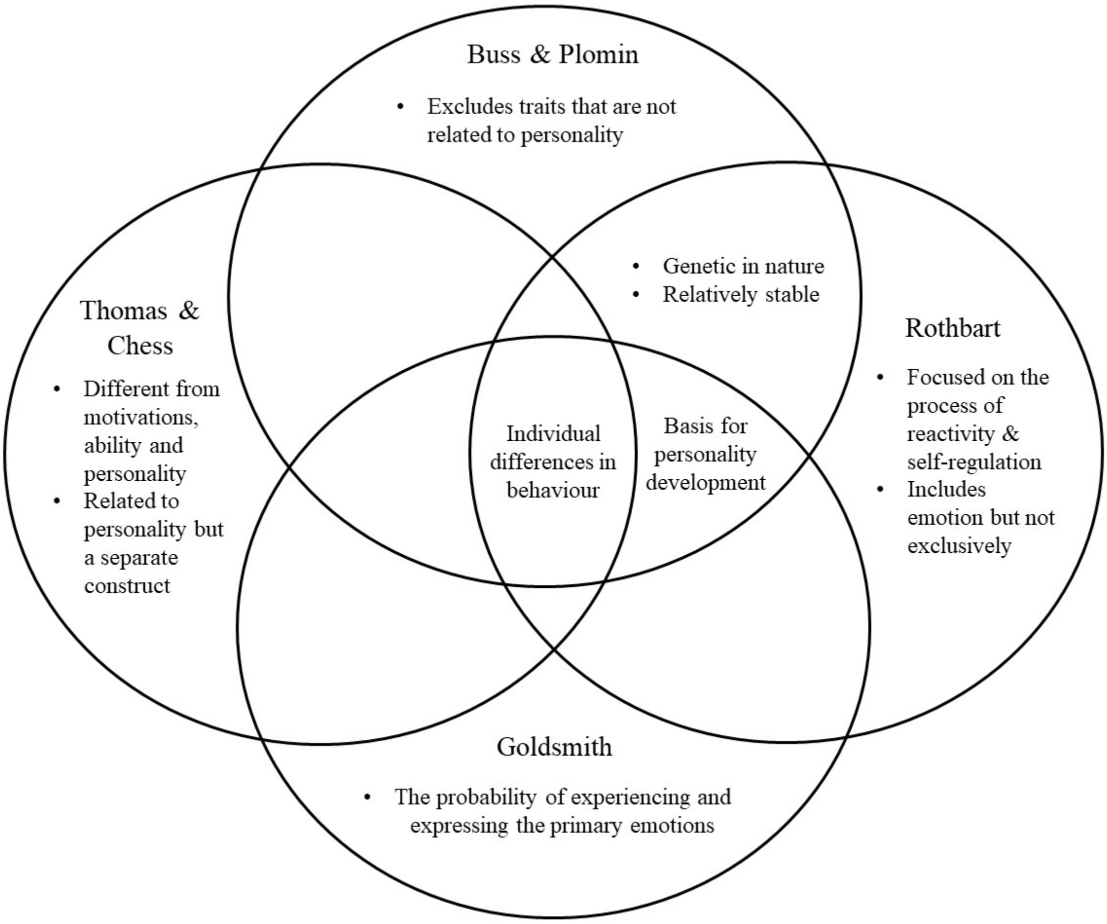

Figure 1.1 A Venn diagram comparing the four conceptual frameworks of temperament presented in this chapter.

All four frameworks are useful theoretical models and appear to have similar psychometric properties, however, the approaches by Rothbart (1986) and Thomas et al.

(1963) appear to be more widely used in research. The NYLS framework (Thomas et al., 1963) is the only model of temperament that has a parent-report measure (i.e., CTS) that can be used with infants as young as 4 weeks of age. Comparatively, other measures, such has the Infant Behavior Questionnaire (Rothbart, 1986), have only been validated for use with infants from three months of age. Thus, the CTS provides researchers with a unique measure of infant temperament that can be implemented into studies of early infant development. The usefulness of providing infants with a temperament profile has been debated, due to the perceived negative connotations with labelling an infant (Rothbart, 1982). However, as profiling temperament provides more information regarding an individual infant's behavioural style, compared to other methods, it is therefore recommended that Carey's (1978a, 1978b) measure is implemented into future research.

1.1.2 The Influence of Individual Differences in Temperament on Child Psychosocial, Behavioural and Cognitive Development

The development of a child is influenced by a broad range of factors. By the time the child is born, they have been exposed to biological and environmental factors that predispose them to certain developmental outcomes (Esper & Furtado, 2014; Kappil et al., 2015; Kingston, Tough, & Whitfield, 2012; Nieuwenhuijsen, Dadvand, Grellier, Martinez, & Vrijheid, 2013). As the child continues to develop outside of the womb, they are additionally exposed to psychosocial factors that can affect their health and wellbeing (Hayiou-Thomas, 2008; Marceau et al., 2013; McDonald, Kehler, Bayrampour, Fraser-Lee, & Tough, 2016; Reiss, 2013). While there are many separate biological and environmental factors that can shape the trajectory of child development, one key child factor that encompasses both domains is temperament.

Temperament is central to the concept of 'goodness-of-fit', put forth by Chess and Thomas (1991). This concept refers to the interaction between a child's temperament and their environment. It is theorised that there is ‘goodness-of-fit’ when a child’s temperament is adequate to meet the demands, expectations and opportunities within their environment (Chess & Thomas, 1991). Alternatively, there is ‘poorness-of-fit’ when a child’s environment does not successfully support their needs. When there is goodness of fit between a child’s temperament and their environment, healthy psychosocial development occurs. However, with poorness of fit comes the difficulty to adapt and to cope with excess stress, in turn affecting a child’s developmental trajectory. As temperament can be assessed early in life and potentially identify difficulty with environmental stressors, it offers a unique opportunity to explore individual differences in child behaviour and development.

As discussed in Section 1.1.1.1, there are several temperament domains that collectively profile a child’s overall behavioural style (Carey & McDevitt, 1978a). A child’s behavioural style plays a role in developmental processes across the lifespan, which can determine the nature of opportunities to learn, socialise and grow. The following section will explore the literature that examined temperamental features associated with child development, including aspects of the mother-infant relationship, behavioural problems, executive functioning and learning, and psychosocial development.

1.1.2.1 Temperament and the Mother-Infant Relationship

The mother-infant relationship is, typically, the first bonding experience for a child. As a result, the quality of this relationship, and the interactions arising from it, plays a vital role in shaping attachment outcomes (Madigan, Hawkins, Plamondon, Moran, & Benoit, 2015; Schoenmaker et al., 2015). Child temperament is one determining factor in the quality of mother-infant interactions, as it can influence parenting style, infant attachment and maternal mental health (Gölcük & Berument, 2019; Groh et al., 2017; Kim, Chow, Bray, & Teti, 2017). Research shows that when a child has more challenging temperament features, such as being difficult to soothe or having a lower ability to persist with difficult tasks, maternal parenting styles are more coercive (Gölcük & Berument, 2019). Whilst overall, there are only weak associations between temperament and attachment, a recent meta-analysis found that more challenging temperament features (e.g., fussiness, fearfulness, frustration) are associated with a resistant child-mother attachment style, one that is characterised by intense separation anxiety yet resists physical comfort from mother, less exploration of environment, and greater fear of strangers (Groh et al., 2017).

Infant temperament, however, is not the only determining factor in mother-infant interactions. Studies also show that maternal mental health is a key influencer of infant attachment and the shared boding experience (Aktar, Colonnesi, De Vente, Majdandžić, & Bögels, 2016). Mothers with more anxiety, depression, and stress symptoms report having an infant with more difficult temperament traits, such as increased frustration and sadness (Dalimonte-Merckling & Brophy-Herb, 2018; Prino et al., 2016). This may be due to maternal biases, resulting from poor mental health, when reporting on their infant's temperament. Alternatively, the infant may be responding to their mother's mood and emotions. These studies are observational; thus causality cannot be determined. Despite this, previous studies suggest that infant temperament, alongside maternal mental health, influences dyadic interactions and attachment. Subsequently, mother-child interactions can be influenced by child behavioural difficulties (e.g., Woltering, Lishak, Elliott, Ferraro, & Granic, 2015), which, in turn, are associated with features of temperament.

1.1.2.2 Temperament, and Internalising and Externalising Behaviour Problems

Children's behavioural problems can be defined in one of two ways: internalising or externalising. Internalising behavioural problems refer to those that are focused inward, such as social withdrawal, anxiety and depression, and somatic complains (American Psychological Association, 2018). Alternatively, externalising behavioural problems are those that are focussed towards others, including aggression, defiance and violence

(American Psychological Association, 2018). Temperament traits that are more challenging, including distress to novelty, anger, and frustration, are associated with externalising behavioural problems, such as relational aggression (Edwards & Hans, 2015; Sirois, Bernier, & Lemelin, 2019). Alternately, children who display more inhibition and negative emotionality are more likely to demonstrate internalising behavioural problems, for example anxiety (Davis, Votruba-Drzal, & Silk, 2015; Paulus, Backes, Sander, Weber, & Von Gontard, 2015). The associations between temperament and behavioural problems may be present due to the constructs not being completely independent. However, understanding how temperament relates to a child's behavioural problems is important, as this interaction may shape their ability to explore and learn in their environment.

1.1.2.3 Temperament, Executive Function and Learning

A child's ability to learn depends on several interrelated factors. One prominent aspect is the influence of temperament on the development of executive function (Marulis, Baker, & Whitebread, 2019; McClelland & Cameron, 2019). Children with more traits of anger, sadness, frustration and fear – those that characterise a difficult temperament style – demonstrate poorer attentional abilities including joint attention (Miramontes, Driggers-Jones, & Dixon Jr, 2018), cognitive shift (Affrunti, Gramszlo, & Woodruff-Borden, 2016) and verbal working memory (Rabinovitz, O'Neill, Rajendran, & Halperin, 2016). Moreover, temperament also directly influences learning in later life (Collins, O'Connor, & McClowry, 2017; Dollar, Perry, Calkins, Keane, & Shanahan, 2017; Gartstein et al., 2016). Infants who display more positive affect and surgency (i.e., extraversion) in the first year of life later demonstrate a greater level of school-readiness (measured by knowledge of foundational concepts related to letters, numbers, colours etc.) in preschool (Gartstein et al., 2016). Alternatively, the temperament trait of anger in preschool children has been reported to be associated with poorer teacher-reported academic competence at age 10 (Dollar et al., 2017).

This study did not report the association between academic test scores and temperament, however, meaning there may be unaccounted biases. While the literature suggests that temperament is associated with academic achievement, it may also be dependent on other factors, such as how a child interacts and socialises with their peers.

1.1.2.4 Temperament and Psychosocial Development

Different styles of temperament have been linked to social development and peer interactions. Children with easier temperament traits, such as higher attentional focusing and inhibitory control, have greater sociability, communication and assertiveness, and less conflict with peers (Acar, Rudasill, Molfese, Torquati, & Prokasky, 2015). Further, more shyness and lower activity level in toddlers is related to more sophisticated theory of mind abilities when preschool aged (Labounty, Bosse, Savicki, King, & Eisenstat, 2016; Mink, Henning, & Aschersleben, 2014). This suggests that toddlers who are more observant and less active have a higher understanding that others have feelings and thoughts that differ from their own in later childhood. This, in turn, has positive implications for developing social skills and interacting with peers (Caputi, Lecce, Pagnin, & Banerjee, 2012). However, children who have a more difficult temperament style, characterised by more negative emotions and difficulty in soothing, have more social avoidance and poorer social competence (Coplan, Ooi, Xiao, & Rose-Krasnor, 2018; Neal, Durbin, Gornik, & Lo, 2017; Verron & Teglasi, 2018). Studies are limited by reliance on parent- and teacher-report measures of temperament and social competence, which may lead to biased responses. Future research should implement more objective researcher-observed measures of social competence to reduce the aforementioned biases. Research has found that when parenting quality is high, compared to low, infants with difficult temperament features have better social adjustment in later childhood (e.g., Stright, Gallagher, & Kelley, 2008). This reiterates that poorer outcomes can be mitigated, when a child's environment is well suited to their needs.

1.1.2.5 Summary of the Influence of Individual Differences in Temperament on Child Psychosocial, Behavioural and Cognitive Development

In summary, previous reports have suggested that temperament plays a role in developmental processes related to the parent-child relationship, learning and socialisation. Infants and children who have a more difficult temperament are more likely to experience maladaptive attachment styles, and have lower academic achievement, more behavioural problems and poorer social functioning than their peers. Challenging temperament features suggest that a child may have difficulty in coping with their environment (Chess & Thomas, 1991). While it is theorised that a child's temperament cannot be directly changed, their environment can be adapted to better support their needs, thus modifying the expression of temperament (Iverson & Gartstein, 2018). Overall, the research in the literature suggests that temperament plays an important role in developmental processes in childhood, including the way in which children interact with caregivers, learn, express behaviours, and socialise with peers. Some children are at an increased risk of poor developmental outcomes, such as those with poorer physical health (e.g., Ferro & Boyle, 2015; Razzaghi, Oster, & Reefhuis, 2015; Valeri, Holsti, & Linhares, 2015). Exploring infant temperament in such populations can potentially highlight clinically meaningful individual differences in child development outcomes.

1.2 Infants Born to Mothers with Asthma during Pregnancy: A Developmentally Vulnerable Cohort

Asthma is one of the most prevalent chronic diseases worldwide. The global prevalence of asthma is estimated to be 4.3%, varying widely from 0.2% in China to 11.2% in Australia (Australian Bureau of Statistics, 2018; To et al., 2012). Asthma is a respiratory disorder that is characterised by symptoms of wheeze, excess mucus, chest tightness and dyspnoea, in which episodes of restricted breathing, known as exacerbations, occur due to the airways becoming obstructed (Global Initiative for Asthma, 2017). The onset of asthma often occurs early in life, with diagnosis peaking in early childhood and declining in older people (Radhakrishnan et al., 2014).

Asthma results in a large number of emergency department visits, hospitalisations, and deaths each year (Akinbami, Moorman, & Liu, 2011; D'Amato et al., 2016; Reddel, Sawyer, Everett, Flood, & Peters, 2015). As a consequence, asthma significantly impacts the quality of life for those affected, with a decrease of exercise (Avallone & McLeish, 2013), loss of work productivity (Hiles et al., 2018; Sadatsafavi et al., 2014), significant healthcare costs (Nunes, Pereira, & Morais-Almeida, 2017), and more sick days at work or school absences (Sullivan et al., 2018). This highlights that asthma continues to be a major public health concern worldwide.

The occurrence of symptoms can be decreased, however, through optimal management (McCracken, Veeranki, Ameredes, & Calhoun, 2017). By reducing the symptoms of one's asthma, disease burden can be alleviated (Simoneau et al., 2018). However, there are a number of barriers to optimal management of asthma including tobacco smoking and obesity (Beasley, Semprini, & Mitchell, 2015). Further, there are certain challenges when managing asthma in special populations, such as pregnant women (McLaughlin, Kable, Ebert, & Murphy, 2015). The following two sections will (a) discuss the effect of asthma during pregnancy on the health of the mother and (b) review the literature relating to the neurodevelopment of children born to mothers with asthma.

1.2.1 Asthma in Pregnancy and the Perinatal Period

Asthma is the leading respiratory disease to complicate pregnancy, occurring in 6-12% of pregnancies worldwide (Clark et al., 2007; Clifton et al., 2009; Kwon, Belanger, &

Bracken, 2003; Rejnö et al., 2014; Tegethoff, Olsen, Schaffner, & Meinlschmidt, 2013). Of pregnant women who suffer from asthma, approximately one third report that their asthmatic condition worsened during pregnancy (Kircher, Schatz, & Long, 2002), with at least 20% of pregnant women with asthma experiencing an exacerbation (Murphy, Clifton, & Gibson, 2006). Further, rates of exacerbations increase to up to 51.9% for pregnant women with severe asthma (Schatz et al., 2003). Women with asthma during pregnancy are at increased risk of multiple adverse perinatal outcomes. Such outcomes include premature labour, pre-eclampsia, placental complications, caesarean section and gestational diabetes (Murphy et al., 2011; Rejnö et al., 2018; Wang et al., 2017). For example, pregnant women with asthma are 1.54 times more likely to develop pre-eclampsia than those without asthma (Murphy et al., 2011). However, these negative effects are reduced when accounting for active asthma management during pregnancy. Adherence to preventer medication and having a written action plan are some management strategies that decrease the chance of exacerbation (Grzeskowiak, Grieger, & Clifton, 2018; Murphy, 2015). Effective management in pregnancy is therefore crucial, in order to reduce the risk of these adverse perinatal outcomes.

Asthma during pregnancy not only negatively affects the mother's health, but it also leads to poorer physical health outcomes for her child, including premature birth, low birthweight and small for gestational age (Liu, Wen, Demissie, Marcoux, & Kramer, 2001; Murphy et al., 2011; Rejnö et al., 2018; Shaked, Wainstock, Sheiner, & Walfisch, 2019). However, this risk is reduced when asthma is well controlled during pregnancy (Grzeskowiak, Smith, Roy, Dekker, & Clifton, 2016; Murphy et al., 2011), with evidence from a meta-analysis demonstrating that pregnant women with active asthma management are less likely to experience premature delivery compared to those with poorly managed asthma (Murphy et al., 2011). Taken together, these findings suggest that active asthma management during pregnancy is pivotal in reducing the risk of poorer infant birth outcomes.

Infants born to mothers with asthma during pregnancy are also at an increased risk of wheeze and the development of childhood asthma (Kashanian, Mohtashami, Bemanian, Moosavi, & Moradi Lakeh, 2017; Martel et al., 2009). Children born to mothers with asthma are 1.7 times more likely to have wheeze symptoms (Mirzakhani et al., 2019; Wright, Cohen, Carey, Weiss, & Gold, 2002). Further, the transmission of asthma is up to 1.4 times more likely to occur when a mother's asthma is inadequately controlled during pregnancy (Liu et al., 2017; Martel et al., 2009). This further supports the argument that physiological changes during pregnancy, incurred due to poor asthma control, may affect the child's likelihood of developing poorer physical health outcomes, such as asthma.

1.2.1.1 Summary of Asthma in Pregnancy and the Perinatal Period

Overall, asthma during pregnancy has several negative physical health implications for mother and child. Pregnant women with asthma are more likely to develop pre-eclampsia and gestational diabetes. Additionally, their child is at greater risk of being born prematurely and developing childhood asthma. However, these detrimental outcomes may be more strongly linked to poor asthma control during pregnancy, rather than asthma status alone. Research suggests that effective management of one's asthma can reduce the likelihood of poor perinatal outcomes. As a result, current research is focused on conducting trials during pregnancy aimed at exploring effective asthma management strategies (e.g., Murphy et al., 2016; Zairina et al., 2016), which has positive implications for maternal and infant health.

1.2.2 The Effect of Maternal Asthma on Child Neurodevelopment

It is well established in the literature that children born to mothers with asthma during pregnancy are at an increased risk of poorer neonatal outcomes, such as low birth weight, small for gestational age and premature birth (e.g., Murphy et al., 2011). Importantly, such neonatal outcomes confer a higher risk for poor child developmental outcomes, for example developmental delays, increased hyperactivity/inattention, and peer problems (Delobel-

Ayoub et al., 2009; Guerra et al., 2014; Schieve et al., 2016; Takeuchi et al., 2016). Children whose mothers have asthma are also at high risk of developing asthma themselves (Kashanian et al., 2017). Children with asthma are reported to have a more challenging temperament (i.e., more difficulties with adapting to change in routine, more sensitive to sensory stimuli) and more behavioural problems (e.g., anxiety, aggression), compared to children without asthma (Kim et al., 1997; Kim, Ferrara, & Chess, 1980; McQuaid, Kopel, & Nassau, 2001). However, little is known about the neurodevelopment and behavioural features of infants born to mothers with asthma during pregnancy. Given the likelihood of subsequent poorer outcomes, it is important to explore the development of children born to mothers with asthma.

Whilst there is a paucity of research about the neurodevelopment and behavioural features of infants born to mothers with asthma, some studies have investigated the effect of asthma on infant cognition (Schatz, Harden, Kagnoff, Zeiger, & Chilingar, 2001) and risk of intellectual disability (ID; Flannery & Liederman, 1994; Langridge et al., 2013; Leonard, de Klerk, Bourke, & Bower, 2006). Using a prospective cohort design, Schatz et al. (2001) assessed the cognitive development of 15-month-old infants born to mothers with well-managed asthma, using the Bayley Scales of Infant and Toddler Development, finding no differences compared to peers born to mothers without asthma. However, as the mothers with asthma in the study had well-controlled asthma, it is not known how infants born to mothers with poorly controlled asthma develop cognitively. Other studies utilising retrospective designs have focused on the effect of maternal asthma on risk of ID in offspring. After adjusting for maternal health conditions and sociodemographic factors, Australian children with an ID have been reported to be 1.25 times more likely to be born to mothers with asthma than without (Langridge et al., 2013; Leonard et al., 2006). However, one case-control study, conducted in the United States, found no increased risk (Flannery & Liederman, 1994). These differences in findings may be due to variation in study design, as confounding variables, such as familial history of neurodevelopmental disorders, were not considered in all studies. As a result, further exploration of the effect of maternal asthma on child ID should use a prospective study design, as this offers the ability to collect more specific exposure data and assess temporal relationships.

There is an emerging interest in the effect of maternal asthma and other autoimmune conditions on child risk of Autism Spectrum Disorder (ASD). After adjusting for a number of maternal (e.g., age, race, health outcomes), child (e.g., sex, gestational age) and sociodemographic (e.g., household income, parental education) factors, children have been reported to be to between 1.3 to 1.6 times more likely to have ASD, if their mother had asthma during pregnancy (Croen, Grether, Yoshida, Odouli, & Van de Water, 2005; Croen et al., 2019; Gong et al., 2019). Further, odds of ASD in offspring were even greater for mothers who had their asthma treated during pregnancy. The research findings are not unanimous, however. Other studies have reported no increased risk for the development of ASD in children born to mothers with asthma (Langridge et al., 2013; Micali, Chakrabarti, & Fombonne, 2004). However, two of these studies had a small sample size (Micali et al., 2004; Mouridsen, Rich, Isager, & Nedergaard, 2007), and thus may not have been appropriately powered to detect an effect. Further, some studies (Langridge et al., 2013; Leonard et al., 2006) showed that maternal asthma was not associated with an increased odds of ASD in offspring, when adjusting for maternal factors (e.g., other health conditions, smoking, pregnancy complications), neonatal outcomes and sociodemographic factors (e.g., race, education, or medical insurance status). As highlighted by Whalen et al. (2019), none of these studies assessed whether differences in asthma medications or management during pregnancy effects child neurodevelopment. Thus, there is an ongoing need to further investigate the role of maternal asthma severity and control in infant behavioural outcomes.

It is acknowledged that the previously reported associations between maternal asthma during pregnancy and neurodevelopmental outcomes of offspring may be the due to poorer perinatal outcomes. As mentioned in section 1.2.1, maternal asthma is associated with an increased risk of premature birth, low birthweight and small for gestational age (Liu et al., 2001; Murphy et al., 2011; Rejnö et al., 2018; Shaked et al., 2019). Further, the likelihood of pregnancy-related conditions (e.g., caesarean section, gestational diabetes, pre-eclampsia) and birth complications (e.g., maternal haemorrhage) are increased for pregnant women with asthma (e.g., Baghlaf, Spence, Czuzoj-Shulman, & Abenhaim, 2019). These pregnancy and perinatal outcomes are known risk factors for child neurodevelopmental outcomes including ASD (e.g., Brumbaugh, Weaver, Myers, Voigt, & Katusic, 2020; Jenabi, Karami, Khazaei, & Bashirian, 2019; Lampi et al., 2012; Modabbernia, Velthorst, & Reichenberg, 2017). It may be that association between maternal asthma during pregnancy and child neurodevelopmental outcomes is mediated by poorer birth-related outcomes. whilst controlling for other associated risk factors.

While the literature suggests that maternal asthma during pregnancy may have a role in the neurodevelopmental outcomes of offspring, less is known about the underlying mechanisms. Prenatal maternal immune activation (MIA) is theorised to be one mechanism. Through work using animal models, studies have shown that prenatal exposure to infection triggers MIA, which in turn leads to changes in offspring brain and behaviour development (Machado, Whitaker, Smith, Patterson, & Bauman, 2015; Patrich, Piontkewitz, Peretz, Weiner, & Attali, 2016; Wang, Yang, Zhang, Yu, & Yao, 2019). While studies with humans are emerging, a current review indicates that maternal immune activation is linked to reduced fetal brain growth and poorer developmental outcomes (Boulanger-Bertolus, Pancaro, & Mashour, 2018). These studies suggest MIA modifies the salience network in the fetal brain, and these changes subsequently influence infant cognitive development. Further, MIA has been linked to the development of ASD (Careaga, Murai, & Bauman, 2017; Patterson, 2011). As immune activation occurs in individuals with asthma (Villa et al., 2016; Wood & Gibson, 2009), this may possibly explain the increased odds of ASD in offspring born to mothers with asthma during pregnancy.

1.2.2.1 Summary of the Effect of Maternal Asthma on Child Neurodevelopment

Overall, the current literature suggests that maternal asthma could confer a greater vulnerability for poorer developmental outcomes in offspring, potentially subsequent to prenatal MIA. However, evidence is mixed. Some studies found a higher likelihood of developing ASD and ID for children born to mothers with asthma during pregnancy, while others did not. Differences in results may be due to methodological variations, such as not controlling for confounding variables due to study design. Premature birth, low birthweight, and birth complications are some factors that are associated with maternal asthma during pregnancy and can increase the risk of developmental problems in children. As a result, further research into this area, using prospective study designs to control for these factors is recommended. Early intervention and treatment are crucial in supporting optimal developmental outcomes (Bradshaw, Steiner, Gengoux, & Koegel, 2015), therefore, it is important to understand ASD risk in infancy in children born to mothers with asthma.

1.3 The Emergence of Autism Spectrum Disorder in Infancy

ASD is a neurodevelopmental disorder characterised by persistent deficits in social communication and interaction, and the presence of restricted, repetitive behaviours and interests (American Psychiatric Association, 2013). Deficits in social communication and interaction are represented in three core features: (1) social-emotional reciprocity, (2) nonverbal communicative behaviours used for social interaction, and (3) developing, maintaining and understanding relationships. In addition, restricted, repetitive behaviours and interests can manifest as any two of the following features: (1) repetitive motor movements, use of objects or speech, (2) insistence on sameness or routine, (3) fixated interests that are abnormal in intensity or focus, and (4) hypo- or hyper-reactivity to sensory events in the environment, and unusual sensory interests. ASD is a neurodevelopmental disorder which means that these core features must emerge during the critical developmental period, that is, prior to entry into school (American Psychiatric Association, 2013). However, a diagnosis may not be given until later in childhood. Furthermore, these features must be persistent and appear across multiple settings, limiting key areas of functioning (e.g., social, work).

While individuals with ASD collectively meet these diagnostic criteria, it has been established that there is great genetic and behavioural heterogeneity within ASD (Betancur, 2011; Georgiades, Szatmari, & Boyle, 2013; Masi, Demayo, Glozier, & Guastella, 2017). Severity, or the level of support an individual requires, is linked to the prognosis of ASD (Hannant, Cassidy, Tavassoli, & Mann, 2016; Magiati, Tay, & Howlin, 2014). Whilst research initially indicated poor prognosis for individuals with ASD, interventions have been found to improve social communication skills and adaptive functioning (Elder, Kreider, Brasher, & Ansell, 2017). Early intervention is vital for improvement of developmental skills and functioning (Fernell, Eriksson, & Gillberg, 2013; Volkmar, 2014). However, there is currently no single known cause for ASD. Evidence from systematic reviews indicate that advancing parental age (Wu et al., 2017), pregnancy-related conditions (e.g., diabetes; Modabbernia et al., 2017), birth complications (e.g., haemorrhage; Modabbernia et al., 2017) and maternal infection during pregnancy (Jiang et al., 2016) are risk factors for ASD. Thus, as ASD cannot be genetically screened or identified through biological testing, an important focus in ASD research is on identifying early behavioural markers of ASD. The following two sections will (a) examine and synthesise the literature on early behavioural markers of ASD in the first year of life, in the areas of social communication, attention, and sensory and motor abilities and (b) discuss the literature pertaining to the temperamental features of infant siblings of children diagnosed with ASD, and children diagnosed with ASD themselves.

1.3.1 Early Behavioural Markers of Autism Spectrum Disorder

ASD is typically diagnosed between the third to fifth years of life (Brett, Warnell, McConachie, & Parr, 2016). Despite this, it can be reliably diagnosed in a research setting as early as two years of age (Barbaro & Dissanayake, 2009; Lord et al., 2006). Over the past three decades, many studies utilising retrospective and prospective designs have investigated atypical behaviours, associated with the later development of ASD, within the first year of life. The retrospective studies (e.g., Maestro et al., 2002) use videos of children diagnosed with ASD and parental questionnaires regarding their child's behaviour, during infancy. The prospective studies (e.g., Zwaigenbaum et al., 2005) utilise longitudinal designs of infants at high-risk for ASD, specifically infant siblings (infant-sibs) of children diagnosed with ASD. These studies use infant-sibs, as there is a higher prevalence of ASD diagnosis in this cohort compared to the general population (~20% vs ~1%; Adak & Halder, 2017; Messinger et al., 2015; Ozonoff et al., 2011). Despite these study designs using different methodologies, both types have identified similar behavioural differences related to social communication, attention, and sensory and motor abilities.

Social communication refers to the use of language in social contexts. It is comprised of four main components including social interaction, social cognition, verbal and nonverbal communication, and language processing (American Speech-Language-Hearing Association, 2019). Most studies in the literature have reported differences between infants later diagnosed with ASD and typically developing infants in the first three areas, during the first year of life. Infants later diagnosed with ASD have poorer social interaction and social cognition abilities including being unable to anticipate other peoples' intentions (Maestro et al., 2002), exhibiting less attuning behaviours (i.e., being aware and responsive to others; Maestro et al., 2002), fewer instances of looking at and orienting towards people (Maestro et al., 2002; Osterling & Dawson, 1994; Ozonoff et al., 2010), and displaying fewer social smiles (Adrien et al., 1993; Bryson et al., 2007; Maestro et al., 2002; Zwaigenbaum et al., 2005). Additionally, infants later diagnosed with ASD have deficits in verbal and nonverbal communication, such as poorer eye contact (Adrien, Perrot, Sauvage, & Leddet, 1992; Barbaro & Dissanayake, 2013; Bryson et al., 2007; Maestro et al., 2005; Zwaigenbaum et al., 2005), fewer gestures (e.g., showing, pointing, giving; Barbaro & Dissanayake, 2013; Osterling & Dawson, 1994; Veness et al., 2012; Zwaigenbaum et al., 2005) and fewer vocalisations (Maestro et al., 2002; Ozonoff et al., 2010; Veness et al., 2012). These deficits have been observed from as early as 6 months of age (Maestro et al., 2002; Maestro et al., 2005), with a decline in eye contact present from two months of age (Jones & Klin, 2013). Consequently, atypical behaviours related to social communication, presenting in the first year of life, may be early indicators of later development of ASD.

Attention is a construct linked to executive function that allows individuals to focus their concentration on a discrete part of the environment, while ignoring other perceivable information (Diamond, 2013). Children with ASD are reported to have more attention deficits compared to typically developing children, indicated by poorer performance on auditory and visual attention tasks (Soskey, Allen, & Bennetto, 2017; Wang et al., 2015). These deficits have been reported in infancy, prior to diagnosis. At 6 months of age, infants later diagnosed with ASD are less likely to spontaneously attend to social scenes, compared to typically developing infants (Chawarska, Macari, & Shic, 2013). By 12 months of age, infants later diagnosed with ASD have poorer visual tracking, more difficulty with disengaging visual attention, and more visual fixation (i.e., maintaining a visual gaze on a single location), compared to infants who develop typically (Bryson et al., 2007; Zwaigenbaum et al., 2005). Additionally, it is more challenging to gain the attention of these infants through name call

(Osterling & Dawson, 1994; Zwaigenbaum et al., 2005). These findings highlight that poorer attention may be a marker for ASD; however, as most differences are not present until 12 months of age, it may not be the most salient predictor.

Lastly, research has also found atypicalities in sensory processing and motor behaviours. Children diagnosed with ASD frequently present with a hypo- or hyper-reactive sensory processing style, which refers to less intense or more intense reactions to sensory stimuli, respectively (Schaaf & Lane, 2015). In the first year of life, studies report that infants later diagnosed with ASD tend to demonstrate more hypo-reactivity, compared to other sensory styles (Maestro et al., 2005). Additionally, a higher proportion of infants later diagnosed with ASD demonstrated more mouthing of objects and aversion to touch compared to typically developing infants (Baranek, 1999). Moreover, infants later diagnosed with ASD demonstrate more repetitive motor behaviours compared to typically developing infants (Adrien et al., 1992; Bryson et al., 2007; Loh et al., 2007), such as arm waving or banging objects. Infants in their first few months of life, who are later diagnosed with ASD, have been observed to demonstrate atypical postures and a high rate of abnormal general movements (e.g., jerky or stiff limb movements; Baranek, 1999; Einspieler et al., 2014). Additionally, infants later diagnosed with ASD have a lower frequency of manual exploration of objects (Bryson et al., 2007; Maestro et al., 2002; Veness et al., 2012). These motor behaviours discriminate between infants later diagnosed with ASD and typically developing infants. However, they are also apparent in infants without ASD but with other developmental concerns (Einspieler et al., 2014; Loh et al., 2007). This suggests that these behaviours may not be unique to ASD. Despite this, sensory-motor behaviours, in conjunction with social communication and attention deficits, indicate an atypical developmental trajectory that may lead to the development of ASD.

In summary, infants who later develop ASD exhibit different behaviours, compared to typically developing infants, in the first year of life. These infants have deficits in social communication and attention, and atypical sensory and motor behaviours, which are apparent by 12 months of age. Further, atypical behaviours related to social communication, such as poor social interaction and limited eye contact, can distinguish between infants with and without a later diagnosis of ASD as early as 6 months of age. Therefore, the presence of atypical behaviours in the first year of life may act as early markers of ASD.

1.3.2 Temperament in Autism Spectrum Disorder

Temperament has been posited to be a behavioural marker for ASD, and offers a unique opportunity to explore individual differences (Zwaigenbaum et al., 2015). Research has investigated the temperament of children diagnosed with ASD, in childhood and prior to diagnosis in infancy (e.g., Macari, Koller, Campbell, & Chawarska, 2017; Ostfeld-Etzion, Feldman, Hirschler-Guttenberg, Laor, & Golan, 2016). The findings of these studies have been synthesised and discussed in detail, in the systematic review in Chapter Two. Briefly, children diagnosed with ASD are reported by their parents to display more negative affect, less extraversion, and less effortful control than typically developing peers. However, when researchers looked into the variability of temperament in children with ASD, they noted that some children with ASD had temperament features comparable to normative samples (Chuang, Tseng, Lu, & Shieh, 2012; Hepburn & Stone, 2006). Thus, these findings warrant the further examination of the variability of temperament in ASD.

In infancy, research has utilised cohorts of infant-sibs, as they are at an increased risk of developing ASD (e.g., Zwaigenbaum et al., 2005). In early infancy, these studies found that infant-sibs, who later developed ASD, were viewed as more manageable, compared to infant-sibs without ASD and typically developing infants. However, by 12 months of age, these infants displayed more challenging temperament features, such as more frustration, compared to infants without a later diagnosis of ASD. While these studies used cohorts of infant-sibs, less is known about the temperament of other infant cohorts at-risk for ASD. Temperament offers the potential for identifying early individual differences in infant-sibs. Thus, the exploration of temperament in other groups at-risk for ASD may provide information useful for screening and early intervention.

In conclusion, the research utilising high-risk infant-sibs provides evidence for infant temperament features to be early behavioural markers for ASD. However, those profiles presented in infancy may not necessarily resemble the patterns of temperament exhibited once diagnosed with ASD in later childhood. Despite this, temperament may be an appropriate construct for identifying clinically significant individual differences within ASD. Therefore, further investigation into the variability of temperament features in at-risk groups and children diagnosed with ASD is warranted.

1.4 Gaps in the Literature

Infancy is a critical period for growth and development (Cameron & Demerath, 2002). There are many factors that influence the trajectory of development, with temperament identified as an important construct (Frick et al., 2018). Temperament is defined as early individual differences in behavioural style (Thomas et al., 1963). It plays an important role in development across infancy and childhood, influencing attachment, social skills, and cognitive and academic outcomes (Chong et al., 2019; Dollar et al., 2017; Kim et al., 2017). Temperament can be reliably assessed in infancy, from as early as 4 weeks of age (Medoff-Cooper et al., 1993). As a result, it offers a unique opportunity to explore the early development of groups vulnerable to poorer health outcomes.

One vulnerable group is infants born to mothers with asthma. Asthma complicates up to 12 percent of pregnancies worldwide (Clifton et al., 2009), and can affect the physical health of both mother and child (Murphy et al., 2011; Murphy et al., 2013). Infants born to mothers with asthma are more likely to be born prematurely, be of low birthweight, and to develop childhood asthma (Murphy et al., 2011). In addition, emerging research suggests that these infants may also be at an increased for later development of ASD (e.g., Gong et al., 2019), which is proposed to be linked due to maternal immune activation during pregnancy (Careaga et al., 2017). ASD is associated with temperament differences, some of which are present as early as 6 months of age (for systematic review, see chapter two). However, to date, there is currently no literature exploring temperament and ASD risk in infants born to mothers with asthma. Exploring differences in temperament of infants born to mothers with asthma may allow for the early identification of those at-risk for poorer developmental outcomes in later childhood.

1.5 Thesis Aim and Research Questions

The general aim of this thesis is to characterise the temperament of infants born to mothers with asthma and explore whether temperament features are associated with autism symptoms within this cohort. This thesis addresses the following three research questions:

1. What are the temperament features of infants born to mothers with asthma at 6 weeks, 6 months and 12 months of age, and how do they compare to infants born to mothers without asthma?
2. Is temperament associated with parent-reported symptoms of autism at 12 months of age, in infants born to mothers with and without asthma, and if so, what temperament features are the best predictors of ASD symptoms?
3. What are the temperament and developmental features of infants born to mothers with asthma who are screened as at-risk of ASD?

1.6 Thesis Statement

This thesis is structured as follows:

1.6.1 Chapter Two

This chapter, a submitted paper currently under review, is a systematic review entitled "The temperament features associated with autism spectrum disorder in childhood: A systematic review". The aim of this review was to synthesise the literature on the temperament of children with ASD, pre- and post-diagnosis. Seventeen articles were identified to meet eligibility criteria and were included in this review.

1.6.2 Chapter Three

This chapter provides an overview of the research projects, the measures and the procedures used to collect data to address the research questions of this thesis. The research projects, the Breathing for Life Trial-Infant Development and the BabyMinds studies, are described including recruitment strategies, participant characteristics and eligibility criteria. An overview of all measures used within the Breathing for Life Trial-Infant Development and the BabyMinds studies is provided, with the measures of temperament (Carey Temperament Scales), ASD risk (First Year Inventory) and covariates discussed in detail. Lastly, the procedures used to collect and code data are described.

1.6.3 Chapter Four

This chapter addresses the first research question of this thesis. It is comprised of two parts. Part One characterises the temperament of infants born to mothers with asthma, at 6 weeks, 6 months and 12 months of age, and compares to the Carey Temperament Scales normative groups. Part Two, extending on Part One, compares the temperament of infants born to mothers with asthma to infants from the general community, at 6 weeks, 6 months and 12 months of age. Additionally, it compares the proportion of infants born to mothers with asthma and community infants who fall within the 'easy', 'average' and 'difficult' ranges within each of the nine Carey Temperament Scales domains. Lastly, the temperament categories (easy, difficult, slow-to-warm-up, intermediate-low, and intermediate-high) of infants born to mothers with asthma and community infant are compared.

1.6.4 Chapter Five

This chapter addresses the second research question of this thesis. This study explores the relationships between the nine temperament domains defined in the CTS and ASD risk score, in infants born to mothers with asthma and infants from the general community. The temperament domains associated with ASD risk were subsequently entered into a multiple regression as predictors, alongside potential covariates, in order to assess which temperament features, if any, best predictors of ASD risk.

1.6.5 Chapter Six

This chapter is the final study chapter and addresses the third research question of this thesis. Using a case series design, six infants born to mothers with asthma screened as at-risk of ASD were profiled on their temperament, alongside sensory processing and general development. Individual profiles were compared, in order to identify similarities and differences between the infants in their development.

1.6.6 Chapter Seven

This chapter is a general discussion on the findings arising from study chapters four through six. It summarises and synthesises the results, linking to previous research, and explores the strengths and limitations of the studies. Lastly, it provides recommendations for future research and an overall conclusion.

Chapter Two: Systematic Review

The Temperament Features Associated with Autism Spectrum Disorder in Childhood: A Systematic Review

2.1 Introduction

The study of individual differences is an important approach in understanding human behaviour and development (Kanai & Rees, 2011). A central construct contributing to individual differences is temperament. Temperament is defined as the observable, individual differences in behavioural style that appears early in life (Thomas et al., 1963). Temperament is comprised of separate domains, or features, which are bidirectional in nature. The individual's temperament features, or temperament profile, describes an individual's overall behavioural style (Carey, 1970). Temperament profiles can be described as 'easy' or 'difficult', depending on where an individual falls on the spectrum within the domains. A temperament profile characterised by positive mood, high approach, quick adaptability to change, predictability of responses and low distractibility is referred to as 'easy', whereas the temperament profile comprised of the opposite features is referred to as 'difficult' (Carey, 1970).

Temperament plays an important role in child development, as it shapes learning (Gartstein et al., 2016; Studer-Luethi et al., 2016), social functioning (Baer et al., 2015) and attachment (Groh et al., 2017). Temperament is also closely associated with individual differences in children's responses to stressors (Messerli-Bürgy et al., 2018; Meyer et al., 2017). Children with more challenging temperament features, such as high negative emotionality and low effortful control, are more likely to display internalised (e.g., inhibited and over-controlled) or externalised (e.g., aggression, hyperactivity) behaviours compared to peers with typical temperament styles (Atherton, Tackett, Ferrer, & Robins, 2017; Davis et al., 2015). These behaviours, in turn, can determine the nature of opportunities to learn and socialise within in the home and school environments (Hymel, Rubin, Rowden, & LeMare, 1990; Ready, LoGerfo, Burkam, & Lee, 2005). While problematic internalising and externalising behaviours are often apparent in neurotypical children, they are more prominent in clinical populations, such as children with developmental disorders (Bauminger, Solomon, & Rogers, 2010; Mazurek & Kanne, 2010; Volker et al., 2010). However, the severity of such behaviours varies considerably in children with developmental disorders (Vaillancourt et al., 2017), indicating substantial heterogeneity both between, and within, these populations.

