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Maternal late pregnancy anxiety and stress is associated with children’s health: a longitudinal study

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ABSTRACT
Aim: Maternal prenatal anxiety and stress (PNS) have been positively associated to physical health problems in offspring in the first year of life. Whether these associations are transient, persistent, or even progressive over time, is as yet unknown. The goal of this study is to investigate associations between late pregnancy PNS and child health from 18 months to age 6.

Methods: Mothers were recruited in late pregnancy, and had uncomplicated, singleton pregnancies without physical health problems. Around week 37 of pregnancy, mothers reported on their PNS by means of questionnaires, and provided saliva for determination of circadian cortisol concentrations. Children’s illnesses in the preceding year were assessed using maternal reports at 30, 48, 60, and 72 months. Antibiotic use was obtained from medical records between one and six years. Multilevel models (N=1474) showed a positive relation between maternal prenatal general and pregnancy-specific anxiety during late pregnancy and offspring respiratory illnesses and symptoms. Interaction effects with time indicated that more PNS was related to more respiratory illnesses until toddlerhood, but not later in life. Furthermore, maternal prenatal cortisol concentrations were related to child digestive illnesses. A steeper maternal cortisol decline over the day was related to more child digestive illnesses, until around three years of age. Finally, children of mothers who suffered more from daily hassles during pregnancy received more antibiotics between one and six years of age. PNS was not related to general and skin illnesses.

Conclusion: Summarizing, this study showed that late pregnancy anxiety and cortisol was associated with children’s respiratory and digestive illnesses till the age of 3.0–3.5 years. Additionally, more daily hassles were related to more prescribed antibiotics between one and six years. These findings point in the direction of possible effects of PNS persisting beyond the first year of life and into toddlerhood, but disappearing at older ages.

INTRODUCTION
Prenatal exposure to maternal anxiety and stress (PNS), as reported by the mother or assessed with stress hormones, is associated with more physical health problems in offspring. Higher levels of reported PNS are associated with preterm birth, lower birth weight (Dunkel Schetter & Tanner, 2012; Shapiro, Fraser, Frasch, & Seguin 2013), obesity, metabolic dysfunction (Entringer, 2013), and more illnesses, and antibiotic treatments (Beijers, Jansen, Riksen-Walraven, & de Weerth, 2010). Higher PNS, as assessed with maternal prenatal cortisol concentrations, is also associated with offspring health (Zijlmans Korpela, Riksen-Walraven, de Vos, & de Weerth, 2015), including lower birth weight (Bolten et al., 2011; D’Anna-Hernandez et al., 2012; Goedhart et al., 2010), shorter gestational age (Diego et al., 2009; Erickson et al., 2001; Mercer et al., 2006), more infant respiratory and skin illnesses (Beijers et al., 2010), and larger systemic vascular resistance and lower artery elasticity (Rondó, Lemos, Pereira, & Souza, 2010; Rondó, Pereira, Lemos, & Ferreira, 2011). However, most studies on the relation between PNS and physical health in offspring focused on early life. Whether the associations are transient, persistent, or even progressive over time, is as yet unknown. The Developmental Origins of Health and Disease (DOHaD) hypothesis states that environmental exposures in utero condition the risk of disease throughout life: in infancy, childhood, and adult life (Gluckman & Hanson, 2004). Furthermore, life course models suggest that health development is a dynamic process, beginning before conception, and continuing throughout life (Halfon, Larson, Lu, Tullis, & Russ, 2014). This suggests that PNS could influence the health development of children already in utero and that the effects may be long-lasting. The goal of this study is to investigate associations between PNS and child health throughout the first six postnatal years. In a previous study on the same sample (Beijers et al., 2010), we found that PNS was associated to more respiratory, general, and skin illnesses, and more antibiotic use during the first postnatal year. Therefore, we hypothesize that children from mothers with higher levels of PNS will suffer from more respiratory, general, and skin illnesses, and receive more antibiotic treatments, during the first six postnatal years.
Methods

