

Diathesis-stress or differential susceptibility? Comparing the theories when determining the outcomes for children born before 33 weeks' gestation

Jacqueline F. Gould^{a,*}, Carolyn Di Fiore^b, Paul Williamson^b, Rachel M. Roberts^c,
Rosalyn H. Shute^b, Carmel T. Collins^a, Maria Makrides^a

^a South Australian Health and Medical Research Institute (Women & Kids), 72 King William Road, North Adelaide, South Australia 5006, Australia

^b Flinders University, Sturt Road, Bedford Park, South Australia 5042, Australia

^c University of Adelaide, North Terrace, Adelaide, South Australia 5005, Australia

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ABSTRACT

Infants born preterm (less than 37 weeks completed gestation) have a higher risk of suboptimal cognitive and behavioral outcomes when compared with their term-born counterparts. The risk and severity of poor outcome increases as gestational age at birth decreases; however, not all children born preterm will develop deficits, and environmental influences post birth may have a role in shaping developmental outcomes. Whilst early preterm birth is not preventable, it may be possible to intervene after birth via the environment in order to improve outcomes. The diathesis-stress theory hypothesizes that vulnerable individuals will have worse outcomes after a negative environmental exposure, whereas the differential susceptibility theory posits that vulnerable (or plastic) individuals can be both adversely and positively affected by environmental factors. These two theories were compared in 535 children born <33 weeks' gestation. The interaction between the degree of prematurity and the home environment (as measured by the Home Screening Questionnaire) at 18 months on cognition (Intelligence Quotient from the Wechsler Abbreviated Scale of Intelligence) and behavior (Total Difficulties Score from the Strengths and Difficulties Questionnaire) at 7 years was explored. Evidence was not found for either theory, although a supportive/stimulating home environment appeared to contribute to a decrease in the risk or severity of suboptimal scores. Future research is needed to establish stronger evidence in order to inform interventions to improve the home environment of children born preterm.

1. Introduction

More than 10% of live births worldwide are now preterm (Chawanpaiboon et al., 2019), that is, born before 37 weeks' gestation. However, where modern neonatal care is available, survival of those born at 26 weeks gestational age reaches 80%; even those born as early as 22 weeks have a 30% chance of survival (Boardman et al., 2020). Nevertheless, preterm birth, and the neurological insults associated with it, place these children at increased risk for a wide range of developmental difficulties (e.g., Hirvonen et al., 2014; Loe, Lee, Luna, & Feldman, 2011). For example, 50–70% of preterm infants develop behavioral difficulties (Aylward, 2005; Bhutta, Cleves, Casey, Craddock, & Anand, 2002; Pinto-Martin et al., 2004; Taylor, Klein, & Hack, 2000). The risk is greater for those born earlier (Aylward, 2005; Boardman et al., 2020). For example, intelligence quotient (IQ) has been estimated

to decrease by 1.5 points for every week born early under 33 weeks' gestation (Johnson, 2007), which is commonly used as a criterion for considering a birth as very preterm (Zmyj, Witt, Weltkamper, Neumann, & Lücke, 2017), although terminology varies between authors.

Preterm birth is usually not preventable, and research in recent years has shifted its focus from survival to understanding morbidity and impairments that may be relatively subtle, with a view to identifying ways of supporting children born early towards optimal cognitive, social and emotional development (Mathewson et al., 2017). Whereas risk increases with earlier birth, not all children have poor outcomes (Bora, Pritchard, Moor, Austin, & Woodward, 2011; Lind et al., 2010). The quality of the home environment is a prime candidate for attention: there is evidence that children at high biological risk show fewer cognitive deficits in the early years if raised in a home environment supportive of their development compared with high risk children from

* Corresponding author.

E-mail addresses: jacqueline.gould@sahmri.com (J.F. Gould), paul.williamson@flinders.edu.au (P. Williamson), rachel.roberts@adelaide.edu.au (R.M. Roberts), ros.shute@flinders.edu.au (R.H. Shute), carmel.collins@sahmri.com (C.T. Collins), maria.makrides@sahmri.com (M. Makrides).

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a less supportive home (Weisglas-Kuperus, Baerts, Smrkovsky, & Sauer, 1993).

The present study was aimed at examining the role of the home environment for the cognitive and behavioral outcomes at 7 years for children born before 33 weeks' gestational age. Specifically, it compared the explanatory power of two developmental theories concerning vulnerability (*diathesis-stress* and *differential susceptibility*) in relation to those outcomes. Only four previous studies have compared these theories in relation to preterm birth, with mixed results, and the focus has previously been on relatively short-term outcomes (up to three years of age). No study has specifically examined stimulation and developmental support in the home environment in testing the diathesis-stress and differential susceptibility theories, and these have different implications for interventions to support optimal development. The present study adds to the available evidence base for children at greatest risk of poor outcomes, those born before 33 weeks' gestation. By way of background, we first discuss the role of the early home environment in children's development, before turning to discussion about each of the two theories under consideration and the evidence that supports them, particularly in relation to preterm birth.

1.1. The early home environment and child development

The enduring importance of the home environment for child outcomes in the general population has been demonstrated by two large population-based studies (Bradley, Corwyn, Pipes McAdoo, & García Coll, 2001; Weisglas-Kuperus et al., 1993). Stimulation in the home environment during infancy has been linked to child pre-academic knowledge (Merz et al., 2014) and school performance years after the home environment assessment (van Doorninck, Caldwell, Wright, & Frankenburg, 1981). Organization of the home environment, parental involvement and availability of play materials have been shown to be protective for children's development (Coscia et al., 2001). The Home Screening Questionnaire (HSQ) assesses the quality and quantity of daily stimulation as well as support for emotional, cognitive and social development in the home between birth and three years of age, and scores are positively associated with concurrently assessed child intelligence (Richter & Grieve, 1991; Zhou, Baghurst, Gibson, & Makrides, 2007), further suggesting the importance of the quality of the home environment for young children's development.