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterised by atypical social communication and interaction, and the presence of restricted, repetitive behaviours, interests or activities (American Psychiatric Association, 2013). Atypical social communication and interaction refers to difficulty with social-emotional reciprocity, nonverbal communicative behaviours, and the development and maintenance of relationships. Restricted and repetitive behaviours can include stereotyped motor movements, insistence on sameness, fixated interests that are atypical in intensity or focus, and hyper- or hypo-reactivity to sensory input. While individuals diagnosed with ASD collectively meet these criteria, functionally, there is a diverse range in the manifestation of symptoms, and their impact on social, behavioural and daily living skills (Weitlauf, Gotham, Vehorn, & Warren, 2014). As a result, there is no intervention approach that suits all individuals diagnosed with ASD. Consequently, researchers in the autism field are seeking methods by which individual differences within ASD can be identified to promote improved customisation of interventions (U.S. Department of Health and Human Services Interagency Autism Coordinating Committee, 2017).

Temperament is one construct that could help explain why some children with ASD develop emotional, social and behavioural problems, while others do not. Additionally, as temperament provides information on an individual's behavioural style (Iverson & Gartstein, 2018), understanding its variance in ASD may assist caregivers and educators with anticipating and managing aspects of the social and physical environment that may not fit an individual child's needs. Little is known, however, about whether there are specific temperament features associated with ASD that could be used to identify individual differences. The purpose of this systematic review is to synthesise the existing literature in order to examine whether there are specific features of temperament associated with ASD, prior to and post diagnosis, in infancy, toddlerhood and childhood.

2.2 Methods

A systematic review of the literature was conducted using the statement on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, Altman, & Prisma Group, 2009).

2.2.1 Search Strategy

In July 2017, a literature search was conducted across six social science and allied health databases: PsycINFO, CINAHL, Academic Search Ultimate, and the Psychology, Nursing & Allied Health, and Social Science databases in ProQuest. The literature was searched for all articles published from database inception until July 2017, using search terms related to temperament and ASD in infant and child populations (Table 2.1 in Appendix B). A manual search identified an additional 70 articles from the reference list of eligible articles and relevant review articles.

2.2.2 Inclusion and Exclusion Criteria

Articles were screened for eligibility against the selection criteria by three independent investigators (CM, AW, and OW). A fourth independent investigator (LC) resolved conflicts in eligibility status. Articles were included if they (1) reported on the temperament of individuals diagnosed with ASD either (a) post diagnosis, in childhood (3-12 years of age) or (b) prior to diagnosis, in infancy (< 3 years of age); (2) were peer-reviewed;

and (3) were published in English. There were no restrictions for inclusion based on study design. Articles were excluded if they (1) reported on adolescents or adults with ASD (>12 years); (2) included a sample with a combined age range (e.g. 10-16 years) and data could not be extracted for children (< 13 years); (3) measured personality rather than temperament; (4) reported on children with ASD as a co-morbid condition (e.g. Fragile X with ASD); and (5) were a review, conference paper, book, thesis or grey literature.

2.2.3 Data Extraction and Quality Assessment

Two investigators (CM, LC) independently extracted the following information: study design, country of recruitment, sample size, gender distribution, age of sample (mean and/or range), method of diagnosis, and temperament measure. Where possible, we extracted statistically significant mean differences in temperament outcomes between infants later diagnosed with ASD or children with ASD, and typically developing comparison groups. The results are synthesised and discussed in two clusters: (1) Those pertaining to the temperament of infants later diagnosed with ASD (i.e. pre-diagnosis) and (2) those pertaining to the temperament of children diagnosed with ASD (i.e. post-diagnosis). The Joanna Briggs Institute Critical Appraisal (JBI-CA) checklists were used by one reviewer (CM) to critically assess the methodological quality of the included studies. All articles were included in the review, regardless of quality assessment outcome. A meta-analysis was not feasible within this review, due to differences in temperament measures and participant samples (e.g., gender, age ranges) between the included articles. Rather, we addressed trends descriptively, taking the heterogeneity of reported temperament outcomes into account.

2.3 Results

The study selection flowchart is presented in Figure 2.1. The search strategy generated 658 unique articles. During title and abstract screening, 559 articles were excluded (primarily as they did not pertain to ASD or temperament). During full-text screening, 82 articles were excluded (see Figure 2.1 for exclusion reasons). Seventeen articles met eligibility criteria for inclusion.

2.3.1 Study Characteristics

The study characteristics of the 17 articles are summarised in Table 2.2 (see Appendix C), Table 2.3 (see Appendix D) and Table 2.4 (see Appendix E). These articles report temperament findings from 13 study cohorts. Six reported on the temperament of infant siblings of children diagnosed with ASD, who are at high-risk for developing ASD. The other

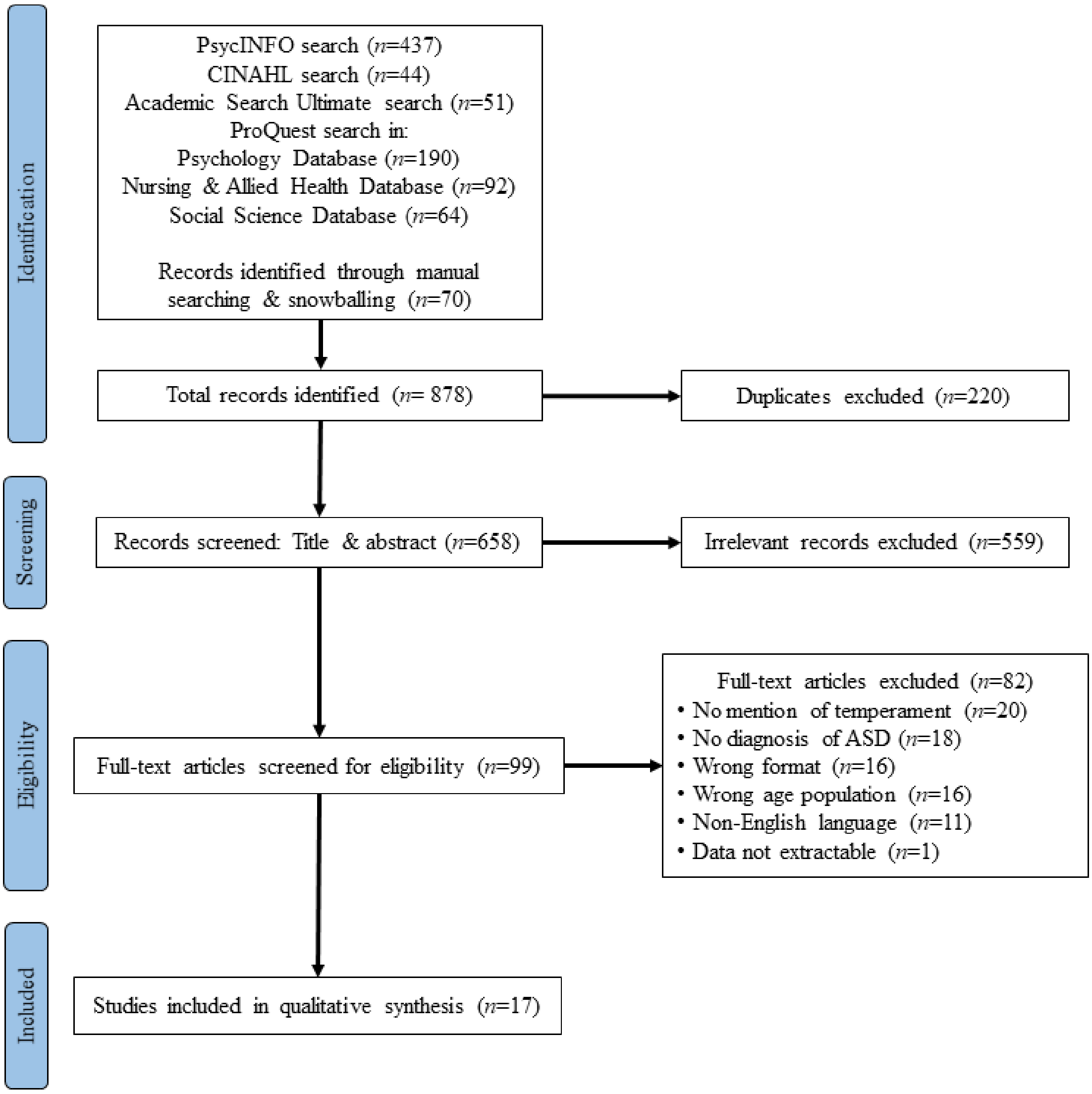

Figure 2.1 PRISMA flow chart of study selection.

11 articles reported on the temperament of children diagnosed with ASD. Most articles were published after the year 2000 (82.4%), with eight articles published within five years prior to the search date. The studies included case-control (*n* = 6), cohort (*n* = 5) and cross-sectional (*n* = 5) designs, with only one case series. The majority of studies were conducted within North America (76.5%). The remaining were conducted in Taiwan (*n* = 1), the United Kingdom (*n* = 1) and Israel (*n* =2). The sample size ranged from nine to 373 participants. Gender was unequally distributed, with more than half of the articles reporting 80% or more males in their sample. The majority of articles utilised parent-report temperament measures, with only one study using a laboratory measure.

2.3.2 Methodological Quality of Included Studies

Table 2.5 reports the percentage of JBI-CA items that met methodological requirements within each article. All articles used appropriate statistical analyses of the data. Most cross-sectional studies described participants and setting in sufficient detail, and used a valid and reliable measure of temperament. The majority of case-control studies appropriately matched cases with controls, identified and managed confounding factors, and measured ASD and temperament with valid and reliable tools. Most cohort studies reported on groups that were from similar populations, addressed confounding factors, and used valid and reliable measures of exposure and outcome. Additionally, the case series met most of the JBI-CA criteria. Some methodological concerns, however, were identified. Most cross-sectional studies did not clearly state how ASD was assessed, and did not identify or control for confounding factors. The case-control studies did not demonstrate that the same eligibility criteria were used for cases and controls, or that ASD was assessed in the same manner across groups.

Table 2.5 Outcome of methodological quality assessment: JBI Critical Appraisal Checklist.

Form Version	Study	% of Items Meeting Requirements
Case Control	Kasari and Sigman (1997)	78
	Konstantareas and Stewart (2006)	78
	Chuang et al. (2012)	33
	Hirschler-Guttenberg, Feldman, Ostfeld-Etzion, Laor, and Golan (2015)	78
	Ostfeld-Etzion et al. (2016)	78
	Macari et al. (2017)	67
Case Series	Bryson et al. (2007)	89
Analytical Cross Sectional	Bagnato and Neisworth (1999)	13
	Bailey, Hatton, Mesibov, Ament, and Skinner (2000)	100
	Hepburn and Stone (2006)	50
	Adamek et al. (2011)	38
	Brock et al. (2012)	75
Cohort	Zwaigenbaum et al. (2005)	100
	Garon et al. (2009)	100
	Clifford, Hudry, Elsabbagh, Charman, and Johnson (2013)	29
	Del Rosario, Gillespie-Lynch, Johnson, Sigman, and Hutman (2014)	100
	Garon et al. (2016)	100

Note: The following items were removed from the forms as they were not applicable to any of the assessed studies: Case Control (item 9), Cohort (items 6, 8, 9 & 10), and Case Series (Item 10).

2.3.3 Associations between Temperament and Autism Spectrum Disorder Pre-Diagnosis

Six articles reported on the temperament characteristics of infant siblings (hereafter, infant-sibs) of children diagnosed with ASD (Table 2.6; Bryson et al., 2007; Clifford et al., 2013; Del Rosario et al., 2014; Garon et al., 2009; Garon et al., 2016; Zwaigenbaum et al., 2005). These articles compared the temperament of infant-sibs later diagnosed with ASD, prior to diagnosis, to typically developing controls or infant-sibs without ASD. Within these articles, infant-sibs and typically developing controls had been assessed for ASD by 36

Table 2.6 Summary of findings on temperament traits in children with ASD.

Age Group	ASD vs. other infant-sibs[a]		ASD vs. typically developing controls/reference samples		
	Surgency/Extraversion	Effortful Control	Negative Affectivity	Surgency/Extraversion	Effortful Control
Infancy (6-36 months)	> approach at 6 months[13] < positive affect at 12 and 24 months[15] > withdrawal at 24 and 36 months[13]	> adaptable to change at 6 and 12 months[13] < effortful control at 24 months[15] < adaptable to change at 24 and 36 months[13]	> distress to limitations at 12 months[4] < soothable at 24 months[12] > sadness at 24 months[12]	< activity level at 6 months[4] < smiling and laughter at 14 months[12] < cuddliness at 14 and 24 months[12] > shyness at 24 months[12] < excitability at 24 months[4] < behavioural approach at 24 months[8]	> duration of orienting at 12 months[4] < low-intensity pleasure at 24 months[12] < inhibitory control at 24 months[4] < attentional shifting at 24 months[4] < effortful emotion regulation at 24 months[8]
Childhood (mean age 2-6 years)			> difficult[1] < soothable[6,16,17] > discomfort[6] < discomfort[9] > arrhythmia[3,10] > anger/frustration[9] > detached[2]	< smiling and laughter[6] > shyness[6,16] > activity level[10,11,16] < excitability[19]7 > high-intensity pleasure[9] < emotional intensity[3,10] > hyper-sensitive/active[2] > underreactive[2] > withdrawal[3,10,11]	< attentional shifting[5,16,17] < low-intensity pleasure[16,17] > low-intensity pleasure[9] < adaptable to change[3,10,11] < persistent[3,10,11] < distractable[3,10,11] < attentional focusing[6,9,16,17] < inhibitory control[6,9,16,17] < perceptual sensitivity[6,16,17] > sensory threshold[3,10,11] > dysregulated[2]

Note: > symbol = more or greater. < symbol = less or lower. Results from Bryson et al. (2007), Hepburn, and Stone (2006) are not reported within this table, as they did not report group differences.
[a]Infant-sibs classified as typically developing or as non-ASD

1. Kasari and Sigman (1997)
2. Bagnato and Neisworth (1999)
3. Bailey et al. (2000)
4. Zwaigenbaum et al. (2005)
5. Hepburn and Stone (2006)
6. Konstantareas and Stewart (2006)
7. Bryson et al. (2007)
8. Garon et al. (2009)
9. Adamek et al. (2011)
10. Brock et al. (2012)
11. Chuang et al. (2012)
12. Clifford et al. (2013)
13. del Rosario et al. (2014)
14. Hirschler-Guttenberg et al. (2015)
15. Garon et al. (2016)
16. Ostfeld-Etzion et al. (2016)
17. Macari et al. (2017)

months of age. Infant-sibs who received a diagnosis of ASD will be referred to as *infant-sibs with ASD,* with age of diagnosis reported afterwards in brackets. Infant-sibs who did not receive a diagnosis of ASD, but may have had some developmental concerns, will be referred to as *infant-sibs without ASD*. Infant-sibs who proceeded to develop typically will be referred to as *typically developing infant-sibs* in order to differentiate them from *typically developing controls* (i.e., infants with no family history of ASD). Results will be synthesised in groups by age: early infancy, later infancy and toddlerhood. Four of the infant-sib articles (Bryson et al., 2007; Garon et al., 2009; Garon et al., 2016; Zwaigenbaum et al., 2005) reported data from the same prospective cohort study. As such, results from these articles will be considered together with the exception of Bryson et al. (2007), who did not describe temperament outcomes in a way that enabled them to be included in the synthesis (i.e., utilising temperament domain names).

2.3.3.1 Temperament Profile: Early Infancy (6 – 7 months)

Three articles reported on the temperament of infant-sibs later diagnosed with ASD in early infancy, at six (Del Rosario et al., 2014; Zwaigenbaum et al., 2005) or seven (Clifford et al., 2013) months of age. Group differences emerged in the temperament domains of *activity, approach* and *adaptability* (from 17 domains assessed; Table 2.7 in Appendix F) between 6-month infants with and without a later diagnosis of ASD. Zwaigenbaum et al. (2005) found that 6-month infant-sibs with ASD (at 24 months), had lower levels of activity compared to 6-month typically developing controls and 6-month infant-sibs without ASD. Conversely, Del Rosario et al. (2014) found no differences in activity level between 6-month infant-sibs with ASD (at 36 months) and 6-month typically developing infant-sibs. However, the 6-month infant-sibs with ASD (at 36 months) were less withdrawn and more adaptive to change compared to those who proceeded to develop typically.

2.3.3.2 Temperament Profile: Late Infancy (12 months – 14 months)

Four articles (three cohorts) reported on the temperament of infant-sibs with a later diagnosis of ASD in late infancy, at 12 (Del Rosario et al., 2014; Garon et al., 2016; Zwaigenbaum et al., 2005) and 14 months of age (Clifford et al., 2013). Together, they assessed 18 temperament domains, with differences emerging in four: *distress to limitations, cuddliness, duration of orienting,* and *smiling and laughter*. Zwaigenbaum et al. (2005) found 12-month infants with ASD (at 24 months) demonstrated more distress to limitations (i.e., frustration) and a longer duration of visual orientation towards objects than 12-month typically developing controls and 12-month infant-sibs without ASD. Within the same cohort, Garon et al. (2016) reported that 12-month infants with ASD (at 36 months) showed less *positive affect* (discriminant function comprised of *smiling and laughter*, *soothability* and reversed *fear*) than infant-sibs without ASD. Additionally, Del Rosario et al. (2014) reported that 12-month infant-sibs with ASD (at 36 months) were more adaptive to change in routine, compared to typically developing infant-sibs. Clifford et al. (2013) found that 14-month infant-sibs with ASD (at 36 months) were lower in *cuddliness* and *smiling and laughter* than typically developing controls.

2.3.3.3 Temperament Profile: Toddlerhood (24 months – 36 months)

Five articles (three cohorts) reported on the temperament of infant-sibs later diagnosed with ASD during toddlerhood, at 24 (Clifford et al., 2013; Del Rosario et al., 2014; Garon et al., 2009; Garon et al., 2016; Zwaigenbaum et al., 2005) and 36 months of age (Del Rosario et al., 2014). Differences emerged in 10 out of 14 temperament domains assessed (six of which were not assessed earlier), between infant-sibs with ASD, and typically developing controls and infant-sibs without ASD: *soothability*, *sadness*, *cuddliness, shyness, approach, inhibitory control, low intensity pleasure, adaptability, attentional shifting,* and *positive anticipation*. Zwaigenbaum et al. (2005) found that 24-month infant-sibs with ASD (at 24 months) were reported to have less inhibitory control, a lower ability to shift attention and to display less excitement about pleasurable activities than typically developing controls and infant-sibs without ASD. Within the same prospective infant-sib cohort, the researchers later found that 24-month infant-sibs later diagnosed with ASD (at 36 months) displayed less behavioural approach and less effortful emotion regulation compared to typically developing controls (Garon et al., 2009), and less positive affect than infant-sibs without ASD (Garon et al., 2016). Clifford et al. (2013) found that 24-month infant-sibs later diagnosed with ASD (at 36 months) were harder to soothe, displayed more sadness, sought less physical comfort, were shyer, and participated less in low intensity activities than typically developing controls. Lastly, Del Rosario et al. (2014) found that 24-month and 36-month infant-sibs with ASD (at 36 months) were more withdrawn and less adaptable to change than typically developing infant-sibs.

2.3.4 Associations between Temperament and Autism Spectrum Disorder Post-Diagnosis

Eleven articles reported on the temperament of children diagnosed with ASD (mean age between 2-6 years; Table 2.6). Of these, two descriptively characterised the temperament of children with ASD, three compared temperament scores to normative reference samples, and six compared temperament scores to typically developing controls. For ease of synthesis, results are grouped by three overarching temperament factors: (1) Negative Affectivity (domains pertaining to negative affect, e.g., sadness, fear), (2) Extraversion/Surgency (domains pertaining to positive affect, e.g., activity level, approach), and (3) Effortful Control (domains pertaining to attention and inhibition, e.g., inhibitory control and distractibility). Domains that do not fall within these factors will be discussed in a fourth section. The definitions of the temperament domains can be found in Table 2.7 (see Appendix F). All differences included in the synthesis were reported as statistically significant. For studies where statistical comparisons were not conducted (Bagnato & Neisworth, 1999; Hepburn & Stone, 2006), findings are reported descriptively.

2.3.4.1 Negative Affectivity

Four articles reported on the domain of *Soothability* or *Falling Reactivity*, or how easily the child can be soothed after a peak in reactivity. Three articles (Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016) reported that children with ASD were harder to soothe than typically developing controls, while one article found no difference compared to a normative reference group (Adamek et al., 2011). Five articles (three case-control, one cohort, one cross-sectional) reported on the *anger* and *frustration* of children with ASD across four cohorts (Adamek et al., 2011; Hirschler-Guttenberg et al., 2015; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016). None of the case-control or cohort studies observed differences between groups (Hirschler-Guttenberg et al., 2015; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016). Only one article (Adamek et al., 2011) reported that their sample of children with ASD had a higher level of anger, compared to a normative reference group.

Four articles reported on the level of *discomfort* of children with ASD, with two finding no significant difference between children with ASD and typically developing controls (Macari et al., 2017; Ostfeld-Etzion et al., 2016). One study (Konstantareas & Stewart, 2006) found children with ASD were reported to display a higher level of discomfort than typically developing controls. In contrast, Adamek et al. (2011) found children with ASD were reported to exhibit less discomfort than the normative reference group. Of note, no articles reported significant differences related to *sadness* (Adamek et al., 2011; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016), *fear* (Hirschler-Guttenberg et al., 2015; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016), or *mood* (Bailey et al., 2000; Brock et al., 2012; Chuang et al., 2012). However, Hepburn and Stone (2006) found that whilst over half of their sample fell within the average range for mood, one third were reported to be primarily negative in mood (i.e. scores > 1 standard deviation from normative mean). Similarly, Chuang et al. (2012) reported that nearly one fifth of their ASD sample scored within the difficult range for mood. Lastly, Kasari and Sigman (1997) constructed a ‘difficultness’ score using five domains (Rhythmicity, Approach, Adaptability, Intensity and Mood) from the Carey Temperament Scales and found that children with ASD were more temperamentally difficult compared to typically developing controls.

2.3.4.2 Extraversion/Surgency

Eight of the 13 articles reported on the domain of *activity level*, with four finding no difference between children with ASD and typically developing controls (Konstantareas & Stewart, 2006; Macari et al., 2017) or normative reference groups (Adamek et al., 2011; Bailey et al., 2000). However, three studies found that children with ASD had a significantly higher level of activity than typically developing controls (Chuang et al., 2012; Ostfeld-Etzion et al., 2016) and norms (Brock et al., 2012). Furthermore, Hepburn and Stone (2006) reported that over half of the children with ASD fell within the average range for level of activity, whilst Chuang et al. (2012) reported that one third fell within the difficult range. The domain of *high intensity pleasure* refers to the frequency of a child engaging in recreational activities with a high physical component (e.g., bike riding). Of the four articles reporting on this feature, one reported that children with ASD engaged in more high intensity activities than the normative reference group (Adamek et al., 2011). The other three articles, which used case-control designs, reported no significant differences (Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016). Only one study reported on a related domain, *positive anticipation*, finding that children with ASD were significantly less excitable in anticipation of pleasurable activities than typically developing children (Macari et al., 2017).

Six articles reported on the bidirectional domain of *Approach-Withdrawal* (Bailey et al., 2000; Brock et al., 2012; Chuang et al., 2012; Hepburn & Stone, 2006; Konstantareas & Stewart, 2006; Ostfeld-Etzion et al., 2016). This domain relates to whether a child approaches new people, objects and environments or tends to withdraw from novel stimuli. Three studies found that children with ASD were reported to be significantly more withdrawn than typically developing controls (Chuang et al., 2012) and normative reference groups (Bailey et al., 2000; Brock et al., 2012). Again, Hepburn and Stone (2006) reported that over half of their ASD sample fell within the average range for this domain, and Chuang et al. (2012) found approximately one third to fall within the difficult range. On a related domain, *shyness*, two articles (Konstantareas & Stewart, 2006; Ostfeld-Etzion et al., 2016) found children with ASD to exhibit more shyness than their typically developing controls, whereas Adamek et al. (2011) found no difference with a normative reference group.

2.3.4.3 Effortful Control

All four articles that reported on *inhibitory control* found that children with ASD were significantly less able to focus on relevant stimuli when irrelevant stimuli were present, compared to typically developing controls (Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016) or a normative reference group (Adamek et al., 2011). In contrast, the three studies that measured *distractibility* found that children with ASD were significantly less distractible compared to typically developing controls (Chuang et al., 2012) or normative reference groups (Bailey et al., 2000; Brock et al., 2012). Hepburn and Stone (2006) reported that over half of their sample fell within the average range for the domain of distractibility. However, one third of their sample was reported to be very difficult to distract, a proportion similar to that reported by Chuang et al. (2012). Furthermore, seven articles reported on *persistence* or *attentional focusing*, finding that children with ASD were less able to pursue tasks in the face of obstacles, compared to typically developing children (Chuang et al., 2012; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016) or normative reference groups (Adamek et al., 2011; Bailey et al., 2000; Brock et al., 2012). In addition, Hepburn and Stone (2006) and Chuang et al. (2012) reported that over 50% and approximately 42% of children with ASD were non-persistent, respectively.

Four studies investigated the *adaptability* domain, which refers to how well a child copes with change to routine. Three of the four studies utilising control or normative reference groups found that children with ASD were significantly less adaptable to change in routine than typically developing children (Chuang et al., 2012) or normative reference groups (Bailey et al., 2000; Brock et al., 2012). Furthermore, Hepburn and Stone (2006) and Chuang et al. (2012) reported that two thirds and approximately one third of their sample were non-adaptable, respectively. Four articles reported on *low intensity pleasure* (i.e., recreational activities with a low physical component, e.g., reading), with inconsistent findings. Of the three case-control studies, two (Macari et al., 2017; Ostfeld-Etzion et al., 2016) reported that children with ASD engaged in a lower level of low intensity pleasure compared to typically developing controls. In contrast, Adamek et al. (2011) found that children with ASD were reported as engaging in a higher level of low intensity pleasure, compared to the normative reference group. Furthermore, Konstantareas and Stewart (2006) found no difference between children with ASD and typically developing children.

Two studies (Konstantareas & Stewart, 2006; Ostfeld-Etzion et al., 2016) reported on the domain of *smiling and laughter*, with one (Konstantareas & Stewart, 2006) finding that children with ASD displayed less smiling and laugher than typically developing controls. Six of the seven studies reporting on the domains of *threshold* or *perceptual sensitivity* found that children with ASD had a significantly lower sensory threshold than typically developing children (Chuang et al., 2012; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016) or normative reference groups (Bailey et al., 2000; Brock et al., 2012). Additionally, Chuang et al. (2012) found a significantly smaller proportion of children with ASD fell within the difficult range on the threshold domain, compared to typically developing peers (7.5% vs 25%). Three studies reported on the domain of *attentional shifting*, with all reporting that children with ASD had a significantly lower ability to shift their attention than typically developing children (Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016). Notably, no articles reported significant differences in the domain of *impulsivity* (Adamek et al., 2011; Konstantareas & Stewart, 2006; Ostfeld-Etzion et al., 2016).

2.3.4.4 Other Domains

There were three articles reporting on the domain of *intensity*. This domain refers to the energy level a child uses in expressing their mood, regardless of direction. For example, one child may cry when they fall over, whereas another may display a sad facial expression. Two studies found that children with ASD were less intense when exhibiting their mood than the normative reference group (Bailey et al., 2000; Brock et al., 2012), whereas Chuang et al. (2012) found no significant difference compared to typically developing controls. Hepburn and Stone (2006), and Chuang et al. (2012) alike, found that the majority of their sample of children with ASD were reported to be mild in emotional intensity. Of the four studies that reported temperament outcomes related to the domain of *rhythmicity*, two found that children with ASD were significantly less predictable in their biological functions than the normative reference group (Bailey et al., 2000; Brock et al., 2012), with the case-control study finding no difference (Chuang et al., 2012). The fourth study (Hepburn & Stone, 2006) found that more than half of the children with ASD fell within the average range for rhythmicity. In an additional study (Bagnato & Neisworth, 1999), children with ASD were reported to be more detached (i.e., disconnected from daily routines), hyper-sensitive (i.e., highly active, inconsolable), underreactive (i.e., unresponsive) and dysregulated (i.e., state disorganization) than the norm.

2.4 Discussion

The aim of this systematic review was to synthesise the literature reporting on the temperament features of children diagnosed with ASD, prior to and after diagnosis. Of the 17 included articles, six were within infancy (i.e., pre-diagnosis) and 11 were within childhood (i.e., post-diagnosis). Within infancy, evidence of an association between specific temperament features and later ASD diagnosis was weak, as only six articles (three cohorts) reported on temperament outcomes. However, these articles suggest that infant-sibs with ASD had temperament features in early infancy that were generally viewed as ‘more manageable’, characterised by less withdrawal and more adaptability to change. By the time of diagnosis, these infants had distinct challenging temperament features, such as more negative affect and more withdrawal. These findings suggest that infants later diagnosed with ASD have a manageable temperament profile in early infancy that becomes more challenging as infants near time of diagnosis. However, alternative explanations need to be considered given the reliance on parent-report measurement methods and infant-sib cohorts. One explanation is that parents are unconsciously comparing the temperament of their older child with ASD to their participating infant, and thus they are reported as less challenging in early infancy. As time progresses and behaviours related to ASD emerge, parents rate their infants differently. However, as the majority of articles were cross-sectional, any conclusions about changes in temperament over time cannot be made.

Eleven articles reported on the temperament of older children diagnosed with ASD. Our synthesis found sufficient evidence to suggest that some temperament features are associated with a diagnosis of ASD in childhood. Seven of the 11 articles report a temperament profile that is characterised by more negative emotions, less excitability and extraversion, and less ability to focus and shift attention. These differences are also supported by Hepburn and Stone (2006), where more than half of their sample were reported to have challenges with adapting to change and persisting with difficult tasks. These differences are not surprising, considering that the diagnostic criteria of ASD involves an insistence on sameness and an inflexible adherence to routines, and, in some cases, hyper-reactivity to sensory input (American Psychiatric Association, 2013).

While the majority of articles reported more challenging temperament characteristics for children with ASD, compared to comparison groups, it is important to consider studies that found more manageable temperament features within their sample. These temperament features include reports of less discomfort (Adamek et al., 2011), greater pleasure from low- and high-intensity activities (Adamek et al., 2011), less intense emotional response (Bailey et al., 2000; Brock et al., 2012), and less distractibility (Bailey et al., 2000; Brock et al., 2012; Chuang et al., 2012). Of note, Hepburn and Stone (2006) found that more than half of their sample fell within the average range for rhythmicity, mood, activity, approach and distractibility. This highlights that many children with ASD are generally considered to have temperament features and profiles that are 'easy' rather than 'difficult'.

To conclude, the results from this systematic review supports the notion that there are some temperamental features that are more frequently present in ASD. However, these behaviours are not necessarily viewed as more challenging by parents. It is also clear that there are significant heterogeneities in expressed behaviours among infants and children with ASD. Thus, each child diagnosed with ASD is not necessarily going to demonstrate the same behavioural style as another. Therefore, this systematic review highlights the importance of developing norms for children with ASD and recording parents' perceptions on whether their child's behaviours are problematic or not.

2.4.1 Limitations and Directions for Future Research

While the included articles provide important information regarding the temperament profile of children with ASD, they are not without limitations. Most of the cross-sectional and case-control studies did not clearly report on how cases of ASD were confirmed in participants. The cross-sectional studies also poorly identified confounding factors and thus did not account for them within their study design. Additionally, no case-control studies were able to clearly demonstrate that the same eligibility criteria were used for both cases and controls. It is important for future research to consider these criteria, as it is possible that factors other than diagnosis of ASD could be contributing to differences in temperament features. These methodological concerns have implications for the generalisability of study findings, specifically, to gender. The majority of included studies had predominantly male children in their samples. As there are known differences in temperament based on gender in typically developing populations (for review, see Else-Quest, Hyde, Goldsmith, & Van Hulle, 2006), future research should investigate whether the temperament profiles of children with ASD also differ as a function of gender.

Regarding the trajectory of temperament features in infants later diagnosed with ASD, only one study directly addressed changes in temperament over time (Del Rosario et al., 2014). Future research should explore this further, as the knowledge of how temperament features change over time may help inform clinical practice surrounding diagnosis and intervention targets. Within the included articles, only two (Chuang et al., 2012; Hepburn & Stone, 2006) reported on the distribution of scores (i.e., % within/above/below 1 standard deviation of the normative mean). Most studies indicated that children with ASD as a group had more challenging temperament features. However, both Hepburn and Stone (2006) and Chuang et al. (2012) highlight that some children with ASD had temperament features comparable to normative samples. Therefore, there is need to further explore temperamental profiles (i.e. distribution of scores), in order to examine the variability in temperament among children with ASD, prior to and post diagnosis.

2.4.2 Conclusions

To the authors' knowledge, this is the first systematic review to synthesise the literature investigating the temperament of children with ASD, prior to and after diagnosis. Our review found sufficient evidence to suggest that some specific temperament features are associated with ASD in childhood. Children diagnosed with ASD were reported by their parents to display more negative affect, less extraversion, and less effortful control. Although, there was large heterogeneity in the studies, which highlights the importance of using an individuals' profiles to identify appropriate intervention. Our review also indicates that infants later diagnosed with ASD were rated as displaying behaviours generally deemed to be 'easier' in early infancy with more challenging behaviours observed closer to time of diagnosis. However, due to the relatively small number of studies in this area, these findings should be interpreted with caution. All six of the articles that reported on the temperament of infants later diagnosed with ASD were conducted with infant siblings of children diagnosed with ASD, with only one assessing changes in temperament over time. Thus, our review supports the need for future research to investigate how temperament features present and change in other infant cohorts at-risk for ASD.

Chapter Three: Methodology

Chapter Synopsis

This chapter will provide a description of the following: a) the research projects used to source data to address the research questions – Breathing for Life Trial-Infant Development and BabyMinds – including recruitment strategies, participant characteristics and eligibility criteria; b) the measures used within this thesis; and c) the procedures used to collect and code data.

3.1 Data Sources

This thesis sourced data from two longitudinal observational studies: The Breathing for Life Trial – Infant Development project and the BabyMinds project. Participants within these studies were recruited from the Hunter and Central Coast regions of New South Wales in Australia. These studies were chosen as they included measures of temperament and risk of ASD, as part of profiling infant development within the first year of life. Data collected from May 2015 until December 2018 was used within this thesis. The Breathing for Life Trial – Infant Development project was chosen to provide data for the at-risk group, due to an increased risk of Autism Spectrum Disorder (ASD) in infants born to mother with asthma (for details, see section 1.2.2). The BabyMinds project was chosen to provide data for the comparison group, due to low risk of neurodevelopmental disorders in the cohort and recruitment occurring in the same region as the BLT-ID project.

3.1.1 The Breathing for Life Trial - Infant Development

The Breathing for Life Trial - Infant Development (BLT-ID) project is a longitudinal cohort study that is investigating the developmental and behavioural outcomes of infants born to mothers with asthma during pregnancy. The BLT-ID is a sub-study of the original Breathing for Life Trial (BLT), which is a multi-site randomised controlled trial (RCT) investigating whether a novel asthma management strategy (use of Fractional Exhaled Nitric Oxide to guide treatment changes) will lead to better maternal and infant health outcomes (Murphy et al., 2016). Thus, the BLT-ID project also aims to examine whether there are differential infant developmental outcomes as a function of maternal RCT treatment group, once the BLT is completed.

3.1.1.1 Recruitment

After the birth of their child, mothers attending BLT follow-up appointments were subsequently invited to participate in the BLT-ID. The BLT-ID tests participants at three time points, when infants are approximately aged 6 weeks (± 2 weeks[1]), 6 months (± 1 month) and 12 months (± 1 month). Participants could enrol into the study at any of the three timepoints. Only mothers who were enrolled in the RCT at the John Hunter Hospital site in New Lambton Heights, Australia were invited to participate in the BLT-ID, due to feasibility at time of study conception.

There were 435 mothers eligible to participate in the BLT-ID during the recruitment period, of which, 295 were invited to participate (Figure 3.1). The remaining 140 mothers were not invited to participate as they did not attend any of their BLT appointments

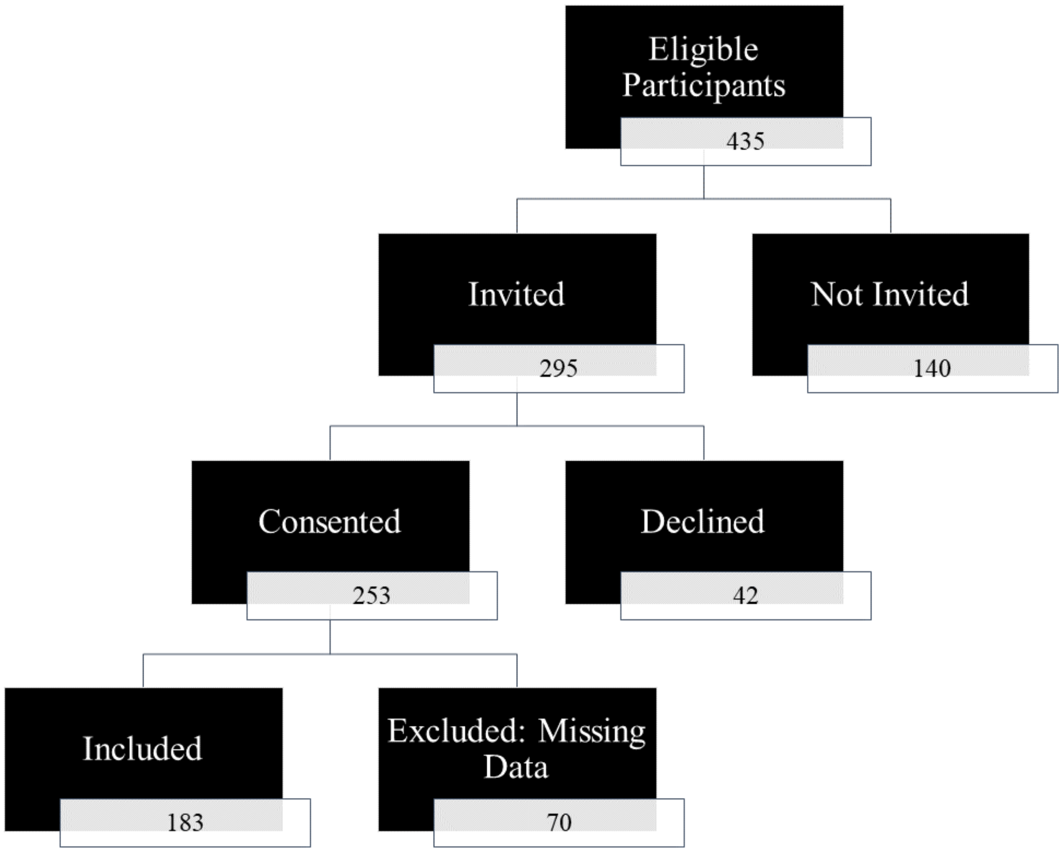

Figure 3.1 A flowchart of the number of participants in each recruitment stage for the BLT-ID study.

[1] At the first timepoint, we aimed to test infants at 6 weeks (±2 weeks). However, due to the health complications experienced by mothers with asthma and their infants, we did test some infants at the first timepoint who were outside the specified age range.

subsequent to the birth of their infant(s). Of the mothers who were invited to participate, 86% (*n* = 253) consented to participate in the BLT-ID. From the pool of mothers who consented to the BLT-ID, 72% (*n* = 183) are included in the studies presented within this thesis. The other 70 mothers were not included due to missing or incomplete data. Mothers who were not invited to participate in the BLT were less likely to have only one child and more likely to be current smokers (all $p < .05$). No significant differences were observed between (a) mothers who were invited versus not invited to participate in the BLT-ID or (b) mothers who consented versus declined participation in the BLT-ID (for more details, see Appendix G).

3.1.1.2 Eligibility Criteria

For the original BLT, pregnant women who had a physician diagnosis of asthma were recruited at a gestational age of 12-22 weeks during antenatal appointments. Women were at least 18 years of age, were randomised into an RCT arm between 12 and 23 weeks gestation and had symptoms of asthma or had used asthma treatment (short acting bronchodilators, or inhaled corticosteroids) in the previous 12 months. Women were included regardless of smoking status at recruitment. Women were excluded if they were drug/alcohol dependent, had a lung disease other than asthma, or had used oral corticosteroids for >14 days in the previous 3 months. Infants were included regardless of gestational age and birth weight. Mothers were excluded from the BLT-ID sub-study if they reported active symptoms of a severe mental illness at time of testing.

3.1.1.3 Ethics Approval

Ethics approval for the BLT-ID study was obtained from the Hunter New England Human Research Ethics Committee (reference number: 15/05/20/4.05) and reciprocal approval was obtained from the University of Newcastle Human Research Ethics Committee (reference number: H-2015-0307). Recruitment commenced in June 2015 and was ongoing until October 2018. No variations were made to the original ethics application for the purpose of this thesis.

3.1.2 BabyMinds: A Study of Infant Development and Parental Wellbeing

BabyMinds (BMs) is a longitudinal study that profiles infant development in the first year of life, in order to examine whether developmental trajectories of infants are impacted by maternal physical, psychological and social states.

3.1.2.1 Recruitment

Participants were recruited through the New South Wales Children and Family Health Nursing Service (CFHN) within the Hunter New England Local Health District. CFHN nurses invited families to participate during routine visits 2-week following the birth of the infant. At this time, mothers were given an information packet (containing an invitation letter, an information statement and a ‘consent to contact’ form) and encouraged to contact the researchers for further information. Posters were additionally displayed at each of the five recruiting CFHN sites and flyers were handed out at CFHN parenting groups. Participants were also recruited from local communities via posters and flyers distributed to antenatal clinics, General Practitioner/Obstetrician and Gynaecologist clinics, university campuses, community events, playgroups, and mother’s groups within the Hunter and Central Coast regions of New South Wales in Australia. Additionally, social media was utilised to recruit participants via paid advertisements on Facebook and via social media engagement on ‘grad photos’ of infant participants posted weekly.

3.1.2.2 Eligibility Criteria

Participants were primary caregivers and their infants from local communities. Caregivers were invited to participate at three time points, when infants were aged 6 weeks (±

2 weeks[2]), 6 months (± 1 month) and 12 months (± 1 month). Caregivers were included in the study if they were over the age of 18 and, alongside their infant(s), did not heavily rely on medical assistance. Within this thesis, participants were excluded from analyses if the mother reported a diagnosis of asthma. Further, all infants from the BMs study included within this thesis were full-term (≥36 weeks gestation) with a healthy birth weight (≥2500g).

