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SGA adults’ differential susceptibility

Differential susceptibility effects of maternal sensitivity in childhood on small for gestational age adults’ wealth

Abstract

Being born small for gestational age (SGA) is considered a developmental vulnerability. Alternatively, SGA may be viewed as a marker for individual susceptibility to environmental experiences. The aim was to test if individuals born SGA are more susceptible to both negative and positive environmental experiences assessed by sensitive parenting in childhood compared to those born appropriate for gestational age (AGA). The target outcome was wealth in young adulthood. 438 participants (SGA n = 109, AGA n = 329) were studied as part of the prospective Bavarian Longitudinal Study of neonatal at-risk children. Maternal sensitivity was observed during a standardized mother-child interaction task, and IQ was assessed with the K-ABC at age 6 years. At age 26, participants’ wealth was assessed with a comprehensive composite score. Individuals born SGA were found to be more susceptible to the effects of sensitive parenting after controlling for gestational age and IQ at age 6 years. When maternal sensitivity was lower than average, SGA adults did worse than AGA adults, but when exposed to above average maternal sensitivity in childhood they obtained significantly higher wealth than their AGA peers by 26 years of age.

Keywords: small for gestational age, differential susceptibility, maternal sensitivity, wealth, Bavarian Longitudinal Study (BLS)
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Introduction

Intrauterine growth restriction (IUGR) is an adaptation to adverse pre-conceptual and prenatal conditions such as malnutrition, poor placental supply, genetic disposition or maternal stress; protecting the development of vital organs (i.e., the brain) while constraining the fetus from reaching its potential size (Gluckman, Hanson, Cooper, & Thornburg, 2008). These unfavorable conditions in utero may affect behavioral functioning and health in later life via prenatal programming during developmental periods of high organ plasticity (Barker, 2007; Gluckman et al., 2008; Workalemahu et al., 2018). IUGR is associated with small for gestational age (SGA) birth, low birth weight (LBW, <2500g), preterm birth (<37 weeks gestational age), and increased long-term morbidity (Raikkonen & Pesonen, 2009).

In addition to poor health outcomes, those born SGA are at increased risk to score lower than their peers born appropriate for gestational age (AGA) in cognitive abilities (Gutbrod, Wolke, Söhne, Ohrt, & Riegel, 2000), mathematics, reading, and fine motor skills at age 5 (Li et al., 2017). Mild cognitive deficits of children born SGA may result in lower academic achievement and a higher likelihood of being recommended for special education than those born AGA (Strauss, 2000). However, there are controversial findings whether being born SGA still affects cognition in adulthood. Some have found that SGA individuals continue to show higher rates of learning difficulties in adolescence (O’Keeffe, O’Callaghan, Williams, Najman, & Bor, 2003) and lower IQ scores in young adulthood (19-20 years of age) compared with AGA peers (Lohaugen et al., 2013). Others reported that SGA birth at term may have few long-term effects on executive function, attentional control (Kulseng et al., 2006), and general IQ into adulthood (Eryigit Madzwamuse, Baumann, Jaekel, Bartmann, & Wolke, 2015; Pyhala et al.,
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2011), indicating the brain’s potential to compensate and catch up after IUGR. These contradictory findings may be the result of individual differences in susceptibility to environmental influences among those born SGA (van der Kooy-Hofland, van der Kooy, Bus, van Ijzendoorn, & Bonsel, 2012; Windhorst et al., 2017).