Considering children of low birthweight (which may overlap with, but is not identical to, preterm birth; Wilcox, 2001), Hoffnung et al. (2013) suggest that the quality of the home environment is of particular importance before 5–6 years of age given the rapidity of developmental change and attainment of milestones, at a time before the child is exposed to other influences such as the school environment. Evidence supports an association between the quality of the home environment for both behavior (McCormick et al., 1996) and cognitive development across the first three and a half years of life (Weisglas-Kuperus et al., 1993) for children of low birthweight. For very preterm children specifically, scores on the HSQ at two years of age have been associated with cognitive, behavioral and social outcomes (Treyvaud et al., 2012). Previous research has also implied that infants born preterm may be more receptive to optimal caregiver responsiveness than full term infants (Landry, Smith, & Swank, 2006; Landry, Smith, Swank, Assel, & Vellet, 2001).

1.2. Diathesis-stress theory

Sameroff and Seifer's (1983) dual-risk theory proposed that if a child has a pre-existing vulnerability (later referred to as a diathesis), they are more prone to develop poor outcomes in the face of later adversity. In the case of preterm birth, it is thought that the diathesis is biological in nature, with brain injury (a common complication of preterm birth) and disruption of in-utero brain growth spurt, creating biological vulnerability that predisposes the child to poorer outcomes in the face of future

stressors, compared with full-term children. The more preterm the child, the poorer the expected outcomes. Conversely, protective factors such as a supportive/stimulating home environment are expected to ameliorate the situation (Goforth, Pham, & Carlson, 2011; Monroe & Simons, 1991). However, the focus of diathesis-stress theory is adversity and maladaptation, with differences in the development of vulnerable individuals and those who are more resilient being evident only under conditions of environmental risk.

A number of studies examining the diathesis-stress model have explored preterm birth, and found some limited support but results are mixed (Jaekel, Pluess, Belsky, & Wolke, 2015; Poehlmann et al., 2011; Wu & Chiang, 2016). Gueron-Sela, Atzaba-Poria, Meiri, and Marks (2015) compared the social and cognitive functioning of preterm (28–33 weeks' gestation) and full-term (>37 weeks' gestation) infants at 12 months of age and found that preterm birth combined with maternal distress at 6 months acted as a risk factor for cognitive outcome (significantly lower cognitive scores in comparison with infants born at term), supporting the diathesis-stress theory for cognitive, but not social, outcomes (paternal distress played no role). Hadfield, O'Brien, and Gerow (2017) too explored the interaction between parental distress (symptoms of stress and depression measures) as well as parental quality of attachment at 9 months of age, and degree of prematurity (full-term: >37 weeks' gestation, late preterm: 34–36 weeks, very preterm: <33 weeks) to influence social-emotional, cognitive and motor skills of children at three years of age. Contrary to Gueron-Sela et al.'s (2015) results, support was not found for the diathesis-stress model when exploring the role of maternal distress or quality of attachment, but was supported in the case of fathers' distress, which significantly moderated the effect of prematurity on cognitive and social-emotional outcomes. Gueron-Sela, Atzaba-Poria, Meiri, and Marks (2016) later showed that when exposed to low levels of co-parental structuring (e.g., ability to jointly structure the play activity) at 6 months of age, the 12-month cognitive scores (in the same preterm infants as their 2015 study) were poorer than the scores of the term-born infants, whereas there was no such difference with high levels of co-parenting, supporting the diathesis-stress theory.

1.3. Differential susceptibility theory

The diathesis-stress theory has been of interest, however a more recent theory for understanding development in the face of adversity is that of differential susceptibility. The theory is built on the suggestion that individuals differ in their neurobiological sensitivity to context, such that some are not only more sensitive to adversity, but also more sensitive to positive environments (Boyce et al., 1995); Boyce & Ellis, 2005; Ellis, Boyce, Belsky, Bakermans-Kranenburg, & Van Ijzendoorn, 2011). According to differential susceptibility theory, sensitivity may be influenced by genetic variations and developmental experiences of nurturing or harshness, may vary over the lifespan, and constitutes adaptation, in an evolutionary sense. Individuals who are more sensitive to both negative and positive environments can be seen as displaying greater plasticity. 'Upregulation' of sensitivity to context was proposed to be promoted by either especially harsh or supportive conditions, whereas 'downregulation' was expected to occur for the majority of children who do not experience these extremes. Such changes are expected to be relatively long-lasting. Evidence consistent with the theory has been found at genetic, epigenetic, neural, neuroendocrine and behavioral levels (Ellis et al., 2011). For example, Davies, Hentges, Coe, Parry, and Sturge-Apple (2021) found that young children's social and psychological outcomes in relation to family climate depend on their temperament: those who respond more readily to environmental stimulation and display behavioral flexibility across contexts are more susceptible to both supportive and adverse family environments.