3.1.2.3 Ethics Approval

Ethics approval for the BMs study was obtained from the University of Newcastle Human Research Ethics Committee (reference number: H-2016-0425) and the Hunter New England Human Research Ethics Committee (reference number: 17/12/13/4.01). Recruitment commenced in May 2017 and was ongoing until December 2018. No variations were made to the original ethics application for the purpose of this thesis.

3.2 Measures

The above-mentioned BLT-ID and BMs studies have overlapping protocols and assessed several areas related to infant development and parental health (see Table 3.2 in Appendix H). For the purpose of this thesis, only the measures used within each of the three study chapters (i.e., chapters four, five and six) will be described in detail (for overview, see Table 3.3).

3.2.1 Primary Outcomes

3.2.1.1 Infant Temperament

The Carey Temperament Scales is a norm-referenced collection of five parent-report questionnaires that measure temperament from one month to 12 years of age. Three of the five questionnaires are used as the measure of infant temperament in this thesis: The Early Infancy Temperament Questionnaire (EITQ; Medoff-Cooper et al., 1993) at 6 weeks, the

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[2] At the first timepoint, we aimed to test infants at 6 weeks (±2 weeks). However, due to the nature of research with young infants, we did test some infants at the first timepoint who were outside the specified age range.

Table 3.3 A brief overview of questionnaires and assessments included in thesis chapters.

Measure	Age Assessed	Brief Description of Measure	Domains
Bayley Scales of Infant and Toddler Development	6 and 12 months	Assesses the developmental level of young children. Screens for developmental delay.	Cognitive Receptive Communication Expressive Communication Fine Motor Gross Motor
Carey Temperament Scales	All	Assesses temperament of infants, toddlers and children.	Activity Rhythmicity Approach Adaptability Intensity Mood Persistence Distractibility Threshold
Edinburgh Postnatal Depression Scale	Time of Enrolment	Screens for risk of postpartum depression.	Total Score
First Year Inventory	12 months	Screens for risk of Autism Spectrum Disorder.	Social-Communication Sensory-Regulatory Total Score
Toddler Sensory Profile 2	All	Assesses sensory processing in infants, toddlers and children.	Infant form: Total Score Toddler form: Seeking/Seeker Quadrant Avoiding/Avoider Quadrant Sensitivity/Sensor Quadrant Registration/Bystander Quadrant

Revised Infant Temperament Questionnaire (RITQ; Carey & McDevitt, 1978a) at 6 months and the Toddler Temperament Scales (TTS; Fullard et al., 1984) at 12 months. The questionnaires include nine domains that measure different areas of behaviour: activity, rhythmicity, approach, adaptability, intensity, mood, persistence, distractibility, and threshold. Domain scores are computed by averaging the responses to the items that load into each domain: There are 76 items for the EITQ, 95 items for the RITQ and 107 items for the TTS. Items are rated on a 6-point Likert scale, from 1 (Almost Never) to 6 (Almost Always). The following are examples of items in the questionnaires, specifically from the distractibility domain: "The infant can be soothed (patted, rocked) when sleepy" (EITQ), "The infant can be distracted from fussing or squirming during procedure (nail cutting, hair brushing, etc.) by a game, singing, TV, etc." (RITQ) and "The child stops eating and looks up when a person walks by" (TTS).

Past research utilising the CTS have found the questionnaires to have acceptable reliability and have been validated within clinical populations (Carey & McDevitt, 1978a; Dukewich, Borkowski, & Whitman, 1996; McDevitt & Carey, 1978; Stroustrup et al., 2016; Tees et al., 2010; Torowicz, Irving, Hanlon, Sumpter, & Medoff-Cooper, 2010; Zhu et al., 2014). For the EITQ, internal consistency ranged from .42 to .76 for the nine domains and test-retest reliability ranged from .43 to .87 (Medoff-Cooper et al., 1993; Torowicz et al., 2010). Within the current study, internal consistency coefficients for the EITQ ranged from .38 to .84 for the nine domains. For the RITQ, internal consistency coefficients ranged from .49 to .71 for the nine categories and .83 for the entire instrument (Carey & McDevitt, 1978a). The test-retest reliability coefficient was .86 (Dukewich et al., 1996). Within the current study, internal consistency coefficients for the RITQ ranged from .42 to .79 for the nine domains. For the TTS, test-retest reliability was satisfactory, with a median correlation of .81 (Fullard et al., 1984). Internal consistency had a median correlation coefficient of .70

across the nine categories, and thus was satisfactory. Within the current study, internal consistency coefficients for the TTS ranged from .34 to .84 for the nine domains.

3.2.1.2 Risk of Autism Spectrum Disorder

The First Year Inventory (FYI; Reznick, Baranek, Reavis, Watson, & Crais, 2007; Turner-Brown, Baranek, Reznick, Watson, & Crais, 2013) is a parent-report questionnaire that screens for risk of ASD at one year of age. The FYI includes 61 questions about infant behaviour that is observed in typically developing infants, but also those who have an increased risk of a later diagnosis of ASD. An example item from the FYI is “Does your baby ignore loud or startling sounds?”. These questions are scored in terms of the frequency of the behaviours observed: Never, Seldom, Sometimes or Often. These items load into one of two risk domains, Social Communication and Sensory Regulatory, and a Total Risk score. The cut-off for the Social-Communication Domain score is 22.5 (94^{th} percentile) and the cut-off for the Sensory-Regulatory Domain is 14.75 (88^{th} percentile). Infants who meet both cut-off scores are deemed as at-risk for the eventual diagnosis of ASD. The FYI has a predictive diagnostic value of 0.31, which indicates that 31% of infants screened as at-risk will receive an eventual diagnosis of ASD. The FYI has been reported to have good internal consistency ($\alpha = .81$ across the 61 items; Reznick et al., 2007). Within the current study, the internal consistency coefficient across the 61 items was .73.

3.2.2 Secondary Outcomes

3.2.2.1 Sociodemographic Characteristics

Sociodemographic information, medical history and birth outcomes were collected at each visit via a brief project-designed questionnaire. This includes information such as maternal/infant date of birth, infant expected due date, infant gender, maternal education level, annual household income, and family illness and medical history. A full version is used at a participant's first appointment and at subsequent appointments they receive a revised (i.e., shorter) version to update their information.

3.2.2.2 Sensory Processing

The Sensory Profile 2 (SP2; Dunn, 2014) is a collection of five norm-referenced parent- and teacher- report questionnaires that assess the level of sensory functioning in children, from birth to 14 years and 11 months, in relation to everyday sensory events. The SP2 was included in this thesis as it is well-established in the literature that sensory processing differences are associated with ASD symptoms (Lane, Molloy, & Bishop, 2014; Niedźwiecka, Domasiewicz, Kawa, Tomalski, & Pisula, 2019; Simpson, Adams, Alston-Knox, Heussler, & Keen, 2019) and is related yet distinct from temperament (e.g., Nakagawa, Sukigara, Miyachi, & Nakai, 2016). This thesis utilised two of the questionnaires from the SP2 to measure sensory processing: The Infant Sensory Profile 2 (ISP2; for 6-week and 6-month-old infants) and the Toddler Sensory Profile 2 (TSP2; for 12-month-old infants). The ISP2 includes 25 items from six domains, while the TSP2 includes 54 items from seven domains. These domains include General Processing, Auditory Processing, Visual Processing, Touch Processing, Movement Processing, Oral Sensory Processing, Behaviour Processing (TSP2 only) and Total Sensory Processing (ISP2 only). Domain scores are computed by summing the responses to the items that load into each individual subscale. Domain scores are only computed if there are no missing responses for items in that particular domain. Items are rated on a 5-point Likert scale from 5 (Almost Always) to 1 (Almost Never). Higher scores indicate more hyper-reactive sensory features, while low scores indicate more hypo-reactive sensory features. The TSP2 can also produce four sensory styles called quadrants, which refer to how likely an infant is to pursue (seeking/seeker), move away from (avoiding/avoider), notice (sensitivity/sensor), or miss (registration/bystander) sensory input. An example of an item from the ISP2 is "My baby becomes upset by sudden everyday sounds" and an example from the TSP2 is "My child needs a routine to stay content or calm". The ISP2 and TSP2 have been used with typically developing and clinical samples (Dunn & Daniels, 2002; Tomchek & Dunn, 2007): Test-retest reliability coefficients ranged from .83 to .97, indicating a high level of consistency in scores across time (Psimas, 2014).

3.2.2.3 Developmental Level

The Bayley Scales of Infant and Toddler Development (3rd edition, Bayley-III; Bayley, 2006) is a norm-referenced assessment tool that measures the developmental functioning of infants aged one to 42 months. The Bayley-III assesses an infant's development in areas of cognitive, language and motor skills, and can be used to assist in the diagnosis of developmental delays. The cognitive scale includes up to 91 items, which assess information processing, memory and habituation skills, reasoning abilities and play skills. The language scale includes two subtests: receptive communication and expressive communication. The receptive communication subtest includes up to 49 items, which assess a child's ability to discriminate between sounds, and their comprehension of and response to verbal stimuli. The expressive communication subtest includes up to 48 items, which assess a child's ability to name objects and actions, respond to questions, and use multiword sentences. The motor scale includes two subtests: fine motor and gross motor. The fine motor subtest includes up to 66 items, which assess motor planning and speed, the use of a pincer grasp, and visual tracking. The gross motor subtest includes up to 72 items, and assesses skills involving the movement of torso and limbs such as balance, jumping, and locomotion. The Bayley-III requires the child to interact with the administrator and test stimuli, in order to score the items on a two-point scale; either 1 (able to demonstrate target behaviour) or 0 (not able to demonstrate target behaviour). The screening version was utilised during the 6-month time point, which includes a subset of items from the complete Bayley-III in order to screen infants for risk of developmental delay in a shorter timeframe. The Bayley-III has been demonstrated to have acceptable reliability and validity (Albers & Grieve, 2006). Internal consistency coefficients ranged from .91 to .93 for scales, and subtest coefficients ranged from .86 to .91, indicating good internal consistency. Across all ages, corrected correlation coefficients for domains were .80 or higher, indicating good test-retest reliability. Within the current study, average interrater reliability coefficients ranged from .83 to .99 for the five subscales.

3.2.2.4 Prenatal Maternal Asthma Severity and Control

The measures of asthma severity and asthma control were only administered to mothers enrolled in the BLT-ID study. Asthma severity and asthma control were classified based on asthma reliver and preventor use, and asthma symptoms (see section 3.3.2.3 for details). This information used to classify maternal asthma severity and asthma control was collected through self-report of asthma reliever and preventer use, and the asthma symptom questions outlined in the Global Initiative for Asthma guidelines (Global Initiative for Asthma, 2017).

3.2.2.5 Maternal Mental Health

The Edinburgh Postnatal Depression Scale (EPDS; Cox, Holden, & Sagovsky, 1987) is a self-report questionnaire that contains 10 items designed to evaluate a mother's emotional distress during pregnancy or in the postpartum period. An example of an item is "I have been so unhappy that I have been crying". Items are rated on a 4-point Likert scale, which is different for each item. Seven of the ten items are reverse scored, so that higher scores indicate a higher risk of depression. The EPDS produces a total score that indicates potential postpartum depression (when $\geq$10). The total score was not produced if any items were missing. Prior research has deemed the EPDS to have good internal consistency (α = .82 to .84; Bergink et al., 2011) and test-retest reliability (r = .91 to .96; Kernot, Olds, Lewis, &

Maher, 2015). Within the current study, the internal consistency coefficient across the 10 items was .86.

3.3 Procedure

3.3.1 Data Collection

Participants were provided with a written information statement prior to consent. Primary caregivers provided written informed consent for themselves and their infant(s) upon entry into the study. Primary caregivers were given a questionnaire packet to complete (for included questionnaires, see Table 3.4 in Appendix H), either prior to or after the laboratory visit, which took approximately 2 hours to complete at each timepoint. The laboratory visits were conducted at the Hunter Medical Research Institute or the University of Newcastle. A full list of the assessments completed is reported in Table 3.4 (see Appendix H). Briefly, sessions lasted approximately 30 minutes at 6 weeks, 1 hour at 6 months and 2 hours at 12 months. At 6 weeks, a 15-minute filmed parent-infant play interaction was conducted. At 6 and 12 months, in addition to the play interaction, infants completed assessments on development (Bayley-III) and sensory functioning (TSFI), alongside an eye-tracking paradigm assessing cognition. Trained clinicians and postgraduate students in psychology or occupational therapy administered the developmental and sensory functioning assessments. After each visit, BLT-ID and BM participants were reimbursed with an AUD$20 gift card and a small gift for the infant. Further, at 6 months and 12 months, caregivers were given a brief developmental report, based on the results from Bayley-III.

Parental mental health and infant development assessments were screened by researchers after each testing session, in order to identify participants that may be at-risk. Those who were at-risk were followed-up by the clinical psychologist and the occupational therapist on the studies. In an attempt to retrieve missing data, reminder texts were sent one week, and three weeks if required, after their visit to remind caregivers of outstanding questionnaires. Furthermore, study ‘post cards’ were sent to enrolled participants approximately 2 weeks before their next visit was due to be scheduled, in order to remind them about participation in follow-up visits. For BLT-ID participants, the RCT baseline data used to assess asthma severity and asthma control during pregnancy were accessed through the BLT database.

3.3.2 Data Coding

3.3.2.1 Carey Temperament Scales

Data was coded in the Statistical Package for the Social Sciences (SPSS version 25; IBM Corporation, 2017) using syntax. SPSS syntax was developed using the hand scoring formula sheets provided with the questionnaires. Each item loads into one of the nine CTS domains, which are averaged in order to obtain nine domain scores. As per the scoring instructions reported in the manual (Behavioral-Developmental Initiatives, 2007), CTS subscale scores were not computed if more than 20% of the items had missing responses. In order to interpret domain scores, they were assigned a *profile label* based on the following: scores that fall one standard below the normative mean are classified as *easy*, scores that fall one standard within the normative mean are classified as *average* and scores that fall one standard above the normative mean are classified as *difficult*. Further, the authors of the CTS (e.g., Carey, 1970; Carey & McDevitt, 1978a, 1978b) state that an infant’s temperament can be categorised into *diagnostic categories*, using the methodology presented in Table 3.4. Briefly, the process involves where an infant’s CTS score falls on five of the CTS domains. Subsequently, an infant’s temperament is assigned one of five diagnostic temperament categories, depending on how many domain scores are below, above or within the normative mean.

Table 3.4 The diagnostic temperament categories within the Carey Temperament Scales.

Diagnostic Temperament Categories	Related Temperament Domains
Difficult	Rhythmicity, Intensity, Approach, Adaptability, Mood • 4 or 5 domain ratings above the normative mean • + at least 2 ratings greater than 1 standard deviation above the normative mean
Intermediate - High	Rhythmicity, Intensity, Approach, Adaptability, Mood • 4 or 5 domain ratings above the normative mean • + 1 rating greater than 1 standard deviation above the normative mean Or • 2 to 3 domain ratings above the normative mean • + 2 to 3 greater than 1 standard deviation above the normative mean
Slow-To-Warm-Up	Activity, Intensity, Approach, Adaptability, Mood • Below the normative mean for Activity and Intensity ratings • Above the normative mean for Approach and Adaptability ratings • Above the normative mean for Mood, but no more than 1 standard deviation above the normative mean.
Intermediate - Low	Rhythmicity, Intensity, Approach, Adaptability, Mood • 3 to 5 domain ratings above the normative mean • + 0 ratings greater than 1 standard deviation above the normative mean Or • 1 to 3 domain ratings above the normative mean • + 1 greater than 1 standard deviation above the normative mean
Easy	Rhythmicity, Intensity, Approach, Adaptability, Mood • 0 to 2 domain ratings above the normative mean • + No ratings greater than 1 standard deviation above the normative mean

Note: Ratings above the normative mean indicate *difficult* scores and ratings below the normative mean indicate *easy* scores.

3.3.2.2 First Year Inventory

Data was coded in the Statistical Package for the Social Sciences (SPSS version 25; IBM Corporation, 2017) using syntax. SPSS syntax was developed using the algorithm provided in a Microsoft Excel spreadsheet by the developers of the FYI. The algorithm created by the instrument authors produces a social-communication risk score, a sensory-regulatory risk score and a total risk score (average of the two domain risk scores). As recommended by a co-developer of the FYI (Baranek, G.T., personal communication with Lane, A.E., August 1, 2018), FYI domain scores were not computed if more than 10% of the items had missing responses (each domain calculated separately). A percentile is provided for each of the risk scores to aid in interpretation, alongside a cut-off score used to identify infants at heighted risk. The cut-off scores used within this thesis were those previously reported by Turner-Brown et al. (2013): 19.2 (≥ 96^{th} percentile) for the Total Risk score, 22.5 (94^{th} percentile) for the Social-Communication Domain score, and 14.75 (88^{th} percentile) for the Sensory-Regulatory Domain. The developers of the FYI recommend that the more stringent two-domain cut-off criterion should be applied, rather than the total cut-off criterion. This is because the two-domain criterion is better to identify infants who are more likely to develop ASD, compared to other developmental concerns, than the total score criterion (i.e., a lower false positive rate). However, for the purpose of this thesis, infants who met the cut-off for the total score and/or the two domain scores will be considered as *at-risk*. The research conducted as part of this thesis was largely exploratory in nature and utilised a small sample of infants. A more liberal approach was taken to increase the likelihood of identifying all possible infants at-risk for developmental concerns in this relatively understudied cohort.

3.3.2.3 Global Initiative for Asthma Guidelines for Asthma Severity and Asthma Control Classifications

Maternal asthma severity and control during pregnancy was classified utilising asthma management and prevention guidelines (Global Initiative for Asthma, 2017). Mothers were described as having: mild asthma if they were using step 1 (reliever alone) or step 2 (low dose inhaled corticosteroids [ICS]) therapy, moderate asthma if they were using step 3 (low dose ICS/long-acting beta-antagonist [LABA] or medium/high dose ICS) therapy or severe asthma if they were using step 4 (medium/high dose ICS/LABA) therapy. Mothers were considered to have well-controlled asthma if they did not experience any of the following symptoms in the previous week: night waking, activity limitation, reliever use >2 times, or daytime symptoms >2 times. Mothers were classified as having partly-controlled asthma or uncontrolled asthma if 1-2 or 3-4 of these symptoms were present, respectively. Asthma severity and asthma control groups were not computed for mothers who did not report on their asthma treatment and asthma symptoms.

Chapter Four: Study One

Early temperament features in infants born to mothers with asthma

Chapter Synopsis

This chapter is the first of three studies contributing to this thesis. This chapter consists of two parts and aims to explore the first research question of this thesis: What are the temperament features of infants born to mothers with asthma at 6 weeks, 6 months and 12 months of age, and how do they compare to infants born to mothers without asthma? Part One explores the temperament of infants born to mothers with asthma during pregnancy and compares each of the nine CTS domain scores to the normative data. Part Two extends upon the methodology used in part one in order to compare the CTS domain scores, domain profiles (i.e., Easy, Average, Difficult) and overall diagnostic temperament category (i.e., Easy, Difficult, Sow-To-Warm-Up, Intermediate) of infants born to mothers with asthma to infants recruited from the Hunter Region and Central Coast communities of New South Wales, Australia. The CTS domain profiles and diagnostic temperament category were also included as they provide meaningful information about individual infant's behavioural styles, as compared to group mean scores, and allow for the exploration of individual differences in temperament. While group mean CTS scores may be comparable between groups, investigating the differences in proportions of temperament categories between groups provides the ability to see whether there are more infants born to mothers with asthma with challenging temperament features compared to infants from the general community.

4.1 Part One: A Comparison with Normative Data, Asthma Control and Asthma Severity

4.1.1 Aims

In this exploratory study, we aimed to: 1) characterise temperament features of infants born to mothers with asthma in the first year of life, as compared to the normative population, and 2) investigate differences in temperament between infants, as a function of maternal asthma severity and asthma control during pregnancy. Given the paucity of research in this area, this investigation was considered exploratory and no hypotheses were proposed.

4.1.2 Data Analysis

Data were analysed using the Statistical Package for the Social Sciences (version 25; IBM Corporation, 2017). GraphPad Software QuickCalcs (Motulsky, 2018) was used to perform chi-squared analyses. JASP was used to conduct Bayesian analyses in order to examine the strength of evidence under the null hypothesis (JASP Team, 2019; van Doorn et al., 2019). As described in van Doorn et al. (2019), Bayes Factors (BF) were used to interpret the strength of evidence using the following guidelines: BF_{10} 1-3 = inconclusive evidence, BF_{10} 3-10 = moderate evidence and BF_{10} >10 = strong evidence. BF_{10} that are >1 provide evidence under the alternative hypothesis and BF_{10} <1 provide evidence under the null hypothesis. Data was analysed cross-sectionally at 6 weeks, 6 months and 12 months. Means and standard deviations were produced for CTS data, sociodemographic characteristics, and asthma severity and control. Additionally, percentages of each response option were produced for the sociodemographic characteristics, as well as maternal asthma severity and control. CTS scores were compared to the normative data using one-sample t-tests. One-sample t-tests were the most appropriate statistical analyses to perform as they determine whether a sample mean is statistically different from a known population mean, and have been used in multiple studies comparing a study sample to normative data (e.g., Gaynor et al., 2015; Noyes, 2007).

Differences in temperament between infants born to mothers with mild asthma vs non-mild (moderate/severe) asthma were examined using independent samples t-test. Differences in temperament between infants born to mothers with well-controlled vs partly-controlled vs uncontrolled asthma were examined using one-way Analysis of Variance. Level of statistical significance was set to $\alpha < 0.05$. Bonferroni corrections were applied for multiple comparisons, with alpha levels reported in the results section.

4.1.3 Results

4.1.3.1 Sample Characteristics

Mothers (n = 183) had a mean age of 30.4 years (SD = 5.1) when their infants (51.9% male, 97.8% singleton) were born (Table 4.1). Most mothers were Caucasian (85.8%), Australian born (88.0%) and well-educated (84.2% had at least completed final year of high school). The mode annual household income range was $80,001 to $180,000. Most mothers had mild asthma (59.6%), which was either partly-controlled (45.9%) or uncontrolled (32.8%; Table 4.2). Most mothers with asthma did not smoke during pregnancy (89.9%) and had a body mass index (BMI; kg/m^2) above the healthy range (73.3%; Table 4.2). From the total asthma sample (n = 183), 80 mothers reported using inhaled corticosteroids (ICS) as their preventer medication (median dose = 500 µg, for 76 out of 80 mothers using ICS). There were four sets of twins; data were randomly selected from one twin of each pair to include in analyses. Further, participants were included if they had complete data for the temperament measure, for at least one time-point: 45.3% of our total sample provided data for more than one time-point described within this chapter. In order to assess for missing data bias, mothers who had temperament data (at any timepoint) and mothers who had missing temperament data (excluded from this study) were compared on their asthma and physical health characteristics. There were no statistically significant differences between mothers who were included versus excluded on any of the characteristics (Appendix G).

Table 4.1 Sociodemographic characteristics of the participants at 6 weeks, 6 months and 12 months of age.

Sociodemographic characteristic		6 weeks *n* = 144	6 months *n* = 83	12 months *n* = 74
Maternal Age, at infant birth (years)				
	Mean (SD)	30.3 (5.1)	30.7 (5.1)	30.8 (5.2)
	Range	20.1 – 43.9	20.7 – 43.9	21.4 – 43.9
Infant Age[a], at participation (weeks)				
	Mean (SD)	6.8 (1.5)	27.5 (1.8)	54.3 (3.0)
	Range	1.7 – 10.4	19.9 – 33.4	42.7 – 64.4
Infant Gender, *n* (%)				
	Male	76 (52.8)	43 (51.8)	39 (52.7)
	Female	68 (47.2)	40 (48.2)	35 (47.3)
Maternal Country of Birth, *n* (%)				
	Australia	131 (91.0)	73 (88.0)	62 (83.8)
	Overseas	8 (5.6)	4 (4.8)	4 (5.4)
	Unspecified[b]	5 (3.5)	6 (7.2)	8 (10.8)
Maternal Ethnicity, *n* (%)				
	Caucasian	126 (87.5)	69 (83.1)	64 (86.5)
	Aboriginal Australian	2 (1.4)	3 (3.6)	2 (2.7)
	Asian	3 (2.1)	2 (2.4)	2 (2.7)
	Mixed	7 (4.9)	3 (3.6)	3 (4.1)
	Other	6 (4.2)	5 (6.0)	3 (4.1)
	Unspecified[b]	0 (0.0)	1 (1.2)	0 (0.0)
Maternal Educational Attainment, *n* (%)				
	< High School Certificate	23 (16.0)	12 (14.5)	11 (14.9)
	High School Certificate	28 (19.4)	15 (18.1)	8 (10.8)
	Trade Certificate/Diploma	48 (33.3)	19 (22.9)	16 (21.6)
	University Degree	39 (27.1)	31 (37.3)	32 (43.3)
	Unspecified[b]	6 (4.2)	6 (7.2)	7 (9.5)
Annual Household Income[c], *n* (%)				
	0 – 18,700	11 (7.6)	5 (6.0)	6 (8.0)
	18,701 – 37,000	13 (9.0)	7 (8.3)	7 (9.3)
	37,001 – 80,000	42 (29.2)	25 (29.8)	17 (22.7)
	80,001 – 180,000	64 (44.4)	40 (47.6)	37 (49.3)
	180,001 and Over	8 (5.6)	3 (3.6)	3 (4.0)
	Unspecified[b]	6 (4.2)	4 (4.8)	5 (6.7)
Parity, *n* (%)				
	Primipara (1 child)	75 (52.1)	42 (50.6)	36 (48.6)
	Multipara (2 children)	42 (29.2)	21 (25.3)	21 (28.4)
	Grand Multipara (≥ 3 children)	27 (18.8)	20 (24.1)	17 (23.0)
	Unspecified[b]	0 (0.0)	0 (0.0)	0 (0.0)
Mental Health Condition[d], *n* (%)				
	No	112 (77.8)	59 (71.1)	51 (68.9)
	Yes	32 (22.2)	24 (28.9)	23 (31.1)
	Anxiety Disorder	20 (13.9)	13 (15.7)	12 (16.2)
	Depressive Disorder	26 (18.1)	21 (25.3)	17 (23.0)
	Borderline Personality Disorder	2 (1.4)	2 (2.4)	1 (1.4)

[a]Adjusted for infant prematurity.
[b]Mothers did not respond to the question(s) pertaining to this information.
[c]Annual household income is reported in Australian dollars.
[d]Frequencies/percentages do not add up to total sample size/100 percent as they are not mutually exclusive.

Table 4.2 Descriptive statistics for asthma and physical health characteristics for mothers with asthma.

Asthma/Health characteristic		6 Weeks n = 144	6 Months n = 83	12 Months n = 74
Body Mass Index, *n* (%)				
	Mean (SD)	31.0 (8.1)	30.7 (7.4)	31.2 (8.3)
	Range	19.2 – 51.4	19.6 – 49.4	19.6 – 49.4
	Underweight	0 (0.0)	0 (0.0)	0 (0.0)
	Health Weight	36 (25.0)	18 (21.7)	20 (27.0)
	Overweight	43 (29.9)	29 (34.9)	20 (27.0)
	Obese	65 (45.1)	35 (42.2)	32 (43.2)
	Unknown[a]	0 (0.0)	1 (1.2)	2 (2.7)
Smoking status, *n* (%)				
	Never	82 (56.9)	50 (60.2)	51 (68.9)
	Ex-Smoker	45 (31.3)	25 (30.1)	18 (24.3)
	Current Smoker	16 (11.1)	8 (9.6)	5 (6.8)
	Unspecified[a]	1 (0.7)	0 (0.0)	0 (0.0)
Asthma severity, *n* (%)				
	Mild	86 (59.7)	52 (62.7)	45 (60.8)
	Moderate	18 (12.5)	11 (13.3)	13 (17.6)
	Severe	38 (26.4)	19 (22.9)	13 (17.6)
	Unknown[a]	2 (1.4)	1 (1.2)	3 (4.1)
Asthma control, *n* (%)				
	Well-controlled	30 (20.8)	15 (18.1)	14 (18.9)
	Partly-controlled	68 (47.2)	43 (51.8)	37 (50.0)
	Uncontrolled	45 (31.3)	25 (30.1)	22 (29.7)
	Unknown[a]	1 (0.7)	0 (0.0)	1 (1.4)
Asthma treatment[b], *n* (%)				
	SABA	137 (95.1)	80 (96.4)	69 (93.2)
	ICS	11 (7.6)	7 (8.4)	9 (12.2)
	ICS/LABA	51 (35.4)	27 (32.5)	22 (29.7)
	LABA	3 (2.1)	1 (1.2)	1 (1.4)
	No asthma treatment specified[a]	2 (1.4)	1 (1.2)	3 (4.1)

[a]This information was not collected at baseline because mothers either did not attend their appointment or they did not specify the information during their appointment.
[b]Frequencies/percentages do not add up to total sample size/100 percent as they are not mutually exclusive.

4.1.3.2 Characterisation of Infant Temperament

Mean CTS domain scores between infants born to mothers with asthma and normative samples were compared at 6 weeks, 6 months, and 12 months of age. Descriptive statistics alongside p-values are reported in Table 4.3 and Bayes Factors are reported in Table 4.4. At the first time point, around 6 weeks of age, average scores were compared to the two

Table 4.3 Comparison between normative Carey Temperament Scales data and our 6 week, 6 month and 12 month-old asthma samples. One sample t-tests were used to determine significant differences between the two groups, and *p*-values are reported here.

Age	CTS Domain	Asthma M (SD)	Normative M (SD)	*p*-value
4-8 Weeks		*n* = 126	*n* = 262	
	Activity	3.65 (0.64)	3.58 (0.65)	.278
	Rhythmicity	3.38 (0.79)	3.12 (0.69)	**.001***
	Approach	2.45 (0.71)	2.58 (0.63)	.046
	Adaptability	2.33 (0.67)	2.49 (0.67)	.016
	Intensity	3.74 (0.88)	3.86 (0.69)	.135
	Mood	2.86 (0.74)	3.21 (0.73)	**<.001***
	Persistence	2.80 (0.92)	2.79 (0.71)	.873
	Distractibility	2.32 (0.73)	2.65 (0.60)	.072
	Threshold	4.28 (0.67)	4.15 (0.57)	.027
9-12 Weeks[a]		*n* = 18	*n* = 142	
	Activity	3.78 (0.81)	3.79 (0.73)	.970
	Rhythmicity	3.18 (0.73)	2.90 (0.71)	.123
	Approach	2.75 (0.80)	2.84 (0.79)	.632
	Adaptability	2.17 (0.49)	2.39 (0.63)	.078
	Intensity	4.12 (0.96)	3.96 (0.68)	.488
	Mood	2.78 (0.97)	2.79 (0.62)	.964
	Persistence	2.37 (0.76)	2.49 (0.54)	.513
	Distractibility	2.22 (0.90)	2.41 (0.58)	.829
	Threshold	4.28 (0.56)	4.32 (0.56)	.768
6 Months		*n* = 83	*n* = 203	
	Activity	4.27 (0.48)	4.40 (0.56)	.015
	Rhythmicity	2.80 (0.76)	2.36 (0.68)	**<.001***
	Approach	2.40 (0.64)	2.27 (0.78)	.068
	Adaptability	2.16 (0.57)	2.02 (0.59)	.035
	Intensity	3.59 (0.60)	3.42 (0.71)	.012
	Mood	2.71 (0.65)	2.81 (0.68)	.172
	Persistence	3.12 (0.80)	3.03 (0.82)	.281
	Distractibility	2.19 (0.62)	2.23 (0.60)	.569
	Threshold	3.85 (0.55)	3.79 (0.76)	.358
12 Months		*n* = 74	*n* = 167	
	Activity	3.92 (0.59)	4.13 (0.80)	**.005***
	Rhythmicity	2.63 (0.80)	2.49 (0.81)	.132
	Approach	2.99 (0.82)	2.97 (1.00)	.844
	Adaptability	3.52 (0.74)	3.42 (0.86)	.242
	Intensity	3.81 (0.54)	4.03 (0.76)	**.001***
	Mood	3.17 (0.63)	2.96 (0.69)	.007
	Persistence	3.77 (0.64)	3.45 (0.83)	**<.001***
	Distractibility	4.43 (0.55)	4.39 (0.76)	.586
	Threshold	3.58 (0.68)	3.61 (0.88)	.713

Abbreviation: CTS = Carey Temperament Scales.
[a]Infants within our 6 week cohort fell across both normative subgroups of the Early Infancy Temperament Questionnaire.
*significant at p <.006, using Bonferroni correction.

Table 4.4 Bayes factors from the comparison of scores on the Carey Temperament Scales (CTS) between infants born to mothers with asthma and normative samples using Bayesian independent samples t-tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
4-8 Weeks				
	Activity	0.186	H_0	Moderate
	Rhythmicity	48.233	H_a	Strong
	Approach	0.701	H_0	Inconclusive
	Adaptability	1.776	H_a	Inconclusive
	Intensity	0.301	H_0	Inconclusive
	Mood	19296.624	H_a	Strong
	Persistence	0.103	H_0	Moderate
	Distractibility	0.497	H_0	Inconclusive
	Threshold	1.099	H_a	Inconclusive
9-12 Weeks[a]				
	Activity	0.256	H_0	Moderate
	Rhythmicity	0.733	H_0	Inconclusive
	Approach	0.277	H_0	Moderate
	Adaptability	1.045	H_a	Inconclusive
	Intensity	0.304	H_0	Inconclusive
	Mood	0.249	H_0	Moderate
	Persistence	0.296	H_0	Moderate
	Distractibility	0.248	H_0	Moderate
	Threshold	0.259	H_0	Moderate
6 Month				
	Activity	2.135	H_a	Inconclusive
	Rhythmicity	9631.788	H_a	Strong
	Approach	0.625	H_0	Inconclusive
	Adaptability	1.071	H_a	Inconclusive
	Intensity	2.660	H_a	Inconclusive
	Mood	0.303	H_0	Inconclusive
	Persistence	0.213	H_0	Moderate
	Distractibility	0.142	H_0	Moderate
	Threshold	0.186	H_0	Moderate
12 Month				
	Activity	5.658	H_a	Moderate
	Rhythmicity	0.386	H_0	Inconclusive
	Approach	0.132	H_0	Moderate
	Adaptability	0.257	H_0	Moderate
	Intensity	28.882	H_a	Strong
	Mood	4.682	H_a	Moderate
	Persistence	343.493	H_a	Strong
	Distractibility	0.149	H_0	Moderate
	Threshold	0.139	H_0	Moderate

Note: H_0 = null hypothesis; H_a = alternative hypothesis.

[a]Infants within our 6-week cohort fell across both normative subgroups of the Early Infancy Temperament Questionnaire.

normative subgroups, as appropriate: 4-8 weeks and 9-12 weeks. The 4-8 week-old infants scored higher in rhythmicity ($t_{(122)} = 3.646$, $p < .001$), lower in adaptability ($t_{(110)} = -2.438$, $p = .016$), lower in mood ($t_{(121)} = -5.251$, $p < .001$) and higher in threshold ($t_{(122)} = 2.235$, $p = .027$) than the normative sample. In other words, they were more arrhythmic in their biological functions, adapted more quickly to change in routine, were less fussy and were more sensitive to sensory events. Bayes Factors indicated that the strength of evidence was inconclusive for adaptability ($BF_{10} = 1.776$) and threshold ($BF_{10} = 1.099$), and strong for rhythmicity ($BF_{10} = 48.233$) and mood ($BF_{10} = 19296.624$). The 9-12 week-old infants[3] did not differ significantly from the normative data; however the sample was very small ($n = 18$).

The 6 month old infants scored lower in activity ($t_{(81)} = -2.476$, $p = .015$), and higher in rhythmicity ($t_{(80)} = 5.190$, $p < .001$), adaptability ($t_{(80)} = 2.146$, $p = .035$) and intensity ($t_{(81)} = 2.573$, $p = .012$) compared to normative data. This indicates that they were less active, more arrhythmic in their biological functions, adapted more slowly to change in routine and were more intense in response. Bayes Factors indicated that the strength of evidence was inconclusive for activity ($BF_{10} = 2.135$), adaptability ($BF_{10} = 1.071$) and intensity ($BF_{10} = 2.660$), and strong for rhythmicity ($BF_{10} = 9631.788$).

The 12 month old infants scored lower in activity ($t_{(68)} = -2.873$, $p = .005$), lower in intensity ($t_{(71)} = -3.481$, $p = .001$), higher in mood ($t_{(71)} = 2.799$, $p = .007$) and higher in persistence ($t_{(71)} = 4.280$, $p < .001$) compared to normative data. This means that they had a lower activity level, were milder in their responses, were fussier and were less persistent when completing challenging tasks. Bayes Factors indicated that the strength of evidence was moderate for activity ($BF_{10} = 5.658$) and mood ($BF_{10} = 4.682$), and strong for intensity ($BF_{10} = 28.882$) and persistence ($BF_{10} = 343.493$). After Bonferroni correction ($\alpha = 0.006$), the

[3] At the first timepoint, we aimed to test infants at 6 weeks (±2 weeks). However, due to the health complications experienced by mothers with asthma and their infants, we did test some infants at the first timepoint who were outside the specified age range. This is the reason for using the two normative subgroups of the EITQ.

differences in adaptability and threshold at 6 weeks, activity, adaptability and intensity at 6 months, and mood at 12 months were not sustained. Bayes Factors indicated that the strength of evidence for all other comparisons was inconclusive to moderate, in favour of the null hypothesis or alternative hypothesis depending on the CTS domain (Table 4.4).

4.1.3.3 Comparison of Infant Temperament between Maternal Asthma Severity and Control Groups

Tables 4.5 and 4.6 report the descriptive statistics and *p*-values for comparisons between infants, as a function of maternal asthma severity and asthma control. Regarding

Table 4.5 Comparison of temperament data between infants born to mothers with mild asthma and non-mild asthma.

Age	CTS Domain	Mild Asthma M (SD)	Non-Mild Asthma[a] M (SD)	*p*-value
6 Week		*n* = 86	*n* = 56	
	Activity	3.69 (0.68)	3.59 (0.61)	0.395
	Rhythmicity	3.47 (0.76)	3.19 (0.82)	0.038
	Approach	2.53 (0.74)	2.42 (0.72)	0.368
	Adaptability	2.39 (0.61)	2.18 (0.67)	0.070
	Intensity	3.77 (0.92)	3.83 (0.87)	0.713
	Mood	2.90 (0.82)	2.74 (0.67)	0.221
	Persistence	2.79 (0.91)	2.69 (0.94)	0.540
	Distractibility	2.34 (0.76)	2.23 (0.74)	0.442
	Threshold	4.24 (0.57)	4.33 (0.76)	0.428
6 Month		*n* = 52	*n* = 30	
	Activity	4.24 (0.48)	4.33 (0.49)	0.411
	Rhythmicity	2.85 (0.76)	2.70 (0.76)	0.386
	Approach	2.38 (0.59)	2.43 (0.73)	0.694
	Adaptability	2.12 (0.50)	2.20 (0.69)	0.508
	Intensity	3.54 (0.59)	3.67 (0.63)	0.329
	Mood	2.72 (0.63)	2.70 (0.70)	0.900
	Persistence	3.10 (0.80)	3.16 (0.81)	0.777
	Distractibility	2.08 (0.55)	2.37 (0.71)	0.039
	Threshold	3.84 (0.54)	3.85 (0.59)	0.913
12 Month		*n* = 45	*n* = 26	
	Activity	3.98 (0.59)	3.79 (0.62)	0.222
	Rhythmicity	2.71 (0.83)	2.52 (0.77)	0.339
	Approach	3.00 (0.81)	2.91 (0.82)	0.634
	Adaptability	3.63 (0.69)	3.31 (0.79)	0.089
	Intensity	3.82 (0.56)	3.78 (0.55)	0.763
	Mood	3.22 (0.65)	3.07 (0.61)	0.344
	Persistence	3.82 (0.62)	3.74 (0.69)	0.625

Table 4.5 (continued).

Age	CTS Domain	Mild Asthma M (SD)	Non-Mild Asthma[a] M (SD)	*p*-value
	Distractibility	4.47 (0.55)	4.34 (0.52)	0.344
	Threshold	3.53 (0.76)	3.65 (0.55)	0.504

Abbreviations: CTS = Carey Temperament Scales.
Note: α = .006, after Bonferroni correction.
[a]Infants born to mothers with moderate asthma and severe asthma were combined into a non-mild group.

Table 4.6 Comparison of temperament data between infants born to mothers with well controlled asthma, partly controlled asthma and uncontrolled asthma.