The adverse and scarce conditions SGA born individuals face in utero in association with IUGR may lead to an increased adaptability to the environment after birth (i.e., being able to survive in unpredictable conditions) (Wadhwa, Buss, Entringer, & Swanson, 2009). Thus, compared with AGA infants, those born SGA may be programmed for a higher susceptibility to environmental influences (Pluess & Belsky, 2011; van der Kooy-Hofland et al., 2012). Accordingly, differential susceptibility theory (DST) proposes that those that have been traditionally viewed as vulnerable to environmental influences in the diathesis-stress framework (Zuckerman, 1999) are in fact more susceptible to environmental impacts, for-better-or-for-worse (Belsky, Bakermans-Kranenburg, & van IJzendoorn, 2007). According to the diathesis-stress framework, individuals born SGA (i.e., those who carry the risk factor) would be predicted to perform worse than those born AGA given adverse environmental conditions (e.g., low sensitive parenting). When reared in an enriched environment (e.g. high maternal sensitivity), those born SGA would do as well as their AGA peers. DST also predicts that those born SGA (i.e., those who carry the susceptibility factor) would perform worse than their AGA peers given an adverse environment (e.g. low maternal sensitivity). The difference is that DST predicts better than average performance of SGA compared with AGA individuals given an enriched environment (e.g., high parental sensitivity). In contrast, those without the risk factor, i.e. born AGA, may be invulnerable and little affected by adverse or enriched environments. The
SGA adults’ differential susceptibility underlying mechanisms that explain why SGA may be a marker for prenatally programmed increased susceptibility that leads to superior outcomes in the context of beneficial postnatal experiences are not yet fully understood. Findings from one study of individuals born with mild perinatal adversity (late preterm (LP, 34-36 weeks gestational age) or SGA at term) suggest that the complex interplay between central nervous system and endocrine system (i.e., the hypothalamic–pituitary–adrenal (HPA) axis) may be altered (Windhorst et al., 2017), which may result in differential registration and subsequently sensitized response to environmental cues. Specifically, harsh parenting disproportionately affected the stress response of those born with mild perinatal risk compared to those without (i.e., term born AGA), suggesting a higher susceptibility to environmental cues among those born SGA or LP (Windhorst et al., 2017). In contrast, if the environment is supportive such as providing a reading intervention, children born LP or SGA at term outperformed their term born AGA peers, suggesting that children born with mild perinatal risk may be more susceptible to environmental stimulation and support than those born without risk (van der Kooy-Hofland et al., 2012). Although individuals born SGA, on average, may experience less favorable long-term outcomes than their AGA peers, we hypothesize that the adverse intrauterine conditions that lead to protection of the brain by down regulating weight gain may result in high individual susceptibility to environmental experiences.

Maternal sensitivity is a key environmental factor, associated with positive developmental outcomes in early and late childhood (DeWolff & van IJzendoorn, 1997). Children who receive sensitive parenting, regardless of their temperament in infancy, have better math, reading, and social skills (Pluess & Belsky, 2010). For those born at neonatal risk,
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Sensitive parenting might be especially important: Maternal sensitivity works to protect against the adverse effects of VP/VLBW birth, positively affecting attention regulation (Jaekel, Wolke, & Chernova, 2012) and academic performance throughout childhood and adolescence (Treyvaud et al., 2016; Wolke, Jaekel, Hall, & Baumann, 2013). For those born SGA, early maternal sensitivity has been found to reduce deficits in cognitive abilities and motor skills compared to their AGA peers, while parental intrusiveness widened the developmental gap between the two groups (Li et al., 2017). Likewise, detrimental effects of insensitive or harsh parenting on later developmental outcomes may be stronger among perinatal at-risk mother-infant dyads (Feldman & Eidelman, 2009; Landry, Smith, Miller-Loncar, & Swank, 1997).

The effects of prenatal risks such as IUGR on childhood outcomes may set children on trajectories of reduced life chances, economically impacting both the individual and society (D’Onofrio et al., 2013; Shah & Kingdom, 2011). However, developmental trajectories can be altered by environmental conditions, and information about the factors involved in potential upward shifts from projected economic underachievement is critical. As a means of understanding long-term development and success in adulthood, wealth has been used as an overall index of real life effects, including measures such as income, financial independence, job stability, and educational attainment (Bilgin, Mendonca, & Wolke, 2018; Copeland, Wolke, Shanahan, & Costello, 2015; Moffitt et al., 2011; Wolke, Copeland, Angold, & Costello, 2013). In the 1970 Birth Cohort Study, adults born SGA had similar educational attainment and worked a similar number of hours, but on average had lower weekly incomes compared with those born AGA (Strauss, 2000). A Swedish study found that those born SGA were more likely to retire early and receive a disability pension (Helgertz & Vågerö, 2014). Considering the cascading
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nature of early adversities, SGA birth likely impacts adult outcomes indirectly, for instance via cognitive functioning and academic success. While these mediating longitudinal factors are important when investigating developmental cascades, ultimate outcomes of interest may be more ecologically valid markers, such as educational attainment and economic success (Shah & Kingdom, 2011). In this respect, most studies have documented the negative consequences of SGA birth, but it is important to start investigating environmental factors that may promote life-course success of individuals born SGA.

The aim of this present study was to investigate the relationship between sensitive parenting in childhood and adult wealth for individuals born SGA compared to those born AGA in the Bavarian Longitudinal Study (BLS). We applied confirmatory-comparative modeling to test our hypothesis that SGA individuals are more susceptible (DST), rather than just more vulnerable, to the long-term effects of sensitive parenting on adult wealth compared to their AGA peers.