As indicated previously, there have been four studies with preterm children that have examined whether differential susceptibility offers a better explanation for outcomes than diathesis-stress. As we observed

above, in some (but not all) studies, a diathesis-stress explanation was supported in some respects. The evidence for differential susceptibility is also mixed. Shah, Robbins, Coelho, and Poehlmann (2013) were the first to explore and find some support for the differential susceptibility theory when gestational age at birth was considered as the plasticity factor. In a subgroup of infants born <30 weeks' gestation, those exposed to negative parenting had the *lowest* cognitive scores at 36 months whilst those exposed to a less negative parenting style had the *highest* cognitive scores, outperforming infants born 34–37 weeks' gestation (Shah et al., 2013). Gueron-Sela et al. (2015) compared the social and cognitive functioning of preterm (28–33 weeks' gestation) and full-term (>37 weeks' gestation) infants at 12 months of age and found support for the differential susceptibility theory for social outcomes in the interactions between preterm birth and maternal emotional distress at 6 months, and between preterm birth and family interactions (child and both parents). However, as reported above, for cognitive outcomes, diathesis-stress offered a stronger explanation. By contrast, the Hadfield et al. (2017) study across the spectrum of gestational ages did not find strong support for either theory, but it did confirm the importance of parental attachment and distress for children's outcomes. We further note that a study focusing on mild perinatal adversity did support a differential susceptibility explanation (Windhorst et al., 2016), with perinatal adversity moderating the relationship between harsh mothering at 3 years and children's hair cortisol concentration (an indicator of chronic stress) at 6 years. 'Perinatal adversity' in that study included only late preterm birth (or being small for gestational age) and so did not address the matter of very or moderately preterm birth. Nevertheless, the findings are of interest given Luciana's (2003) suggestion that earlier preterm birth might offer a greater opportunity for recovery, which implies that preterm infants born at earlier gestations might be even more likely to yield findings consistent with differential susceptibility theory. Furthermore, whereas preterm differential susceptibility studies have focused on children under 6 years of age, it has been suggested, on evolutionary grounds, that there may be a 'switch point' around 6 years of age when earlier rearing patterns become translated into more stable behavioral patterns, with differential susceptibility becoming more pronounced (Davies et al., 2021).

1.4. The present study

Through the lens of both the diathesis-stress and the differential susceptibility theories, children born preterm are at risk of poor developmental outcomes resulting from the early brain injury and altered development. Follow-up, and assessment are necessary for early detection and intervention in order to minimize the extent of poor outcomes. Clinical practice, where resources permit, is to follow-up and assess the most medically at-risk (typically based on gestational age at birth or birthweight) preterm infants to determine need for medical devices (such as hearing aids or glasses), or support from allied health professionals. The diathesis-stress and the differential susceptibility theories imply that follow-up and screening of the home environment of preterm infants is also important in order to identify and intervene with families where the home environment is poor. Under the diathesis-stress theory the aim of an intervention would be to improve a poor home environment to bring children's development as far as possible up to the level of their full-term peers. Conversely, parents who are able to provide a home environment that is stimulating and supportive of their very preterm children's development could be reassured that their child is already unlikely to have a poor developmental outcome, and additional supportive resources may be unnecessary. The implication of the differential susceptibility theory on the other hand is that the earlier the gestation at birth, the greater the vulnerability but the potential for recovery may also be greatest (Luciana, 2003). Hence, there may be more motivation and support for intervention and parents may expect positive developmental outcomes. However, clear evidence of benefit is necessary to justify resources required to implement screening and

support.

Investigations of the diathesis-stress and differential susceptibility theories to date have all restricted environmental exposure to parent-child interactions and/or parental mental health (Gueron-Sela et al., 2015, 2016; Hadfield et al., 2017; Jaekel et al., 2015; Poehlmann et al., 2011), with the exception of Wu and Chiang (2016) who only measured effects on motor development. Interestingly, findings differ greatly between these studies so that there is no consensus about which theory can best explain the interaction between preterm birth and later environmental factors, whereas longer-term outcomes have been largely unexamined. Furthermore, despite demonstrated links between stimulation/developmental support in the home environment and positive outcomes for children, these links have not been explored in testing the diathesis-stress or differential susceptibility theories.

The present study aimed to add to the literature around the susceptibility of infants born less than 33 weeks preterm to the environment. We examined the interaction between biological risk (degree of prematurity) and a measure of stimulation at 18 months that included a broad range of stimuli within the home, such as the family situation and sources of cognitive and emotional support, to affect later child cognitive and behavioral functioning. Child cognition was to be assessed at 7-years (corrected age), by when cognitive measures are considered stable and predictive of adult intelligence (IQ), and hence results can indicate likely long-term effects of the early home environment (Luttikhuisen dos Santos, de Kieviet, Konigs, van Elburg, & Oosterlaan, 2013). Importantly, an assessment of behavioral functioning was also included, as preterm samples are known to experience high rates of behavioral difficulties (Allotey et al., 2018; Aylward, 2005; Bhutta et al., 2002; Pinto-Martin et al., 2004; Taylor et al., 2000; Zmyj et al., 2017).

Both the diathesis stress and differential susceptibility theories predict a moderating role of prematurity on the impact of the home environment on child cognition and behavior but they reflect different patterns, specifically in terms of the benefits of a supportive home environment. In general, an unsupportive home environment would be assumed to be detrimental to these outcomes. The diathesis-stress model would be supported if the negative impact of unsupportive home environment was greater for those who were more premature; as the home environment becomes more supportive, the more premature children would have smaller relative deficits in the outcomes with only a small (or no) deficit in the most supportive environments. In contrast, the differential susceptibility theory predicts that, although an unsupportive home environment would also be assumed to be more detrimental for those who were more premature, a supportive home environment would actually lead to a relative *benefit* for those who were more premature. In statistical terms, the diathesis-stress theory reflects a non-crossover interaction whereas the differential susceptibility theory reflects a cross-over interaction. Determining whether either theory can explain the interaction between prematurity and the home environment in predicting child abilities would be crucial to funding support for families with preterm infants.