Age	CTS Domain	Well Controlled Asthma M (SD)	Partly Controlled Asthma M (SD)	Uncontrolled Asthma M (SD)	*p*-value
6 Week		*n* = 30	*n* = 68	*n* = 45	
	Activity	3.69 (0.59)	3.60 (0.70)	3.73 (0.65)	.621
	Rhythmicity	3.29 (0.79)	3.36 (0.75)	3.41 (0.85)	.809
	Approach	2.45 (0.81)	2.37 (0.64)	2.65 (0.74)	.119
	Adaptability	2.38 (0.60)	2.15 (0.58)	2.51 (0.74)	.024
	Intensity	3.88 (0.89)	3.72 (0.88)	3.80 (0.91)	.720
	Mood	2.95 (0.72)	2.66 (0.65)	3.04 (0.91)	.027
	Persistence	2.87 (1.06)	2.65 (0.86)	2.83 (0.88)	.448
	Distractibility	2.21 (0.78)	2.19 (0.67)	2.53 (0.82)	.052
	Threshold	4.29 (0.60)	4.20 (0.68)	4.38 (0.63)	.383
6 Month		*n* = 15	*n* = 43	*n* = 25	
	Activity	4.32 (0.42)	4.25 (0.39)	4.27 (0.63)	.863
	Rhythmicity	2.54 (0.70)	2.92 (0.78)	2.75 (0.74)	.229
	Approach	2.32 (0.48)	2.49 (0.65)	2.31 (0.70)	.458
	Adaptability	1.99 (0.37)	2.23 (0.65)	2.13 (0.53)	.352
	Intensity	3.71 (0.43)	3.48 (0.59)	3.71 (0.68)	.211
	Mood	2.77 (0.51)	2.68 (0.62)	2.74 (0.78)	.882
	Persistence	3.32 (0.75)	3.05 (0.80)	3.14 (0.82)	.540
	Distractibility	2.05 (0.51)	2.19 (0.62)	2.28 (0.69)	.539
	Threshold	3.83 (0.48)	3.89 (0.54)	3.79 (0.62)	.762
12 Month		*n* = 14	*n* = 37	*n* = 22	
	Activity	4.31 (0.60)	3.81 (0.52)	3.82 (0.62)	.018
	Rhythmicity	2.56 (0.61)	2.67 (0.94)	2.64 (0.68)	.902
	Approach	2.91 (0.81)	3.09 (0.97)	2.87 (0.54)	.567
	Adaptability	3.70 (0.72)	3.44 (0.84)	3.52 (0.59)	.542
	Intensity	3.74 (0.40)	3.89 (0.52)	3.72 (0.65)	.488
	Mood	3.46 (0.61)	3.05 (0.59)	3.19 (0.68)	.121
	Persistence	4.00 (0.56)	3.69 (0.58)	3.79 (0.77)	.318
	Distractibility	4.39 (0.42)	4.40 (0.60)	4.44 (0.53)	.953
	Threshold	3.71 (0.56)	3.55 (0.70)	3.54 (0.74)	.718

Note: α = .006, after Bonferroni correction.

asthma severity, infants born to mothers with mild asthma scored higher in rhythmicity at 6 weeks (p = .038) and lower in distractibility at 6 months (p = .039) compared to infants born to mothers with non-mild (i.e., moderate or severe) asthma. This indicates that they were less predictable in their biological functions and more easily soothed. Bayes Factors, reported in Table 4.7, indicated that the strength of evidence was inconclusive for both rhythmicity (BF_{10}

Table 4.7 Bayes factors from the comparison of temperament between infants born to mothers with mild asthma and non-mild asthma using Bayesian independent samples t-tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
6 Week				
	Activity	0.270	H_0	Moderate
	Rhythmicity	1.352	H_a	Inconclusive
	Approach	0.268	H_0	Moderate
	Adaptability	0.861	H_0	Inconclusive
	Intensity	0.198	H_0	Moderate
	Mood	0.371	H_0	Inconclusive
	Persistence	0.223	H_0	Moderate
	Distractibility	0.246	H_0	Moderate
	Threshold	0.248	H_0	Moderate
6 Month				
	Activity	0.322	H_0	Moderate
	Rhythmicity	0.333	H_0	Inconclusive
	Approach	0.259	H_0	Moderate
	Adaptability	0.291	H_0	Moderate
	Intensity	0.363	H_0	Inconclusive
	Mood	0.241	H_0	Moderate
	Persistence	0.246	H_0	Moderate
	Distractibility	1.569	H_a	Inconclusive
	Threshold	0.242	H_0	Moderate
12 Month				
	Activity	0.496	H_0	Inconclusive
	Rhythmicity	0.374	H_0	Inconclusive
	Approach	0.281	H_0	Moderate
	Adaptability	0.896	H_0	Inconclusive
	Intensity	0.266	H_0	Moderate
	Mood	0.375	H_0	Inconclusive
	Persistence	0.282	H_0	Moderate
	Distractibility	0.374	H_0	Inconclusive
	Threshold	0.310	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

= 1.352) and distractibility (BF_{10} = 1.569). Differences also emerged in infant temperament characteristics when comparing groups as a function of maternal asthma control. At 6 weeks, infants born to mothers with partly-controlled asthma during pregnancy scored lower in adaptability (*p* = .021) and mood (*p* = .029) compared to infants born to mothers with uncontrolled asthma. This indicates that they were more able to adapt to change and had a more positive mood. Bayes Factors, reported in Table 4.8, indicated that the strength of

Table 4.8 Bayes factors from the comparison of temperament between infants born to mothers with well controlled asthma, partly controlled asthma and uncontrolled asthma using Bayesian independent samples t-tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
6 Week				
	Activity	0.121	H_0	Moderate
	Rhythmicity	0.088	H_0	Strong
	Approach	0.469	H_0	Inconclusive
	Adaptability	0.478	H_0	Inconclusive
	Intensity	0.098	H_0	Strong
	Mood	0.567	H_0	Inconclusive
	Persistence	0.151	H_0	Moderate
	Distractibility	0.951	H_0	Inconclusive
	Threshold	0.173	H_0	Moderate
6 Month				
	Activity	0.131	H_0	Moderate
	Rhythmicity	0.366	H_0	Inconclusive
	Approach	0.223	H_0	Moderate
	Adaptability	0.261	H_0	Moderate
	Intensity	0.415	H_0	Inconclusive
	Mood	0.129	H_0	Moderate
	Persistence	0.185	H_0	Moderate
	Distractibility	0.182	H_0	Moderate
	Threshold	0.147	H_0	Moderate
12 Month				
	Activity	0.380	H_0	Inconclusive
	Rhythmicity	0.136	H_0	Moderate
	Approach	0.200	H_0	Moderate
	Adaptability	0.204	H_0	Moderate
	Intensity	0.226	H_0	Moderate
	Mood	0.627	H_0	Inconclusive
	Persistence	0.298	H_0	Moderate
	Distractibility	0.132	H_0	Moderate
	Threshold	0.162	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

evidence was inconclusive for adaptability ($BF_{10} = 0.478$) and mood ($BF_{10} = 0.567$). At 6 months, there were no statistically significant differences in temperament scores between infants based on asthma control. At 12 months, infants born to mothers with well-controlled asthma during pregnancy scored higher in activity compared to infants born to mothers with partly-controlled ($p = .020$) or uncontrolled asthma ($p = .040$), indicating a higher activity level. Bayes Factors indicated that the strength of evidence was inconclusive for activity ($BF_{10} = 0.380$). None of these differences in asthma severity of asthma control were sustained after Bonferroni correction ($\alpha = 0.006$). Bayes Factors indicated that the strength of evidence for all other comparisons was inconclusive to strong, in favour of the null hypothesis (see Tables 4.7 & 4.8).

4.2 Part Two: A Comparison with Community Infants

4.2.1 Aims and Hypotheses

In this study, we extend on Part One by introducing a community recruited comparison group and exploring the temperament profiles and diagnostic categories at 6 weeks, 6 months and 12 months from birth. Firstly, we aimed to investigate differences in temperament scores (for each of the nine CTS domains) between the infants born to mothers with asthma and infants from the general community. Our second aim was to characterise the temperament profiles (i.e., Easy, Average, or Difficult for each of the nine CTS domains) of infants born to mothers with asthma and compare the proportions in each group to infants from the general community. Our third aim was to characterise the temperament diagnostic categories (i.e., Easy, Difficult, Slow-To-Warm-Up, Intermediate-High, Intermediate-Low) of infants born to mothers with asthma and compare the proportions in each group to infants from the general community.

Based on the results from part one, it was firstly hypothesised that infants born to mothers with asthma would be more arrhythmic than infants from the general community.

Secondly, it was hypothesised that infants born to mothers with asthma would be more positive in mood compared to infants from the general community. Thirdly, it was hypothesised that infants born to mothers with asthma would have a lower activity level than infants from the general community. It was also hypothesised that infants born to mothers with asthma would be milder in their response than infants from the general community. Lastly, it was hypothesised that infants born to mothers with asthma would be less persistent in completing challenging tasks, compared to infants from the general community. Aims two and three were considered exploratory and no hypotheses were proposed.

4.2.2 Data Analyses

Data were analysed using the Statistical Package for the Social Sciences (version 25; IBM Corporation, 2017). JASP was used to conduct Bayesian analyses in order to examine the strength of evidence under the null hypothesis (JASP Team, 2019; van Doorn et al., 2019). As described in van Doorn et al. (2019), Bayes Factors (BF) were used to interpret the strength of evidence using the following guidelines: BF_{10} 1-3 = inconclusive evidence, BF_{10} 3-10 = moderate evidence and BF_{10} >10 = strong evidence. BF_{10} that are >1 provide evidence under the alternative hypothesis and BF_{10} <1 provide evidence under the null hypothesis. Data was analysed cross-sectionally at 6 weeks, 6 months and 12 months. Means and standard deviations were produced for sociodemographic characteristics (i.e., maternal age, infant age) and CTS data. Additionally, percentages of each response option were produced for the sociodemographic characteristics (i.e., infant gender, maternal country of birth, maternal ethnicity, maternal educational attainment, annual household income, parity). Independent samples t-tests and chi-squared tests were performed in order to test for differences between infants born to mothers with asthma and community infants on the sociodemographic characteristics. Pearson correlation coefficients were used to determine any association between Edinburgh Postnatal Depression Scale (EPDS) total scores and CTS domain scores.

CTS domain scores were compared between groups in each age group using independent samples t-test. Differences in temperament profiles and diagnostic categories between groups were examined using chi-squared tests. Cohen's *d* and Cramer's V were used to calculate effect sizes for independent samples t-tests and chi-squared tests, respectively. Level of statistical significance was set to $\alpha < 0.05$. Bonferroni corrections were applied for multiple comparisons, with alpha levels reported in the results section.

4.2.3 Results

4.2.3.1 Preliminary Analyses

Participants were included if they had data for at least one temperament domain, at any time-point: 45.3% of our asthma sample and 41.5% of our community sample provided data for more than one time-point described within this chapter. In order to assess participation bias, participant groups were compared on their sociodemographic characteristics (Table 4.9). Mothers with asthma were significantly younger at infant birth, less likely to be born overseas, less likely to have an annual household income over $180,000, more likely to have 3 or more children, and less likely to have obtained a university degree, compared to mothers from the general community (all $p < .05$). Infants born to mothers with asthma were significantly older during participation than community infants, at the 12-month visit ($p = .008$). There were no statistically significant differences between the two groups on infant gender or self-reported maternal mental health condition (all $p > .05$).

Due to the small sample size within this study, analyses where covariation can be measured were not utilised. However, in order to examine whether maternal mental health was a potential covariate, associations between Edinburgh Postnatal Depression Scale (EPDS) total scores and CTS domain scores were analysed using Pearson correlation coefficients. For the asthma group, there were statistically significant correlations between

Table 4.9 Sociodemographic characteristics of the participants in the asthma group and community group at 6 weeks, 6 months and 12 months of age.

Sociodemographic characteristic		6 weeks		6 months		12 months	
		Asthma *n* = 144	Community *n* = 34	Asthma *n* = 83	Community *n* = 46	Asthma *n* = 74	Community *n* = 45
Maternal Age, at infant birth (years)							
	Mean (SD)	**30.3 (5.1)**	**33.3 (4.5)**	**30.7 (5.1)**	**32.6 (4.5)**	30.8 (5.2)	32.2 (4.5)
	Range	20.1 – 43.9	26.3 – 49.8	20.7 – 43.9	25.6 – 49.2	21.4 – 43.9	24.0 – 49.2
Infant Age[a], at participation (weeks)							
	Mean (SD)	6.8 (1.5)	6.7 (1.1)	27.5 (1.8)	27.3 (1.4)	**54.3 (3.0)**	**53.0 (1.8)**
	Range	1.7 – 10.4	5.4 – 11.4	19.9 – 33.4	24.6 – 30.4	42.7 – 64.4	45.6 – 56.1
Infant Gender, *n* (%)							
	Male	76 (52.8)	16 (47.1)	43 (51.8)	20 (43.5)	39 (52.7)	24 (53.3)
	Female	68 (47.2)	18 (52.9)	40 (48.2)	26 (56.5)	35 (47.3)	21 (46.7)
Maternal Country of Birth, *n* (%)							
	Australia	**131 (91.0)**	**25 (73.5)**	**73 (88.0)**	**38 (82.6)**	62 (83.8)	40 (88.9)
	Overseas	**8 (5.6)**	**9 (26.5)**	**4 (4.8)**	**8 (17.4)**	4 (5.4)	4 (8.9)
	Unspecified[b]	5 (3.5)	0 (0.0)	6 (7.2)	0 (0.00	8 (10.8)	1 (2.2)
Maternal Ethnicity, *n* (%)							
	Caucasian	126 (87.5)	12 (35.3)	69 (83.1)	26 (56.5)	64 (86.5)	39 (86.7)
	Aboriginal Australian	2 (1.4)	0 (0.0)	3 (3.6)	0 (0.0)	2 (2.7)	0 (0.0)
	Asian	3 (2.1)	2 (5.9)	2 (2.4)	3 (6.5)	2 (2.7)	3 (6.7)
	Mixed	7 (4.9)	0 (0.0)	3 (3.6)	1 (2.2)	3 (4.1)	1 (2.2)
	Other	6 (4.2)	0 (0.0)	5 (6.0)	1 (2.2)	3 (4.1)	0 (0.0)
	Unspecified[b]	0 (0.0)	20 (58.8)	1 (1.2)	15 (32.6)	0 (0.0)	2 (4.4)
Maternal Educational Attainment, *n* (%)							
	< High School Certificate	23 (16.0)	1 (2.9)	**12 (14.5)**	**1 (2.2)**	**11 (14.9)**	**1 (2.2)**
	High School Certificate	**28 (19.4)**	**1 (2.9)**	**15 (18.1)**	**2 (4.3)**	8 (10.8)	2 (4.4)
	Trade Certificate/Diploma	**48 (33.3)**	**4 (11.8)**	19 (22.9)	8 (17.4)	16 (21.6)	6 (13.3)
	University Degree	**39 (27.1)**	**25 (73.6)**	**31 (37.3)**	**32 (69.6)**	**32 (43.3)**	**34 (75.6)**
	Unspecified[b]	6 (4.2)	3 (8.8)	6 (7.2)	3 (6.5)	7 (9.5)	2 (4.4)

Table 4.9 (continued).

Sociodemographic characteristic	6 weeks		6 months		12 months	
	Asthma *n* = 144	Community *n* = 34	Asthma *n* = 83	Community *n* = 46	Asthma *n* = 74	Community *n* = 45
Annual Household Income[c], *n* (%)						
0 – 18,700	11 (7.6)	0 (0.0)	5 (6.0)	2 (4.3)	6 (8.0)	1 (2.2)
18,701 – 37,000	13 (9.0)	2 (5.7)	7 (8.3)	2 (4.3)	7 (9.3)	1 (2.2)
37,001 – 80,000	**42 (29.2)**	**3 (8.6)**	**25 (29.8)**	**6 (13.0)**	17 (22.7)	9 (19.6)
80,001 – 180,000	64 (44.4)	18 (51.4)	40 (47.6)	24 (52.2)	37 (49.3)	30 (65.2)
180,001 and Over	**8 (5.6)**	**12 (34.3)**	**3 (3.6)**	**11 (23.9)**	3 (4.0)	5 (10.9)
Unspecified[b]	6 (4.2)	0 (0.0)	4 (4.8)	1 (2.2)	5 (6.7)	0 (0.0)
Parity, *n* (%)						
Primipara (1 child)	75 (52.1)	17 (50.0)	42 (50.6)	27 (58.7)	**36 (48.6)**	**30 (66.7)**
Multipara (2 children)	42 (29.2)	14 (41.2)	21 (25.3)	14 (30.4)	21 (28.4)	12 (26.7)
Grand Multipara (≥ 3 children)	27 (18.8)	1 (2.9)	**20 (24.1)**	**2 (4.3)**	**17 (23.0)**	**2 (4.4)**
Unspecified[b]	0 (0.0)	2 (5.9)	0 (0.0)	3 (6.5)	0 (0.0)	1 (2.2)
Mental Health Condition[d], *n* (%)						
No	112 (77.8)	27 (79.4)	59 (71.1)	39 (84.8)	51 (68.9)	37 (82.2)
Yes	32 (22.2)	7 (20.6)	24 (28.9)	7 (15.2)	23 (31.1)	8 (17.8)
Anxiety Disorder	20 (13.9)	3 (8.8)	13 (15.7)	2 (4.3)	12 (16.2)	3 (6.7)
Depressive Disorder	26 (18.1)	6 (17.6)	21 (25.3)	6 (13.0)	17 (23.0)	4 (8.9)
Borderline Personality Disorder	2 (1.4)	0 (0.0)	2 (2.4)	0 (0.0)	1 (1.4)	1 (2.2)

Note: Statistically significant differences ($\alpha = .05$) between sociodemographic characteristics between the asthma group and community group are denoted by bold text.

[a]Adjusted for infant prematurity.

[b]Mothers did not respond to the question(s) pertaining to this information.

[c]Annual household income is reported in Australian dollars.

[d]Frequencies/percentages do not add up to total sample size/100 percent as they are not mutually exclusive.

EPDS total scores and activity (6 weeks), rhythmicity (6 weeks), approach (6 months), adaptability (6 weeks, 6 months, 12 months), intensity (6 weeks, 12 months), mood (6 weeks, 6 months, 12 months), and distractibility (6 weeks, 6 months; all $p < .05$). For the community group, there were statistically significant correlations between EPDS total scores and activity (6 weeks), rhythmicity (12 months), intensity (12 months) and distractibility (6 weeks; all p <.05). No other significant correlations between EPDS total scores and CTS domain scores were observed (all $p > .05$; for details see Table 4.10 in Appendix I).

4.2.3.2 Sample Characteristics

Mothers with asthma (n = 183) had a mean age of 30.4 years (SD = 5.1) when their infants (51.9% male, 97.8% singleton) were born (Table 4.9). Most mothers were Caucasian (85.8%) and Australian-born (88.0%), with the majority having attained a degree no higher than a trade qualification (62.3%). Within the community sample, mothers (n = 82) had a mean age of 32.5 years (SD = 4.4) when their infants (51.2% male, 100% singleton) were born (Table 4.9). Similar to the asthma group, most mothers without asthma were Caucasian (86.3%) and Australian-born (81.2%), however, the majority had a university degree (76.8%). The mode annual household income range for both samples was $80,001 to $180,000.

4.2.3.3 Differences in Temperament Domain Scores

Mean CTS domain scores between infants born to mothers with and without asthma were compared at 6 weeks, 6 months, and 12 months of age. Descriptive statistics alongside p-values, effect sizes and confidence intervals are reported for both groups in Table 4.11. Sample sizes for each CTS domain are reported in Table 4.12 (Appendix J). At 6 weeks, infants born to mothers with asthma scored significantly lower in mood than the community infants ($t_{(171)} = -2.310$, $p = .022$, $d = -.442$). Bayes Factors indicated that the strength of evidence was inconclusive for mood ($BF_{10} = 2.179$). There were no statistically significant

Table 4.11 Comparison between infants born to mothers with and without asthma on Carey Temperament Scales data of 6 week, 6 month and 12 month-old samples.

Age	CTS Domain	Asthma M (SD)	Community M (SD)	*p*-value	Cohen's *d*	95% CI	
6 Weeks		*n* = 144	*n* = 34			Lower	Upper
	Activity	3.66 (0.66)	3.67 (0.57)	0.956	-0.011	-0.261	0.247
	Rhythmicity	3.36 (0.79)	3.43 (0.76)	0.614	-0.096	-0.370	0.220
	Approach	2.49 (0.73)	2.63 (0.73)	0.330	-0.191	-0.421	0.142
	Adaptability	2.31 (0.65)	2.49 (0.76)	0.200	-0.268	-0.457	0.097
	Intensity	3.79 (0.89)	3.79 (0.79)	0.984	-0.004	-0.337	0.331
	Mood	2.85 (0.77)	3.18 (0.69)	0.022	-0.442	-0.620	-0.049
	Persistence	2.75 (0.91)	3.08 (0.95)	0.064	-0.366	-0.693	0.020
	Distractibility	2.31 (0.75)	2.52 (0.63)	0.137	-0.298	-0.506	0.070
	Threshold	4.28 (0.65)	4.35 (0.56)	0.577	-0.107	-0.309	0.173
6 Months		*n* = 83	*n* = 46				
	Activity	4.27 (0.48)	4.32 (0.60)	0.614	-0.093	-0.241	0.143
	Rhythmicity	2.80 (0.76)	2.96 (0.76)	0.248	-0.214	-0.440	0.114
	Approach	2.40 (0.64)	2.56 (0.71)	0.203	-0.237	-0.401	0.086
	Adaptability	2.16 (0.57)	2.15 (0.53)	0.974	0.006	-0.200	0.207
	Intensity	3.59 (0.60)	3.49 (0.51)	0.360	0.169	-0.111	0.304
	Mood	2.71 (0.65)	2.81 (0.56)	0.391	-0.159	-0.324	0.128
	Persistence	3.12 (0.80)	3.14 (0.64)	0.933	-0.015	-0.282	0.259
	Distractibility	2.19 (0.62)	2.17 (0.50)	0.821	0.042	-0.188	0.237
	Threshold	3.85 (0.55)	3.95 (0.65)	0.365	-0.171	-0.318	0.118
12 Months		*n* = 74	*n* = 45				
	Activity	3.92 (0.59)	3.97 (0.64)	.704	-0.076	-.287	.195
	Rhythmicity	2.63 (0.80)	2.63 (0.57)	.997	0.184	-.271	.271
	Approach	2.99 (0.82)	2.89 (0.92)	.527	0.121	-.219	.426
	Adaptability	3.52 (0.74)	3.56 (0.64)	.808	-0.048	-.306	.239
	Intensity	3.81 (0.54)	3.80 (0.63)	.949	0.012	-.211	.225
	Mood	3.17 (0.63)	3.10 (0.56)	.560	0.111	-.160	.294
	Persistence	3.77 (0.64)	4.13 (0.76)	.008	-0.515	-.618	-.094
	Distractibility	4.43 (0.55)	4.65 (0.55)	.034	-0.410	-.433	-.017
	Threshold	3.58 (0.68)	3.50 (0.75)	.569	0.109	-.190	.344

Abbreviations: CTS = Carey Temperament Scales.
*significant at p <.006, using Bonferroni correction.

differences between infants born to mothers with and without asthma at the 6-month time point. At 12 months, infants born to mothers with asthma scored significantly lower in persistence ($t_{(114)} = -2.694$, $p = .008$, $d = -.515$) and distractibility ($t_{(115)} = -2.146$, $p = .034$, $d = -.433$) compared to the community infants. Bayes Factors indicated that the strength of evidence was inconclusive for distractibility (BF_{10} = 1.561) but moderate for persistence (BF_{10} = 4.949). None of the differences at 6 weeks or 12 months were sustained after Bonferroni correction ($\alpha = 0.006$). Bayes Factors indicated that the strength of evidence for all other comparisons were inconclusive to moderate, in favour of the null hypothesis (See Table 4.13).

Table 4.13 Bayes factors from the comparison of temperament between infants born to mothers with asthma and community infants using Bayesian independent samples t-tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
6 Week	Activity	0.211	H_0	Moderate
	Rhythmicity	0.227	H_0	Moderate
	Approach	0.316	H_0	Inconclusive
	Adaptability	0.453	H_0	Inconclusive
	Intensity	0.205	H_0	Moderate
	Mood	2.179	H_a	Inconclusive
	Persistence	0.969	H_0	Inconclusive
	Distractibility	0.566	H_0	Inconclusive
	Threshold	0.233	H_0	Moderate
6 Month	Activity	0.220	H_0	Moderate
	Rhythmicity	0.360	H_0	Inconclusive
	Approach	0.412	H_0	Inconclusive
	Adaptability	0.196	H_0	Moderate
	Intensity	0.287	H_0	Moderate
	Mood	0.274	H_0	Moderate
	Persistence	0.196	H_0	Moderate
	Distractibility	0.201	H_0	Moderate
	Threshold	0.289	H_0	Moderate
12 Month	Activity	0.224	H_0	Moderate
	Rhythmicity	0.201	H_0	Moderate
	Approach	0.241	H_0	Moderate
	Adaptability	0.212	H_0	Moderate
	Intensity	0.202	H_0	Moderate
	Mood	0.235	H_0	Moderate
	Persistence	4.949	H_a	Moderate
	Distractibility	1.561	H_a	Inconclusive
	Threshold	0.234	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

As there were no significant differences between infants born to mothers with asthma and community infants in temperament, post-hoc analyses using one-sample t-tests were conducted in order to determine whether our community infants differed from the CTS normative sample (Table 4.14). Results showed, after Bonferroni correction ($\alpha = .006$), that infants from our local community were significantly higher in: rhythmicity at 6 months ($t_{(45)} = 5.342$, $p <.001$), persistence at 12 months ($t_{(43)} = 5.900$, $p <.001$), and distractibility at 12 months ($t_{(43)} = 3.151$, $p = .003$). Bayes Factors, reported in Table 4.15, indicated that the strength of evidence was strong for rhythmicity ($BF_{10} = 6104.502$), persistence ($BF_{10} = 31395.579$) and distractibility ($BF_{10} = 11.337$). For all other comparisons, Bayes Factors indicated that the strength of evidence was inconclusive to moderate, in favour of the null hypothesis or alternative hypothesis depending on the CTS domain (See Table 4.15).

4.2.3.4 Differences in Temperament Profile Distributions

The distribution of profile scores between infants born to mothers with and without asthma were compared at 6 weeks, 6 months, and 12 months of age (Table 4.16). The majority of infants fell within the average range on most CTS domains, across the three age groups. At 6 weeks, there was a significantly higher proportion of infants born to mothers with asthma within the easy range in the mood domain, compared to community infants (29.5% vs 8.8%; $\chi^2_{(2)} = 7.175$, $p = .028$, V = .204). Bayes Factors, reported in Table 4.17, indicated that the strength of evidence was inconclusive for mood ($BF_{10} = 2.814$).

At 6 months, more than one third of infants born to mothers with asthma (42%) and community infants (43.5%) fell within the difficult range for rhythmicity. At 6 months, there was a significantly lower proportion of infants born to mothers with asthma within the difficult range in the activity domain, compared to community infants (3.7% vs 15.3%; $\chi^2_{(2)} = 6.816$, $p = .033$, V = .231). Additionally, at 6 months, there were significantly higher proportions of infants born to mothers with asthma within the difficult range of the distractibility domain, compared to community infants (16.9% vs 4.4%; $\chi^2_{(2)} = 9.023$, $p = .011$, V = .266). Bayes Factors indicated that the strength of evidence was inconclusive for

Table 4.14 Comparison between normative Carey Temperament Scales (CTS) data and our 6 week, 6 month and 12 month-old community samples.

Age	CTS Domain	Community M (SD)	Normative M (SD)	*p*-value
4-8 Weeks		*n* = 32	*n* = 262	
	Activity	3.61 (0.54)	3.58 (0.65)	.783
	Rhythmicity	3.38 (0.74)	3.12 (0.69)	.052
	Approach	2.67 (0.73)	2.58 (0.63)	.517
	Adaptability	2.47 (0.77)	2.49 (0.67)	.891
	Intensity	3.78 (0.81)	3.86 (0.69)	.611
	Mood	3.17 (0.66)	3.21 (0.73)	.751
	Persistence	3.09 (0.95)	2.79 (0.71)	.093
	Distractibility	3.09 (0.95)	2.65 (0.60)	.017
	Threshold	4.39 (0.55)	4.15 (0.57)	.019
9-12 Weeks[a]		*n* = 2	*n* = 142	
	Activity	4.56 (0.27)	3.79 (0.73)	.152
	Rhythmicity	4.20 (1.13)	2.90 (0.71)	.351
	Approach	2.00 (0.47)	2.84 (0.79)	.240
	Adaptability	2.80 (0.85)	2.39 (0.63)	.618
	Intensity	3.92 (0.59)	3.96 (0.68)	.934
	Mood	3.32 (1.48)	2.79 (0.62)	.702
	Persistence	2.94 (1.15)	2.49 (0.54)	.680
	Distractibility	2.94 (1.15)	2.41 (0.58)	.633
	Threshold	3.70 (0.14)	4.32 (0.56)	.102
6 Months		*n* = 46	*n* = 203	
	Activity	4.32 (0.60)	4.40 (0.56)	.363
	Rhythmicity	2.96 (0.76)	2.36 (0.68)	**< .001**[*]
	Approach	2.56 (0.71)	2.27 (0.78)	.008
	Adaptability	2.15 (0.53)	2.02 (0.59)	.098
	Intensity	3.49 (0.51)	3.42 (0.71)	.328
	Mood	2.81 (0.56)	2.81 (0.68)	.992
	Persistence	3.14 (0.64)	3.03 (0.82)	.264
	Distractibility	2.17 (0.50)	2.23 (0.60)	.399
	Threshold	3.95 (0.65)	3.79 (0.76)	.115
12 Months		*n* = 45	*n* = 167	
	Activity	3.97 (0.64)	4.13 (0.80)	.124
	Rhythmicity	2.63 (0.57)	2.49 (0.81)	.101
	Approach	2.89 (0.92)	2.97 (1.00)	.542
	Adaptability	3.56 (0.64)	3.42 (0.86)	.171
	Intensity	3.80 (0.63)	4.03 (0.76)	.019
	Mood	3.10 (0.56)	2.96 (0.69)	.096
	Persistence	4.13 (0.76)	3.45 (0.83)	**<.001**[*]
	Distractibility	4.65 (0.55)	4.39 (0.76)	**.003**[*]
	Threshold	3.50 (0.75)	3.61 (0.88)	.345

[a]Infants within our 6-week cohort fell across both normative subgroups of the Early Infancy Temperament Questionnaire.
[*]significant at p <.006, using Bonferroni correction.

Table 4.15 Bayes factors from the comparison of temperament between community infants and Carey Temperament Scales normative sample using Bayesian independent samples t-tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
4-8 Weeks				
	Activity	0.205	H_0	Moderate
	Rhythmicity	1.130	H_a	Inconclusive
	Approach	0.237	H_0	Moderate
	Adaptability	0.209	H_0	Moderate
	Intensity	0.216	H_0	Moderate
	Mood	0.198	H_0	Moderate
	Persistence	0.738	H_0	Inconclusive
	Distractibility	2.929	H_a	Inconclusive
	Threshold	2.579	H_a	Inconclusive
9-12 Weeks[a]				
	Activity	1.523	H_a	Inconclusive
	Rhythmicity	0.931	H_0	Inconclusive
	Approach	1.184	H_a	Inconclusive
	Adaptability	0.634	H_0	Inconclusive
	Intensity	0.526	H_0	Inconclusive
	Mood	0.588	H_0	Inconclusive
	Persistence	0.599	H_0	Inconclusive
	Distractibility	0.624	H_0	Inconclusive
	Threshold	1.829	H_a	Inconclusive
6 Month				
	Activity	0.238	H_0	Moderate
	Rhythmicity	6104.502	H_a	Strong
	Approach	4.836	H_a	Moderate
	Adaptability	0.596	H_0	Inconclusive
	Intensity	0.253	H_0	Moderate
	Mood	0.160	H_0	Moderate
	Persistence	0.291	H_0	Moderate
	Distractibility	0.227	H_0	Moderate
	Threshold	0.538	H_0	Inconclusive
12 Month				
	Activity	0.529	H_0	Inconclusive
	Rhythmicity	0.587	H_0	Inconclusive
	Approach	0.193	H_0	Moderate
	Adaptability	0.409	H_0	Inconclusive
	Intensity	2.236	H_a	Inconclusive
	Mood	0.611	H_0	Inconclusive
	Persistence	31395.579	H_a	Strong
	Distractibility	11.337	H_a	Strong
	Threshold	0.248	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales.

Note: H_0 = null hypothesis; H_a = alternative hypothesis.

[a]Infants within our 6-week cohort fell across both normative subgroups of the Early Infancy Temperament Questionnaire.

Table 4.16 Carey Temperament Scales profile groups for infants born to mothers with and without asthma in 6 weeks, 6 month and 12-month samples.

Age	CTS Domain	Group	Easy % (*n*)	Average % (*n*)	Difficult % (*n*)	*p*-value	Effect Size Cramer's V
6 Weeks							
	Activity	Asthma	10.1 (13)	72.1 (93)	17.8 (23)	.720	.064
		Community	6.5 (2)	71.0 (22)	22.6 (7)		
	Rhythmicity	Asthma	8.5 (12)	64.5 (91)	27.0 (38)	.746	.058
		Community	8.8 (3)	70.6 (24)	20.6 (7)		
	Approach	Asthma	21.1 (30)	64.1 (91)	14.8 (21)	.841	.045
		Community	18.8 (6)	62.5 (20)	18.8 (6)		
	Adaptability	Asthma	24.2 (31)	66.4 (85)	9.4 (12)	.072	.184
		Community	21.4 (6)	53.6 (15)	25.0 (7)		
	Intensity	Asthma	28.6 (40)	52.1 (73)	19.3 (27)	.966	.020
		Community	27.3 (9)	51.5 (17)	21.2 (7)		
	Mood	Asthma	29.5 (41)	59.7 (83)	10.8 (15)	.028	.204
		Community	8.8 (3)	70.6 (24)	20.6 (7)		
	Persistence	Asthma	25.5 (35)	50.4 (69)	24.1 (33)	.141	.152
		Community	9.4 (3)	62.5 (20)	28.1 (9)		
	Distractibility	Asthma	39.4 (54)	50.4 (69)	10.2 (14)	.189	.141
		Community	22.6 (7)	61.3 (19)	16.1 (5)		
	Threshold	Asthma	12.9 (18)	62.9 (88)	24.3 (34)	.789	.052
		Community	8.8 (3)	67.6 (23)	23.5 (8)		
6 months							
	Activity	Asthma	15.9 (13)	80.5 (66)	3.7 (3)	.033	.231
		Community	21.7 (10)	63.0 (29)	15.3 (7)		
	Rhythmicity	Asthma	8.6 (7)	49.4 (40)	42.0 (34)	.118	.184
		Community	0.0 (0)	56.5 (26)	43.5 (20)		
	Approach	Asthma	5.1 (4)	77.2 (61)	17.7 (14)	.539	.100
		Community	4.3 (2)	69.6 (32)	26.1 (12)		
	Adaptability	Asthma	8.6 (7)	74.1 (60)	17.3 (14)	.727	.071
		Community	13.0 (6)	69.6 (32)	17.4 (8)		
	Intensity	Asthma	6.1 (5)	76.8 (63)	17.1 (14)	.559	.095
		Community	4.3 (2)	84.8 (39)	10.9 (5)		
	Mood	Asthma	23.2 (19)	62.2 (51)	14.6 (12)	.331	.131
		Community	13.0 (6)	73.9 (34)	13.0 (6)		

Table 4.16 (continued).

Age	CTS Domain	Group	Easy % (*n*)	Average % (*n*)	Difficult % (*n*)	*p*-value	Effect Size Cramer's V
	Persistence	Asthma	13.3 (11)	66.3 (55)	20.5 (17)	.066	.205
		Community	2.2 (1)	82.6 (38)	15.2 (7)		
	Distractibility	Asthma	21.7 (18)	61.4 (51)	16.9 (14)	.011	.266
		Community	8.9 (4)	86.7 (39)	4.4 (2)		
	Threshold	Asthma	7.5 (6)	83.8 (67)	8.8 (7)	.484	.108
		Community	6.8 (3)	77.3 (34)	15.9 (7)		
12 months							
	Activity	Asthma	15.9 (11)	79.7 (55)	4.3 (3)	.506	.112
		Community	22.5 (9)	70.0 (28)	7.5 (3)		
	Rhythmicity	Asthma	8.1 (6)	74.3 (55)	17.6 (13)	.312	.140
		Community	2.2 (1)	84.4 (38)	13.3 (6)		
	Approach	Asthma	4.2 (3)	84.7 (61)	11.1 (8)	.003	.313
		Community	24.4 (11)	62.2 (28)	13.3 (6)		
	Adaptability	Asthma	11.6 (8)	71.0 (49)	17.4 (12)	.644	.089
		Community	7.1 (3)	78.6 (33)	14.3 (6)		
	Intensity	Asthma	18.1 (13)	75.0 (54)	6.9 (5)	.652	.085
		Community	13.3 (6)	82.2 (37)	4.4 (2)		
	Mood	Asthma	8.3 (6)	68.1 (49)	23.6 (17)	.344	.135
		Community	6.7 ()	80.0 (36)	13.3 (6)		
	Persistence	Asthma	2.9 (2)	78.6 (55)	18.6 (13)	.060	.222
		Community	2.3 (1)	59.1 (26)	38.6 (17)		
	Distractibility	Asthma	9.6 (7)	82.2 (60)	8.2 (6)	.195	.167
		Community	4.5 (2)	77.3 (34)	18.2 (8)		
	Threshold	Asthma	12.7 (9)	77.5 (55)	9.9 (7)	.712	.077
		Community	17.8 (8)	71.1 (32)	11.1 (5)		

Note: 'Easy' refers to scores < 1 standard deviation below the normative mean. 'Average' refers to scores within one standard deviation of the normative mean. 'Difficult' refers to scores > 1 standard deviation above the normative mean.

Table 4.17 Bayes factors from the comparison of temperament profile distribution between infants born to mothers with asthma and community infants using Bayesian chi-squared tests.

Age	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence
6 Week				
	Activity	0.070	H_0	Strong
	Rhythmicity	0.068	H_0	Strong
	Approach	0.078	H_0	Strong
	Adaptability	0.728	H_0	Inconclusive
	Intensity	0.078	H_0	Strong
	Mood	2.814	H_a	Inconclusive
	Persistence	0.586	H_0	Inconclusive
	Distractibility	0.385	H_0	Inconclusive
	Threshold	0.068	H_0	Strong
6 Month				
	Activity	1.067	H_a	Inconclusive
	Rhythmicity	0.382	H_0	Inconclusive
	Approach	0.067	H_0	Strong
	Adaptability	0.065	H_0	Strong
	Intensity	0.054	H_0	Strong
	Mood	0.155	H_0	Moderate
	Persistence	0.670	H_0	Inconclusive
	Distractibility	4.307	H_a	Moderate
	Threshold	0.072	H_0	Strong
12 Month				
	Activity	0.086	H_0	Strong
	Rhythmicity	0.100	H_0	Moderate
	Approach	11.177	H_a	Strong
	Adaptability	0.072	H_0	Strong
	Intensity	0.054	H_0	Strong
	Mood	0.123	H_0	Moderate
	Persistence	0.495	H_0	Inconclusive
	Distractibility	0.171	H_0	Moderate
	Threshold	0.067	H_0	Strong

Abbreviations: CTS = Carey Temperament Scales.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

activity (BF_{10} = 1.067) but moderate for distractibility (BF_{10} = 4.307).

Lastly, at 12 months, there was a significantly lower proportion of infants born to mothers with asthma within the easy range in the approach domain, compared to community infants (4.2% vs 24.4%; $\chi^2_{(2)} = 11.473$, $p = .003$, V = .313). Bayes Factors indicated that the strength of evidence was strong for approach (BF_{10} = 11.177). After Bonferroni correction (α = 0.006), only the difference in profile distributions found in the approach domain at 12 months was sustained. Bayes Factors indicated that the strength of evidence for all other comparisons was inconclusive to strong, in favour of the null hypothesis (See Table 4.17).

4.2.3.5 Differences in Temperament Diagnostic Category Distributions

The distribution of diagnostic temperament categories between infants born to mothers with and without asthma were compared at 6 weeks, 6 months, and 12 months of age (Tables 4.18 & 4.19). The largest proportion of infants born to mothers with asthma were categorised as easy, across the three age groups (30.4% - 44.8%), with no more than one quarter being categorised as difficult (12.8%-25.3%). In contrast, the largest proportion of

Table 4.18 Carey Temperament Scales diagnostic temperament categories for infants born to mothers with and without asthma in 6 weeks, 6 month and 12-month samples.

Age	Diagnostic Category	Asthma	Community	*p*-value	Effect Size Cramer's V
6 Weeks	Easy	44.8 (56)	23.1 (6)		
	Intermediate – Low	27.2 (34)	38.5 (10)		
	Intermediate – High	14.4 (18)	23.1 (6)	.314	.177
	Slow-To-Warm-Up	0.8 (1)	0.0 (0)		
	Difficult	12.8 (16)	15.4 (4)		
6 months	Easy	30.4 (24)	30.4 (14)		
	Intermediate – Low	26.6 (21)	26.1 (12)		
	Intermediate – High	12.7 (10)	8.7 (4)	.456	.171
	Slow-To-Warm-Up	5.1 (4)	0.0 (0)		
	Difficult	25.3 (20)	34.8 (16)		
12 months	Easy	34.8 (24)	33.3 (14)		
	Intermediate – Low	26.1 (18)	38.1 (16)		
	Intermediate – High	14.5 (10)	4.8 (2)	.471	.179
	Slow-To-Warm-Up	10.1 (7)	9.5 (4)		
	Difficult	14.5 (10)	14.3 (6)		

community infants were categorised as intermediate-low at 6 weeks (38.5%) and 12 months (38.1%), yet difficult at 6 months (34.8%). Within the asthma sample, there was one infant at 6 weeks, and four infants at 6 months, who were categorised as slow-to-warm-up. However, no infants from the community sample were categorised as slow-to-warm-up at these time points. At 6 weeks, there was almost double the proportion of infants born to mothers with asthma who had an easy temperament than community infants (44.8% vs 23.1%). However, there were no statistically significant differences in the distribution of temperament categories in any of the age groups (all $p > .05$). Bayes Factors indicated that the strength of evidence for all comparisons was strong, in favour of the null hypothesis (see Table 4.19).

Table 4.19 Bayes factors from the comparison of temperament diagnostic categories between infants born to mothers with asthma and community infants using Bayesian chi-squared tests.

CTS Diagnostic Category	BF_{10}	Direction of Evidence	Strength of Evidence
6 Week	0.088	H_0	Strong
6 Month	0.040	H_0	Strong
12 Month	0.077	H_0	Strong

Abbreviations: CTS = Carey Temperament Scales.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

Chapter Five: Study Two

The relationship between temperament features and autism symptoms in infants born to mothers with asthma

Chapter Synopsis

This chapter aims to explore the second research question of this thesis: Is temperament associated with parent-reported symptoms of autism at 12 months of age, in infants born to mothers with and without asthma, and if so, what temperament features are the best predictors of ASD symptoms? This chapter firstly reports on how temperament features, at 6 weeks, 6 months and 12 months of age, of infants born to mothers with asthma relate to autism symptoms at 12 months of age, compared to community infants. Subsequently, this chapter will explore which temperament features, at 6 weeks, 6 months and 12 months of age, best predicts autism symptoms at 12 months of age.

5.1 Aims and Hypotheses

In this study, I explored whether temperament features in the first year of life were associated with autism symptoms measured at 12 months of age, in infants born to mothers with asthma and infants from the general community. The primary aim was to investigate whether scores on the Carey Temperament Scale (CTS) domains, at 6 weeks, 6 months and 12 months of age, were associated with First Year Inventory (FYI) total risk scores at 12 months of age in both cohorts. The secondary aim was to explore whether scores on the CTS domains, at 6 weeks, 6 months and 12 months of age, were associated with FYI social communication and sensory regulatory risk scores at 12 months of age in both cohorts. The relationships between temperament and autism symptoms were examined in each cohort separately, in order to highlight differences in relationships between the two groups. As there is limited extant research in this field, the following hypotheses were applied to both cohorts.