**Methods**

**Participants and Design**

Data were collected as part of the geographically defined Bavarian Longitudinal Study (BLS). Written informed consent was obtained from parents within 48 hours of child birth and from adult participants at the 26 years follow up. Original ethical approval was given by the University of Munich Children’s Hospital and the Landesaerztekammer Bayern, ethical approval for the adult follow up was given by the University Hospital Bonn Ethical Board (reference #159/09). Regular neurological and psychological test batteries, behavior observations, and parent interviews were used to assess participants’ development throughout childhood and
SGA adults’ differential susceptibility into adulthood. At age 6 and 26 years, participants were assessed for one whole day by trained psychologists, pediatricians, and research nurses who were blind to their background characteristics. This study assesses a whole population sample of 682 individuals born very preterm/very low birthweight (VP/VLBW) and matched term born comparison participants (Wolke & Meyer, 1999). Of the VP/VLBW infants recruited at birth, 411 were presumed alive, living in Germany, and eligible for inclusion at 26 years of age, and 260 (63.3%) participated in the adult assessment (see Appendix Figure 1). The BLS VP/VLBW participants did not differ from adults who dropped out in terms of gestational age, birth weight, duration of hospitalization, gender, maternal age, parental marital status, and childhood cognitive scores, but had fewer prenatal complications and were of higher socioeconomic status (SES) (Eryigit Madzwamuse et al., 2015). Of the term-born comparison children, 308 individuals were eligible for inclusion and 229 (74.4%) participated at 26 years. Participants who had childhood parenting and IQ as well as adulthood wealth data (209 VP/VLBW and 229 term comparisons; of these 109 were SGA and 329 AGA, respectively) were included in the current analyses.

Measures

**Biological variables at birth.** Gestational age was determined from maternal reports of the last menstrual period and serial ultrasounds during pregnancy. Birth weight was documented in the birth records. Infants were classified as SGA if they weighed less than the sex specific 10\(^{\text{th}}\) percentile for their respective gestational age according to national standard weight charts (1985-1986) (Riegel, Ohrt, Wolke, & Österlund, 1995).

**Maternal sensitivity.** At age six, maternal sensitivity was observed and rated during a structured dyadic cooperation task using a standardized coding system, the “Assessment of
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Mother-Child-Interaction with an Etch-a-Sketch (AMCIES) (Wolke, Rios, & Unzer, 1995). Raters (psychologists) received extensive training, bimonthly feedback, and frequent refreshers. Rating scales consisted of three subscales for the mother (Verbal Control, Non-Verbal Control, and Criticism, all reverse-coded) and one subscale for mother-child joint behavior (Harmony) (Jaekel, Pluess, Belsky, & Wolke, 2015; Wolke, Jaekel, et al., 2013). According to principal component and reliability analyses, they were combined into a comprehensive index of Maternal Sensitivity (Cronbach’s α=.58), reflecting a multidimensional construct that involves responsive, supportive and prompt behaviors that are adapted to the child’s needs. The AMCIES coding system has established high inter-rater reliabilities (Jaekel et al., 2012). The in vivo rated scores show excellent convergence with video-rated scores of Maternal Sensitivity (Wolke, Jaekel, et al., 2013) (N: 565, intraclass-correlation coefficient of .76, \(p<0.001\), for two master raters).

**IQ.** At age 6, children’s intelligence was assessed with the German version of the Kaufman Assessment Battery for Children, K-ABC Mental Processing Composite (MPC) score (Melchers & Preuss, 1991).

**Adult wealth score.** Wealth was a composite score derived from a life-course interview and questionnaires at 26 years of age, including information about participants’ financial independence, occupational stability, and qualifications. Example items that indicated poor economic success included ‘receiving social benefits’, ‘no secondary school or profession oriented educational qualifications’, and ‘unemployed at present or in the past’ (please see Appendix Table 1 for details). Items were binary coded and then summed into a comprehensive
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wealth index score. Scores were reverse coded for analysis (i.e. higher scores indicate higher wealth).

**Analytic Approach**

Analyses were conducted using SPSS 23 (SPSS Inc., Chicago, IL). Descriptive characteristics are reported according to SGA versus AGA birth status. Maternal sensitivity and adult wealth scores were z-standardized according to the term born comparison participants in the sample. All reported regression slopes are unstandardized, but can be interpreted like betas based on z-standardized continuous scores; reported tests are two-tailed using $\alpha = .05$. All models are controlled for gestational age and IQ at age 6. Exploratory regression models were used to identify the main effects for SGA birth and maternal sensitivity (model 1). For model 2, an interaction effect between SGA birth and maternal sensitivity was added. Confirmatory model testing was performed by fitting data to four different reparametrized regression models (3 a-d). This method systematically varies parameters in order to test how well DST versus diathesis stress explains the data (Widaman et al., 2012).