2. Method

2.1. Participants

Participants were enrolled in a randomized controlled trial of high-dose docosahexaenoic acid intervention in the neonatal period. The primary outcome of the trial, child development, suggested little evidence of benefit of the intervention (Collins et al., 2015; Makrides et al., 2009). We repurposed the data set (combining the intervention groups into one cohort) to compare the diathesis-stress and the differential susceptibility theories. Infants were recruited into the original trial shortly after birth between 2001 and 2005 from five Australian perinatal centers. Eligibility for enrolling into the trial was defined as a birth before 33 weeks' gestational age. Exclusion criteria for the trial included major congenital or chromosomal abnormalities, multiple birth where

not all infants were eligible, and involvement in other trials of fatty acid supplementation, or for whom tuna oil was contraindicated. Children were excluded from the current analyses if they had a diagnosis of Autism Spectrum Disorder (due to possible effect on the validity of behavioral and cognitive assessments) or if data were missing for the variables of interest (maternal education, home environment, child cognitive and behavioral outcome).

2.2. Measures

2.2.1. Home environment (at age 18 months)

Home Screening Questionnaire (HSQ). The HSQ (Coons, Gay, Fandal, Ker, & Frankenburg, 1981) is a 30-item parent-completed questionnaire that assesses the quality and quantity of cognitive, social, and emotional support as well as stimulation in the home environment. It was developed to indicate home environments that are more likely to support optimal child development and measures parental involvement with the child, organization of the physical environment, provision of appropriate play materials, and variety in daily activities. Example items include “how often does your child get out of the house (backyard, for a walk, to the store etc.),” “Does the father (or other adult male) provide some caregiving (such as babysitting, feeding, putting to bed, etc.) for the child?” and “how often do you actively play with your child at this age?” as well as an inventory of common toys. Originally based on the objective Home Observation for Measurement of the Environment interview which takes 45–90 min to be completed by an interviewer at a visit to the home, the HSQ was developed as a screen of the home environment that can be quickly and effectively completed by caregivers at a clinic appointment (Frankenburg & Coons, 1986). It has been tested and validated in a sample of over 900 children (Frankenburg & Coons, 1986). Items are scored based on a set of rules for credits and penalties to form a total home environment score that ranges from zero to 43. It was thus developed as a single-factor dichotomous screener and, according to the manual, scores of 32 and below are indicative of a nonoptimal home environment (for example use of physical punishment or limited availability of stimulation at home) and scores ranging from 33 to 43 reflect an optimal home environment (for example, provision of appropriate play materials and opportunity for variety in daily stimulations) (Coons et al., 1981). The HSQ has good validity and reliability against the objective Home Observation for Measurement of the Environment tool (Nair et al., 2009) and acceptable internal consistency ($\alpha = 0.74$) and test-retest reliability ($r = 0.82$; Coons et al., 1981). The HSQ was completed by someone who was familiar with the child and the child’s home, such as a parent, grandparent or legal guardian.

2.2.2. Cognitive ability (at age 7 years)

Wechsler Abbreviated Scale of Intelligence (WASI). The WASI (Harcourt Assessment, 1999) is a brief, reliable measure of general intellectual ability for individuals aged 6–90 years. Four subtests (Vocabulary, Similarities, Block Design and Matrix Reasoning) provide a Full-Scale Intelligence Quotient (FSIQ), age standardized to a mean of 100 and SD of 15. When administered to children aged 6–16 years, the WASI has good internal consistency ($\alpha = 0.71$ in the current sample), high test-retest stability ($r = 0.88$ – 0.93), and is strongly correlated with the Wechsler Intelligence Scale for Children – 3rd Edition ($r = 0.87$).

2.2.3. Behavior

Strengths and Difficulties Questionnaire (SDQ). The SDQ – Parent Version (Goodman, 1997) is widely used to measure child behavioral functioning. The questionnaire consists of 25 items, with five subscales each consisting of five items. The subscales assess emotional symptoms, conduct problems, hyperactivity/inattention, and peer relationship problems, as well as prosocial behavior, which captures a strength in functioning and was not used in the present study. A parent scores each item on a three-point rating scale ranging from zero to two, depending on whether items are ‘not true’, ‘somewhat true’ or ‘certainly true’. High

scores indicate poor adjustment and more behavior problems. A Total Difficulties score is calculated by summing scores across all subscales, except prosocial behavior (Goodman, 2001). It has been shown to have good concurrent and predictive validity (Goodman, 1997, 2001; Mathai, Anderson, & Bourne, 2004), high test-retest reliability with a mean 0.62 (Goodman, 2001) and high discriminant validity (Goodman, 1997). The SDQ has an average odds ratio of 15.7 for having a psychiatric disorder with a high, rather than low, parent-rated SDQ scale score (Goodman, 2001). The SDQ has demonstrated internal consistency and was completed by a parent or legal guardian (Cronbach $\alpha = 0.76$).

2.2.4. Control variables

SES has previously been associated with home environment (Coscia et al., 2001), behavior (Burnson, Poehlmann, & Schwichtenberg, 2013), cognitive ability (Wong & Edwards, 2013) and prematurity (Goldenberg, Culhane, Iams, & Romero, 2008). SES, determined by the highest level of completed maternal education (to match Gueron-Sela et al., 2015), was categorized as 1 = did not complete secondary school, 2 = completed secondary school, 3 = post-secondary education such as a certificate or diploma, 4 = university degree, and entered as a covariate in analyses.