There has been no research published on the temperament of children with autism prior to 6 months of age, hence the analyses between CTS domains at 6 weeks of age and FYI total risk at 12 months were considered exploratory in nature. Based on the findings of prior research synthesised in the systematic review (see chapter two), it was hypothesised that the CTS domains of activity, approach and adaptability at 6 months would be negatively correlated with FYI total risk at 12 months of age. This means that lower levels of motor activity, greater approach to novelty, and faster adaptability to change in routine would be associated with greater autism symptoms. Additionally, it was hypothesised that the CTS domains of mood at 12 months would be positively correlated, and adaptability and distractibility at 12 months would be negatively correlated, with FYI total risk at 12 months of age. This means that increased fussiness, faster adaptability to change in routine, and less distractibility would be associated with greater autism symptoms. Lastly, any CTS domains where there were associations of interest with the FYI total risk score were subsequently explored as predictors of FYI total risk.

5.2 Data Analysis

Data were analysed using the Statistical Package for the Social Sciences (version 25; IBM Corporation, 2017). JASP was used to conduct Bayesian analyses in order to examine the strength of evidence under the null hypothesis (JASP Team, 2019; van Doorn et al., 2019). As described in van Doorn et al. (2019), Bayes Factors (BF) were used to interpret the strength of evidence using the following guidelines: BF_{10} 1-3 = inconclusive evidence, BF_{10} 3-10 = moderate evidence and BF_{10} >10 = strong evidence. BF_{10} that are >1 provide evidence under the alternative hypothesis and BF_{10} <1 provide evidence under the null hypothesis. Summary statistics (i.e., means, standard deviations, percentages) were produced for sociodemographic characteristics, CTS data and FYI data. Independent samples t-tests and chi-squared tests were performed to test for differences between participants in the asthma group and participants in the community group on the following: maternal age at infant birth, infant gender, maternal country of birth, maternal ethnicity, maternal educational attainment, annual household income, and parity.

Pearson correlation coefficients were used to test for associations between CTS domain scores, sociodemographic characteristics, Edinburgh Postnatal Depression Scale (EPDS) total scores, and FYI total, social communication and sensory regulatory risk scores. The strength of significant correlations was interpreted using the following: .1 to .3 (-.1 to -.3) as weak, .3 to .5 (-.3 to -.5) as moderate, and .5 to 1.0 (-.5 to -1.0) as strong. Multiple linear regression using the enter method was used to test whether CTS domains were predictors of FYI total, social communication and sensory regulatory risk scores, in the asthma and community groups separately. Due to a small sample that had CTS data at all three time points, separate regression models were run at 6 weeks, 6 months and 12 months of age if there were any CTS domains that significantly correlated with FYI total risk. Multi-collinearity was assessed with the tolerance and VIF statistics: Multi-collinearity was deemed to be present if the tolerance value was less than .200 and the VIF value was simultaneously 10 or greater. Level of statistical significance was set to $\alpha < 0.05$.

5.3 Results

5.3.1 Preliminary Analyses

In order to assess participation bias, participants in the asthma group and community group were compared on their sociodemographic characteristics (Table 5.1). Mothers with asthma were significantly more likely to have three or more children, and less likely to have obtained a university degree, compared to mothers from the general community (all $p < .05$). Infants born to mothers with asthma were significantly older during participation than community infants ($p < .05$). No significant correlations between the sociodemographic characteristics and FYI total risk scores were identified (all $p > .05$). Due to the small sample size within this study, analyses where covariation can be measured were not utilised. However, in order to examine whether maternal mental health was a potential covariate, the association between the Edinburgh Postnatal Depression Scale (EPDS) total score and the FYI total score was analysed using Pearson correlation coefficients. For the asthma group, there was a statistically significant correlation between EPDS total score and FYI total score ($n = 52$, r = .330, $p = .017$). For the community group, there was no statistically significant correlation between EPDS total score and FYI total score ($n = 41$, r = .120, $p = .456$). There were two sets of twins in the asthma group; data were randomly selected from one twin of each pair for inclusion in analyses. Participants were included if they had data for the FYI and the CTS for at least the third time-point (i.e., ~12 months of age). Of the total sample ($n = 117$), 28.2% provided data at 12 months only, 34.2% provided data at 12 months and either 6 weeks or 6 months, and 37.6% provided data at all three time points described within this

Table 5.1 Sociodemographic characteristics of the participants in the asthma and community groups at time of assessment of autism symptoms. Independent samples t-tests and chi-squared tests were used to assess differences in characteristics.

Sociodemographic characteristic		Infants-Asthma $n = 72$	Infants-Community $n = 45$	*p*-value
Maternal Age at infant birth (years)				.105
	Mean (SD)	30.7 (5.2)	32.2 (4.5)	
	Range	21.5 – 43.9	24.0 – 49.2	
Infant Age, at participation (weeks)				.009
	Mean (SD)	54.3 (3.0)	53.0 (1.8)	
	Range	42.7 – 64.4	45.6 – 56.1	
Infant Gender		*n* (%)	*n* (%)	.930
	Male	39 (54.2)	24 (53.3)	
	Female	33 (45.8)	21 (46.7)	
Maternal Country of Birth		*n* (%)	*n* (%)	.580
	Australia	60 (83.3)	40 (88.9)	
	Overseas	4 (5.6)	4 (8.9)	
	Unspecified	8 (11.1)	1 (2.2)	
Maternal Ethnicity		*n* (%)	*n* (%)	.354
	Caucasian	62 (86.1)	39 (86.7)	
	Australian Aboriginal	2 (2.8)	0 (0.0)	
	Asian	2 (2.8)	3 (6.7)	
	Mixed	3 (4.2)	1 (2.2)	
	Other	3 (4.2)	0 (0.0)	
	Unspecified	0 (0.0)	2 (4.4)	
Maternal Educational Attainment		*n* (%)	*n* (%)	.008
	< High School Certificate	11 (15.3)	1 (2.2)	
	High School Certificate	8 (11.1)	2 (4.4)	
	Trade Certificate/Diploma	15 (20.8)	6 (13.3)	
	University Degree	31 (43.1)	34 (75.6)	
	Unspecified	7 (9.7)	2 (4.4)	
Annual Household Income[a]		*n* (%)	*n* (%)	.167
	0 – 18,700	5 (6.9)	1 (2.2)	
	18,701 – 37,000	7 (9.7)	1 (2.2)	
	37,001 – 80,000	17 (23.6)	9 (20.0)	
	80,001 – 180,000	36 (50.0)	29 (64.4)	
	180,001 and Over	3 (4.2)	5 (11.1)	
	Unspecified	4 (5.6)	0 (0.0)	
Parity		*n* (%)	*n* (%)	.029
	Para 1	36 (50.0)	30 (66.7)	
	Para 2	20 (27.8)	12 (26.7)	
	Para ≥3	16 (22.2)	2 (4.4)	
	Unspecified	0 (0.0)	1 (2.2)	
Maternal Mental Health Condition[a]		*n* (%)	*n* (%)	.165
	No	51 (70.8)	37 (82.2)	
	Yes	21 (29.2)	8 (17.8)	

Abbreviations: Para 1 = 1 child; Para 2 = 2 children; Para ≥3 = 3 or more children.
[a]Australian dollars.
[b]Anxiety disorder, depressive disorder and/or borderline personality disorder.

chapter.

5.3.2 Sample Characteristics

Mothers with asthma (*n* = 72) had a mean age of 30.7 years (*SD* = 5.2) when their infants (54.2% male, 97.2% singleton) were born (Table 5.1). The majority of mothers with asthma were Caucasian, Australian born, well educated (i.e. at least completed final year of high school) and had a median annual household income range of $80,001 to $180,000. During pregnancy, most mothers had mild asthma (59.7%) that was either partly-controlled (51.4%) or uncontrolled (29.2%). Most mothers with asthma did not smoke during pregnancy (68.1%) and had a body mass index (BMI; kg/m^2) above the healthy range (72.2%; Table 5.2). There were 30 mothers who reported using inhaled corticosteroids as their preventer medication during pregnancy (median dose = 500 µg, for *n* = 28). Mothers without asthma (*n* = 45) had a mean age of 32.2 years (*SD* = 4.5) when their infants (53.3% male, 100% singleton) were born (Table 5.1). The majority of mothers were Caucasian, Australian born, university educated, and had a median annual household income range of $80,001 to $180,000.

5.3.3 Association between Infant Temperament and Autism Symptoms

Table 5.3 reports the summary statistics and sample sizes for the CTS and FYI data for both groups (see Appendix K). Table 5.4 reports the Pearson correlation coefficients between the FYI and the CTS at 6 weeks, 6 months and 12 months of age for infants born to mothers with asthma. There were moderate, positive, statistically significant correlations between rhythmicity ($p = .035$), adaptability ($p = .001$), mood ($p = .001$), persistence ($p = .003$) and distractibility ($p = .012$) at 6 weeks of age, and FYI total risk at 12 months of age. There were moderate to strong, positive, statistically significant correlations between rhythmicity ($p = .002$), approach ($p = .004$), adaptability ($p < .001$), mood ($p = .001$) and distractibility ($p < .001$) at 6 months of age, and FYI total risk at 12 months of age. There was

Table 5.2 Descriptive statistics for asthma and physical health characteristics for mothers with asthma.

Asthma/Health characteristic		*n*	%	M (SD)	Range
Body Mass Index				31.1 (8.2)	19.6 – 49.4
	Underweight	0	0.0		
	Health Weight	20	27.8		
	Overweight	19	26.4		
	Obese	31	43.1		
	Unknown[a]	2	2.8		
Smoking status					
	Never	49	68.1		
	Ex-Smoker	18	25.0		
	Current Smoker	5	6.9		
	Unspecified[a]	0	0.0		
Asthma severity					
	Mild	43	59.7		
	Moderate	13	18.1		
	Severe	13	18.1		
	Unknown[a]	3	4.2		
Asthma control					
	Well-controlled	13	18.1		
	Partly-controlled	37	51.4		
	Uncontrolled	21	29.2		
	Unknown[a]	1	1.4		
Asthma treatment[b]					
	SABA	67	93.1		
	ICS	8	11.1		
	ICS/LABA	22	30.6		
	LABA	1	1.4		
	No asthma treatment specified[a]	3	4.2		

[a]This information was not collected at baseline because mothers either did not attend their appointment or they did not specify the information during their appointment.
[b]Frequencies/percentages do not add up to total sample size/100 percent as they are not mutually exclusive.

a weak, negative correlation between FYI total risk and distractibility at 12 months of age ($p = .017$). Additionally, there were moderate, positive, statistically significant correlations between FYI total risk and rhythmicity ($p = .001$), approach ($p = .009$), adaptability ($p = .001$), mood ($p < .001$) and persistence ($p = .005$) at 12 months of age.

Regarding FYI social communication risk, there were moderate, positive, statistically significant correlations with rhythmicity ($p = .043$), adaptability ($p = .031$), mood ($p = .034$), persistence ($p = .001$) and distractibility ($p = .037$) at 6 weeks. At 6 months, there were

Table 5.4 Pearson correlation coefficients between First Year Inventory and Carey Temperament Scale scores for infants born to mothers with asthma (*n* = 72) at 6 weeks (T1), 6 months (T3) and 12 months (T3) of age.

		Total	Social Communication	Sensory Regulatory
Activity	T^1	.220	-.062	**.450***
	T^2	-.089	-.127	-.032
	T^3	.034	.030	.029
Rhythmicity	T^1	**.314***	**.304***	.248
	T^2	**.436***	**.351***	**.427***
	T^3	**.398***	**.273***	**.418***
Approach	T^1	.181	.120	.197
	T^2	**.410***	.278	**.454***
	T^3	**.312***	.194	**.350***
Adaptability	T^1	**.494***	**.338***	**.516***
	T^2	**.565***	**.401***	**.609***
	T^3	**.413***	**.316***	**.404***
Intensity	T^1	.088	.083	.070
	T^2	.065	.013	.103
	T^3	.173	.025	**.268***
Mood	T^1	**.476***	**.323***	**.512***
	T^2	**.482***	**.363***	**.498***
	T^3	**.440***	**.314***	**.453***
Persistence	T^1	**.434***	**.500***	.272
	T^2	.185	.162	.169
	T^3	**.334***	**.369***	.216
Distractibility	T^1	**.375***	**.315***	**.343***
	T^2	**.567***	**.500***	**.516***
	T^3	**-.282***	**-.260***	-.232
Threshold	T^1	-.188	-.233	-.098
	T^2	-.035	-.128	.064
	T^3	-.108	-.184	-.011

*Correlation is significant at the .05 level.

moderate, positive, statistically significant correlations between FYI social communication risk and rhythmicity (p = .016), adaptability (p = .005), mood (p = .011) and distractibility (p < .001). At 12 months, there were weak to moderate, positive, statistically significant correlations with rhythmicity (p = .020), adaptability (p = .009), mood (p = .008) and persistence (p = .002). Further, there was a weak, negative, statistically significant correlation between distractibility at 12 months and FYI social communication risk (p = .029).

Regarding FYI sensory regulatory risk, there were moderate to strong, positive, statistically significant correlations with activity (*p* = .002), adaptability (*p* = .001), mood (*p* < .001) and distractibility (*p* = .023) at 6 weeks. At 6 months, there were moderate to strong, positive, statistically significant correlations between rhythmicity (*p* = .003), approach (*p* = .001), adaptability (*p* < .001), mood (*p* < .001) and distractibility (*p* < .001) and FYI sensory regulatory risk. At 12 months, there were weak to moderate, positive, statistically significant correlations between rhythmicity (*p* < .001), approach (*p* = .003), adaptability (*p* = .001), intensity (*p* = .025) and mood (*p* < .001) and FYI sensory regulatory risk. No other significant correlations between CTS domain scores with FYI risk scores for infants born to mothers with asthma were identified (*p* >. 05). Bayes Factors indicated that the strength of evidence for significant correlations ranged from inconclusive to strong (See Table 5.5 in Appendix L). Bayes Factors indicated that the strength of evidence for all other correlations ranged from inconclusive to moderate, in favour of the null hypothesis or alternative hypothesis depending on the CTS domain (See Table 5.5 in Appendix L).

Table 5.6 reports the Pearson correlation coefficients between the FYI and the CTS at 6 weeks, 6 months and 12 months of age for community infants. There was a moderate, positive, statistically significant correlation between distractibility (*p* = .025) at 6 months of age and FYI total risk at 12 months of age. There were moderate, positive, statistically significant correlations between rhythmicity (*p* = .020) and mood (*p* = .005) at 12 months of age, and FYI total risk at 12 months of age. Regarding FYI social communication risk, there was a strong, negative, statistically significant correlation with rhythmicity at 6 weeks (*p* = .034) and a moderate, positive, statistically significant correlation with rhythmicity at 12 months (*p* = .005). Regarding FYI sensory regulatory risk, there were moderate, positive, statistically significant correlations with mood at 12 months (*p* = .030) and distractibility at 6 months (*p* = .029). No other significant correlations between CTS domain scores with FYI

Table 5.6 Pearson correlation coefficients between First Year Inventory and Carey Temperament Scale scores for community infants (*n* = 45) at 6 weeks (T1), 6 months (T3) and 12 months (T3) of age.

		Total	Social Communication	Sensory Regulatory
Activity	T^1	.387	-.225	.594
	T^2	.178	-.103	.328
	T^3	.190	.191	.094
Rhythmicity	T^1	-.398	**-.706***	.076
	T^2	.169	.178	.046
	T^3	**.346***	**.413***	.108
Approach	T^1	.370	.022	.397
	T^2	.167	.123	.096
	T^3	.153	.080	.145
Adaptability	T^1	.532	.145	.489
	T^2	.039	-.186	.229
	T^3	.251	.238	.134
Intensity	T^1	.353	.113	.327
	T^2	.168	-.011	.227
	T^3	-.031	-.073	.024
Mood	T^1	-.441	-.431	-.186
	T^2	.207	.101	.169
	T^3	**.413***	.287	**.323***
Persistence	T^1	-.018	.244	-.195
	T^2	.082	-.161	.259
	T^3	-.180	-.151	-.122
Distractibility	T^1	.186	.152	.095
	T^2	**.455***	.166	**.445***
	T^3	-.137	-.178	-.034
Threshold	T^1	.162	-.355	.464
	T^2	-.007	-.155	.153
	T^3	.090	.106	.030

*Correlation is significant at the .05 level.

risk scores for community infants were identified ($p >. 05$). Bayes Factors indicated that the strength of evidence for significant correlations ranged from inconclusive to moderate (See Table 5.7 in Appendix M). Bayes Factors indicated that the strength of evidence for all other correlations ranged from inconclusive to moderate, in favour of the null hypothesis or alternative hypothesis depending on the CTS domain (see Table 5.7 in Appendix M).

5.3.4 Infant Temperament as a Predictor of Autism Symptoms

For infants born to mothers with asthma, the following temperament domains significantly correlated with FYI total risk and were subsequently entered into a multiple regression model as predictors: Persistence (6 weeks & 12 months), approach (6 & 12 months), and rhythmicity, adaptability, mood and distractibility at all three time points. As fewer participants had temperament data at 6 weeks and 6 months, three separate regression models were tested; one for each timepoint. Table 5.8 provides information regarding

Table 5.8 Standardised and unstandardised regression coefficients for the Carey Temperament Scale domains at 6 weeks (T1), 6 months (T2) and 12 months (T3) entered into each model as predictors of First Year Inventory (FYI) risk scores for infants born to mothers with asthma.

Model	FYI Risk	Variable	B	SE B	*β*	*p*	Tolerance	VIF
1. T1	Total Score	Rhythmicity	-.208	2.043	-.019	.920	.615	1.626
		Adaptability	3.256	2.380	.287	.181	.481	2.079
		Mood	2.766	2.350	.304	.248	.317	3.155
		Persistence	2.037	1.665	.229	.230	.604	1.655
		Distractibility	-1.584	2.580	-.158	.544	.322	3.109
2. T2	Total Score	Rhythmicity	1.400	1.586	.140	.383	.536	1.866
		Approach	-4.126	2.733	-.297	.139	.348	2.878
		Adaptability	6.118	2.624	.439	**.025**	.379	2.637
		Mood	.971	2.096	.080	.646	.447	2.237
		Distractibility	4.825	2.047	.391	**.023**	.489	2.044
3. T3	Total Score	Rhythmicity	1.490	1.161	.153	.204	.756	1.323
		Approach	.881	1.119	.093	.434	.766	1.306
		Adaptability	1.027	1.535	.096	.506	.525	1.906
		Mood	2.183	1.745	.176	.216	.545	1.835
		Persistence	2.630	1.456	.219	.076	.730	1.370
		Distractibility	-3.700	1.564	-.261	**.021**	.884	1.132

Abbreviations: *p* = *p*-value; VIF = Variance Inflation Factor.
Note: Tolerance and VIF are collinearity statistics.

the regression coefficients and multi-collinearity statistics for the predictor variables entered into each model. Multi-collinearity was not present for any predictor variable across the three models (all Tolerance > .020 and VIF <10). Using the 6-week temperament domains, a significant model emerged ($F_{(5,32)}$= 3.029, p = .024), explaining 22% of the variance in FYI total risk (Adjusted R^2 = .215). Bayes Factors indicated that the strength of evidence for the model was moderate, in favour of the alternative hypothesis (BF_{10} = 3.955). None of the entered predictors (i.e., rhythmicity, adaptability, mood, persistence & distractibility) significantly contributed to the predictive value of the model. Using the 6 month temperament domains, a significant model emerged ($F_{(5,41)}$= 6.652, p = <.001), explaining 38% of the variance in FYI total risk (Adjusted R^2 = .381). Bayes Factors indicated that the strength of evidence for the model was strong, in favour of the alternative hypothesis (BF_{10} = 179.378). Of the entered predictors (i.e., rhythmicity, approach, adaptability, mood & distractibility), adaptability and distractibility contributed significantly to the predictive value of the model, with a positive relationship to FYI total risk. Using the 12 month temperament domains, a significant model emerged ($F_{(6,60)}$= 5.477, p = <.001), explaining 29% of the variance in FYI total risk (Adjusted R^2 = .289). Bayes Factors indicated that the strength of evidence for the model was strong, in favour of the alternative hypothesis (BF_{10} = 425.468). Of the entered predictors (i.e., rhythmicity, approach, adaptability, mood, persistence & distractibility), distractibility was the only entered predictor to contribute significantly to the predictive value of the model, with a negative relationship to FYI total risk.

For community infants, the distractibility domain at 6 months, and the rhythmicity and mood domains at 12 months significantly correlated with FYI total risk and were subsequently entered into a multiple regression model as predictors. As fewer participants had temperament data at 6 months, two separate regression models were tested; one for 6 months and one for 12 months. Table 5.9 provides information regarding the regression coefficients and multi-collinearity statistics for the predictor variables entered into each model. Multi-collinearity was not present for any predictor variable across the two models (all Tolerance > .200 and VIF <10). Using the 6-month temperament domain, a significant model emerged ($F_{(1,22)}$= 5.758, p = .025), explaining 17% of the variance in FYI total risk (Adjusted R^2 = .171). Bayes Factors indicated that the strength of evidence for the model was inconclusive, in favour of the alternative hypothesis (BF_{10} = 2.638). The only entered predictor was distractibility, which contributed significantly to the predictive value of the model, with a positive relationship to FYI total risk. Using the 12 month temperament domains, a significant model emerged ($F_{(2,42)}$= 5.644, p = .007), explaining 27% of the variance in FYI total risk (Adjusted R^2 = .174). Bayes Factors indicated that the strength of evidence for the model was inconclusive, in favour of the alternative hypothesis (BF_{10} = 2.589). Of the entered predictors (i.e., rhythmicity & mood), mood contributed significantly to the predictive value of the model, with a positive relationship to FYI total risk.

Table 5.9 Standardised and unstandardised regression coefficients for the Carey Temperament Scale domains at 6 months (T2) and 12 months (T3) entered into each model as predictors of First Year Inventory (FYI) risk scores for community infants.

Model	FYI Risk	Variable	B	SE B	*β*	*p*	Tolerance	VIF
1. T2	Total Score	Distractibility	6.302	2.626	.455	**.025**	1.000	1.000
2. T3	Total Score	Rhythmicity	2.098	1.412	.221	.145	.853	1.173
		Mood	3.187	1.441	.328	**.032**	.853	1.173

Abbreviations: p = p-value; VIF = Variance Inflation Factor.
Note: Tolerance and VIF are collinearity statistics.

Chapter Six: Study Three

Temperament profiles of infants born to mothers with asthma at-risk for autism spectrum disorder: A case-series

Chapter Synopsis

This chapter aims to explore the third and final research question of this thesis: What are the temperament and developmental features of infants born to mothers with asthma who are at-risk for ASD? Using a case series design, this chapter reports on the temperament, sensory and developmental profiles of infants born to mothers with asthma, who screened at-risk on the First Year Inventory. I present each case individually and describe their temperament, sensory features, and cognitive, language and motor development, at three timepoints during the first year of life. Subsequently, I synthesise the profiles of the cases to identify similarities and differences in the developmental features.

6.1 Aims

In this study, I used a case series design to profile the temperament, sensory and developmental features of infants born to mothers with asthma who were identified as at-risk for Autism Spectrum Disorder (ASD). The first aim was to profile the temperament (measured by the Carey Temperament Scales [CTS]) of infants at-risk for ASD (measured by the First Year Inventory [FYI]). Second, I aimed to characterise the sensory features (measured by the Sensory Profile 2 [SP2]), and cognitive, language and motor development (measured by the Bayley Scales of Infant and Toddler Development [Bayley-III]) of infants at-risk for ASD. Lastly, I aimed to synthesise the temperament, sensory and developmental features of each case, in order to identify similarities and differences in these areas.

6.2 Data Analysis

A case series design, or multiple-case study, was used to explore the early development of infants born to mothers with asthma at-risk for ASD. A case study is an empirical method used to examine a subject (i.e., case) in an in-depth and detailed manner, using a real-world context (Yin, 2018). In this study, six separate case studies are presented, followed by a cross-case analysis in order to synthesise the features of the cases. The scores on the nine domains of the CTS were compared to normative data in order to profile temperament. The scores on the SP2 were compared to normative data in order to profile sensory processing: At 6 weeks and 6 months the total score of the ISP2 was used, while the four quadrants of the TSP2 were used at 12 months. The scores on the domains of the Bayley-III were compared to normative data in order to profile cognitive, language and motor development: At 6 months, the raw scores of the cognitive, receptive communication, expressive communication, fine motor and gross motor domains of the screening version were used, while the composite scores of the cognitive, language and motor domains were used at 12 months. The categories used to describe where an infant's score fell compared to the normative sample are presented in Table 6.1.

Table 6.1 Descriptive categories for the Carey Temperament Scales, Sensory Profile 2 and Bayley Scales of Infant and Toddler Development.

Measure	Descriptor	Score Range
CTS	Easy	< 1 standard deviation below the normative mean
	Average	1 standard deviation within the normative mean
	Difficult	> 1 standard deviation below the normative mean
SP2	Much Less Than Others	< 2 standard deviations below the normative mean
	Less Than Others	Between 1 and 2 standard deviations below the normative mean
	Just Like the Majority of Others	1 standard deviation within the normative mean
	More Than Others	Between 1 and 2 standard deviations above the normative mean
	Much More Than Others	> 2 standard deviations above the normative mean
Bayley-III: Screening Test[a]	At-Risk	Ranges from: 0-2 to 0-7
	Emerging	Ranges from: 3-4 to 8-10
	Competent	Ranges from: 6-24 to 11-28
Bayley-III: Full Test	Very Superior	> 3 standard deviations above the normative mean
	Superior	Between 2 and 3 standard deviations above the normative mean
	High Average	Between 1 and 2 standard deviations above the normative mean
	Average	1 standard deviation within the normative mean
	Low Average	Between 1 and 2 standard deviations below the normative mean
	Borderline	Between 2 and 3 standard deviations below the normative mean
	Extremely Low	< 3 standard deviations below the normative mean

[a]Score range is dependent on the age of the infant and the subtest domain.

6.3 Results

During the data collection period (May 2015 until December 2018), there were 76 infants born to mothers with asthma who had a complete FYI. Of these, seven infants were screened at-risk for ASD. One infant was excluded from this case series analysis due to familial risk of ASD (i.e., older siblings diagnosed with ASD). All included infants (3 male) were born full-term (>36 weeks gestation) with a healthy birthweight (≥2500g). Descriptive data for sociodemographic and maternal asthma characteristics for cases are reported in tables 6.2 and 6.3, respectively. Mothers had mild (n = 4) or moderate (n = 2) asthma, that was

Table 6.2 Descriptive data for sociodemographic characteristics of each case.

Case	Gender	Infant Age[a]	Maternal Age[b]	Maternal Country of Birth	Maternal Ethnicity	Parity
1	Female	12.27	28.32	Australia	Other	Para ≥3
2	Male	12.30	30.02	Australia	White	Para ≥3
3	Female	12.30	42.48	Overseas	White	Para 2
4	Male	12.30	30.66	Australia	White	Para 2
5	Female	12.30	32.56	N/A	White	Para 2
6	Male	13.77	21.45	Australia	White	Para 1

[a]at autism risk (FYI) assessment, in months.
[b]at infant birth in years.
[c]at timepoint three.

Table 6.3 Descriptive statistics of maternal asthma characteristics for each case.

Case	Asthma Severity	Asthma Control	Asthma Treatment
1	Moderate	Uncontrolled	SABA, ICS
2	Moderate	Partly-controlled	SABA, ICS/LABA
3	Mild	Uncontrolled	SABA
4	Mild	Partly-controlled	SABA
5	Mild	Uncontrolled	SABA
6	Mild	Uncontrolled	SABA

Abbreviations: ICS = Inhaled Corticosteroids; LABA = Long-Acting Beta Agonists; SABA = Short-Acting Beta Agonists.

either partly-controlled (n = 2) or uncontrolled (n = 4). Table 6.4 reported the total scores, alongside domain scores, on the FYI for each case. Infants fell within the 98th to 100th percentile for the total score, the 90th to 100th percentile for the sensory regulatory domain score, and the 94th to 100th percentile for the social communication domains score. All cases were screened as 'at-risk' on the total score criterion, with four cases screened at-risk on the two-domain criterion. Case 4 was not at-risk on the sensory regulatory domain and Case 1 was not at-risk on the social communication domain. In the following sections, the temperament, sensory and general developmental features of each case are individually described. Subsequently, the profiles cases are synthesised to highlight similarities and differences between cases.

Table 6.4 Descriptive statistics of first year inventory total and domain scores for each case.

Case	Total	Sensory Regulatory Domain	Social Communication Domain
1	20.63	25.00	16.25
2	43.75	43.75	43.75
3	21.50	16.50	26.50
4	21.63	14.25	29.00
5	26.88	24.00	29.75
6	26.75	30.50	23.00

6.3.1 Case Descriptions

6.3.1.1 Case 1: Female

6.3.1.1.1 Timepoint: 6 months

At 6 months, Case 1 fell within the average range for the activity, adaptability, intensity, persistence and threshold CTS domains. This indicates that she was comparable to the majority of normative infants in her activity level, ability to adapt to change, energy of response, level of persistence in completing challenging tasks, and sensory threshold. For the CTS domains of rhythmicity, approach, mood and distractibility, however, she fell within the difficult range. This indicates that she was less predictable in her biological functions, slower to approach novel stimuli, fussy, and difficult to soothe. The overall diagnostic temperament category for Case 1 at 6 months was Difficult. Regarding sensory processing, no differences were observed from normative infants. Lastly, Case 1 fell within the *competent* range on the cognitive, receptive communication, expressive communication, fine motor and gross motor domains.

6.3.1.1.2 Timepoint: 12 months

At 12 months, Case 1 fell within the average range for all nine CTS domains. This indicates that she was comparable to the majority of normative infants in her activity level, predictability of biological functions, approach novel stimuli, ability to adapt to change, energy of response, mood, level of persistence in completing challenging tasks, ability to soothe, and sensory threshold. The overall diagnostic temperament category for Case 1 at 12 months was Slow-To-Warm-Up. Regarding sensory processing, Case 1 fell within the *just like the majority of others* range for the seeking/seeker, avoiding/avoider and registration/bystander quadrants. This implies that she sought, moved away from, and missed sensory input at the same rate as the majority of normative infants. For the sensitivity/sensor quadrant, she fell within the *more than others* range, indicating that she noticed sensory input at a higher rate than the majority of normative infants. Lastly, Case 1 fell within the *high average* range for cognitive skills, *low average* range for language skills, and *average* range for motor skills.

6.3.1.2 Case 2: Male

6.3.1.2.1 Timepoint: 6 weeks

At 6 weeks, Case 2 fell within the average range for the activity, intensity, distractibility and threshold CTS domains. This indicates that he was comparable to the majority of normative infants in his activity level, energy of response, ability to be soothed, and sensory threshold. For the CTS domains of rhythmicity, approach, adaptability, mood and persistence, he fell within the difficult range. This indicates that he was less predictable in his biological functions, slower to approach novel stimuli and adapt to change, fussier and less persistent in completing challenging tasks. The overall diagnostic temperament category for Case 2 at 6 weeks was Difficult. There was no sensory processing score for Case 2 at this timepoint due to missing data.

6.3.1.2.2 Timepoint: 6 months

Case 2 had the same temperament profile as previously described at 6 weeks, with the exception of the distractibility CTS domain. At 6 months, he fell within the difficult range for distractibility, indicating that he was more difficult to soothe compared to the norms. The overall diagnostic temperament category for Case 2 at 6 months was again Difficult. Regarding sensory processing, he exhibited more sensory behaviours than the majority of normative infants. Lastly, Case 2 fell within the *competent* range on the cognitive, receptive communication, expressive communication, and fine motor domains, and the *at-risk* range on the gross motor domain.

6.3.1.2.3 Timepoint: 12 months

At 12 months, Case 2 had the same temperament profile as the 6 weeks and 6 months timepoints, with the exception of the intensity and distractibility CTS domains. At this timepoint, he fell within the difficult range for intensity and the easy range for distractibility. This indicates that he was more intense in his responses and less distractible compared to normative data. Case 2 changed from the difficult range at 6 months to the easy range at 12 months for distractibility. However, the interpretation of the domain inverts between the two versions of the CTS; high scores on the 6-month version indicate less distractibility while high scores on the 12-month version indicate more distractibility. Thus, he was less distractible at both 6 months and 12 months. The overall diagnostic temperament category for Case 2 at 12 months was again Difficult. Regarding sensory processing, Case 2 fell within the *just like the majority of others* range for the seeking/seeker, quadrant, indicating that he sought sensory input at the same rate as the majority of normative infants. For the avoiding/avoider, he fell within the *more than others* range, indicating that he moved away from sensory input at a higher rate than the majority of normative infants. Additionally, he fell within the *much more than others* range for the sensitivity/sensor and registration/bystander quadrants. This indicates that he both noticed and missed sensory input at a much higher rate than the majority of normative infants. Lastly, Case 2 fell within the *average* range for cognitive skills, and the *low average* range for language and motor skills.

6.3.1.3 Case 3: Female

6.3.1.3.1 Timepoint: 6 weeks

At 6 weeks, Case 3 fell within the average range for the rhythmicity, approach, adaptability, mood and distractibility CTS domains. This indicates that she was comparable to the majority of normative infants in her predictability of biological functions, approach to novel stimuli, ability to adapt to change, mood and ability to be soothed. For the CTS domains of activity, intensity and threshold, she fell within the easy range. This indicates that she had a lower activity level, was mild in energy of response, and had a higher sensory threshold. Lastly, Case 3 fell within the difficult range for the persistence CTS domain, indicating that she was less persistent in completing challenging tasks. The overall diagnostic temperament category for Case 3 at 6 weeks was Easy. Regarding sensory processing, she had sensory behaviours comparable to the majority of normative infants.

6.3.1.3.2 Timepoint: 6 months

Case 3 had a similar temperament profile to the previous, with the descriptive range for activity, rhythmicity, approach, adaptability, mood and distractibility remaining the same. At 6 months, she changed from the easy range for intensity and threshold, and the difficult range for persistence, into the average range. This indicates that she was comparable to the majority of normative infants in her energy of response, sensory threshold and persistence in completing challenging tasks. The overall diagnostic temperament category for Case 3 at 6 months was Slow-To-Warm-Up. Regarding sensory processing, she again had sensory behaviours comparable to the majority of normative infants. Lastly, Case 3 fell within the *competent* range on the cognitive, expressive communication and fine motor domains, and the *emerging* range on the receptive communication and gross motor domains.

6.3.1.3.3 Timepoint: 12 months

At 12 months, Case 3 had the same temperament profile as the 6 weeks and 6 months timepoints for the domains of approach, adaptability and mood. The scores for the domains of persistence and threshold were within the same range as the 6-month time point. At this timepoint, she fell within the difficult range for rhythmicity, the easy range for intensity and distractibility, and the average range for activity. This indicates that she was comparable to the normative infants in her activity level, yet less predictable in her biological functions, less intense in her responses and less distracted by extraneous stimuli. The overall diagnostic temperament category for Case 3 at 12 months was Intermediate - Low. Regarding sensory processing, Case 3 fell within the *just like the majority of others* range for all four quadrants. This implies that she sought, moved away from, noticed and missed sensory input at the same rate as the majority of normative infants. Lastly, Case 3 fell within the *average* range for cognitive skills, *low average* range for language skills, and *borderline* range for motor skills.

6.3.1.4 Case 4: Male

6.3.1.4.1 Timepoint: 6 weeks

At 6 weeks, Case 4 fell within the average range for the rhythmicity, intensity, distractibility and threshold CTS domains. This indicates that he was comparable to the majority of normative infants in his predictability of biological functions, energy of response, ability to be soothed, and sensory threshold. For the CTS domains of activity and approach, he fell within the difficult and easy ranges, respectively. This indicates that he had a higher activity level and was quicker to approach to novel stimuli. Items with the adaptability and persistence domains had missing responses and thus domain scores were not calculated. There was no diagnostic temperament category at this timepoint due to the missing domain scores. Regarding sensory processing, he had sensory behaviours comparable to the majority of normative infants.

6.3.1.4.2 Timepoint: 6 months

Case 4 had a similar temperament profile at 6 months to the previous timepoint, with the descriptive range for rhythmicity, approach, intensity, distractibility and threshold remaining the same. At 6 months, he changed from the difficult range for activity and the easy range for mood, into the average range. This indicates that he was comparable to the majority of normative infants in his level of activity and type of emotional responses. Case 4 also scored within the average range for adaptability and persistence, domains that were unavailable at the 6-week timepoint. This indicated that he was comparable to the majority of normative infants in his ability to adapt to change and persistence in completing challenging tasks. The overall diagnostic temperament category for Case 4 at 6 months was Easy. Regarding sensory processing, he again had sensory behaviours comparable to the majority of normative infants. Lastly, Case 4 fell within the *competent* range on the cognitive, expressive communication and fine motor domains, and the *emerging* range on the receptive communication and gross motor domains.

6.3.1.4.3 Timepoint: 12 months

At 12 months, Case 4 had the same temperament profile as the 6 weeks and 6 months timepoints for the rhythmicity domain. The scores for the domains of mood and persistence were within the same range as the 6-month timepoint. At this timepoint, he fell within the average range for approach and the easy range for distractibility. This indicates that he was comparable to the normative infants in his approach to novel stimuli, yet less distracted by extraneous stimuli. Items with the activity, adaptability, intensity and threshold domains had missing responses and thus domain scores were not calculated. There was no diagnostic temperament category at this timepoint due to the missing domain scores. Regarding sensory processing, Case 4 fell within the *just like the majority of others* range for all four quadrants. This implies that he sought, moved away from, noticed and missed sensory input at the same rate as the majority of normative infants. Lastly, Case 4 fell within the *high average* range for cognitive skills, *low average* range for language skills, and *average* range for motor skills.

6.3.1.5 Case 5: Female

6.3.1.5.1 Timepoint: 12 months

Case 5 fell within the average range for the domains of rhythmicity, approach, intensity, and threshold. This indicates that she was comparable to the majority of normative infants in her predictability of biological functions, approach to novel stimuli, energy of response, and sensory threshold. For the domains of adaptability, mood, persistence and distractibility, she fell within the difficult range, while she fell within the easy range for activity. This indicates that she was slower to adapt to change, fussier in mood, less persistent in completing challenging tasks, less distracted by extraneous stimuli, and had a lower activity level. The overall diagnostic temperament category for Case 5 at 12 months was Difficult. Regarding sensory processing, Case 5 fell within the *just like the majority of others* range for all four quadrants. This implies that she sought, moved away from, noticed and missed sensory input at the same rate as the majority of normative infants. Lastly, Case 5 fell within the *average* range for cognitive, language and motor skills.

6.3.1.6 Case 6: Male

6.3.1.6.1 Timepoint: 6 weeks

At 6 weeks, Case 6 fell within the average range for the approach, distractibility and threshold CTS domains. This indicates that he was comparable to the majority of normative infants in his approach to novel stimuli, ability to be soothed and sensory threshold. For the CTS domains of rhythmicity, mood and persistence, he fell within the difficult range. This indicates that he was less predictable in his biological functions, fussy in mood, and less persistent in completing challenging tasks. Items with the activity, adaptability and intensity domains had missing responses and thus domain scores were not calculated. There was no diagnostic temperament category at this timepoint due to the missing domain scores. Regarding sensory processing, he had sensory behaviours comparable to the majority of normative infants.

6.3.1.6.2 Timepoint: 6 months

Case 6 had a similar temperament profile to the previous, with the descriptive range for rhythmicity, approach, distractibility and threshold remaining the same. At 6 months, he changed from the difficult range for mood and persistence into the average range. This indicates that he was comparable to the majority of normative infants in his type of emotional responses and persistence in completing challenging tasks. Case 6 also fell within the average range of the domains of activity, adaptability and intensity, which were unavailable at the 6-week timepoint. This indicates that he was also comparable to the majority of normative infants in his level of activity, approach to novel stimuli, and energy of response. The overall diagnostic temperament category for Case 6 at 6 months was Intermediate – Low. Regarding sensory processing, he again had sensory behaviours comparable to the majority of normative infants. Lastly, Case 6 fell within the *competent* range on the receptive communication, expressive communication and gross motor domains, and the *emerging* range on the cognitive and fine motor domains.

6.3.1.6.3 Timepoint: 12 months

At 12 months, Case 6 had the same temperament profile as the 6 weeks and 6 months timepoints for the domains of approach and distractibility. The domains of activity, adaptability, intensity, and persistence were within the same range as the 6-month time point. At this timepoint, he fell within the average range for rhythmicity, the difficult range for mood and the easy range for threshold. This indicates that he was comparable to the normative infants in the predictability of his biological functions, yet with fussier mood and higher sensory threshold. The overall diagnostic temperament category for Case 6 at 12 months was again Intermediate - Low. Regarding sensory processing, Case 6 fell within the *just like the majority of others* range for the seeking/seeker and avoiding/avoider quadrants. This implies that he both sought and moved away from sensory input at the same rate as the majority of normative infants. For the sensitivity/sensor and registration/bystander quadrants, he fell within the *more than others* range, indicating that he both noticed and missed sensory input at a higher rate than the majority of normative infants. Lastly, Case 6 fell within the *borderline* range for cognitive, language and motor skills.

6.3.2 Synthesis of At-Risk Infant Profiles

6.3.2.1 Temperament Profile

Temperament domain scores and profiles are presented in tables 6.5 and 6.6, respectively. Across the three timepoints, most infants were reported to have a typical temperament profile among most of the nine domains of temperament. However, all infants were reported to have difficult temperament features during at least one timepoint, particularly within the *rhythmicity* (n = 4), *mood* (n = 5) and *persistence* (n = 4) domains. The only domain where no infants were reported to fall within the difficult range was *threshold*. This suggests that, as a group, these infants may be unpredictable in their biological functions, fussy in mood, and not persistent in completing challenging tasks, yet have no difficulties with processing sensory information, compared to the norms. Fewer infants were reported to have easy temperament features, as indicated by falling less than one standard deviation from the normative mean. Of note, however, *distractibility* was the only domain where half of the cases were reported to be less distractible than the norm. There does not

Table 6.5 Carey temperament scales domain scores for each case at the 6 weeks (T1), 6 month (T2) and 12 month (T3) timepoints.

Case	1			2			3			4			5			6		
	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3
Activity	N/A	4.15	3.42	3.57	4.54	3.75	2.75	3.54	3.50	4.25	3.92	N/A	N/A	N/A	3.25	N/A	3.91	4.50
Rhythmicity	N/A	3.83	2.90	4.89	3.50	4.73	3.10	2.83	4.18	2.70	2.50	2.09	N/A	N/A	2.36	4.10	3.33	3.18
Approach	N/A	3.50	3.67	3.83	3.80	5.58	2.17	2.73	3.67	1.83	1.36	2.73	N/A	N/A	3.67	2.17	2.18	2.45
Adaptability	N/A	2.36	3.89	4.11	4.20	5.00	2.00	2.45	3.44	N/A	1.64	N/A	N/A	N/A	4.67	N/A	2.50	3.56
Intensity	N/A	3.89	3.30	3.83	3.80	4.88	2.67	2.90	2.80	4.00	3.70	N/A	N/A	N/A	4.60	N/A	3.33	4.00
Mood	N/A	3.60	3.54	4.00	3.67	4.50	3.09	3.20	2.92	2.00	2.70	2.73	N/A	N/A	4.31	4.44	2.40	3.85
Persistence	N/A	3.13	3.55	4.13	4.25	4.91	3.63	3.25	3.91	N/A	2.38	3.44	N/A	N/A	5.45	3.71	3.63	3.82
Distractibility	N/A	3.00	4.55	3.00	3.60	3.18	2.14	2.70	3.09	2.33	2.60	3.36	N/A	N/A	5.64	3.17	2.30	3.73
Threshold	N/A	3.67	3.50	4.50	4.00	4.43	2.60	3.70	3.00	4.10	3.60	N/A	N/A	N/A	3.38	4.00	3.40	2.25

Note: N/A = Temperament data not available due to missing responses or participant not being tested at timepoint.