Both DST and diathesis stress models predict that a below average environment (i.e., low maternal sensitivity) will result in lower adult wealth for SGA adults compared with their AGA peers. However, DST predicts that an above average environment (i.e., high sensitivity) will result in significantly higher adult wealth for SGA compared with AGA adults who received similarly high levels of sensitivity in childhood. In contrast, diathesis stress predicts that an above average environment will result in SGA adult wealth equal to AGA peers (i.e., catch-up). In addition, each theoretical model has a strong and a weak version: Strong DST (reparameterized regression model 3a, respectively) and strong diathesis stress (3c) predict that
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individuals born AGA are not affected by the environment (i.e., a regression line with a slope of 0). In contrast, weak DST (3b) and weak diathesis stress (3d) models predict that those born AGA are influenced by the environment but to a lesser degree than those born SGA. Finally, results of each model were compared to determine which model provides the best fit to the data.

Results

On average, SGA adults were born at a lower gestational age and birth weight, experienced lower maternal sensitivity, were more likely to suffer from cognitive impairment in childhood, and obtained lower adult wealth scores than AGA adults (see Table 1).

Regression modeling confirmed that maternal sensitivity at age 6 predicted higher wealth at age 26 (B = .23, p= .002) for both AGA and SGA adults (model 1). Adding the interaction effect between SGA birth and maternal sensitivity (model 2) revealed that the positive effect of sensitivity on adult wealth was stronger among SGA compared to AGA adults, (B = .44, p= .004).

Figure 1 depicts that adult wealth of individuals born AGA who experienced below average maternal sensitivity did not significantly differ from those born AGA who experienced above average maternal sensitivity. However, individuals born SGA did worse than their AGA peers when experiencing below average maternal sensitivity but did increasingly better than AGA peers when experiencing above average levels of maternal sensitivity.

Differential Susceptibility Versus Diathesis Stress Model Fitting
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For models 3 a-d, data was fit to four reparametrized regression models to compare the fit of strong DST (model 3a), weak DST (model 3b), strong diathesis stress (model 3c), and weak diathesis stress (model 3d) in adults born SGA versus AGA. Model fit values indicated that DST (models 3a and 3b) better fit the data than diathesis stress (models 3c and 3d) (see Table 2).

While both DST models showed similar fit, the amount of variance explained by each model was not significantly different, thus suggesting that the more parsimonious DST strong model (3a) had the best fit.

- Table 2 about here -

Discussion

This is the first study to show that individuals born SGA are more susceptible, not more vulnerable, to the long-term effects of sensitive parenting in childhood on wealth in adulthood compared to those born AGA. Confirmatory model testing showed that maternal sensitivity played a significant role in predicting the wealth outcomes of adults born SGA, while wealth of individuals born AGA was only minimally affected by parenting. SGA children who had received lower than average maternal sensitivity fared worse than AGA peers, but SGA children who had experienced higher than average maternal sensitivity attained higher wealth in adulthood than their AGA peers. These findings support the conclusion that individuals born SGA are highly susceptible, for better-or-for worse, to environmental influences. In contrast, AGA born individuals were little affected by the environmental influences tested here, maternal sensitivity at age 6 years.

Traditionally, SGA birth has been viewed as a vulnerability predisposing children to developmental difficulties. Indeed, just looking at the overall difference in wealth did show, on
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average, poorer outcomes for SGA compared to AGA adults. This is consistent with findings of
cognitive and academic difficulties in childhood (Gutbrod et al., 2000; Li et al., 2017) that may
lead to lower educational attainment and adult wealth after SGA birth. However, others have
found that SGA birth may not represent a risk factor for neurocognitive outcomes in adulthood
(Eryigit Madzwamuse et al., 2015; Pyhala et al., 2011). According to the new results presented
here, these inconsistent findings may be explained by environmental variations within the SGA
population. Due to SGA born individuals’ heightened susceptibility to environmental influences,
their long-term developmental trajectories are a complex product of early deficits, individual
neurodevelopmental resources, and continued environmental influences. Understanding what
environmental factors SGA individuals are susceptible to, over and above maternal sensitivity,
will be an essential step in designing interventions that support life-course outcomes. Examples
of potential environmental factors that may help SGA individuals to thrive include peer
relationships, educational quality, and cognitive stimulation, but their protective effects in SGA
children have not been investigated.