2.3. Procedure

A number of baseline demographic characteristics were gathered at enrollment into the original trial and participants were then followed up at 18 months and 7 years’ corrected age. Measures at enrollment included gestational age, birth weight, infant sex, order of birth (if multiple birth) and maternal education, used as a proxy for socioeconomic status (SES). Clinical Index for Babies (CRIB) scores were also noted; these neonatal scores are predictive of initial risk of mortality and correlate with a number of measures, including gestational age (Ezz-Eldin, Hamid, Youssef, & Nabil, 2015). At 18 months’ corrected age, caregivers completed a questionnaire assessing the quality of the home environment. At 7 years’ corrected age, children completed a cognitive assessment and caregivers completed a questionnaire assessing child behavior. All procedures were approved by the Women’s and Children’s Health Network Human Research Ethics Committee. Written informed consent was obtained from parents prior to enrolling in the trial and participating in the 7-year follow-up study.

2.3.1. Statistical analyses

The analytic strategy comprised two parts: (a) preliminary analyses in which the independent effects of degree of prematurity and home environment on child cognitive and behavioral outcomes were evaluated; and (b) tests of moderation in accord with the hypotheses.

Analyses presented here base degree of prematurity on the categories used by Shah et al. (2013) in their examination of the differential susceptibility theory: <30 weeks (very preterm) and 30 to <33 weeks (moderately preterm; in the current sample, there was no late preterm group). Data are nested in structure, whereby individual children are nested within mothers (i.e., twins/triplets nested within one mother). As such, some variables are assessed at the individual child level, such as the outcome measures and the degree of prematurity. Other variables are assessed at the family level, such as home environment and maternal education. We used linear mixed-effects modelling with R data analysis and graphics programming environment.

For each dependent variable, we ran two linear mixed-effects models allowing for a random intercept. For the first model, we included home environment (HSQ), degree of prematurity (gestational age at birth category), and maternal education as additive predictors so that each effect represented a conditional effect controlling for the other variables in the model. For the second model, we added the product term between gestational age group and home environment to assess the interaction. Furthermore, the continuous predictor variables were centered by subtracting the sample mean from all participant values in order to aid

interpretability of the fixed effects—meaning that the effects can be interpreted as at average levels of the variables controlled for.

Roisman et al. (2012) recommend rigorous statistical techniques when evaluating interaction effects. Consequently, a Regions of Significance analysis was applied when significant interaction effects were found to determine the moderator values for which the independent and dependent variables are significantly correlated. To further quantify the evidence, a Proportion Affected Index was calculated in order to estimate the proportion that was differentially affected by gestational age. This represents the proportion of the sample who have scores in the regions of significance (at each end of the home environment continuum). Roisman et al. (2012) suggest that a Proportion Affected Index of less than 16% should give reason to question whether the data are consistent with differential susceptibility theory.

We also planned additional analyses to consider singleton and multiple births separately due to the potential confounding of shared genetics and environment. We repeated all analyses with singletons only, however the sample of multiples was too small to conduct meaningful analyses.

3. Results

3.1. Participants

As per the exclusion criteria for the current analyses, 122 children were removed from the data set: 19 children were excluded due to a diagnosis of Autism Spectrum Disorder and 103 children were excluded due to missing data on the variables of interest (see Fig. 1). Of the 535 children (from 441 families) included in data analyses, seven children did not have a full-scale IQ (FSIQ) and seven other children did not have an SDQ score. Thus 528 children (from 437 families) were used in the analysis of FSIQ, and 528 children (from 434 families) were used in the analysis of SDQ scores.

Missing case analyses were conducted, using linear mixed effects models, to determine whether those included in the sample were significantly different from those excluded. Excluded cases did not include those omitted due to an Autism Spectrum Disorder diagnosis. Cases with missing data were more likely to be of a younger gestational age ($t(113) = 2.18, p = .032$), lower in birth weight ($t(113) = 2.68, p = .009$), assessed as being greater in neonatal clinical risk ($t(109) = 2.94, p = .004$), had higher FSIQ ($t(100) = 2.17, p = .032$), and lower total difficulties scores ($t(97) = 2.53, p = .013$). Excluded participants were more likely to identify as Aboriginal than Caucasian ($Z = 8.28, p < .001$)

or Asian ($Z = 5.36, p < .001$). There were no differences in maternal education, HSQ, or gender.

Demographic information stratified by degree of prematurity is shown in Table 1. There were differences for Clinical Risk Index for Babies scores, in which newborn clinical risk decreases as gestational age at birth increases. As expected, birth weight significantly differed according to degree of prematurity with birth weight increasing as gestational age at birth increased. No group differences were found for gender, although small numbers in some categories led to very low statistical power.

3.2. Cognitive outcomes

Linear mixed effects analyses were conducted with IQ scores entered as the outcome variable. A test of the null model revealed significant between-family variation, with 43.9% of the variation in IQ scores between families ($ICC1 = 0.439$), justifying the necessity for a multi-level analysis.

Analyses (see Table 2) revealed significant effects of both maternal education and degree of prematurity on IQ. These show an almost 9 IQ points difference between the lowest and highest maternal education categories, and that children born <30 weeks' gestation (estimated $M = 97.23, SE = 1.24$) had significantly lower IQ than children born 30–33 weeks' gestation (estimated $M = 101.41, SE = 1.24$) among families with average maternal education and HSQ. There was no significant interaction between prematurity group and HSQ.

Table 1

Demographic Information according to degree of prematurity (using Shah et al.'s (2013) classification)^a.

Characteristics, mean (SD)	< 30 wks	30- < 33 wks
Gestational age, weeks	27.59 (0.08)	30.69 (0.08)
Birth weight, g	1021 (19.94)	1594 (18.71)
Clinical Risk Index for Babies	3.37 (0.15)	0.70 (0.15)
Maternal education ^b	2.69 (0.06)	2.21 (0.06)
Child gender, n (%)		
Male	140 (47)	157 (53)
Female	123 (46)	147 (54)

^a Statistics are estimated means (standard errors) from linear mixed effects models except for gender where they are frequencies (percentages within each gender).