Table 6.6 Carey temperament scales profile groups for each case at the 6 weeks (T1), 6 month (T2) and 12 month (T3) timepoints.

Case	1			2			3			4			5			6		
	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3	T^1	T^2	T^3
Activity	N/A	A	A	A	A	A	E	E	A	D	A	N/A	N/A	N/A	E	N/A	A	A
Rhythmicity	N/A	D	A	D	D	D	A	A	D	A	A	A	N/A	N/A	A	D	D	A
Approach	N/A	D	A	D	D	D	A	A	A	E	E	A	N/A	N/A	A	A	A	A
Adaptability	N/A	A	A	D	D	D	A	A	A	N/A	A	N/A	N/A	N/A	D	N/A	A	A
Intensity	N/A	A	A	A	A	D	E	A	E	A	A	N/A	N/A	N/A	A	N/A	A	A
Mood	N/A	D	A	D	D	D	A	A	A	E	A	A	N/A	N/A	D	D	A	D
Persistence	N/A	A	A	D	D	D	D	A	A	N/A	A	A	N/A	N/A	D	D	A	A
Distractibility	N/A	D	A	A	D	E	A	A	E	A	A	E	N/A	N/A	D	A	A	A
Threshold	N/A	A	A	A	A	A	E	A	A	A	A	N/A	N/A	N/A	A	A	A	E

Abbreviations: A = Average; D = Difficult; E = Easy.

Note: N/A = Temperament data not available due to missing responses or participant not being tested at timepoint.

appear to be any apparent differences in temperament profiles between cases who met the two-domain criteria and cases who only met the total cut-off criteria. Regarding the diagnostic temperament categories (Table 6.7), infants were more frequently categorised within a more challenging temperament cluster (i.e., Difficult, Slow-To-Warm-Up), compared to an easier temperament cluster (i.e., Easy, Intermediate – Low). Overall, there were no distinguishing temperament features for the infants as a group, however, half of the infants presented with difficult temperament features across the timepoints.

Table 6.7 Carey temperament scales diagnostic temperament categories for each case at the 6 weeks, 6 month and 12 month timepoints.

Case	6 weeks	6 months	12 months
1	N/A	Difficult	Slow-To-Warm-Up
2	Difficult	Difficult	Difficult
3	Easy	Slow-To-Warm-Up	Intermediate - Low
4	N/A	Easy	N/A
5	N/A	N/A	Difficult
6	N/A	Intermediate - Low	Intermediate - Low

Note: N/A = Temperament data not available due to missing responses or participant not being tested at timepoint.

6.3.2.2 Sensory Profile

Sensory scores and profiles are presented in table 6.8 for 6 weeks and 6 months, and table 6.9 for 12 months. At 6 weeks (n = 3) and 6 months (n = 5), all infants had typically sensory processing features, with the exception of Case 2 who, at the 6-month timepoint, was reported to engage in sensory behaviours more than the norm. At 12 months (n = 6), all infants were reported to seek sensory input (seeking/seeker quadrant) at the same rate as normative infants. Most infants, except Cases 2 and 6, had typical sensory features relating to the degree to which they move away from (avoiding/avoider quadrant) and miss (registration/bystander quadrant) sensory input. Lastly, within the sensitivity/sensory quadrant, half of the infants were reported to detect sensory input at a higher rate than the norm. There does not appear to be any apparent differences in sensory profiles between cases who met the two-domain criteria and cases who only met the total cut-off criteria. Looking at all three timepoints, it appears that the infants fell into one of two distinct sensory processing profiles: one that was comparable to the norm and one that involved moving away from, detecting and/or missing sensory input at a higher rate compared to norm.

Table 6.8 Infant Sensory Profile 2 total score for each case at the 6 weeks and 6 month timepoints.

Case	6 weeks	6 months
1	N/A	46[a]
2	N/A	65[b]
3	50[a]	45[a]
4	44[a]	45[a]
5	N/A	N/A
6	51[a]	41[a]

Note: N/A = sensory data not available due to missing questionnaire or participant not being tested at that timepoint. Descriptive categories for total scores are indicated by superscript lettering.
[a]Just Like the Majority of Others
[b]More Than Others

Table 6.9 Toddler Sensory Profile 2 quadrant scores for each case at the 12 month timepoint.

Case	Seeking/Seeker	Avoiding/Avoider	Sensitivity/ Sensor	Registration/Bystander
1	25[a]	20[a]	30[b]	19[a]
2	33[a]	33[b]	46[c]	33[c]
3	25[a]	15[a]	22[a]	20[a]
4	35[a]	13[a]	19[a]	12[a]
5	35[a]	15[a]	25[a]	14[a]
6	33[a]	17[a]	34[b]	22[b]

Note: Descriptive categories for quadrants are indicated by superscript lettering.
[a]Just Like the Majority of Others
[b]More Than Others
[c]Much More Than Others

6.3.2.3 Cognitive, Language and Motor Developmental Profile

There were no overall patterns of cognitive, language and motor development that may be used to distinguish or categorise the infants. However, there did appear to be trends in these areas of development at the domain level (Tables 6.10 and 6.11). At 6 months, apart from Case 6, infants had developmentally appropriate cognitive skills. Most infants had

Table 6.10 Bayley scales of infant and toddler development raw scores for each case at the 6 month timepoint.

Case	Cognitive	Receptive Communication	Expressive Communication	Fine Motor	Gross Motor
1	7[c]	12[c]	9[c]	10[c]	7[c]
2	10[c]	6[c]	6[c]	8[c]	4[a]
3	14[c]	7[b]	8[c]	10[c]	10[b]
4	15[c]	7[b]	7[c]	10[c]	9[b]
5	N/A	N/A	N/A	N/A	N/A
6	5[b]	8[c]	5[c]	6[b]	9[c]

Note: N/A = Bayley-III data not available due to participant not being tested at that timepoint. Descriptive categories for domains are indicated by superscript lettering.
[a]At-Risk
[b]Emerging
[c]Competent

Table 6.11 Bayley scales of infant and toddler development composite scores for each case at the 12 month timepoint.

Case	Cognitive	Language	Motor
1	110[d]	86[b]	103[c]
2	95[c]	89[b]	85[b]
3	95[c]	83[b]	76[a]
4	115[d]	86[b]	97[c]
5	95[c]	97[c]	97[c]
6	75[a]	77[a]	70[a]

Note: Descriptive categories for domains are indicated by superscript lettering.
[a]Borderline
[b]Low Average
[c]Average
[d]High Average

developmentally appropriate language skills at 6 months, however one third (Cases 3 & 4) had less developed receptive communication skills. Regarding motor skills at 6 months, infants varied from the at-risk to competent level, particularly within the gross motor domain. At 12 months, apart from Case 6, infants had *average* to *high average* skills pertaining to cognitive development. The opposite pattern is noted for language development at 12 months, with all infants except Case 5 demonstrating skills within the *low average* range or below. Lastly, regarding motor development at 12 months, infants ranged in ability from the *borderline* level to *average* level. Only one infant scored below average for all three areas of development (Case 6). There did not appear to be any apparent differences in cognitive, language or motor development between cases who met the two-domain criteria and cases who only met the total cut-off criteria. Overall, it appears that these infants had developmentally appropriate cognitive skills and less developed language skills yet varied in their motor development. This pattern was noted from 6 months, although the pattern of less-developed language skills did not appear until 12 months of age.

Chapter Seven: Discussion

Chapter Synopsis

This chapter is final chapter of this thesis and will provide a discussion of the findings, implications and limitations of the research presented within this thesis and provide directions for future research. Firstly, I summarise the findings of each study, comparing to previous literature, and discuss the theoretical and clinical implications pertaining to my findings. Secondly, I describe the limitations of this thesis and subsequently provide directions for future research. Lastly, I provide a conclusion to this thesis by summarising the aforementioned sections.

7.1 Key Findings and Implications: Study-by-Study Synthesis

7.1.1 Study One: Early temperament features in infants born to mothers with asthma

7.1.1.1 Summary of Findings from Study One

Study One consisted of two parts that aimed to characterise the temperament of infants born to mothers with asthma during pregnancy. The findings will be discussed in sections 7.1.1.1.1 and 7.1.1.1.2 below.

7.1.1.1.1 Part One: A Comparison with Normative Data, Asthma Control and Asthma Severity

The aim of Part One was to characterise temperament features of infants born to mothers with asthma in the first year of life, as compared to a normative population, and investigate differences in temperament between infants, as a function of maternal asthma severity and asthma control during pregnancy. As this study was exploratory, no hypotheses were proposed. At 6 weeks, infants were more arrhythmic and more positive in mood than the normative sample. Similarly, the 6-month-old infants also showed greater arrhythmia, compared to the normative sample. This indicates that infants born to mothers with asthma had less predictable biological functions, such as sleep-wake cycles, feeding and bowel movements. At 12 months, infants were reported as being less active, less intense and less persistent than the normative sample, indicating less motor activity, less energetic responses and less time spent pursuing challenging tasks.

There were some differences in infant temperament based on maternal asthma severity and asthma control during pregnancy. Mothers with mild asthma during pregnancy had infants at 6 weeks of age who were less predictable in their biological functions, compared to mothers with moderate/severe asthma. At 6 months, infants born to mothers with mild asthma during pregnancy were more easily soothed than infants born to mothers with moderate/severe asthma. Mothers with uncontrolled asthma during pregnancy had infants, at 6 weeks, who were slower to adapt to change in routine, compared to mothers with partly-controlled asthma. Further, infants born to mothers with controlled asthma had a higher level of motor activity at 12 months, than infants born to mothers with partly-controlled and uncontrolled asthma. However, the differences in temperament as a function of maternal asthma severity and asthma control did not remain significant after correcting for multiple comparisons.

7.1.1.1.2 Part Two: A Comparison with Community Infants

The objective of Part Two was to extend on the findings of Part One by introducing a community recruited comparison group. The first aim was to investigate differences in temperament domain scores between infants born to mothers with asthma and infants from the general community. The second aim was to characterise the temperament profiles of infants born to mothers with asthma and compare the proportions in each group to infants from the general community. Lastly, the third aim was to characterise the temperament diagnostic categories of infants born to mothers with asthma and compare the proportions in each group to infants from the general community. It was hypothesised that infants born to mothers with asthma would be (1) more arrhythmic, (2) more positive in mood, (3) lower in activity level, (4) milder in their response, and (5) less persistent in completing challenging tasks, compared to infants from the general community.

Regarding differences in domain scores, infants born to mothers with asthma were more positive in mood at 6 weeks, more persistent in completing challenging tasks at 12 months, and less distractible at 12 months, compared to community infants. However, these differences did not remain significant after correcting for multiple comparisons. Thus, none of the hypotheses were supported. Looking at the distribution of domain profiles, more infants born to mothers with asthma were positive in mood at 6 weeks and difficult to soothe at 6 months, compared to community infants. Further, fewer infants born to mothers with asthma were high in motor activity at 6 months or quick to approach novel stimuli (e.g., toys, people) at 12 months, compared to community infants. Rather, more infants born to mothers with asthma were within the average bounds for activity level and approach than community infants. Interestingly, at 6 months, nearly half of infants born to mothers with asthma and community infants were arrhythmic, that is, unpredictable in their biological functions (e.g., sleep-wake cycles, feeding etc.). After correcting for multiple comparisons, only the difference in profile distributions found in the approach domain at 12 months was sustained. Lastly, regarding the distribution of diagnostic temperament categories, more infants born to mothers with asthma were categorised as easy overall, compared to community infants. This indicates that they were more likely to be predictable in their biological function, fast to approach novel stimuli and adapt to change, positive in mood and mild in response. However, there were no significant differences in the distribution of temperament categories at any of the three time points.

7.1.1.2 Discussion of Findings from Study One

Our results regarding the temperament of children born to mothers with asthma are not clear. On the one hand, our sample of infants born to mothers with asthma during pregnancy were more arrhythmic, and less fussy in mood, active, intense in response and able to pursue challenging tasks than normative peers. However, no evidence was found to suggest that infants born to mothers with asthma have different temperament features, compared to infants recruited from the general community. There is also inconclusive evidence for the impact of severity and control of maternal asthma on infant temperament outcomes. In this section, I will firstly discuss the long-term associations of difficult temperament with functional outcomes relevant to the current cohort. I will then discuss the implications of our findings concerning maternal asthma severity and control during pregnancy. After this I will address potential explanations for the inconsistencies in our findings by arguing that our samples (a) differed from the Carey Temperament Scales (CTS) norms due to temporal and cultural reasons and (b) had insufficient sample sizes.

7.1.1.2.1 The Temperament of Infants Born to Mothers with Asthma: Long-Term Associations of Difficult Temperament with Functional Outcomes

Some infants in our sample were reported to experience temperament difficulties, particularly related to arrhythmia and fussy mood. Arrhythmia of biological functions refers to less predictability of feeding schedules, sleep-wake cycles and elimination habits (Medoff-Cooper et al., 1993). Arrhythmia has been reported in approximately 25% of infants in the general population (Cook, Mensah, Bayer, & Hiscock, 2019), which is similar to our sample at the 6 weeks (27%) and 12 month (18%) timepoints, yet lower than the 42% observed in our sample at 6 months. Arrhythmia has recently been linked to differences in infant feeding methods, whereby infants who are breastfed are reported to have more sleep difficulties than bottle fed infants (Galbally, Lewis, McEgan, Scalzo, & Islam, 2013; Kielbratowska, Kazmierczak, Michalek, & Preis, 2015). Infant feeding method, rather that maternal asthma, may explain the moderate proportion of arrhythmic infants in our sample, considering that similar rates of arrhythmia were found in our community infants.

Issues relating to arrhythmia, such as sleeping difficulties, usually resolve between three to five months of age (Henderson, France, Owens, & Blampied, 2010; St James-Roberts, Roberts, Hovish, & Owen, 2015). Poorer quality of sleep and feeding difficulties, however, have been linked to lesser cognitive and language abilities, and greater hyperactivity-impulsivity (Malas et al., 2017; Scher, 2005; Touchette et al., 2007). This suggests that arrhythmia in infancy may be an early indicator of poorer developmental outcomes. Not only is arrhythmia linked to functional outcomes for children, it also plays a role in the health and well-being of caregivers (Bayer, Hiscock, Hampton, & Wake, 2007;

Martin, Hiscock, Hardy, Davey, & Wake, 2007). By promoting timely and extended sleep, parents can support healthy development in their infants and contribute positively to their own well-being (Bayer et al., 2007; Bernier, Carlson, Bordeleau, & Carrier, 2010; Seehagen, Konrad, Herbert, & Schneider, 2015).

Negative infant affect generally refers to crying, irritability and general fussiness. Extended periods of crying peaks at 6 weeks of age and declines as the infant ages (Wolke, Bilgin, & Samara, 2017). In our sample, 11-24% infants were negative in mood across the three timepoints, which was similar to our community sample. Infant negative mood has been linked to in utero drug exposure (Edmondson & Smith, 1994; O'Connor, 2001). A more common explanation of fussiness in our sample, however, may be the presence of colic (i.e., excessive crying), which occurs in 1 out of 5 infants and is related to increased temperamental difficultness (Lester, Zachariah Boukydis, Garcia-Coll, Hole, & Peucker, 1992; Lucassen et al., 2001).

Negative infant affect has previously been linked to poorer maternal mental health (Barroso, Hartley, Bagner, & Pettit, 2015; Petzoldt, 2018; Rode & Kiel, 2016). Higher rates of infant crying and fussiness have been reported by mothers experiencing symptoms of depression and anxiety (Martini et al., 2017; Petzoldt, 2018; Prino et al., 2016; Rode & Kiel, 2016; Shapiro, Jolley, Hildebrandt, & Spieker, 2018). Similarly, in our sample, the more symptoms of depression mothers reported, the fussier they reported their infant to be (for details, see section 4.2.3.1). As mentioned in section 1.1.2.1, causal relationships cannot be determined, as this research is observational in design. However, research shows that infant negative mood and maternal depression symptoms are related to the quality of the mother-infant bonding experience (Nolvi et al., 2016; Tester-Jones, O'Mahen, Watkins, & Karl, 2015). Thus, the interaction of these two factors may lead to poorer quality of mother-infant interactions, which hinders infant growth and well-being (Bernier, Calkins, & Bell, 2016;

Murray et al., 2016; Niedźwiecka, Ramotowska, & Tomalski, 2018). Supporting mothers who experience poorer mental health in the postpartum period, providing parents with psychoeducation on infant temperament, and soothing fussy infants via kangaroo care (i.e., skin-to-skin contact) may help improve mother-infant interactions (Accortt & Wong, 2017; Akbari et al., 2018; Tsivos, Calam, Sanders, & Wittkowski, 2015; Werner et al., 2016).

The only significant finding was in the distribution for the approach domain at 12 months, which showed strong evidence that more infants born to mothers with asthma fell within the average range than community infants in this domain. This suggests that infants born to mothers with asthma may be less varied in the way they approach new people, objects and situations. Research has shown associations between higher levels of approach and better verbal and non-verbal communication skills (Chong et al., 2019), and decreased behavioural problems (Liang et al., 2019). These outcomes, in turn, support the development of better social skills (Anthony et al., 2005; Cochet, Jover, Rizzo, & Vauclair, 2017; Lipscombe et al., 2016). Therefore, tracking infant temperament, via parent report, may be a useful adjunct to the early care and monitoring of young children born to mothers with asthma.

7.1.1.2.2 The Influence of Maternal Asthma Severity and Asthma Control during Pregnancy on Infant Temperament

This section will discuss the implications of the findings pertaining to maternal asthma severity and asthma control during pregnancy. Maternal asthma severity does not appear to be related to infant temperament in this cohort. While there were some differences in rhythmicity and distractibility, these differences were not sustained after correction for multiple comparisons. However, Bayes factors for these comparisons (previously reported in section 4.1.3.3) provided inconclusive evidence, which indicates an insufficient sample size to detect an effect. Thus, the effect of maternal asthma severity during pregnancy on infant temperament is not clear. Maternal asthma treatment during pregnancy was used to measure asthma severity, as it is the clinically preferred method due to being an objective assessment (Taylor et al., 2008). Despite this, the method of using asthma medication as a proxy for asthma severity is not without limitation. Mothers were classified into one of the three asthma severity groups (i.e., mild, moderate or severe), depending on the type and dosage of asthma medication they received during pregnancy (for further details, see section 3.3.2.3). Health practitioners have reported a lack of confidence in treating asthma in pregnancy (Lim, Stewart, Abramson, & George, 2011). This suggests that some mothers may not receive asthma medication they require during pregnancy. Therefore, some mothers in our sample may have been classified into a severity group they otherwise would not have been if another method of assessing asthma severity was used (e.g., spirometry, i.e., lung function).

Similar to asthma severity, there were differences in temperament based on maternal asthma control, yet not after correction for multiple comparisons. Infants born to mothers with uncontrolled asthma differed from infants born to mothers with partly-controlled asthma, yet not well-controlled asthma, on adaptability. This difference may not be clinically meaningful, as it is not biologically plausible. Biologically, it would be expected that infants born to mothers with uncontrolled asthma would additionally differ from infants born to mothers with well-controlled asthma. This is because mothers with partly-controlled and uncontrolled asthma experienced greater asthma symptoms than mothers with well-controlled asthma. Bayes factors for this comparison (previously reported in section 4.1.3.3), however, provided inconclusive evidence indicating an insufficient sample size to detect an effect.

While there were no statistically significant differences in infant motor activity based on maternal asthma control, the observed relationship between maternal asthma control and level of motor activity in infants at 12 months is important. Infants born to mothers with asthma are at an increased risk of developing asthma themselves (Kashanian et al., 2017). It is not currently known how many infants in our sample will receive an eventual diagnosis of asthma. However, there is evidence to suggest that older children who have been diagnosed with asthma display less physical activity than their non-asthmatic peers (for review, see Williams, Powell, Hoskins, & Neville, 2008). Our finding suggests that these behavioural characteristics that have been linked to childhood asthma may be apparent early in life. It could be that less participation in movement indicates less energy availability. Physical inactivity is a modifiable health risk behaviour that increase the risk of chronic diseases, such as diabetes, cardiovascular disease and cancer (Australian Institute of Health Welfare, 2019). By targeting health risk behaviours early on, intervention could be introduced to increase positive health behaviour change that reduces the risk of disease in later life. For example, programs such as ‘Dads And Daughters Exercising and Empowered’ (DADEE; Morgan et al., 2018) and ‘Study of Health and Activity in Preschool Environments’ (SHAPES; Pate et al., 2016) have been effective in primary school-aged children as young as four, and could be modified to implement in earlier life. Despite the differences in infant temperament based on maternal asthma severity and asthma control not remaining significant after correcting for multiple comparisons, they support the future examination of the relationship between maternal asthma and infant behaviour using well-powered studies.

7.1.1.2.3 Reason for Discrepancies in the Findings of Comparisons between Infants Born to Mothers with Asthma, Community Controls and Normative Samples

There are two potential reasons behind why our sample of infants born to mothers with asthma differed from the CTS normative sample in some temperament domains, yet not our community sample. The first one relates to the sociocultural differences between CTS normative infants and our Australian infants. The second one is related to sample size and statistical power. Both of these arguments will be discussed below.

7.1.1.2.3.1 Practical Considerations for Using the Carey Temperament Scales in Australian Cohorts

Study One found that there were differences between infants born to mothers with asthma compared to the normative sample, yet not our community controls. It was also found that our community controls differed from the normative sample. The normative data were collected in samples of American infants born during the 1970's to 1990's, whilst our sample were Australian infants who were born in the current decade. Thus, the differences we observed between our asthma sample and normative peers in Part One of Study One may be temporal or cultural. This notion is further supported by the post-hoc analyses that compared the temperament of our community sample to the normative sample (for details, see section 4.2.3.3). Australian-born infants from our local community were less predictable in their biological functions (rhythmicity), less persistent when completing challenging tasks (persistence) and more distractible (distractibility) than normative American infants. Of note, the differences from the norms for rhythmicity and persistence were observed with both the asthma sample and community sample. This posits the question of whether the CTS norms should be used with contemporary Australian cohorts.

In response to this question, researchers in the state of Victoria developed Australian norms for the CTS through the Australian Temperament Project (ATP; Oberklaid, Sanson, & Prior, 1986; Sanson, Prior, & Oberklaid, 1985; Sanson, Smart, Prior, Oberklaid, & Pedlow, 1994; Sewell, Oberklaid, Prior, Sanson, & Kyrios, 1988). These norms were constructed to be Australian equivalents to the Revised Infant Temperament Questionnaire (RITQ; ages 4-11 months), the Toddler Temperament Scale (TTS; ages 12-35 months) and the Child Behaviour Questionnaire (ages 3-7 years). The Australian equivalents of the RITQ and TTS were developed with large samples (*n* = 2443 for RITQ; *n* = 1188 for TTS) of infants, aged four to eight months for the RITQ and 15 to 29 months for the TTS. Results showed that the

Australian sample was rated by their parents to be less active (RITQ), more arrhythmic in biological functions (RITQ, TTS), less adaptable to change (RITQ), less intense in emotional response (RITQ, TTS), less persistent in completing challenging tasks (TTS) and less easily distracted (TTS) than the original normative samples of American infants (Sanson et al., 1985; Sewell et al., 1988). In Part One, it was reported that our 6-month sample were more arrhythmic, and our 12-month sample were less intense and less persistent, than normative peers. This replicates some of the findings that were reported by the ATP. This supports the notion that the observed differences in temperament between our sample and the CTS norms may be cultural. No other differences found in the ATP were replicated in our 6-month or 12-month asthma samples. However, our samples were smaller in comparison to that of the ATP (83 vs 2443 for RITQ; 74 vs 1188 for TTS), which may have led to insufficient statistical power.

The developers of the original CTS have stated that care needs to be taken when interpreting the CTS and they recommend that country-specific norms are developed for use in samples outside of the United States (Carey & McDevitt, 2015). However, I was not able to implement the Australian norms into our studies across the three timepoints, due to the lack of Australian norms for the Early Infancy Temperament Questionnaire which were used at the 6-week time point. Additionally, the sample of infants used to develop Australian norms for the TTS were older than our sample (i.e., 15-29 months [ATP] vs 11-16 months [current sample]). Previous research, outside of the ATP, has found differences in temperament when comparing infants to the CTS normative data in the United Kingdom (Chong, Chittleborough, Gregory, Lynch, & Smithers, 2015) and Taiwan (Prior, Kyrios, & Oberklaid, 1986). Therefore, there is the need to use contemporary, country-specific CTS norms across all ages, as the original norms are not suitable for use in some populations outside of the United States.

7.1.1.2.3.2 Insufficient Sample Size and Statistical Power

In Study One, it was found that our asthma sample differed from the CTS norms in several domains, yet not our community infants. The CTS included 262 infants in the EITQ normative sample, 203 infants in the RITQ normative sample and 167 in the TTS normative sample. Our asthma and community samples were smaller in comparison. Our asthma sample included 144 infants at the 6-week timepoint, 83 infants at the 6-month timepoint and 74 infants at the 12-month timepoint. Our community sample included 34 infants at the 6-week timepoint, 46 infants at the 6-month timepoint and 45 infants at the 12-month timepoint. The Bayesian analyses presented in Study One demonstrated inconclusive evidence for an effect in some CTS domains, when comparing infants in the asthma group to those in the community group or norms (for details, see Chapter Four). This indicates that the sample was not sufficient to detect an effect across all CTS domains, and thus Study One was under-powered. Study One did, however, have a larger sample than previously published temperament studies conducting similar analyses (Hughes, Shults, McGrath, & Medoff-Cooper, 2002; Jacobson & Melvin, 1995; Torowicz et al., 2010). These studies report significant findings, although they did not correct for multiple companions unlike in our study. Thus, these studies may also have been under-powered. Study One did find moderate to strong evidence that infants born to mothers with asthma in our sample did not differ on some temperament domains across the three timepoints. Despite this, future research using a well-powered sample (i.e., minimum of 516 infants[4]) is required in order to determine

[4] In Bayesian statistics, sample size grows exponentially alongside the expected Bayes Factor (S. Brown, personal communication, April 21, 2020). Thus, doubling a Bayes Factor until it is decisive (i.e., < .300 under H_0 or > 3 under H_a) can determine the required sample size (S. Brown, personal communication, April 21, 2020). Using this method, the weakest Bayes Factor (i.e., BF_{10}= .969) of this thesis was halved until a decisive Bayes Factor was achieved (i.e., BF_{10}= .242). Using the expected Bayes Factor as a guide, the current sample size (i.e., 129 at 6 months) was multiplied by four. This suggests that an additional 387 infants (516 in total, across both groups) would be required to determine whether the two cohorts different in their CTS scores.

whether the temperament features of infants born to mothers with asthma are the same as infants from the general population.

As previously noted, there was a larger sample size for the asthma group compared to the community group, however this was primarily due to the BLT-ID and BMs studies commencing at different times (i.e., June 2015 and May 2017, respectively). Mothers completed a large battery of questionnaire measures, alongside one to three hours laboratory visits. This testing burden may have contributed to more missing data and thus a smaller pool of participants to include within this thesis. Despite this, the questionnaire battery has enabled our team to look at several constructs pertaining to infant development across the first year of life, which provides the possibility of future explorations on links between early development and later childhood conditions.

7.1.1.5 Conclusions for Study One

In our sample, infants born to mothers with asthma had some differences in their temperament features compared to normative samples, yet not community infants. This has implications for using the CTS norms in Australian contexts, as the differences with the normative sample may be cultural or temporal. As a result, there is the need for implementing contemporary Australian-developed norms across all ages. The findings also suggest that our infants born to mothers with asthma are not at an increased risk for temperament difficulties, those that are linked to poorer developmental outcomes in later childhood. Maternal asthma severity and asthma control during pregnancy did not appear to significantly influence infant temperament. However, the study was under-powered, in some analyses, to detect significant effects. Despite this, some infants born to mothers with asthma fell outside the average range, in particular the domains of rhythmicity and mood. This promotes the tracking of temperament in this group, as these temperament differences have been found to be linked to later difficulties in cognition, mother-child interactions and attention. Overall, emerging trends in the data support the future exploration of the relationships between maternal asthma and infant behavioural development with a well-powered sample.

7.1.2 Study Two: The relationship between temperament features and autism symptoms in infants born to mothers with asthma

7.1.2.1 Summary of Findings from Study Two

The primary aim of this study was to investigate whether temperament features, assessed at 6 weeks, 6 months and 12 months of age, were associated with autism symptoms at 12 months of age, in infants born to mothers with and without asthma. It was hypothesised that activity, approach and adaptability at 6 months would be negatively correlated with autism symptoms at 12 months of age. Additionally, it was hypothesised that mood at 12 months would be positively correlated, and adaptability and distractibility at 12 months would be negatively correlated, with autism symptoms at 12 months of age. All other relationships between temperament features at 6 weeks, 6 months and 12 months, and autism symptoms at 12 months were exploratory in nature. The secondary aim was to explore whether temperament features, assessed at 6 weeks, 6 months and 12 months of age, were associated with social communication and sensory regulatory symptoms at 12 months of age, in infants born to mothers with and without asthma.

Within our sample of infants born to mothers with asthma, there were positive associations between rhythmicity, adaptability and mood, and autism symptoms, at all three time points. This means that the hypotheses that activity and approach at 6 months, and adaptability at 6 and 12 months would be negatively correlated with autism symptoms were not supported. However, the hypothesis that mood at 12 months would be positively correlated with autism symptoms was supported. These associations were also observed within the social communication domain, and the sensory regulation domain apart from rhythmicity at 6 weeks. This indicates that the more arrhythmic, slower to adapt to change and fussier infants were reported to be at 6 weeks, 6 months and 12 months, the more symptoms consistent with autism they had at 12 months. Additionally, there were positive associations between distractibility at 6 weeks and 6 months, and a negative association at 12 months, and autism symptoms. This supports the hypothesis that distractibility at 12 months would be negatively correlated with autism symptoms. These associations were also observed within the social communication domain, and the sensory regulation domain, apart from the 12-month timepoint. Higher scores on distractibility indicate less distractibility on the 6 weeks and 6 months measures, and more distractibility on the 12 months measure. Thus, the associations indicate that the less distractible infants were at 6 weeks, 6 months and 12 months, the greater their autism symptoms at 12 months. At 6 weeks and 12 months, there was a positive association between persistence and autism symptoms, indicating that the less persistent in completing challenging tasks infants were, the greater their autism symptoms. These relationships were also observed within the social communication domain. Additionally, there was a positive association between approach, at 6 and 12 months, and autism symptoms at 12 months. These relationships were also observed within the sensory regulatory domain. This shows that the more withdrawn infants were at 6 and 12 months, the greater their autism symptoms at 12 months. Further, activity at 6 weeks and intensity at 12 months were positively associated with sensory regulatory symptoms, yet not total autism risk. This indicates that the more motor activity infants had at 6 weeks and the more intense emotive responses infants had at 12 months, the more sensory regulation symptoms present at 12 months. None of the temperament domains assessed at 6 weeks were predictors of total autism symptoms. Adaptability assessed at 6 months, and distractibility assessed at 6 and 12 months, were predictors of total autism symptoms.

In comparison, there were fewer associations between temperament features and autism symptoms for infants recruited from the general community. Distractibility, measured at 6 months, was positively associated with autism symptoms at 12 months, indicating that the harder infants were to soothe, the greater their autism symptoms. Additionally, at 12 months, rhythmicity and mood were positively associated with autism symptoms at 12 months. The associations show that the more arrhythmic and fussy infants were, the greater their autism symptoms. This supports the hypothesis that mood at 12 months would be positively correlated with autism symptoms. No other hypotheses were supported. Rhythmicity was negatively associated at 6 weeks and positively associated at 12 months with social communication symptoms at 12 months. Distractibility at 6 months and mood at 12 months were positively associated with sensory regulatory symptoms at 12 months. Distractibility assessed at 6 months was a predictor of total autism risk at 12 months for the community group, alongside mood assessed at 12 months.

7.1.2.2 Discussion of Findings from Study Two

Study Two found that many temperament features were associated with more autism symptoms in infants born to months with asthma. In this section, I will firstly discuss the observed associations between temperament with autism symptoms relevant to extant infant-sib studies and the diagnostic criteria for ASD. I will then discuss the relationships between temperament and autism symptoms of infants born to mothers with asthma, comparing to community infants, describing how temperament may be a better predictor of autism symptoms in at-risk cohorts. After this I will address the limitations in measuring infant behaviour pertaining to (a) biases in parental report and (b) construct validity.

7.1.2.2.1 The Relationship Between Temperament and Autism Symptoms in Infants Born to Mothers with Asthma: Links to Infant-Sib Studies and Diagnostic Criteria

It was found that autism symptoms were related to fussier mood at 12 months of age in infants born to mothers with asthma. This is inconsistent with most of the studies exploring the relationship between mood, or domains pertaining to specific emotions, and children with and without ASD (see systematic review, section 2.3.4) where findings suggest no differences in anger, frustration, sadness, fear or mood (Adamek et al., 2011; Bailey et al., 2000; Brock et al., 2012; Chuang et al., 2012; Hirschler-Guttenberg et al., 2015; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016). While I found an association between mood and autism symptoms in infants born to mothers with asthma, other studies have found no differences in children with ASD. This suggests that temperament features related to mood and emotion may not be salient features of ASD in later childhood. This may be due the temperament domains being sensitive enough to measure emotions in at-risk infants, yet not children with diagnosed with ASD.

Lower levels of distractibility at 12 months of age was associated with autism symptoms in infants born to mothers with asthma. Distractibility in infancy is initially related to soothability and later becomes a salient part of attention (Behavioral-Developmental Initiatives, 2007; Medoff-Cooper et al., 1993; Nakagawa & Sukigara, 2019). The concept non-distractibility can be described as a poorer ability to switch or disengage attention, rather than the ability to focus well (Buetti & Lleras, 2016). Studies using eye-tracking technology have found that children with ASD have less ability to disengage their attention, compared to typically developing peers (e.g., Mo, Liang, Bardikoff, & Sabbagh, 2019; Sabatos-DeVito, Schipul, Bulluck, Belger, & Baranek, 2016). The finding that less distractibility is associated with more autism symptoms is therefore in line with previous findings. Previous research suggests that infant behaviours such as poorer visual tracking, more difficulty with disengaging visual attention and more visual fixation are signs of poorer attentional abilities in later childhood that are subsequently associated with ASD (Bryson et al., 2007; Landry & Bryson, 2004; Möricke et al., 2019; Zwaigenbaum et al., 2005). More specifically, 12-month infant-sibs later diagnosed with ASD (at 24 months) have a longer duration of visual orientation towards objects than typically developing controls and infant-sibs without ASD

(Zwaigenbaum et al., 2005). By screening for the behaviours linked to poorer attentional disengagement (i.e., low distractibility) in infancy, infants at higher risk for ASD may be identified earlier.

The associations between autism symptoms and approach and adaptability were in the opposite direction to what was originally hypothesised, based on infant-sib studies previously discussed in section 2.3.3. Infant-sibs later diagnosed with ASD have been reported to be less withdrawn and more adaptive to change than typically developing peers (Del Rosario et al., 2014). In the current study, however, it was found that more withdrawal from new situations, objects and people was related to greater autism symptoms. Further, the slower an infant was to adapt to change in routine, the more autism symptoms they had. The discrepancies in findings between our sample and that of the infant-sib study can be explained by several reasons. Firstly, the differences in findings may be cultural, as our cohort was of Australian-born infants whereas the sample in the infant-sib study were American-born (Del Rosario et al., 2014). Research demonstrates that child temperament varies from culture to culture (e.g., Krassner et al., 2017), posited to result from cultural values and customs surrounding child-rearing practices (Gherasim, Brumariu, & Alim, 2017; Jaramillo, Rendón, Muñoz, Weis, & Trommsdorff, 2017). Secondly, it is not known whether our infants will go on to develop ASD, whereas infants were later diagnosed with ASD in the infant-sib studies (Del Rosario et al., 2014). It may be that our findings differed from the infant-sib study due confirmed diagnoses of ASD in their sample. Thirdly, it is possible that temperament features present differently in at-risk infants, depending on the type of risk status (i.e., maternal asthma during pregnancy vs familial risk). The observed direction of these relationships, however, are in line with DSM-5 criteria for ASD. Specifically, children with ASD have poorer social communication and interaction skills, and many have a strong preference for sameness and a lack of change (American Psychiatric Association, 2013). It is possible that social withdrawal may stem from a poorer ability to socially communicate and interact. Additionally, it is not surprising that autism symptoms would be higher in infants who were slower to adapt to change in routine, if children with ASD have a preference for routines.

I originally hypothesised that greater autism symptoms would be associated with lower levels of activity at 6 months, however, no relationship between activity and autism symptoms was observed. As reported in section 2.3.4.2, some studies found the activity level of children with ASD to be higher than children without ASD (Chuang et al., 2012; Ostfeld-Etzion et al., 2016), however, others have found no differences (Konstantareas & Stewart, 2006; Macari et al., 2017). Upon revising the studies in section 2.3.4.2, the differences between the studies may be due to differing proportions of mothers and father reporting on temperament, considering that parents report on their child's behaviour differently (e.g., Davé, Nazareth, Senior, & Sherr, 2008; Sollie, Larsson, & Mørch, 2013). Additionally, the two studies that found differences in activity were based in non-western countries (i.e., China, Israel), whereas the studies that found no differences were based in western countries (i.e., Canada, United States). Collectivist versus individual societies hold different beliefs surrounding parenting and child behaviour (Aytac, Pike, & Bond, 2019; Song et al., 2017). Thus, discrepancies in results may also be cultural.

Several significant associations between temperament features at 6 weeks and autism symptoms were identified. Specifically, rhythmicity, adaptability and mood were continuously correlated with autism risk, from 6 weeks of age. However, there were no temperament features assessed at 6 weeks that were significant predictors of autism risk, despite a significant model. This indicates that the temperament variables in the model together explain a significant amount of variance, rather than uniquely predicting autism symptoms. These findings are not able to be directly compared to extant literature, as no published studies have examined the relationship between temperament and ASD prior to 6 months of age (see systematic review in Chapter Two).

Most of the literature pertaining to parents' perceptions of their children with ASD in early infancy suggest that parents do notice early signs of ASD before they are diagnosed, but typically only from 6 months of age (Barbaro & Dissanayake, 2009; Young, Brewer, & Pattison, 2003). For example, parents have reported that, before 2 years of age, their children with ASD displayed a lack of, or atypical, social attention and communication behaviours such as eye-contact, pointing gestures, responding to name, seeking contact with parents, and interest in other children (Barbaro & Dissanayake, 2009). It is not developmentally appropriate for infants younger than 6 months of age to display these social attention and communication behaviours (First Words Project, 2018). Thus, this would explain why parents have not reported differences in their child's behaviour prior to 6 months of age. Parents can observe differences in these behaviours as their child grows older because they are able to observe them in other (typically developing) children.

Section 2.3.4, however, presented studies that have shown that children with ASD (mean age 2-6 years) are arrhythmic, less distractible, slower to adapt to change and less able to pursue challenging tasks (Adamek et al., 2011; Bailey et al., 2000; Brock et al., 2012; Chuang et al., 2012; Konstantareas & Stewart, 2006; Macari et al., 2017; Ostfeld-Etzion et al., 2016), which were similarly found with our asthma cohort at 6 weeks in study two. This suggests that temperament patterns may be related to behavioural symptoms consistent with ASD as early as 6 weeks of age. However, it is not known whether temperament features are associated with a diagnosis of ASD in our asthma cohort. Of note, the threshold domain was not associated with autism risk scores, at any of the time points. Most interesting, the threshold domain was not associated with the sensory regulatory domain, both of which include items pertaining to sensory behaviours. This is surprising considering that sensory symptoms have been well-established in the literature as prevalent in ASD (e.g., Lane et al., 2014; Niedźwiecka et al., 2019; Simpson et al., 2019). However, it may be that such sensory features present in individuals with ASD in later childhood and beyond have not yet emerged in early infancy.

7.1.2.2.2 The Differences in Relationships between Infants Born to Mothers with Asthma and Community Infants

In our sample, more temperament domains were associated with autism symptoms in infants born to mothers with asthma, compared to community infants. For infants born to mothers with asthma, there were six temperament domains that were associated with autism symptoms across the three timepoints. However, only three temperament domains were related to autism symptoms in community infants. Distractibility at 6 months, and rhythmicity and mood at 12 months were the only temperament domains that were associated with autism symptoms in both samples. However, activity, intensity and threshold were temperament domains that were not associated with autism symptoms at any timepoint in either sample.

These findings suggest that temperament may be a salient predictor of autism risk in at-risk cohorts, such as infants born to mothers with asthma, yet not the general population. There were more temperament domains associated with autism symptoms in infant born to mothers with asthma, compared to community infants. Further, there were more associations between temperament features and autism symptom across the three timepoints for infant born to mothers with asthma than community infants. This has implications for the early identification of autism risk in infancy. ASD cannot be genetically screened or identified through biological testing, thus the diagnosis of ASD relies on identifying behavioural features (American Psychiatric Association, 2013). Parents are typically the main informants on a child's behaviour. Providing psychoeducation to parents on their child's temperament can help them understand how their child reacts to their environment (Carey, 1985). By being more attune to their child's behaviour, parents can not only modify their parenting style to accommodate their child's needs but may also identify developmental concerns earlier (Iverson & Gartstein, 2018). The number of significant associations within the community group may be the result of a smaller sample size. Bayesian analyses, reported in section 5.3.3, indicated that there was inconclusive evidence for many of the correlational analyses within the community group. This suggests that there was not a large enough sample needed to detect an effect. Therefore, larger, well-powered samples are required to confirm whether there are differences in how temperament relates to autism symptoms in infants born to mothers with asthma and infants from the general population.