The current findings are consistent with the hypothesis that scarce intra-uterine
conditions program those born SGA to be more adaptive to unstable postnatal environments
(Pluess & Belsky, 2011; van der Kooy-Hofland et al., 2012). Why may SGA birth, as a marker of
IUGR, increase individuals’ ability to register and process stimuli, i.e., environmental sensitivity
(Pluess, 2015)? One may speculate that nature has created a mechanism that allows infants
who experienced IUGR to respond and adapt to certain anticipated challenges and
opportunities presented by their postnatal environments (Pluess et al., 2018). Such ontogenetic
adaptation may be achieved, for instance, by small alterations of the complex interplay
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between central nervous system and endocrine system (i.e., the hypothalamic–pituitary–adrenal (HPA) axis) (Windhorst et al., 2017), ideally fine-tuning the organism’s reaction to environmental cues (Ellis, Boyce, Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2011; Pluess, 2015). Such prenatally programmed susceptibility / environmental sensitivity over time may then result in a stronger longitudinal effect of environmental conditions on susceptible individuals’ behavioral outcomes (Pluess, 2015; Pluess et al., 2018).

Thus, as predicted by DST, above average maternal sensitivity was positively associated with wealth among SGA born adults. When experiencing higher than average maternal sensitivity those born SGA demonstrated higher adult wealth than their AGA adult peers. SGA children who experience highly sensitive parenting possibly thrive in later life because sensitive maternal behavior provides the support and scaffolding needed to avoid a trajectory of reduced life chances caused by the early neurodevelopmental risks associated with SGA birth. While high maternal sensitivity works to improve life course outcomes for those born with a neonatal risk, below average maternal sensitivity is detrimental to outcomes of highly susceptible SGA born individuals. This heightened reactivity to positive exposures of highly susceptible individuals suggests that they may be more receptive to interventions (Bakermans-Kranenburg & van IJzendoorn, 2015; Belsky & van Ijzendoorn, 2015, 2017; Lionetti et al., 2018). The findings of this study point towards new strategies to identify target groups that may benefit most from childhood interventions that help support sensitive parenting of school-aged children born SGA (Jaekel, 2016; McCormick, 1997).

Strengths and Limitations
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Previous studies have supported DST among SGA children born at term (van der Kooy-Hofland et al., 2012; Windhorst et al., 2017), but DST has not been supported among other neonatal at-risk groups (Jaekel et al., 2015). The severity of neurodevelopmental risk and subsequent medical complications associated with very low birth weight and preterm birth might overpower the conflicting effect of potentially increased susceptibility, making it difficult to confirm high susceptibility among SGA children born preterm (Li et al., 2017). However, those born SGA do not per se experience the same severity of cognitive impairments as other neonatal at-risk groups (Gutbrod et al., 2000; Shah & Kingdom, 2011) that may overshadow high susceptibility and limit developmental plasticity. While 78% of the SGA individuals in our sample were also born preterm, we controlled our analyses for gestation and childhood IQ, thereby disentangling susceptibility across the full gestational range of SGA born participants and conflicting cognitive deficits associated with preterm birth.

Those lost to follow-up did not differ from adult participants with regard to the rate of SGA birth, sex, and neonatal risk, however, as in most other longitudinal studies low SES families were less likely to continue participation studies (Hille, Elbertse, Gravenhorst, Brand, & Verloove-Vanhorick, 2005). Our study used quality assessments such as our maternal sensitivity assessment, a reliable comprehensive observational measure with an excellent intra-class-correlation coefficient, and a comprehensive composite wealth score at age 26. Nevertheless, maternal sensitivity was observed post-infancy, and despite its well-known long-term stability effects reported here may differ from parenting assessed at earlier or later ages. Given significant changes in neonatal and obstetric care over the past three decades there is room to wonder if our results are generalizable to neonatal at-risk children born today. However, so far
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there is little evidence that increased survival rates have led to higher quality of survival (Moore et al., 2012; Pierrat et al., 2017). Indeed, comparison of Bavarian Longitudinal Study findings with more recent cohorts have shown that the underlying processes and mechanisms do not differ as a function of time (Wolke et al., 2015). This suggests that the findings presented here are valid, nevertheless they require replication.

**Conclusion**

Individuals born SGA are more susceptible rather than vulnerable to sensitive parenting in childhood than their AGA peers. If maternal sensitivity was lower than average, SGA adults had lower wealth than their AGA born peers but when sensitive parenting was above average, they had higher wealth in young adulthood than those born AGA. Intrauterine malnourishment alters susceptibility to environmental experiences in a for-better-or-for-worse way. Interventions that can help to increase parental sensitivity may be an important avenue aimed at improving life-long outcomes of children born SGA.
**References**


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