^b Maternal education: 1 ≤12 years of study, 2 = high school degree, 3 = certificate/diploma, 4 = university degree.

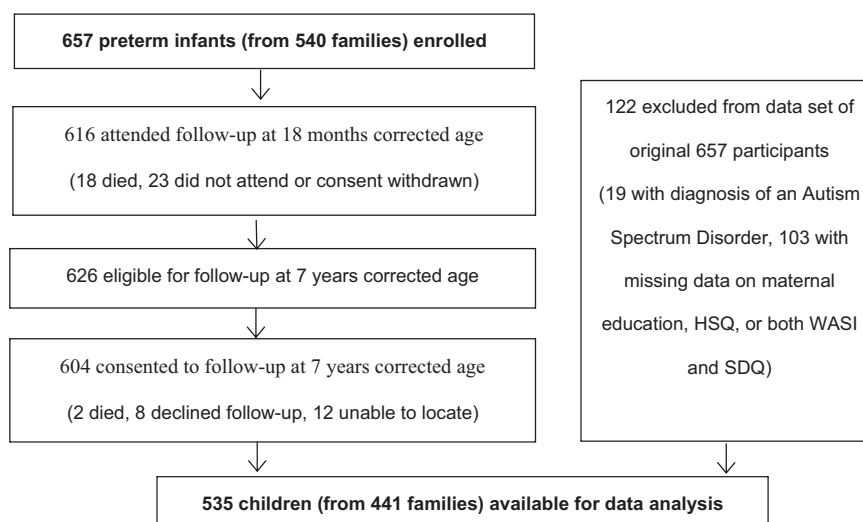


Fig. 1. Participant flow from enrollment at birth to 7 years' corrected age and exclusions from the current data analysis. HSQ = Home Screening Questionnaire, SDQ = Strengths and Difficulties Questionnaire, WASI = Wechsler Abbreviated Scale of Intelligence.

Table 2

Interactions between the degree of prematurity (using Shah et al.'s (2013) classification) and home environment at 18 months when predicting Intelligence Quotient at 7 years ^a.

Predictors	Coefficient	SE	t	p
Model 1				
Maternal education ^b	3.02***	0.51	5.93	< 0.01
Home Environment	0.29	0.17	1.69	0.09
Prematurity: <30 vs. 30- < 33 wks	4.17***	1.11	3.76	< 0.01
Model 2				
Maternal education ^b	3.01***	0.51	5.90	< 0.01
Home Environment	0.19	0.23	0.82	0.42
Prematurity: <30 vs. 30- < 33 wks	4.15***	1.11	3.74	< 0.01
Prematurity x HSQ	0.22	0.33	0.66	0.51

^a Linear mixed effects analyses with the Home Screening Questionnaire ($N_{children} = 528$; $N_{families} = 434$).

^b Maternal education: 1 ≤12 did not complete secondary school, 2 = completed secondary school, 3 = certificate/diploma, 4 = university degree.

*** $p < .001$.

3.3. Behavioral outcomes

Linear mixed effects analyses were conducted with SDQ total difficulties scores as the outcome variable. The multi-level analysis test of the null model revealed significant between-family variation in SDQ scores (interclass correlation: ICC1 = 0.397).

HSQ was negatively related to behavioral difficulties. Children born <30 weeks' gestation (estimated $M = 10.91$, $SE = 1.24$) had significantly higher (worse) SDQ scores than children born 30- < 33 weeks' gestation (estimated $M = 9.38$, $SE = 1.24$) among families with average maternal education and HSQ. The second model revealed a significant interaction between prematurity group and HSQ (see Fig. 2a).

At higher HSQ scores (indicating more favorable home environments), very preterm children had higher SDQ scores (indicating more behavior problems). Although the direction of the difference is swapped at lower levels of home environment, the 95% confidence bands show greater uncertainty and no significant differences between those born <30 weeks' gestation or 30- < 33 weeks' gestation (see Fig. 2b, where the slight negative slope of the regression line for infants born <30 weeks' gestation is non-significant as shown by the coefficient for HSQ in the lower portion of Table 3), indicating that home environment is only related (negatively) to behavior scores for those born 30- < 33 weeks' gestation. Further exploration of the regions of significance demonstrated a significant difference between those born <30 weeks' gestation or 30- < 33 weeks' gestation only at the high end of the HSQ continuum where higher scores indicate a more optimal home environment; specifically, for HSQ scores greater than 32. Significant regions were not apparent at both ends of the x-axis, providing evidence that the data do not conform to the differential susceptibility theory. To further quantify the evidence, a proportion affected index indicated that approximately 12.3% of cases fall below the point at which the regression lines intersect (i.e., where the regression line in Fig. 2a cuts the zero difference grid-line) and 64.4% of cases fell within the regions of significance, which may have implications for statistical power in the region of lower home environment scores.

3.4. Additional analyses

Exploratory, supplementary analyses were conducted with only singletons to account for the possibility that multiple births result in different consequences. The PROCESS macro (Hayes, 2018) yielded a similar pattern of results to the original analyses (shown in the Supplementary materials).