7.1.2.2.3 The Limitations in Measuring Infant Behaviour

Many CTS domains were associated with the total, social communication and sensory regulatory risk scores on the First Year Inventory (FYI). While the association between temperament features and autism has been established in the literature (see systematic review in Chapter Two), there are limitations that need to be considered when interpreting the relationships that I found, particularly related to maternal biases and construct validity. Parent -reported measures of child development are cost-effective and time-efficient to administer. They are most useful because detailed information can be gathered, due to the parent's in-depth knowledge about their child's behaviours. However, it has been well-documented that parent-report measures are prone to respondents' biases, which may lead to over- or underestimating a child's development (e.g., Ringoot et al., 2015; Stokes, Pogge, Wecksell, & Zaccario, 2011). In our studies, both the CTS and FYI questionnaires were completed by the mothers, compared to other caregivers. The scores on the CTS and FYI may reflect the mothers' biased ideations of their infants' behaviour, due to their own personalities and experiences, and not necessarily reflect the true temperament and autism risk of the infant. It is therefore not surprising that the CTS domains and FYI total risk score were significantly correlated, in particular the mood domain. Future studies may want to additionally measure parental psychological functioning (e.g., stress, depression etc) and parent-child attachment to determine the impact of such factors on child characteristics assessed via parent report.

The FYI is a quick and efficient screening tool for ASD symptoms, with 31% of infants screened as at-risk receiving an eventual diagnosis of ASD (Turner-Brown et al., 2013). However, including a screening tool for autism risk that is based on researcher observation, such as the Autism Detection in Early Childhood (ADEC; Young & Nah, 2016) assessment, would help reduce the influence of parental bias. The ADEC is an interactive measure that involves a set of activities requiring child participation, so that trained administers can observe their behaviours (Young & Nah, 2016). These activities aim to target developmentally appropriate behaviours that also indicate risk of ASD when a child responds to them inappropriately (e.g., response to name call, use of gestures, pretend play). Parents are usually present during the assessment, yet they are instructed not to prompt their child. As this assessment does not involve parents reporting on their child's behaviour, it provides a more objective measure of ASD risk. The ADEC has a predictive diagnostic value of 0.22, which indicates that 22% of infants screened as at-risk will receive an eventual diagnosis of ASD. This proportion is lower than the FYI, which has a predictive diagnostic value of 0.31. Further, the FYI does not require child participation, which reduces the chance of collecting inaccurate information due to infant fatigue or fussiness. Considering that infants within our studies completed two to three hours of assessments in our laboratory, it was not deemed possible to include a researcher-observed assessment of ASD risk, as they commonly became fatigued. In-person diagnostic evaluations, used in conjunction with parent-report measures, would be better suited in studies where a stand-alone visit is feasible, so that the infant is more attentive and willing to engage with the researcher.

Associations between temperament features and ASD have been reported in the literature (see systematic review in chapter two), which makes it likely that the CTS and FYI domains would be correlated. However, an alternative explanation for the many relationships between the CTS domains and the FYI scores is construct validity. Construct validity is the degree to which a measure actually tests the theoretical construct it claims to assess (Cronbach & Meehl, 1955). The CTS is a measure of temperament and the FYI is a measure of autism symptoms, thus they are both assessing behavioural features. Subsequently, it is expected that there would be correlations between the domains of the two questionnaires, especially if there is risk of ASD in our cohorts. The developers of the CTS (Carey & McDevitt, 1978a; Fullard et al., 1984; Medoff-Cooper et al., 1993) and FYI (Reznick et al., 2007; Turner-Brown et al., 2013) did not report on the measures' construct validity in the original studies. However, the observed relationships may highlight an overlap in the behaviours assessed though the items on the CTS and FYI. Looking at the FYI, it has two constructs within the sensory-regulatory domain – Regulatory Patterns and Reactivity – which may have accounted for the observed relationships, as reactivity and self-regulation are theoretical aspects of temperament (Rothbart, 1981). Despite this, Section 5.3.3 previously reported the same number of significant correlations between the CTS domains and sensory-regulatory domain as the social-communication domain.

Overall, the CTS is one of the most widely used measure of infant temperament. Additionally, the FYI is currently the only parent-report screening tool for ASD risk in infancy (i.e., 12 months of age). Further examination into the construct validity of measures when exploring the relationship between behavioural constructs is therefore warranted. Using a large sample of children with ASD would be most beneficial in determining the degree of overlap between the CTS and the FYI, and whether the behaviours assessed in the measures are inherent of an ASD diagnosis. The research presented in this thesis was limited in assessing infant behaviour up to one year of age. Thus, a diagnosis of ASD in the infants has not been determined. A longitudinal study using high-risk infant siblings would be better targeted in examining whether a diagnosis of ASD in later childhood can be predicted from temperament in the first year of life.

7.1.2.5 Conclusions for Study Two

Many associations between temperament domains and autism symptoms were observed in infants born to mothers with asthma. In particular, infants who were fussier, less easily distracted, more withdrawn and less adaptable to change in routine had more autism symptoms. These findings support previous research that suggests that children with ASD have difficulties in disengaging their attention, social interaction and changing routine. Fewer associations were observed in community controls, which may be due to a smaller sample size. Differences in temperament may therefore be early indicators of autism risk in infants born to mothers with asthma. However, future research is needed in order to determine whether early temperament features predict later diagnosis of ASD in this cohort.

7.1.3 Study Three: Temperament profiles of infants born to mothers with asthma at-risk for autism spectrum disorder: A case-series

7.1.3.1 Summary of Findings from Study Three

The aim of this study was to profile the temperament, sensory and global development of infants born to mothers with asthma who were at-risk of ASD, using a case series design, in order to identify similarities and differences in these areas. Most infants (4 out of 6) had mainly typical temperament features across the nine domains compared to norms, although all infants did have at least one difficult temperament feature. Infants faced particular challenges within the rhythmicity, mood and persistence domains. This indicates that they had unpredictable biological functions, were fussier, and had greater difficulties completing challenging tasks. None of the infants were identified as difficult on the threshold domain, suggesting no low thresholds for sensory stimuli. In comparison, infants in the total sample had fewer easy temperament features than difficult. However, half of the cases were less distractible than the norm, which is considered by the CTS to be an easier temperament trait. This indicates that the temperament profile labels (i.e., Difficult, Easy etc.) may not necessarily be useful when characterising groups at-risk for ASD. Looking at the diagnostic categories, more infants were categorised within a challenging temperament cluster (i.e., Difficult, Slow-To-Warm-Up) compared to being categorised within an easier temperament cluster (i.e., Easy, Intermediate – Low). Regarding their sensory profiles, infants had overall typical sensory features at 6 weeks and 6 months. However, at 12 months, half of the sample had a distinct sensory profile involving moving away from, detecting and/or missing sensory input at a higher rate than the norm. Of note, half of the infants detected sensory input at a higher rate than the norm. Lastly, there are no overall patterns of cognitive, language or motor development within this group of infants. However, looking at the individual domains, it appears that these infants had developmentally appropriate cognitive skills and underdeveloped language skills, but varied in their motor development.

7.1.3.2 Discussion of Findings from Study Three

Study Three showed that our sample of at-risk infants born to mothers with asthma had differences in temperament domains across the three timepoints, one of two sensory subtypes at 12 months, and underdeveloped language skills at 12 months. However, there was heterogeneity within the sample, particularly across the temperament domains and in gross motor skills. In this section, I will firstly discuss the developmental profiles of the at-risk infants within the current sample, linking to current literature on the developmental features of children diagnosed with ASD. I will then discuss the usefulness of temperament labels, in relation to whether they relate to parent perceptions of child behaviour. After this, I will address the limitations of using the First Year Inventory as a screening tool for risk of ASD.

7.1.3.2.1 The Developmental Profiles of Infants Born to Mothers with Asthma At-Risk on the First Year Inventory: Links to the Development of Children with Autism Spectrum Disorder

This section will discuss the implications of this study pertaining to the developmental profiles of infants born to mothers with asthma at-risk on the First Year Inventory. I will discuss the areas of development in the following order: (1) temperament profiles, (2) sensory processing, and (3) cognitive, language and motor development.

7.1.3.2.1.1 Temperament Profiles

There were no consistent temperament profiles across all nine CTS domains. Between the six cases, infants fell within all three ranges (i.e., Easy, Difficult, Average) across the nine domains. However, many did fall within the average range at multiple points in time. Looking within cases, only one infant (Case 1, timepoint 3) fell within the same range (i.e., Average) for all nine temperament domains. These findings highlight heterogeneity in temperament features, not only between, but also within cases. Similar heterogeneity has been reported in published studies on the temperament of infant-sibs later diagnosed with ASD (Bryson et al., 2007) and children with ASD (Chuang et al., 2012; Hepburn & Stone, 2006). As ASD is a heterogenous disorder (Weitlauf et al., 2014), the variation in domain profiles between and within infants is not surprising.

Some infants did fall within the extremities of some temperament domains. Half of the infants at-risk for ASD were arrhythmic, fussy, less able to pursue challenging tasks and difficult to distract. These patterns of behaviour are similar to what has been previous reported in infant-sibs who later develop ASD (Bryson et al., 2007; Garon et al., 2016; Zwaigenbaum et al., 2005). Half of the cases were reported to be difficult to distract, which is important because it indicates an early tendency to perseveration. Perseveration, the inability to switch tasks or cease a repetitive response, has been documented in individuals with ASD and can manifest as a difficult to disengage from specific objects or the display of stereotyped behaviours (Landry & Al-Taie, 2016; Miller, Ragozzino, Cook, Sweeney, & Mosconi, 2015; Poljac, Hoofs, Princen, & Poljac, 2017). Interestingly, none of the infants were identified as difficult on the threshold domain, suggesting no issues with sensory hyperreactivity. However, sensory hyper-reactivity (in conjunction with hypo-reactivity) is part of the diagnostic criteria and has been observed in children with ASD, particularly related to auditory, smell/taste and tactile stimuli (Dickie, Baranek, Schultz, Watson, & McComish, 2009; Kirby, Boyd, Williams, Faldowski, & Baranek, 2017; McCormick, Hepburn, Young, & Rogers, 2016). It is possible that the threshold domain of the CTS is not sensitive enough to showcase sensory hyper-reactivity in our sample.

Looking at the diagnostic categories, there was no single category that encompassed all at-risk infants, potentially due to the heterogeneity in temperament that was observed at the domain level. This finding suggests that the diagnostic categories do not effectively describe an infant's temperament, because they do not highlight which aspects of the environment are poorly suited to an infant's needs. The diagnostic categories are calculated with five of the nine CTS domains, which means that four domains are not represented in the categories (for more details, see section 3.3.2.1). Further, due to the method of calculating diagnostic categories, an infant may have temperament features that are not in line with the diagnostic category they are classified within. For example, an infant may fall within the difficult range for four of the five domains but fall within the easy range on a single domain. This would mean that they would be classified into the difficult diagnostic category, which does not highlight that they fell below the mean in one of the domains. Thus, the diagnostic categories should not be used when information of a specific child's temperament features (e.g., activity level, mood) is required, such as when looking at individual differences to tailor interventions. By exploring the domain profiles, rather than group differences or diagnostic categories, researchers would be able to identify the aspects of the environment that do not suit a child's needs. Therefore, I recommend that future research exploring temperament and ASD utilise the domain profiles, as these uncover which aspects of the environment should be modified to better support a child's needs.

7.1.3.2.1.2 Sensory Processing

The sensory features in this sample of at-risk infants were comparable to the normative sample during the first half of life. However, at 12 months of age, there were two distinct sensory profiles present in the sample; one that was comparable to the norm, and another that involves avoiding, detecting and missing sensory input at a higher rate that the norm. This finding is significant because it supports a pattern of hyper-reactivity, which has been discussed in the literature as apparent in children with ASD (e.g., Lane et al., 2014; Niedźwiecka et al., 2019; Simpson et al., 2019). Further, this finding supports previous research which suggests that there are two sensory subtypes - sensory adaptive and sensory reactive - present in infants at-risk for ASD (Philpott-Robinson, Lane, & Harpster, 2016). Alongside temperament, sensory processing differed between and within infants, which again is not unexpected and in line with the heterogeneity of ASD.

Many children with ASD have sensory processing difficulties, however these difficulties may present as hyper-reactivity or hypo-reactivity to sensory input (American Psychiatric Association, 2013; Tomchek & Dunn, 2007). The sensory profile 2 (SP2) findings are inconsistent with the CTS domain of threshold, as no infants fell within the difficult range on the threshold domain, suggesting no issues with sensory hyper-reactivity. This finding is supported by Chuang et al. (2012), who found that less than 10% of children with ASD were described as being hyper-reactive on the threshold domain of the CTS. It may be that the items within the sensory profile 2 involve different sensory behaviours than the items within the threshold domain of the CTS. Upon closer inspection of the threshold domain, it appears that items pertain to oral and tactile sensory stimuli, whereas the SP2 encompasses a broader range of sensory processing areas. It is possible that infants in our sample have sensory symptoms in areas other than oral and tactile sensory stimuli. Children may have sensory processing difficulties in one domain yet not another (e.g., sound vs touch; Dunn, 2014), which may also explain why infants were described as hyper-reactive on the SP2 and not the CTS. Previous research has identified sensory sub-types in children with ASD, which suggests that children with ASD can experience the same sensory stimuli differently (for review, see DeBoth & Reynolds, 2017). Thus, the findings of study three, alongside previous literature, suggest that sensory features of children with ASD may be useful to delineate in order to tailor interventions to a child's specific needs, in turn increasing the likelihood of positive outcomes.

7.1.3.2.1.3 Cognitive, Language and Motor Development

Infants within this study had similar developmentally appropriate cognitive skills, yet motor skills varied between infants with some falling within the borderline range and others within the average range. However, these infants collectively had less developed language skills, although this was not observed until 12 months of age. The Bayley-III is not designed as a screening tool for risk of ASD per se, but can be useful to better characterise a child's strengths and weaknesses (Bayley, 2006). However, health care providers may find it useful to administer an ASD screening tool with infants who perform below average on the language domains, as poorer social communication and interaction is a key criterion in receiving a diagnosis of ASD (American Psychiatric Association, 2013). Unfortunately, developmental assessments, such as the Bayley-III and Griffiths Scales of Child Development (Green et al., 2016), are not routinely administered to all infants born in Australia. Rather, infants who are born with poorer perinatal outcomes, such as prematurity and low birthweight, are eligible. Less-developed language skills have been observed in children diagnosed with ASD (for review, see Eigsti, de Marchena, Schuh, & Kelley, 2011). Therefore, the ability to screen infants who have underdeveloped language skills may lead to the identification of those who are at-risk for ASD.

7.1.3.2.2 The Usefulness of Research Labels Versus Parent Perceptions of Temperament in an ASD Context

The method of categorising infant temperament into easy versus difficult ranges was described in section 3.2.1.1. To reiterate, the process involves identifying how many standard deviations below or above the normative mean an infant's score is on each CTS domain. Thus, the terms "easy", "average" and "difficult" refer to an infant who falls more than one standard deviation below the mean, within one standard deviation of the mean, and more than one standard deviation above the mean, respectively. In this sense, the terms do not necessarily represent to a parent's perception of their child, but rather a descriptor for where the infant's domain score falls on a spectrum. Considering this, a specific category label is unlikely to be synonymous for behaviours associated with autism risk. For example, in this study, most infants fell within the difficult range for rhythmicity, yet the easy range for distractibility.

The notion that one single temperament category (i.e., easy, average, difficult) does not encompass all temperament features associated with autism risk echoes the findings of Hepburn and Stone (2006). In their study, Hepburn and Stone found much heterogeneity in their sample. Over half of the children with ASD fell within the average range for distractibility, approach, mood and activity. However, at least one third of the sample fell within the within the "easy" range for distractibility, and the "difficult" range for mood, persistence and adaptability. The findings suggest that some children with ASD were very difficult to distract, negative in mood, less persistence when completing challenging tasks and slower to adapt to change. My findings, in addition to those of Hepburn and Stone (2006), support using temperament categories in a different manner, such as by deriving temperament groupings based on the sample one is studying.

Researchers in the temperament field have utilised cluster analyses to obtain groupings of temperament styles in their samples. Cluster analysis involves statistically dividing data of a particular measure, in order to identify groups that are more similar than others (StatSoft, 2013). Studies using this analysis have found differing temperament groups in typically developing infants, using labels that best reflect the most salient temperament features of each category (Janson & Mathiesen, 2008; Prokasky et al., 2017; Sanson et al., 2009). For example, a temperament cluster characterised by high activity, low shyness, high approach to novelty and low irritability has been labelled as bold (Prokasky et al., 2017), nonreactive/outgoing (Sanson et al., 2009) and confident (Janson & Mathiesen, 2008). In simple terms, a child within this cluster could be described as active, excitable, friendly and fearless.

Identifying temperament clusters could help with communicating complex information of a child’s behaviour to parents and teachers in a simple manner. Parents and teachers, in turn, are then able to tailor their interactions with a child, in order to support best outcomes. Unfortunately, I did not have a sample of at-risk infants large enough to conduct such analyses. Conducting such analyses in a larger sample of at-risk infants may allow for the identification of temperament profiles specific to at-risk infants and enable the exploration of how temperament differs from low risk peers. Overall, the temperament findings of this study show that both “difficult” and “easy” temperament features may indicate risk for ASD. This, in turn, highlights the need to accurately interpret what each temperament profile means, in order to identify environmental factors that are do not accommodate the child’s needs. Thus, I recommend that temperament domains are carefully examined when profiling temperament.

7.1.3.2.3 The Limitations of Using the First Year Inventory as a Screening Tool for Autism Spectrum Disorder

The FYI is a parent-report screening tool for an eventual diagnosis of ASD, which is administered at an infant' first birthday (for detailed description, see section 3.2.1.2; Reznick et al., 2007; Turner-Brown et al., 2013). The validation study showed that of the children who met the cut-off, 85% had a developmental disorder or concern by three years of age, yet only 31% who met the two-domain criterion received a diagnosis of ASD (Turner-Brown et al., 2013). This suggests that approximately half of the cases in this study will have some form of developmental difficulty, yet only one case will receive a diagnosis of ASD. Thus, while this study has profiled the temperament, sensory, cognitive, language and motor development of infants at-risk on the FYI, it is not known whether these profiles are predictive of ASD in this cohort.

The FYI appears to be a promising, easy-to-use screening tool overall for developmental disorders, with 85% of at-risk infants having developmental concerns by three years of age. However, it is not known which infants in our cohort developed ASD or other developmental concerns. Therefore, further work with this cohort would benefit from a 2 to 3-year follow-up, in order to conduct an ASD assessment. This would allow us to explore whether the FYI is an appropriate screening tool for infants born to mother with asthma, and whether early behavioural features are associated with a later diagnosis of ASD, or indeed other developmental disorders, in this cohort.

7.1.3.3 Conclusions for Study Three

There are no clear overall temperament profiles for infants born to mothers with asthma at-risk for ASD. Although, half of the infants presented with differences in temperament features across the timepoints. Specifically, infants were less predictable in their biological functions, fussier, less determined to complete challenging tasks, and more difficult to distract than normative peers. Sensory features of the at-risk infants were overall typical in the first six months of life. However, two subtypes - sensory adaptive and sensory reactive - appeared by 12 months. Cognitive skills were developmentally appropriate within at-risk infants, yet language skills were underdeveloped, and motor skills varied.

These findings suggest that differences in temperament, reactive sensory patterns and underdeveloped language skills in the first year of life are developmental features of infants born to mothers with asthma at-risk of ASD. These developmental features have been observed in children diagnosed with ASD. Identifying these developmental features in infancy may help in tailoring early intervention, as they provide information on how an infant engages with their environment. Future research needs to be conducted, however, in order to determine whether the at-risk infants within the sample develop ASD.

7.1.4 Overall Synthesis of Findings

This thesis firstly reviewed extant literature and found that children with ASD differ in their temperament features, compared to typically developing peers. Parents of children diagnosed with ASD report that their children displayed more negative affect, less extraversion, and less effortful control. It appears that infants later diagnosed with ASD initially have easier temperament features that become more challenging closer to time of diagnosis. However, the studies that reported on the temperament of children with ASD pre-diagnosis only examined the temperament on infant siblings of children diagnosed with ASD. Future research needs to examine temperament features in other infant cohorts at-risk for ASD.

One such cohort is infants born to mothers with asthma. Through original research, this thesis found that infants born to mothers with asthma differ in their temperament compared to normative samples, yet not community infants. This emphasises a need for appropriate norms to use within Australian contents. No evidence was found to suggest that infants born to mothers with asthma as a cohort, regardless of maternal asthma severity and asthma control, are at an increased risk for temperament difficulties. Some infants born to mothers with asthma did displayed differences in temperament, particularly those who were found to be associated with more autism symptoms. This suggests that differences in temperament may be indicators of higher autism risk, or other developmental disorders, in infants born to mothers with asthma. Across the sample of infants born to mother with asthma who screened at-risk for ASD, temperament features outside the average range, two subtypes and underdeveloped language skills were observed.

Overall, findings suggest that tracking temperament would be a useful adjunct to the developmental monitoring of infants born to mothers with asthma. Temperament differences have been linked to poorer developmental outcomes in later childhood, including those associated with a diagnosis of ASD. Identifying these developmental features in infancy may help detect infants at an increased risk of ASD. Future research is needed, however, in order to determine whether these developmental features predict later diagnosis of ASD in this cohort. Therefore, this thesis supports the further exploration of the relationships between maternal asthma and infant behavioural development within a well-powered sample.

7.2 Limitations

This thesis should be considered in light of some methodological qualities. This section will discuss (a) potential covariates and (b) sample characteristics and ascertainment bias.

7.2.1 Potential Covariates

There are several factors that may link maternal asthma to the differences in temperament that were not accounted for in this thesis. Two perinatal outcomes that are salient indicators of developmental outcomes in later life are gestational age and birth weight (Jarjour, 2015; Mathewson et al., 2017; Raju, Buist, Blaisdell, Moxey-Mims, & Saigal, 2017;

Upadhyay et al., 2019). As discussed in section 1.2.1, infants born to mothers with asthma are at an increased risk of being born prematurity and/or with a low birth weight, compared to infants born to mothers without asthma. However, it is not known whether there was a higher proportion of premature and/or low birthweight infants in our asthma cohort compared to our community sample. Preterm birth is a known risk factor the development of ASD (Agrawal, Rao, Bulsara, & Patole, 2018), and there is literature to suggest that the temperament of premature infants differs from full-term peers (Caravale et al., 2017; Litt et al., 2019; Pérez-Pereira, Fernández, Resches, & Gómez-Taibo, 2016). As the infants born to mothers with asthma were participating in an ongoing RCT at the time this thesis was written (see section 3.1.1 for details), I was not able to conduct analyses using gestational age and birthweight to explore whether these factors influenced the findings. However, considering that there were no differences in temperament between infants in the asthma cohort and infants in the community cohort, this suggests that any influence of gestational age and birthweight was limited.

Maternal substance use during pregnancy may also be a potential covariate for the research presented in this thesis. There is a body of literature showing that tobacco smoking and alcohol consumption during pregnancy has harmful effects of the developing fetus, such as restricting fetal growth (Bandoli et al., 2016; Ekblad, Korkeila, & Lehtonen, 2015; Polańska, Jurewicz, & Hanke, 2015). This, in turn, may alter brain structure, which subsequently could shape an infant’s temperament. Maternal substance use during pregnancy could be an explanation for why a large proportion of infants, in both groups, were reported to be more arrhythmic and more negative in mood compared to the norms.

Maternal mental health may also have influenced the findings. Mothers who have depression report their infant’s temperament as more challenging, such as fussier and more difficult to soothe (Nomura et al., 2019; Zhang et al., 2018). Section 4.2.3.1 reported associations between some temperament domains with maternal depression symptoms. Any observed differences in temperament may have be due to maternal biases when reporting on temperament. However, due to the pre-existing small sample size, analyses that allowed for covariation could not be conducted. Additionally, maternal biases may have influenced autism risk in infants, as autism risk was measured using the FYI, a parent-report questionnaire. As observed with temperament, autism risk was associated with maternal depression symptoms in our sample (for further details, see section 5.3.1). Mothers may have over- or underestimated their child's behaviours, which could have led to an inaccurate level of autism risk.

Lastly, it is not guaranteed that the mothers within the community sample did not have asthma. In a sociodemographic questionnaire, mothers were asked the following question: "Do you suffer from any chronic illnesses or chronic mental health conditions?". However, there was no specific question that asked if they had a diagnosis of asthma. Some mothers did report a diagnosis of asthma and were excluded from this thesis; however, some mothers may have not disclosed their diagnosis. In the general Australian population, approximately 12.3% of women have asthma (Australian Bureau of Statistics, 2018). Using this figure as a guideline, it would be expected that 11 (out of 86) mothers in the community sample would have asthma. Considering that four mothers who self-reported asthma had been excluded from this thesis prior to analyses, it is unlikely that the remaining 7 mothers would have influenced the findings. Nevertheless, including a closed response question pertaining to asthma status at the time of enrolment could remove this covariate as a concern in future studies. Overall, the exploratory design employed in this thesis, coupled with low variance in the sample, did not allow me to undertake more sophisticated analyses to explore the mediating/moderating impact of the aforementioned factors. I therefore recommend that future research includes these factors in the study design when exploring the link between maternal asthma and infant behavioural development.

7.2.2 Sample Characteristics and Recruitment Bias

This section will discuss the recruitment bias pertaining to the sociodemographic, asthma and physical health characteristics of the participant samples within in this thesis. The mothers with asthma had participated in a set of consecutive research studies to be included within the studies presented in this thesis. Mothers with asthma initially participated in an extensive RCT of a novel asthma management strategy during pregnancy (Murphy et al., 2016). Half of the mothers with asthma were randomised to an intervention that involved monthly assessments of their asthma with an experienced respiratory nurse, as well as treatment changes every two months according to their airway inflammation and symptoms. The mothers with asthma randomised to the control group also received additional care, in the form of an asthma assessment and the provision of self-management education at their baseline visit. In order to participate in the BLT-ID study, mothers had first consented to their infant having lung function testing during quiet sleep at 6 weeks of age, a process that can take several hours. Only after this was attempted were they able to continue into the BLT-ID study that provided the data for this thesis. For mothers to bring their infants to these lengthy appointments, infants would have been healthy enough to not be in critical care (e.g., Neonatal Intensive Care Unit). Infants who born without complications (e.g., gestational age ≥36 weeks, birth weight ≥2500g, no congenital malformations etc.) tend to have better developmental outcomes (e.g., meeting developmental milestones; Levine et al., 2015; Zwicker & Harris, 2008). Therefore, it is likely that our samples were biased towards high-functioning mothers and typically developing infants.

The notion that our sample of mothers with asthma may have been biased is further supported by analyses (presented in section 3.1.1.1), indicating that mothers with asthma who were not invited to participate in the BLT-ID (i.e., those that did not attend any of their BLT infant follow-up appointments) were less likely to have only one child and more likely to be current smokers than those who were invited. This may be due to several potential reasons. Regarding the differences in number of children, mother who did not attend any of their BLT appointments may have done so due to increased stress that comes with parenting multiple children. Mothers parenting more than one child report greater risk factors (e.g., stressful life events and low social support) for parenting difficulties, compared to mothers parenting only one child (Hickey et al., 2019). Alternatively, a simpler reason may be that these mothers were not able to find care for their older children (i.e., those not participating in the BLT) and may have found it difficult to bring them to the BLT appointments. Regarding the differences in smoking status, mothers who were current smokers may not have attended any BLT appointments due to having more severe and uncontrolled asthma. People with asthma who are current smokers are more likely to have more severe and uncontrolled asthma, compared to those who do not smoke (Grzeskowiak et al., 2016; Murphy, Clifton, & Gibson, 2010; Sheehan & Phipatanakul, 2015). Asthmatics who have more severe and uncontrolled asthma experience greater asthma symptoms (Althuis, Sexton, & Prybylski, 1999; Shaw et al., 2015). These asthma symptoms may have limited the ability of mothers who were current smokers to attend BLT appointments.

It is also possible that the mothers who were current smokers had poorer mental health. Whilst the prevalence of smoking is around 12% in the general Australian population (Australian Institute of Health and Welfare, 2016), approximately half of people with a mental health condition are current smokers (Bartlem et al., 2015). People with a mental health condition (e.g., anxiety, depression) face challenges that may hinder their ability to work, participate in leisure and socialise (Bjørngaard, Bjerkeset, Vaag, & Ose, 2015; Clarke & Fox, 2017; Pieris & Craik, 2004). As a result, mothers who were current smokers may have had a mental health problem that decreased their likelihood of attending the BLT appointments. However, a simpler explanation could be that mothers who smoked did not attend their BLT appointments due the *Smoke-Free Environment Act 2000* (New South Wales Legislation, 2018) applicable to the hospital campus where the research studies were conducted. As each testing session could take up to three hours, it is not surprising that mothers who were current smokers were less likely to attend their BLT appointment. Overall, regardless of the reasons for not attending BLT appointments, the differences between mothers with asthma who did and did not attend their BLT appointments suggest that our asthma sample may not be representative of the broader asthma population.

Within our comparison group of mother-infant dyads from the local community, researchers did not approach mothers to participate. Rather, these mothers had to be actively motivated to contact our researchers, via the methods described on section 3.1.2.1. As a result, it is possible that mothers in the community group might have the ability to cope well as a parent and have less concerns regarding their infant's development. This is further supported by the analyses reported in sections 4.2.3.1 and 5.3.1, which demonstrated that participants from the general community were more homogenous than our sample of mothers with asthma. Mothers from the general community were older, less likely to have three or more children, and more likely to be born overseas, have a household income in the highest bracket and a university degree, compared to mothers with asthma. Further, infants their infants were younger during participation at the 12-month time point. Therefore, participants recruited from the local community may not be representative of the general population, which may explain the differences in temperament between the two groups.

In summary, the asthma sample may have been biased towards high-functioning mothers, as they participated in several consecutive studies. Mother with asthma who were invited to the infant development follow-up study (BLT-ID) were also more likely to have only one child and to be current smokers, compared to those who did not attend the RCT follow-up appointments, and were not invited. Additionally, mothers from the general community differed in several sociodemographic characteristics, compared to mothers with asthma, which suggests that they are from less diverse backgrounds. Therefore, our samples may not be representative of their respective populations and any findings presented in this thesis must be interpreted with caution.

7.3 Directions for Future Research

The aim of this thesis was to characterise the temperament of infants born to mothers with asthma and explore whether temperament features are associated with risk of ASD within the cohort. This research has provided evidence that there are no significant differences in temperament between infants born to mothers with and without asthma, nor as a function of asthma severity and control. However, the sample may not have been large enough to detect an effect. Further, many temperament features are associated with autism risk in this cohort and may be early indictors of autism risk from as early as 6 months of age. Lastly, there are no single temperament, sensory or developmental profiles in infants born to mothers with asthma who were at-risk for autism, which may reflect the heterogeneity of the disorder.

7.3.1 Potential Extensions of this Thesis

Future research could extend upon this thesis by firstly conducting a follow-up study to clinically evaluate a subset of participants at 3-5 years of age, using ASD diagnostic tools such as the ADI-R and the ADOS-2. By obtaining the diagnostic status of participants in the samples, retrospective analyses pertaining to maternal asthma as a risk factor for ASD could be conducted. The predictive validity of the FYI in our sample could be assessed. This would help evaluate the usefulness of the FYI as a screening tool for ASD, in our sample of Australian infants born to mothers with asthma. Subsequently, we could investigate whether the infants born to mothers with asthma in our sample are at an increased risk of ASD, compared to our low-risk sample. This would be an important contribution to the existing research on maternal asthma as a risk factor for ASD, as evidence is currently mixed (for details, see section 1.2.2). Further, a follow-up study would strengthen the research in this thesis, as it would allow for analyses of whether temperament in the first year of life is related to a later ASD diagnosis in infants born to mothers with asthma, rather than purely ASD risk.

Secondly, it may be useful to investigate whether temperament features of infants born to mothers with asthma change over time. As discussed in section 1.1.2, infant temperament is an important predictor of later childhood developmental outcomes. Understanding how temperament changes over time can inform us about early differences in developmental trajectories, that may indicate the emergence of ASD or other neurodevelopmental disorders. While it would have been interesting to examine changes in temperament across the first year of life in this thesis, not enough mothers completed the temperament measure across all three sessions.

Infants born to mothers with asthma are more likely to develop symptoms of persistent wheeze than infants born to mothers without asthma (Martinez et al., 1995; Rusconi et al., 1999). There is some evidence to suggest that infants who experience wheeze in the first year of life are less active than non-wheezy infants, and that arrythmia predicts later development of asthma in wheezy infants (Priel, Henik, Dekel, & Tal, 1990). However, infant wheeze was not explored within this thesis. Further research could expand upon this thesis by examining the relationship between infant wheeze and infant temperament, which may be useful in the further exploration of activity level and arrhythmia.

Lastly, as mentioned in section 3.1.1, mothers with asthma were recruited subsequent to participation in an RCT of a novel asthma management strategy during pregnancy (Murphy et al., 2016). In a recent systematic review, Whalen et al. (2019) highlights the importance of optimal asthma management during pregnancy, and the potential effect this has on child development. However, as the RCT is currently ongoing, it was not possible to analyse the data as a function of RCT treat group at the time of conducting the research within this thesis. Another future extension, in the future, would be to retrospectively analyse the data to see if there are differences in infant behaviour between the intervention and treatment-as-usual groups.

7.3.2 Exploring the Mechanisms Underlying the Relationship Between Asthma and Child Behaviour

Future research should also investigate the potential mechanisms underlying the relationship between maternal asthma and infant behavioural outcomes. Three potential mechanisms include maternal asthma exacerbations during pregnancy, childhood asthma, and gut microbiome. As previously posited in section 1.2.2., maternal immune activation has been linked to poorer neurodevelopmental outcomes, including ASD. Asthma exacerbations may also contribute to differences in infant behaviour and neurodevelopment. Previous research has established a link between maternal asthma exacerbations during pregnancy and poorer perinatal outcomes in offspring (e.g., low birth weight; Murphy et al., 2006), which subsequently influence later child development (Howe, Sheu, Hsu, Wang, & Wang, 2016). However, it is not known whether asthma exacerbations are directly linked to poorer neurodevelopmental outcomes and atypical behaviour. While we found few, albeit non-significant, differences in temperament as a function of asthma control, we were not able to determine whether temperament or autism risk were associated with asthma exacerbations. A path for future research is to examine the effects of asthma exacerbations during pregnancy on infant neurodevelopment, in order to identify whether presence of exacerbations is a risk-factor for poorer developmental outcomes.

Infants born to mothers with asthma are at an increased risk of developing asthma themselves (Kashanian et al., 2017). As mentioned in section 1.2.2, there is some literature to indicate that children with asthma have behavioural differences surrounding difficulties with adapting to change in routine, more sensitive to sensory stimuli, anxiety and aggression (Kim et al., 1997; Kim et al., 1980; McQuaid et al., 2001). Rather than maternal asthma shaping infant behaviour, the differences observed could be due to the emergence of asthma symptoms within the infants. Thus, a future direction could be to follow infants born to mothers with asthma into early childhood and analyse whether there are differences in infant behaviour as a function of the presence of asthma.

Gut microbiome has also been previously posited as a mediating factor between childhood asthma (Fujimura & Lynch, 2015) and child behaviour (Cenit, Nuevo, Codoñer-Franch, Dinan, & Sanz, 2017). Emerging research has observed relationships between infant temperament and gut microbiome (Aatsinki et al., 2019; Christian et al., 2015). Specifically, greater positive affect and extraversion is associated with greater gut microbiome diversity (Christian et al., 2015), with greater negative affect and fear associated with less diverse gut microbiome. Further, infants with a gut microbiota composition of *Bifidobacterium/Enterobacteriaceae* attend to a single object longer than infants with other compositions. Additionally, maternal asthma during pregnancy has been linked to reduced *Lactobacillus* in the gut of male offspring, a microbe that influences infant growth (Koleva et al., 2017). Changes in infant gut microbiome secondary to maternal immune status may result in differences in infant temperament and could be a potential explanation for the findings, particularly related to the rhythmicity, mood and approach domains, in this sample. Overall, while this thesis provides ‘peace of mind’ to mothers with asthma that their infants are not at an increased risk for temperament difficulties, it also supports the need to further investigate the role of maternal asthma, particularly regarding asthma control, in infant behavioural outcomes using high-powered studies.

7.5 Conclusion

Asthma complicates up to 12% of pregnancies, leading to negative health consequences for both mother and child. Further, emerging research suggests that infants born to mothers with asthma are at an increased risk for the development of ASD. ASD is not typically diagnosed until the preschool years, as there are no genetic tests available for the disorder. Thus, there is a large research interested into the early behavioural features associated with the disorder in infancy. One important construct to the study of individual differences in behaviour is temperament. Understanding early temperament features associated with ASD can help inform early intervention, which is vital for achieving a child's best outcomes.

In this cohort of infants born to mothers with asthma during pregnancy, I observed temperament profiles that, for the most part, were comparable to infants from the general community at 6 weeks, 6 months and 12 months of age. However, associations between temperament domains and autism risk were observed in both infants born to mothers with asthma and community infants, with less distractibility predicting higher autism risk from 6 months of age across both groups. While half presented with difficult temperament features, I found no specific temperament profiles for infants born to mothers with asthma at-risk for ASD. Lastly, at-risk infants overall had developmentally appropriate cognitive skills, yet emerging language skills. However, infants were differentiated by their sensory features and motor skills.

Overall, I found no evidence that infants born to mothers with asthma are at-risk for temperament difficulties, compared to infants from the general community. However, difficult temperament features, alongside sensory processing and language difficulties, may be an early indicator of higher autism risk for infants born to mothers with asthma. While there were no clear temperament profiles for infants at-risk for ASD, the lack of a single profile may potentially help explain the heterogeneity within ASD. Thus, this thesis supports future examinations of behavioural development in infants born to mothers with asthma during pregnancy using a well-powered sample, as well as the analysis of longer-term developmental outcomes to understand links between early behavioural features and later childhood functioning.

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Appendices

Appendix A: Table 1.1

Table 1.1 Definitions of the temperament domains within selected conceptual frameworks.

Temperament Framework	Domain	Description
Child Psychiatric Framework of Thomas, Chess & Colleagues[a]	Activity	The motor component present in a given child's functioning, and the diurnal proportion of active and inactive periods.
	Rhythmicity	The predictability and/or the unpredictability…[of behaviour related to]…the sleep-wake cycle, hunger, feeding pattern, and elimination schedule.
	Approach	The nature of the response to a new stimulus, be it a new food, new toy, or new person.
	Adaptability	Responses to new or altered situations. One is not concerned with the nature of the initial responses, but with the frequency with which they were successfully modified in desired directions.
	Intensity	The energy level of response, irrespective of its quality or direction.
	Mood	The amount of pleasant, joyful, and friendly behavior, as contrasted with unpleasant, crying, and unfriendly behavior.
	Distractibility	The effectiveness of extraneous environmental stimuli in interfering with, or in altering the direction of, the ongoing behavior.
	Persistence	The continuation of an activity in the face of obstacles to the maintenance of the activity direction.
	Threshold	The intensity level of stimulation that is necessary to evoke a discernible response, irrespective of the specific form that the response might take or the sensory modality affected. The behaviors utilised are those concerning reactions to sensory stimuli, environmental objects, and social contacts.
Emotionality, Activity and	Emotionality	Emotionality…is equivalent to distress. The dimension varies from an

Table 1.1 (continued).

Temperament Framework	Domain	Description
Sociability Framework of Buss & Plomin[b]		almost stoic lack of reaction to intense emotional reactions that are out of control. Examples of the high extreme are crying, tantrums, difficulty in being soothed, a low threshold for the aversive stimuli that trigger distress, and intense activation of the sympathetic division of the autonomic nervous system. Emotionality clearly involves emotional arousal and, to a lesser extent, behavioral arousal.
	Activity	Activity…[has]…two major components of which are tempo and vigor. Individuals vary from lethargy to an almost hypomanic push of energetic behavior. Activity involves behavioral arousal, specifically, elevated amplitude and rate of responses. Such behavioral arousal is different from the physiological and experiential arousal that occurs in emotionality.
	Sociability	Sociability…is the preference for being with others rather than being alone. No normal person is expected to be a hermit, but there are wide variations in the need to be with others. Sociable individuals seek to share activities, to receive attention from others, and to be involved in the back-and-forth responsivity that characterizes social interaction.
Psychobiological Framework of Rothbart & Colleagues[c]	Activity Level	Gross motor activity, including rate and extent of locomotion.
	Anger	Negative affectivity related to interruption of ongoing tasks or goal blocking.
	Attentional Shifting	Capacity to maintain attentional focus on task-related channels.
	Cuddliness	Expression of enjoyment and molding of the body to being held by a caregiver.
	Discomfort	Negative affectivity related to sensory qualities of stimulation, including intensity; rate; or complexities of light, movement, sound, and texture.
	Distress to Limitations	Fussing, crying or showing distress while (a) in a confining place or

Table 1.1 (continued).

Temperament Framework	Domain	Description
		position; (b) in caretaking activities; (c) unable to perform a desired action.
	Duration of Orienting	Capacity to maintain attentional focus on task-related channels.
	Fear	Negative affectivity, including unease, worry, or nervousness, which is related to anticipated pain or distress and/or potentially threatening situations.
	High Intensity Pleasure	Pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty, and incongruity.
	Impulsivity	Speed of response initiation.
	Inhibitory Control	Capacity to plan and to suppress inappropriate approach responses under instructions or in novel or uncertain situations.
	Low Intensity Pleasure	Pleasure or enjoyment related to situations involving low stimulus intensity, rate, complexity, novelty, and incongruity.
	Perceptual Sensitivity	Detection of slight, low-intensity stimuli from the external environment.
	Positive Anticipation	Amount of excitement and anticipation for expected pleasurable activities.
	Sadness	Negative affectivity and lowered mood and energy related to exposure to suffering, disappointment, and object loss.
	Shyness	Slow or inhibited (versus rapid) speed of approach and discomfort (versus comfort) in social situations.
	Smiling & Laughter	Positive affect in response to changes in stimulus intensity, rate, complexity, and incongruity.
	Soothability	Rate of recovery from peak distress, excitement, or general arousal.
Emotion Systems Framework of Goldsmith & Colleagues[d]	Activity Level	Limb, trunk, or locomotor movement during a variety of daily situations, including free play, confinement, or quiet activities.
	Pleasure	Smiling, laughter, and other hedonically positive vocalizations or playful activity in a variety of nonthreatening or familiar situations.
	Social Fearfulness	Inhibition, distress, withdrawal (vs. approach), or signs of shyness in novel or uncertainty-provoking situations of a social nature.

Table 1.1 (continued).

Temperament Framework	Domain	Description
	Anger Proneness	Crying, protesting, hitting, pouting, or other signs of anger in situations involving conflict with another child or the caregiver.
	Interest/Persistence	Duration of task engagement in ongoing solitary play or other activities.

[a] Descriptions are quoted from Thomas, Chess, Birch, Hertzig, and Korn (1963), p. 40-42
[b] Descriptions are quoted from Goldsmith et al. (1987), p. 512
[c] Descriptions are quoted from Gartstein and Rothbart (2003), p. 72; Rothbart, Ahadi, Hershey, and Fisher (2001), p. 1406
[d] Descriptions are quoted from Goldsmith (1996), p. 223

Appendix B: Table 2.1

Table 2.1 Database search terms.

	AND:	AND:	AND:
autism	diagnos*	TI (temperament OR temperamental)	child*
OR	OR	OR	OR
ASD	high-risk	AB (temperament OR temperamental)	infan*
OR	OR	OR	OR
autism spectrum disorder	genetic risk	SU (temperament OR temperamental)	toddler*
OR	OR		OR
autistic disorder	familial risk		baby
OR	OR		OR
PDD-NOS	prematur*		babies
OR	OR		OR
Pervasive Developmental Disorder-Not Otherwise Specified	sibling*		newborn
	OR		
OR	disorder		
Asperger Syndrome	OR		
OR	(autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 symptom*		
Asperger’s			
OR			
Childhood Disintegrative Disorder			
	OR		
	(autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 sign*		
	OR		
	(autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 marker*		
	OR		
	(autis* OR Pervasive Developmental Disorder-		

Table 2.1 (continued).

	AND:	AND:	AND:
	Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 trait* OR (autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 indicator* OR (autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 precursor* OR (autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5 risk		

Note: *Indicates that the search included the term and any other possible terms stemming from it (e.g., diagnos* captured diagnosis, diagnostic, diagnose, diagnosed). '(autis* OR Pervasive Developmental Disorder-Not Otherwise Specified OR Asperger* OR Childhood Disintegrative Disorder) adj5…' is a search phrase that requires the word autis* (or Pervasive Developmental Disorder-Not Otherwise Specified or Asperger* or Childhood Disintegrative Disorder) to be within 5 words of the following search term in a section of text (e.g., 'autis* adj5 marker*' could detect 'temperament may act as a behavioural marker for autism').

Appendix C: Table 2.2

Table 2.2 The characteristics of the included studies.

Article	Country	Design	Sample Size	Chronological Age (Months) M ± SD (range)	% Male
1. Kasari and Sigman (1997)	USA	Case-Control	ASD = 28 TD = 28	ASD = 42.39 ± 11.61 TD = 20.29 ± 8.26	ASD = 92.9 TD = 85.7
2. Bagnato and Neisworth (1999)	USA	Cross-sectional	ASD = 36	15-45	Not reported
3. Bailey et al. (2000)	USA	Cross-sectional	ASD = 31	64.1 (36 – 95)	100
4. Zwaigenbaum et al. (2005)	Canada	Prospective Cohort	T1: Autism-Sibs = 1 LR = 12 T2: Autism-Sibs = 4 LR = 19 T3: Not reported	Age is for all infant-sibs T1: Autism-Sibs = 6.44 ± .50 LR = 6.15 ± .43 T2: Autism-Sibs = 12.50 ± .75 LR = 12.81 ± .77 T3: Not reported	Not reported
5. Hepburn and Stone (2006)	USA	Cross-sectional	ASD = 110	57.3 ± 15.4 (23 - 94)	86
6. Konstantareas and Stewart (2006)	Canada	Case-Control	ASD = 19 TD = 23	ASD = 6.16 yrs (3 - 10) TD = 6.37 yrs	ASD = 63 TD = Not reported
7. Bryson et al. (2007)	Canada	Case Series	ASD-Sibs = 9	Not reported	66.7
8. Garon et al. (2009)	Canada	Prospective Cohort	ASD-Sibs = 34 Non-ASD Sibs = 104 LR = 73	Not reported	ASD-Sibs = 64.7 Non-ASD Sibs = 49.0 LR = 47.9
9. Adamek et al. (2011)	USA	Cross-Sectional	ASD = 111	4.2 ± 1.5 yrs (2 - 8)	82
10. Brock et al. (2012)	USA	Cross-sectional	ASD = 54	56.17 ± 13.67 (36 - 84)	83.3

Table 2.2 (continued).

Article	Country	Design	Sample Size	Chronological Age (Months) M ± SD (range)	% Male
11. Chuang et al. (2012)	Taiwan	Cross-sectional	ASD = 67 TD = 44	ASD = 64.21 ± 9.01 TD = 63.59 ± 10.14	ASD = 85.1 TD = 50.0
12. Clifford et al. (2013)	UK	Retrospective Cohort	ASD-Sibs = 17 LR = 48	Age not reported separately T1 = 7.2 ± 1.1 T2 = 13.7 ± 1.5 T3 = 23.7 ± 1.0	ASD-Sibs = 64.7 LR = 41.7
13. Del Rosario et al. (2014)	USA	Prospective Cohort	T1: ASD-Sibs = 11 TD-Sibs = 7 T2: ASD-Sibs = 16 TD-Sibs = 13 T3: ASD-Sibs = 10 TD-Sibs = 15 T4: ASD-Sibs = 10 TD-Sibs = 18 T5: ASD-Sibs = 10 TD-Sibs = 27	T1: ASD-Sibs = 6.5 ± .9 TD-Sibs = 6.0 ± .4 T2: ASD-Sibs = 12.4 ± .6 TD-Sibs = 12.6 ± .6 T3: ASD-Sibs = 18.4 ± .4 TD-Sibs = 18.6 ± .6 T4: ASD-Sibs = 24.4 ± .6 TD-Sibs = 24.6 ± .6 T5: ASD-Sibs = 37.8 ± 4.0 TD-Sibs = 36.6 ± .5	ASD-Sibs = 85.7 TD-Sibs = 51.5
14. Hirschler-Guttenberg et al. (2015)	Israel	Case-Control	ASD = 39 TD = 40	ASD = 63.38 ± 12.35 TD = 53.56 ± 13.83	ASD = 87.2 TD = 85.0
15. Garon et al. (2016)	Canada	Prospective Cohort	ASD-Sibs = 95 Non-ASD Sibs = 278	Not reported	ASD-Sibs = 69.5 Non-ASD Sibs = 50.4

Table 2.2 (continued).

Article	Country	Design	Sample Size	Chronological Age (Months) M ± SD (range)	% Male
16. Ostfeld-Etzion et al. (2016)	Israel	Case-Control	ASD = 25 TD = 32	ASD = 63.38 ± 12.35 (36 - 82) TD = 53.56 ± 13.83 (29 - 78)	ASD = 80.0 TD = 81.3
17. Macari et al. (2017)	USA	Case-Control	ASD = 165 TD = 92	ASD = 26.46 ± 5.77 TD = 24.88 ± 5.57	ASD = 81.8 TD = 76.1

Abbreviations: ASD = Autism Spectrum Disorder; ASD-sibs = infant-sibs later diagnosed with ASD; infant-sibs = infant siblings of children with ASD; LR = low-risk controls; Non-ASD sibs = infant-sibs not diagnosed with ASD but may have other developmental concerns; PDD-NOS = Pervasive Developmental Disorder-Not Otherwise Specified; T = time point; TD = typically developing; UK = United Kingdom; USA = United States of America.

Note: Age is reported in months, unless otherwise specified.

Appendix D: Table 2.3

Table 2.3 Eligibility criteria and Autism Spectrum Disorder diagnosis of the included studies.

Article	Eligibility	ASD Diagnosis
1. Kasari and Sigman (1997)	• ASD group met criteria for at least 2/3 of the diagnostic tools	• Clinician diagnosis using DSM-IV by a psychiatrist or psychologist • CARS score ≥32 • ABC score ≥70
2. Bagnato and Neisworth (1999)	• Not reported	• Clinician diagnosis by early intervention provider or psychologist
3. Bailey et al. (2000)	• No suspected or confirmed diagnosis of ASD with FXS • Enrolment in the state-wide autism program	• Clinician diagnosis using ○ CARS and DSM-IV ○ Direct observation of the child ○ Parental report ○ Medical records ○ School observations
4. Zwaigenbaum et al. (2005)	• Infant-sibs were recruited by 6 months • LR group had ○ no 1st/2nd degree relatives with ASD ○ a term gestation ○ a birth weight >2500g	• ADOS classification of autism
5. Hepburn and Stone (2006)	• Documented diagnosis of AD, PDD-NOS or Asperger's • Chronological age between 36-96 months • Absence of severe motor, sensory or medical conditions	• Clinician diagnosis
6. Konstantareas and Stewart (2006)	• Not reported	• Clinician diagnosis using CARS, ADOS or ADI-R

Table 2.3 (continued).

Article	Eligibility	ASD Diagnosis

7. Bryson et al. (2007)	• No
	  ○ neurological conditions
	  ○ genetic conditions
	  ○ severe sensory and motor impairments
		• Clinician diagnosis using ADI-R, ADOS and DSM-IV-TR

8. Garon et al. (2009)	• Term gestation • LR group had no 1st/2nd degree relative with ASD • Probands had no genetic, chromosomal or neurological disorders	• Clinician diagnosis using ADI-R, ADOS and DSM-IV-TR
9. Adamek et al. (2011)	• Diagnosis of ASD	School assessment of ASD by Department of Health–approved evaluator or Clinician diagnosis using ADOS

10. Brock et al. (2012)	• No known
	  ○ Genetic conditions
	  ○ Seizure disorders
	  ○ Epilepsy
	  ○ Uncorrected hearing or visual impairments
	  ○ Significant dysmorphic features or physical impairments
		• Clinician diagnosis
		• Met criteria on ADI-R and/or ADOS
		• Met criteria on DSM-IV

11. Chuang et al. (2012)	• Not reported	• Clinician diagnosis using DSM IV-TR • Catastrophic Illness Card with a diagnosis of autism
12. Clifford et al. (2013)	• Infant-sibs had older sibling with author-confirmed diagnosis of ASD • TD group had ○ A term gestation	Researcher diagnosis using International Statistical Classification of Diseases and Related Health Problems (10th revision)

Table 2.3 (continued).

Article	Eligibility	ASD Diagnosis
	○ A normal birth weight ○ No 1st degree relative with ASD	
13. Del Rosario et al. (2014)	• Infant-sibs of children with PDD-NOS and Asperger's disorder • Infants without ASD but with developmental concerns were excluded	• Clinician diagnosis using ADOS, MSEL, VABS, Social Communication Questionnaire and DSM-V
14. Hirschler-Guttenberg et al. (2015)	• Excluded from ASD group if failed to meet ASD criteria • Excluded from TD group if neuro-psychiatric diagnoses present	• Clinician diagnosis using DSM-V • Confirmed by authors using ADOS
15. Garon et al. (2016)	• Term gestation • No chromosomal or neurological disorders	• Clinical judgement using DSM-V and ADI-R
16. Ostfeld-Etzion et al. (2016)	• ASD group met ASD criteria • TD group had no neuro-psychiatric diagnoses	• Clinician diagnosis using DSM-V • Confirmed by authors using ADOS
17. Macari et al. (2017)	• Not reported	• Clinical best estimate diagnosis using ○ parent interview ○ developmental and medical history ○ MSEL ○ VABS ○ ADOS ○ DSM-IV

Abbreviations: ADI-R = Autism Diagnostic Interview-Revised; ADOS = Autism Diagnostic Observation Schedule; ASD = Autism Spectrum Disorder; ASD-sibs = infant-sibs later diagnosed with ASD; CARS = Childhood Autism Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; infant-sibs = infant siblings of children with ASD; LR = low-risk controls; MSEL = Mullen Scales of Early Learning; Non-

ASD sibs = infant-sibs not diagnosed with ASD but may have other developmental concerns; PDD-NOS = Pervasive Developmental Disorder-Not Otherwise Specified; TD = typically developing; VABS = Vineland Adaptive Behavior Scales.

Appendix E: Table 2.4

Table 2.4 The temperament measures, assessors and outcomes of the included studies.

Article	Temperament Measure(s)	Temperament Assessor	Comparison Group	Temperament Outcome(s)
1. Kasari and Sigman (1997)	Behavioral Style Questionnaire	Parents; % mothers not specified	Typically developing	Higher scores on *difficultness*[a]
2. Bagnato and Neisworth (1999)	Temperament and Atypical Behavior Scale	Not specified	Normative reference	Higher[b] scores on Detached, Hyper-sensitive/active, Underactive, and Dysregulated
3. Bailey et al. (2000)	Behavioral Style Questionnaire	Mothers	Normative reference	Higher scores on Adaptability, Persistence, Approach and Rhythmicity Lower scores on Intensity, Distractibility and Threshold
4. Zwaigenbaum et al. (2005)	Infant Behavior Questionnaire Toddler Behavior Assessment Questionnaire	Parents; % mothers not specified	Typically developing Infant-sibs without ASD	6 mo: Lower score on Activity Level 12 mo: Higher scores on Distress to Limitations and Duration of Orienting 24 mo: Lower scores on Attentional Shifting, Inhibitory Control and Positive Anticipation
5. Hepburn and Stone (2006)	Behavioral Style Questionnaire	Mothers	None; descriptive	Over half of sample were in the average range for Activity, Rhythmicity, Approach, Mood and Distractibility Over half were in the difficult range for Persistence Two thirds were in the difficult range for Adaptability One third was in the difficult range for Mood and Distractibility

Table 2.4 (continued).

Article	Temperament Measure(s)	Temperament Assessor	Comparison Group	Temperament Outcome(s)
6. Konstantareas and Stewart (2006)	Children's Behavior Questionnaire	Parents; % mothers not specified	Typically developing	Higher scores on: Discomfort and Shyness Lower scores on: Attentional Focusing*, Soothability*, Inhibitory Control*, Attentional Shifting*, Perceptual Sensitivity, and Smiling and Laughter
7. Bryson et al. (2007)	Infant Behavior Questionnaire Toddler Behavior Assessment Questionnaire	Not specified	None; descriptive	Temperament outcomes were not clearly described
8. Garon et al. (2009)	Toddler Behavior Assessment Questionnaire-Revised	Parents; % mothers not specified	Typically developing Infant-sibs without ASD	Lower on Behavioural Approach[a] and Emotion Regulation[a]
9. Adamek et al. (2011)	Children's Behavior Questionnaire-Short Form	Parents; 87% mothers	Normative reference	Higher scores on Anger/Frustration, High Intensity Pleasure and Low Intensity Pleasure Lower scores on Discomfort, Inhibitory Control and Attentional Focusing
10. Brock et al. (2012)	Behavioral Style Questionnaire	Parents; % mothers not specified	Normative reference	Lower scores on Intensity, Threshold and Distractibility Higher scores on Activity, Approach, Adaptability, Rhythmicity and Persistence
11. Chuang et al. (2012)	Behavioral Style Questionnaire (Chinese version)	Parents; % mothers not specified	Typically developing	Higher scores on Activity, Approach, Adaptability and Persistence Lower scores on Threshold and Distractibility

Table 2.4 (continued).

Article	Temperament Measure(s)	Temperament Assessor	Comparison Group	Temperament Outcome(s)
12. Clifford et al. (2013)	Infant Behavior Questionnaire-Revised Early Childhood Behavior Questionnaire	Parents; % mothers not specified	Typically developing	7 mo: Lower scores on Approach 14 mo: Lower scores on Smiling and laughter, and Cuddliness 24 mo: Lower scores on Soothability, Low-Intensity Pleasure and Cuddliness 24 mo: Higher scores on Sadness and Shyness
13. Del Rosario et al. (2014)	Revised Infant Temperament Questionnaire Toddler Temperament Scale Behavioral Style Questionnaire	Parents; % mothers not specified	Infant-sibs with typical development	6 mo: Lower scores on Adaptability and Approach 12 mo: Lower scores on Adaptability 24 mo & 36 mo: Higher scores on Adaptability and Approach
14. Hirschler-Guttenberg et al. (2015)	Laboratory Temperament Assessment Battery	Researchers	Typically developing	No differences were found on the two administered tasks, Fear and Anger/Frustration
15. Garon et al. (2016)	Infant Behavior Questionnaire Toddler Behavior Assessment Questionnaire-Revised	Parents; % mothers not specified	Infant-sibs without ASD	12 mo: Lower scores on Positive Affect 24 mo: Lower scores on Positive Affect and Effortful Control
16. Ostfeld-Etzion et al. (2016)	Children’s Behavior Questionnaire	Mothers	Typically developing	Higher scores on Activity Level and Shyness Lower scores on Attention Focusing*, Attention Shifting, Soothability, Inhibitory Control*, Perceptual Sensitivity* and Low-Intensity Pleasure

Table 2.4 (continued).

Article	Article	Article	Article	Article
17. Macari et al. (2017)	Toddler Behavior Assessment Questionnaire - Supplement	Parents; 74.5% mothers for ASD group, % mothers for TD group not specified	Typically developing	Lower scores on Attentional Focusing, Attentional Shifting, Inhibitory Control, Low-Intensity Pleasure, Soothability, Positive Anticipation and Perceptual Sensitivity

Note: Unless otherwise stated, all group differences presented are statistically significant.

*Statistically significant after multiple comparisons analysis

[a]Author-constructed domain

[b]Descriptive difference

Appendix F: Table 2.7

Table 2.7 Definitions of selected temperament domains, by framework.

Temperament Framework	Domain	Description
Carey & Colleagues[a]	Activity	The motor component present in a child's functioning, and the diurnal proportion of active and inactive periods.
	Rhythmicity	The predictability and/or the unpredictability…[of behaviour related to]…the sleep-wake cycle, hunger, feeding pattern, and elimination schedule.
	Approach	The nature of the response to a new stimulus, be it a new food, new toy, or new person.
	Adaptability	Responses to new or altered situations. One is not concerned with the nature of the initial responses, but with the frequency with which they were successfully modified in desired directions.
	Intensity	The energy level of response, irrespective of its quality or direction.
	Mood	The amount of pleasant, joyful, and friendly behavior, as contrasted with unpleasant, crying, and unfriendly behavior.
	Distractibility	The effectiveness of extraneous environmental stimuli in interfering with, or in altering the direction of, the ongoing behavior.

Table 2.7 (continued).

Temperament Framework	Domain	Description
	Persistence	The continuation of an activity in the face of obstacles to the maintenance of the activity direction.
	Threshold	The intensity level of stimulation that is necessary to evoke a discernible response, irrespective of the specific form that the response might take or the sensory modality affected. The behaviors utilised are those concerning reactions to sensory stimuli, environmental objects, and social contacts.
Rothbart & Colleagues[b]	Activity Level	Gross motor activity, including rate and extent of locomotion.
	Anger	Negative affectivity related to interruption of ongoing tasks or goal blocking.
	Attentional Shifting	Capacity to maintain attentional focus on task-related channels.
	Cuddliness	Expression of enjoyment and molding of the body to being held by a caregiver.
	Discomfort	Negative affectivity related to sensory qualities of stimulation, including intensity; rate; or complexities of light, movement, sound, and texture.
	Distress to Limitations/Frustration	Fussing, crying or showing distress while (a) in a confining place or position; (b) in caretaking activities; (c) unable to perform a desired action.

Table 2.7 (continued).

Temperament Framework	Domain	Description
	Duration of Orienting/Attentional Focusing	Capacity to maintain attentional focus on task-related channels.
	Fear	Negative affectivity, including unease, worry, or nervousness, which is related to anticipated pain or distress and/or potentially threatening situations.
	High Intensity Pleasure	Pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty, and incongruity.
	Impulsivity	Speed of response initiation.
	Inhibitory Control	Capacity to plan and to suppress inappropriate approach responses under instructions or in novel or uncertain situations.
	Low Intensity Pleasure	Pleasure or enjoyment related to situations involving low stimulus intensity, rate, complexity, novelty, and incongruity.
	Perceptual Sensitivity	Detection of slight, low-intensity stimuli from the external environment.
	Positive Anticipation/Approach	Amount of excitement and anticipation for expected pleasurable activities.
	Sadness	Negative affectivity and lowered mood and energy related to exposure to suffering, disappointment, and object loss.
	Shyness	Slow or inhibited (versus rapid) speed of approach and

Table 2.7 (continued).

Temperament Framework	Domain	Description
		discomfort (versus comfort) in social situations.
	Smiling & Laughter	Positive affect in response to changes in stimulus intensity, rate, complexity, and incongruity.
	Soothability	Rate of recovery from peak distress, excitement, or general arousal.
Bagnato & Colleagues[c]	Detached	Aloof, self-absorbed, disconnected from daily routines (active avoidance).
	Hyper-sensitive/active	Overreactive, low sensory threshold, highly active, impulsive, inconsolable, negative, and defiant.
	Underreactive	Unresponsive, high sensory threshold, poor awareness, low alertness (passive avoidance suggesting neurophysiological origins).
	Dysregulated	State disorganization and dyscontrol (suggesting a neurophysiological basis).

[a] Descriptions are quoted from Thomas et al. (1963), p. 40-42
[b] Descriptions are quoted from Gartstein and Rothbart (2003), p. 72; Rothbart, Ahadi, Hershey, and Fisher (2001), p. 1406
[c] Descriptions are quoted from Bagnato and Neisworth (1999), p. 102

Appendix G: Analysis for Recruitment Bias, Consent Bias and Missing Data Bias in the Breathing for Life Trial – Infant Development Study

In order to assess recruitment bias, mothers who (a) were invited and not invited and (b) consented versus declined to participate in the BLT-ID were compared on the following: age at birth of infant, number of children, body mass index, smoking status, inhaled corticosteroid use, asthma severity and asthma control. Mothers who were not invited to participate in the BLT-ID (i.e., those who did not attend any BLT appointments) were less likely to have only one child ($p = .012$) and more likely to be current smokers ($p < .001$; Table 3.1). There were no statistically significant differences between mothers who consented to participate in the BLT-ID and mothers who declined to participate on any of the characteristics (Table 3.1). Of mothers who consented to the BLT-ID, the aforementioned characteristics were compared between those who had complete temperament data (included in thesis) and those who had missing temperament data (excluded from thesis), in order to assess for missing data bias. There were no statistically significant differences between mothers who had complete temperament data and mothers who had missing temperament data on any of the characteristics (Table 3.1).

Table 3.1 Comparisons of demographic, asthma and physical health characteristics between mothers who (a) were invited and not invited to participate, (b) consented and declined to participate, and (c) had no missing temperament data (included) and missing temperament data (excluded).

Characteristic	(a) Invitation		(b) Consent		(c) Missing Data		(a)	(b)	(c)
	Invited n = 295	Not Invited n = 140	Consented n = 253	Declined n = 42	No n = 183	Yes n = 70	*p*-value	*p*-value	*p*-value
Maternal Age[a], Mean (SD)	30.18 (5.29)	29.32 (5.76)	30.37 (5.27)	29.03 (5.35)	30.36 (5.11)	30.39 (5.70)	.123	.129	.972
Parity, *n* (%)									
Primipara (1 child)	**153 (52.8)**	**49 (37.4)**	126 (50.8)	27 (64.3)	89 (48.6)	37 (56.9)			
Multipara (2 children)	77 (26.6)	43 (32.8)	70 (28.2)	7 (16.7)	55 (30.1)	15 (23.1)	**.012**	.211	.469
Grand Multipara (≥ 3 children)	60 (20.7)	39 (29.8)	52 (21.0)	8 (19.0)	39 (21.3)	13 (20.0)			
Body Mass Index, *n* (%)									
Mean (SD)	30.98 (8.33)	29.87 (8.08)	30.64 (7.88)	32.98 (10.48)	30.89 (8.09)	30.00 (7.33)	.203	.092	.430
Underweight	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Health Weight	78 (26.7)	36 (27.5)	65 (26.0)	13 (31.0)	47 (26.0)	18 (26.1)	.176	.458	.967
Overweight	86 (29.5)	41 (31.3)	77 (30.8)	9 (21.4)	55 (30.4)	22 (31.9)			
Obese	128 (43.8)	52 (39.7)	108 (43.2)	20 (47.6)	79 (43.6)	29 (42.0)			
Smoking status, *n* (%)									
Never	167 (57.0)	69 (50.4)	144 (57.4)	23 (54.8)	104 (57.1)	40 (58.0)			
Ex-Smoker	98 (33.4)	32 (23.4)	83 (33.1)	15 (35.7)	60 (33.0)	23 (33.3)	**<.001**	.943	.960
Current Smoker	**28 (9.6)**	**36 (26.3)**	24 (9.6)	4 (9.5)	18 (9.9)	6 (8.7)			
ICS Use, *n* (%)									
Yes	127 (43.6)	43 (33.6)	112 (45.0)	15 (35.7)	80 (44.4)	32 (46.4)	.054	.263	.784
No	164 (56.4)	85 (66.4)	137 (55.0)	27 (64.7)	100 (55.6)	37 (53.6)			
Asthma severity, *n* (%)									
Mild	180 (61.9)	85 (66.4)	152 (61.0)	28 (66.7)	109 (60.6)	43 (62.3)			
Moderate	42 (14.4)	18 (14.1)	36 (14.5)	6 (14.3)	26 (14.4)	10 (14.5)	.609	.728	.955
Severe	69 (23.7)	25 (19.5)	61 (24.5)	8 (19.0)	45 (25.0)	16 (23.2)			
Asthma control, *n* (%)									
Well-controlled	53 (18.2)	25 (18.7)	49 (19.6)	4 (9.5)	37 (20.4)	12 (17.4)			
Partly-controlled	134 (45.9)	62 (46.3)	113 (45.2)	21 (50.0)	84 (46.4)	29 (42.0)	.982	.291	.540
Uncontrolled	105 (36.0)	47 (35.1)	88 (35.2)	17 (40.5)	60 (33.1)	28 (40.6)			

[a]at infant birth (years)

Appendix H: Table 3.2

Table 3.2 A brief overview of questionnaires and assessments included in the Breathing for Life Trial – Infant Development and BabyMinds studies.

Participant	Measure	Description	Timepoint		
			6w	6m	12m
Infant					
	Bayley Scales of Infant and Toddler Development	Researcher-administered. Assesses the developmental level of young children. Screens for developmental delay.	✗	✓	✓
	Carey Temperament Scales	Parent-reported. Assesses temperament of infants, toddlers and children.	✓	✓	✓
	Eye Tracking Paradigm	Researcher-administered. A battery of four tasks designed to assess an infant's cognitive control, specifically habituation/dishabituation, smooth pursuit, joint attention and visual expectation.	✗	✓	✓
	First Year Inventory	Parent-reported. Screens for risk of Autism Spectrum Disorder.	✗	✗	✓
	Macarthur Communication Development Inventory – Australian English (OZI)	Parent-reported. Assesses an infant's acquisition of Australian English language through vocabulary.	✗	✗	✓
	Mother-Infant Play Session	Researcher-administered. A 15-minute video and audio recorded play interaction. The first half is free play and the second half is facilitated play, with age-appropriate toys.	✓	✓	✓
	Sensory Profile 2	Parent-reported. Assesses sensory processing in infants, toddlers and children.	✓	✓	✓
	Social-Emotional and Adaptive Behaviour Questionnaire	Parent-reported. Assesses social-emotional development and adaptive behaviour skills.	✗	✓	✓
	Test of Sensory Function in Infants	Researcher-administered. Assesses sensory defensive behaviours in children.	✗	✓	✓

Table 3.2 (continued).

Participant	Measure	Description	Timepoint		
			6w	6m	12m
Mother					
	Achenbach System for Empirically Based Assessment: Adult Self-Report	Self-reported. Assesses adaptive and maladaptive behaviours.	✓	✓	✓
	Adult ADHD Self-Report Scale Symptom Checklist[a]	Self-reported. Screens for symptoms associated with attention-deficit/hyperactivity disorder.	✓*	✗	✗
	Asthma Control Questionnaire[b]	Self-reported. Assesses the level of an individual's asthma symptom control.	✓	✓	✓
	Behavior Rating Inventory of Executive Function – Adult[c]	Self-reported. Assesses an adult's everyday functioning to gain an understanding of their executive function.	✓	✓	✓
	Edinburgh Postnatal Depression Scale	Self-reported. Screens for risk of postpartum depression.	✓*	✗	✗
	Parenting Stress Index – Short Form	Self-reported. Assesses the level of stress an individual is experiencing in relation to parenting.	✓	✓	✓

*Administered at first visit; administered at 6 or 12 months if participants were first enrolled at that point in time.
[a]This measure of only completed by mothers within the BMs study.
[b]This measure of only completed by mothers within the BLT-ID study.
[c]This measure is completed by mothers and fathers within the BLT-ID study.

Appendix I: Table 4.10

Table 4.10 Pearson correlation coefficients between Edinburgh Postnatal Depression Scale and Carey Temperament Scale scores for asthma and community groups at 6 weeks (T1), 6 months (T3) and 12 months (T3) of age.

Timepoint	CTS Domain	EPDS for Asthma Group (n = 141)	EPDS for Community Group (n = 77)
T1			
	Activity	**.212***	**.545***
	Rhythmicity	**.216***	.237
	Approach	.091	.277
	Adaptability	**.296***	.087
	Intensity	**.225***	-.237
	Mood	**.300***	.153
	Persistence	.036	-.125
	Distractibility	**.349***	**.487***
	Threshold	-.025	.080
T2			
	Activity	.092	.081
	Rhythmicity	.167	.044
	Approach	**.293***	.032
	Adaptability	**.435***	.083
	Intensity	.054	.185
	Mood	**.454***	.054
	Persistence	.145	-.044
	Distractibility	**.477***	-.049
	Threshold	.067	.225
T3			
	Activity	.258	.099
	Rhythmicity	.043	**.396***
	Approach	.035	-.235
	Adaptability	**.332***	.074
	Intensity	**.348***	**.356***
	Mood	**.387***	.131
	Persistence	.252	-.163
	Distractibility	.030	-.161
	Threshold	.101	-.021

Abbreviations: CTS = Carey Temperament Scales; EPDS = Edinburgh Postnatal Depression Scale.
Note: Sample size differs from total n depending on timepoint and CTS domain.
*Correlation is significant at the .05 level.

Appendix J: Table 4.12

Table 4.12 Sample sizes for infants born to mothers with and without asthma by Carey Temperament Scales domain at 6 weeks, 6 months and 12 months of age.

Age Group	CTS Domain	Asthma	Community
6 weeks			
	Activity	129	31
	Rhythmicity	141	34
	Approach	142	32
	Adaptability	128	28
	Intensity	140	33
	Mood	139	34
	Persistence	137	32
	Distractibility	137	31
	Threshold	140	34
6 months			
	Activity	82	46
	Rhythmicity	81	46
	Approach	79	46
	Adaptability	81	46
	Intensity	82	46
	Mood	82	46
	Persistence	83	46
	Distractibility	83	45
	Threshold	80	44
12 months			
	Activity	69	40
	Rhythmicity	74	45
	Approach	72	45
	Adaptability	69	42
	Intensity	72	45
	Mood	72	45
	Persistence	72	44
	Distractibility	73	44
	Threshold	71	45

Abbreviations: CTS = Carey Temperament Scales.

Appendix K: Table 5.3

Table 5.3 Summary statistics for Carey Temperament Scales and First Year Inventory scores.

Measure	Domain	Group	N	M	SD	Min	Max
EITQ[a]							
	Activity	Asthma	43	3.70	0.56	2.63	5.38
		Community	8	3.34	0.28	3.13	4.00
	Rhythmicity	Asthma	45	3.25	0.71	1.50	5.30
		Community	9	3.11	0.84	1.70	3.90
	Approach	Asthma	45	2.46	0.53	1.17	3.83
		Community	8	2.58	0.77	1.67	3.83
	Adaptability	Asthma	41	2.34	0.69	1.40	4.11
		Community	8	2.01	0.72	1.33	3.50
	Intensity	Asthma	44	3.93	0.89	2.00	5.67
		Community	9	3.86	0.95	2.60	5.00
	Mood	Asthma	43	2.92	0.86	1.64	5.64
		Community	9	2.93	0.51	1.80	3.45
	Persistence	Asthma	44	2.79	0.88	1.00	4.43
		Community	8	2.96	0.69	1.75	4.00
	Distractibility	Asthma	44	2.32	0.78	1.00	4.29
		Community	7	2.27	0.77	1.43	3.17
	Threshold	Asthma	44	4.41	0.61	2.60	5.40
		Community	9	4.47	0.54	3.70	5.50
RITQ[a]							
	Activity	Asthma	48	4.26	0.46	3.23	5.23
		Community	25	4.32	0.71	2.85	5.69
	Rhythmicity	Asthma	47	2.74	0.78	1.50	4.25
		Community	25	2.95	0.89	2.00	5.50
	Approach	Asthma	47	2.33	0.56	1.18	3.80
		Community	25	2.56	0.79	1.45	4.09
	Adaptability	Asthma	48	2.14	0.56	1.27	4.20
		Community	25	2.04	0.51	1.36	3.00
	Intensity	Asthma	48	3.59	0.65	2.10	4.90
		Community	25	3.49	0.55	2.60	4.80
	Mood	Asthma	48	2.70	0.65	1.30	4.10
		Community	25	2.76	0.60	1.80	4.00
	Persistence	Asthma	48	3.16	0.81	1.00	4.71
		Community	24	3.11	0.68	2.00	4.88
	Distractibility	Asthma	47	2.14	0.63	1.00	3.60
		Community	24	2.10	0.39	1.20	2.80
	Threshold	Asthma	47	3.83	0.54	2.60	5.50
		Community	24	3.94	0.60	2.89	5.40
TTS[a]							
	Activity	Asthma	67	3.90	0.57	2.42	5.10

Table 5.3 (continued).

Measure	Domain	Group	N	M	SD	Min	Max
		Community	40	3.97	0.64	2.67	5.17
	Rhythmicity	Asthma	72	2.62	0.80	1.10	4.91
		Community	45	2.63	0.57	1.55	4.00
	Approach	Asthma	70	2.99	0.83	1.50	5.58
		Community	45	2.89	0.92	1.27	5.08
	Adaptability	Asthma	67	3.50	0.73	1.78	5.00
		Community	42	3.56	0.64	2.22	4.67
	Intensity	Asthma	70	3.80	0.54	2.60	5.00
		Community	45	3.80	0.63	2.11	5.20
	Mood	Asthma	70	3.15	0.63	1.58	4.50
		Community	45	3.10	0.56	1.92	4.38
	Persistence	Asthma	70	3.77	0.65	2.33	5.45
		Community	44	4.13	0.76	2.10	5.91
	Distractibility	Asthma	71	4.41	0.55	3.09	5.64
		Community	44	4.65	0.55	3.18	5.70
	Threshold	Asthma	69	3.58	0.67	1.71	5.13
		Community	45	3.50	0.75	2.00	5.25
FYI							
	Social Communication	Asthma	72	7.85	8.87	0.00	43.75
		Community	45	7.62	7.11	0.00	28.25
	Sensory Regulatory	Asthma	72	8.79	9.07	0.00	43.75
		Community	45	9.28	7.49	0.00	24.75
	Total Risk	Asthma	72	8.32	7.80	0.00	43.75
		Community	45	8.45	5.41	0.00	18.25

Abbreviations: EITQ = Early Infancy Temperament Questionnaire; FYI = First Year Inventory; M = mean; Min = minimum; max = maximum; N = sample size; RITQ = Revised Infant Temperament Questionnaire; SD = standard deviation; TTS = Toddler Temperament Scale.

[a]Age appropriate form from Carey Temperament Scales

Appendix L: Table 5.5

Table 5.5 Bayes factors from the Bayesian Pearson correlation coefficients between First Year Inventory and Carey Temperament Scale scores for infants born to mothers with asthma.

		6 Weeks			6 Months			12 Months		
FYI Domain	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence
Total										
	Activity	0.502	H_0	Inconclusive	0.214	H_0	Moderate	0.158	H_0	Moderate
	Rhythmicity	1.586	H_a	Inconclusive	17.134	H_a	Strong	52.399	H_a	Strong
	Approach	0.368	H_0	Inconclusive	9.725	H_a	Moderate	4.425	H_a	Moderate
	Adaptability	35.009	H_a	Strong	872.302	H_a	Strong	55.972	H_a	Strong
	Intensity	0.220	H_0	Moderate	0.198	H_0	Moderate	0.408	H_0	Inconclusive
	Mood	29.319	H_a	Strong	61.083	H_a	Strong	182.114	H_a	Strong
	Persistence	12.537	H_a	Strong	0.389	H_0	Inconclusive	7.396	H_a	Moderate
	Distractibility	3.970	H_a	Moderate	955.376	H_a	Strong	2.398	H_a	Inconclusive
	Threshold	0.387	H_0	Inconclusive	0.187	H_0	Moderate	0.220	H_0	Moderate
Social Communication										
	Activity	0.205	H_0	Moderate	0.258	H_0	Moderate	0.157	H_0	Moderate
	Rhythmicity	1.363	H_a	Inconclusive	3.111	H_a	Inconclusive	2.057	H_a	Inconclusive
	Approach	0.250	H_0	Moderate	1.026	H_a	Inconclusive	0.528	H_0	Inconclusive
	Adaptability	1.858	H_a	Inconclusive	8.653	H_a	Moderate	4.228	H_a	Moderate
	Intensity	0.216	H_0	Moderate	0.181	H_0	Moderate	0.152	H_0	Moderate
	Mood	1.653	H_a	Inconclusive	4.114	H_a	Moderate	4.610	H_a	Moderate
	Persistence	60.406	H_a	Strong	0.324	H_0	Inconclusive	18.988	H_a	Strong
	Distractibility	1.531	H_a	Inconclusive	101.729	H_a	Strong	1.549	H_a	Inconclusive
	Threshold	0.577	H_0	Inconclusive	0.260	H_0	Moderate	0.460	H_0	Inconclusive
Sensory Regulatory										
	Activity	15.852	H_a	Strong	0.184	H_0	Moderate	0.157	H_0	Moderate
	Rhythmicity	0.689	H_0	Inconclusive	14.006	H_a	Strong	100.273	H_a	Strong

Table 5.5 (continued).

		6 Weeks			6 Months			12 Months		
FYI Domain	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence
	Approach	0.420	H_0	Inconclusive	26.696	H_a	Strong	11.305	H_a	Strong
	Adaptability	62.268	H_a	Strong	4956.861	H_a	Strong	41.913	H_a	Strong
	Intensity	0.207	H_0	Moderate	0.228	H_0	Moderate	1.767	H_a	Inconclusive
	Mood	73.696	H_a	Strong	96.621	H_a	Strong	300.532	H_a	Strong
	Persistence	0.881	H_0	Inconclusive	0.342	H_0	Inconclusive	0.724	H_0	Inconclusive
	Distractibility	2.321	H_a	Inconclusive	166.696	H_a	Strong	0.950	H_0	Inconclusive
	Threshold	0.228	H_0	Moderate	0.199	H_0	Moderate	0.151	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales; FYI = First Year Inventory.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.

Appendix M: Table 5.7

Table 5.7 Bayes factors from the Bayesian Pearson correlation coefficients between First Year Inventory and Carey Temperament Scale scores for community infants.

		6 Weeks			6 Months			12 Months		
FYI Domain	CTS Domain	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence	BF_{10}	Direction of Evidence	Strength of Evidence
Total										
	Activity	0.638	H_0	Inconclusive	0.350	H_0	Inconclusive	0.382	H_0	Inconclusive
	Rhythmicity	0.670	H_0	Inconclusive	0.338	H_0	Inconclusive	2.587	H_a	Inconclusive
	Approach	0.614	H_0	Inconclusive	0.335	H_0	Inconclusive	0.302	H_0	Inconclusive
	Adaptability	0.961	H_0	Inconclusive	0.252	H_0	Moderate	0.665	H_0	Inconclusive
	Intensity	0.597	H_0	Inconclusive	0.337	H_0	Inconclusive	0.190	H_0	Moderate
	Mood	0.760	H_0	Inconclusive	0.395	H_0	Inconclusive	8.694	H_a	Moderate
	Persistence	0.430	H_0	Inconclusive	0.267	H_0	Moderate	0.366	H_0	Inconclusive
	Distractibility	0.491	H_0	Inconclusive	2.686	H_a	Inconclusive	0.275	H_0	Moderate
	Threshold	0.439	H_0	Inconclusive	0.253	H_0	Moderate	0.220	H_0	Moderate
Social Communication										
	Activity	0.488	H_0	Inconclusive	0.278	H_0	Moderate	0.386	H_0	Inconclusive
	Rhythmicity	2.900	H_a	Inconclusive	0.350	H_0	Inconclusive	8.747	H_a	Moderate
	Approach	0.430	H_0	Inconclusive	0.292	H_0	Moderate	0.212	H_0	Moderate
	Adaptability	0.453	H_0	Inconclusive	0.361	H_0	Inconclusive	0.587	H_0	Inconclusive
	Intensity	0.422	H_0	Inconclusive	0.248	H_0	Moderate	0.207	H_0	Moderate
	Mood	0.735	H_0	Inconclusive	0.277	H_0	Moderate	1.092	H_a	Inconclusive
	Persistence	0.499	H_0	Inconclusive	0.328	H_0	Inconclusive	0.300	H_0	Inconclusive
	Distractibility	0.479	H_0	Inconclusive	0.336	H_0	Inconclusive	0.358	H_0	Inconclusive
	Threshold	0.600	H_0	Inconclusive	0.325	H_0	Inconclusive	0.234	H_0	Moderate
Sensory Regulatory										
	Activity	1.226	H_a	Inconclusive	0.837	H_0	Inconclusive	0.231	H_0	Moderate
	Rhythmicity	0.413	H_0	Inconclusive	0.254	H_0	Moderate	0.236	H_0	Moderate

Table 5.7 (continued).

FYI Domain	CTS Domain	6 Weeks BF$_{10}$	6 Weeks Direction of Evidence	6 Weeks Strength of Evidence	6 Months BF$_{10}$	6 Months Direction of Evidence	6 Months Strength of Evidence	12 Months BF$_{10}$	12 Months Direction of Evidence	12 Months Strength of Evidence
	Approach	0.652	H_0	Inconclusive	0.274	H_0	Moderate	0.287	H_0	Moderate
	Adaptability	0.834	H_0	Inconclusive	0.441	H_0	Inconclusive	0.271	H_0	Moderate
	Intensity	0.564	H_0	Inconclusive	0.436	H_0	Inconclusive	0.188	H_0	Moderate
	Mood	0.450	H_0	Inconclusive	0.338	H_0	Inconclusive	1.794	H_a	Inconclusive
	Persistence	0.472	H_0	Inconclusive	0.522	H_0	Inconclusive	0.254	H_0	Moderate
	Distractibility	0.465	H_0	Inconclusive	2.393	H_a	Inconclusive	0.192	H_0	Moderate
	Threshold	0.817	H_0	Inconclusive	0.322	H_0	Inconclusive	0.189	H_0	Moderate

Abbreviations: CTS = Carey Temperament Scales; FYI = First Year Inventory.
Note: H_0 = null hypothesis; H_a = alternative hypothesis.