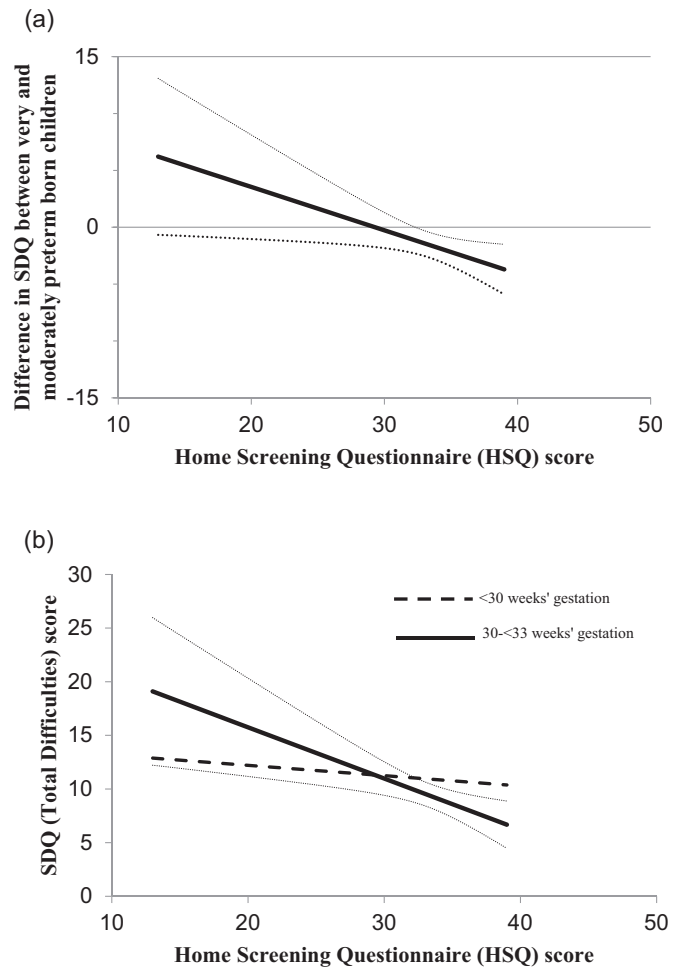


Fig. 2. Behavioral outcomes for preterm children analyzed where degree of prematurity categorized as defined by Shah et al. (2013)

(a) Difference in Strengths and Difficulties Questionnaire scores between children born <30 versus 30- < 33 weeks' gestation as a function of the Home Screening Questionnaire (HSQ) score. ^{a,b,c,d}

^a The effect of HSQ is conditioned.

^b The straight line (regression line) indicates the difference between the two categories at different HSQ scores.

^c The horizontal line at zero on the y-axis represents no difference between the two groups. Points on the regression line above zero on the y-axis indicates greater total difficulties for the infants born 30-<33 weeks' gestation, whereas points below zero on the y-axis indicate greater total difficulties for infants born <30 weeks' gestation.

^d The curved lines represent the 95% confidence bands for the regression line. The confidence band (contains the zero on the y-axis) indicates no significant difference between the groups. Thus, although we see that at lower HSQ scores (< 33), the data suggests that infants born 30-<33 weeks' gestation have greater difficulties, the differences in this region are all non-significant. In contrast, for higher HSQ scores, there is a significant difference between the groups with those born <30 weeks' gestation having (significantly) greater behavioral difficulties.

(b) Difference in Strengths and Difficulties Questionnaire scores between children born <30 versus 30- < 33 weeks' gestation as a function of the HSQ score (a slight clockwise rotation of Fig. 2a including the effect of HSQ on total difficulties for both groups).

4. Discussion

In the present study we tested whether degree of prematurity should be considered a vulnerability (diathesis-stress) or a plasticity (differential susceptibility) factor for the development of children born before 33 weeks' gestation. Although an interaction was found for behavioral

Table 3

Interactions between the degree of prematurity (using Shah et al.'s (2013) classification) and home environment at 18 months when predicting behavioral problems on the Strengths and Difficulties Questionnaire at 7 years^a.

Predictors	Coefficient	SE	t	p
Model 1				
Maternal education ^b	-0.32	0.26	1.25	0.21
Home Environment	-0.24**	0.08	2.89	0.01
Prematurity: <30 vs. 30- < 33 wks	-1.53**	0.56	2.73	0.01
Model 2				
Maternal education ^b	-0.30	0.26	1.18	0.24
Home Environment	-0.10	0.11	0.89	0.37
Prematurity: <30 vs. 30- < 33 wks	-1.49**	0.56	2.67	0.01
Prematurity x Home Environment	-0.34*	0.16	2.11	0.04

^a Linear mixed effects analyses with the Home Screening Questionnaire ($N_{children} = 528$; $N_{families} = 437$).

^b Maternal education: 1 \leq 12 did not complete secondary school, 2 = completed secondary school, 3 = certificate/diploma, 4 = university degree

* $p < .05$.

** $p < .01$.

difficulties, we did not find substantial evidence to support either theory when examining the potential for a moderating effect of gestational age on the relationship between stimulation and developmental support in the early home environment and cognitive and behavioral outcomes at 7 years. Although there have been some suggestive results in past studies, no consistent support for either theory has emerged to date, with preterm samples (Gueron-Sela et al., 2015, 2016; Hadfield et al., 2017; Shah et al., 2013).

Our study had some strengths. Importantly, we assessed two neurological domains in which preterm samples commonly experience difficulties and suboptimal functioning: behavior and cognition. These domains may be differentially influenced by both the home environment and preterm birth, but results on both outcome measures were consistent. We had the advantage of a robust measure of cognition at an age where IQ is considered reasonably predictive of adult functioning, unlike the early childhood assessments (Luttikhuis dos Santos et al., 2013) used in other comparisons of the diathesis-stress and differential susceptibility theories (Gueron-Sela et al., 2015, 2016; Hadfield et al., 2017). Furthermore, capacity for recovery after brain injury is ideally assessed longitudinally as adverse outcomes may become apparent as the brain matures, particularly if one function recovers at the expense of others (Luciana, 2003) and developmental problems are often not apparent until children are in the formal school environment when academic and social demands highlight deficits and handicaps (Nadeau, Boivin, Tessier, Lefebvre, & Robaey, 2001).

We also specifically examined developmental support and stimulation in the home environment as a likely malleability factor for cognitive and behavioral outcomes. There has, to our knowledge, only been one other study that explored stimulation in the home environment, rather than parenting style or emotional distress. Wu and Chiang (2016) used a modified and abbreviated version of the Home Observation for Measurement of the Environment (HOME) interview and based susceptibility on birth weight rather than gestational age. The authors reported no evidence for the differential susceptibility theory but some favoring the diathesis-stress theory for explaining the role of the environment in motor development (Wu & Chiang, 2016). Our study adds to the existing literature by using a broad measure of (stimulation in) the home environment that has already been associated with child development (Richter & Grieve, 1991), and intelligence quotient (Zhou et al., 2007) as well as cognitive, behavioral and social outcomes in a preterm sample (Treyvaud et al., 2012). Despite there being a substantial delay between our measure of home environment and child outcomes, it was clear that stimulation and developmental support in the early home environment was positively associated with the cognitive and behavioral functioning

of children born <33 weeks' gestation. Similarly, a previous study reported that children at high biological risk (in terms of low birth weight combined with other medical complications) appeared to catch up on their cognitive development over the first 3.5 years of life when they were in a stimulating home environment, measured with the HOME interview (Weisglas-Kuperus et al., 1993); in that study, children's cognitive development declined if they were in a poorly stimulating environment whether they were at high or low biological risk. The possibility of improving the home environment for children at risk of poor development should be further explored. The HSQ is a freely available, easy to use screening tool that could be simple and effective to implement, although further work could explore whether there are other measures that are more sensitive to specific aspects of the home.

There were a number of limitations to note as the study used a pre-existing data set that was designed and collected to assess the effect of a high-dose docosahexaenoic acid intervention in the neonatal period on child development, (Collins et al., 2015; Makrides et al., 2009). Hence, possible confounders such as maternal IQ or depression were not available, although we were able to control for maternal education. Unlike previous studies, there was no preterm group >33 weeks or full-term reference group.

Although it is possible that the lack of evidence for either theory in our study was because all infants born <33 weeks' gestation may be similarly vulnerable or plastic, some suggestions to the contrary were detectable in previous studies (Gueron-Sela et al., 2015, 2016; Hadfield et al., 2017). Three previous studies exploring the two theories captured the mental health of mothers and fathers individually and results differed according to whether maternal or paternal mental health was used as the environmental exposure variable (Gueron-Sela et al., 2015, 2016; Shah et al., 2013). We were unable to explore maternal and paternal factors individually, as a single caregiver completed the questionnaires. Whilst the majority were mothers, relationship to the child was not recorded on the questionnaires and therefore we were unable to analyze results according to the relationship of the caregiver to the child. However, the home environment measure we employed is not related to a specific caregiver but to the home environment as a whole and therefore would not be expected to differ substantially between parents from the same household. The lack of a parental mental health measure also meant that it was not available for inclusion in analyses for the SDQ, as maternal mental health problems may cause over-estimation of children's difficulties (Najman et al., 2000).

It is possible that the delay between the measure of home environment and the assessments of child cognition and behavior may have missed relevant changes to the home environment. Another possible limitation is that both home environment and child behavior were completed by a single caregiver, whereas multi-informant reports are often preferred for their ability to provide a more valid measure of certain behaviors due to the potential for biases associated with parent-report of behavior (e.g., Bora et al., 2011; Conrad, Richman, Lindgren, & Nopoulos, 2010). However, results for behavior were similar to cognition. An objective measure (not completed by a caregiver) of home environment, particularly one that reflects parenting styles and interactions as well as variety of stimulation, may have provided additional information about environmental exposure.

In sum, despite a number of limitations, the present study adds to the small number that have compared the diathesis-stress and differential susceptibility theories in relation to developmental outcomes for children born preterm. Previous studies have yielded mixed results, and neither theory was supported in the case of the present sample. The evidence to date, then, does not have clear implications for interventions, except to say broadly that factors such as promoting attachment, reducing parental distress and providing a stimulating home environment are to be encouraged. Much remains to be learned about the developmental processes associated with preterm birth, as evidenced by two recently-published study protocols. One is the Boardman et al. (2020) Scottish study aimed at examining the

association of neuroanatomical differences with outcomes for children born preterm. The other is a scoping literature review study prompted by previous findings on preterm birth as an environmental sensitivity factor, which Lionetti et al. (2021, p. 1) describe as ‘controversial.’ They examined the evidence concerning a broad range of potentially relevant factors and are open to the possibility that findings will continue to produce a complex picture. Lionetti and colleagues also mention the potential relevance of a newer concept, ‘vantage sensitivity’, that focuses on the ‘bright side’ of differential susceptibility (de Villiers, Lionetti, & Pluess, 2018, p.545 & 547), and that may assist understanding of individual differences in response to psychological interventions for those born preterm.

CRediT authorship contribution statement

CDF, JFG, RR, RS, PW Conceptualization; MM, CTC, JFG, PW Data curation; PW, RS, CDF Formal analysis; MM Funding acquisition; MM, CTC, JFG Investigation; RS, RR, JFG, CDF Methodology; Project administration JFG, MM, CTC, RR; MM, CTC, JFG Resources; CDF, PW Software; Supervision; RR, JFG Validation; CDF, JFG, RR, RS, PW Visualization; CDF, JFG, RS, PW, RR Roles/Writing - original draft; JFG, CDF, RR, RS, PW, CTC, MM Writing - review & editing.

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Declaration of competing interest

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Appendix A. Supplementary data

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