Participants and procedure

This study is part of an ongoing longitudinal study in which 192 mothers were followed from week 37 of pregnancy on. Inclusion criteria were an uncomplicated, singleton pregnancy, clear understanding of the Dutch language, no drug use, and no current physical health problems. The 174 participants of the earlier health assessment study (first 12 months, Beijers et al., 2010) were born a term (≥37 weeks, Mean =40.21 weeks, SD =16.18) and had normal 5-min Apgar scores (≥7, Mean =9.67, SD =.61), and were followed again at 30 months (N =167), 48 months (N =159), 60 months (N =161), and 72 months (N =149). Reasons for drop out were lack of time or other personal circumstances. There were no differences in the maternal PNS variables (general anxiety, pregnancy-related anxiety, daily hassles, pregnancy-related daily hassles, maternal evening cortisol, maternal cortisol decline) between participating mothers and drop outs (N =25, independent samples t-tests p’s >.05). The Ethical Committee of the Faculty of Social Sciences (Radboud University, Nijmegen, Netherlands) approved the study following the Helsinki Declaration (ECG 300107 and ECG 22111/130112) and mothers gave written informed consent.

Around week 37 of pregnancy, mothers filled out questionnaires about their experienced levels of stress and anxiety, and reported on their demographics. Furthermore, they collected saliva samples to determine circadian cortisol concentrations. Postnatally, the mothers also filled out questionnaires about anxiety and stress at 3, 6, 12, 30, 48, and 72 months.

In the first six years of life, maternal reports on children’s illnesses and health complaints were obtained by semi-structured interviews as follows: at age 30 months (pencil and paper questionnaire), 48 months (pencil and paper questionnaire), 60 months (phone interview), and 72 months (online questionnaire). Furthermore, from the 174 mothers, 130 mothers gave written permission to request their children’s medical records (prescribed medications) from their general practitioners. These records were used to assess antibiotic use. There were no differences in the maternal PNS variables between mothers who gave permission to request the medical records and mothers who did not give permission (N =44, independent samples t-test p’s >.05).

Measurements

Infant health

Mothers reported on their child’s health during the past year (30, 48, 60, and 72 months). They were asked how often the child had a specific illness or health complaint (e.g., having a cold) ending with an open question about possible illnesses that were not asked for. Basically, the same questionnaire was used at all-time points. The items were classified following the International Classification of Primary Care (ICPC; Lamberts & Wood, 1987). The classes used in this study were identical to those of Beijers et al. (2010), namely Respiratory, Digestive, Skin, and General. For each time point, a sum score per class was created by adding up all the illnesses and health complaints. See Table 1 for illnesses and complaints reported in our sample.

The number of antibiotic treatments from age one to six was obtained from medical records. This time period was chosen because in a previous article on this sample the relation between PNS and antibiotic use was examined between 0 and 12 months of age (Beijers et al., 2010).

General anxiety

Maternal prenatal anxiety symptoms were measured using a Dutch translation of the 20-item state anxiety subscale of the State-Trait Anxiety Inventory (STA; α =.93) (Spielberger, 1983; van der Ploeg, Defares, & Spielberger, 1981). Items were scored on a 4-point scale, with a higher score indicating more anxiety.

Pregnancy-related anxiety

Pregnancy-related anxiety was measured using the Pregnancy-Related Anxieties Questionnaire-Revised (PRAQ-R; van den Bergh, 1990). Two subscales, scored on 5-point scales, were used, namely “fear of giving birth” (three items, α =.70) and “fear of bearing a handicapped child” (four items, α =.83). Higher scores indicated more anxiety.

Daily hassles

The occurrence and intensity of daily hassles was measured using a 49-item Dutch questionnaire (Alledaagse Problemen Lijst, APL, test-retest reliabilities between 0.76 and 0.87; Vingerhoets, Jeninga, & Menges, 1989). Participants had to check if they encountered a daily hassle during the past 2 months and scored on a 4-point scale how much it bothered them. Example items are “you had a conflict with your partner”, and “family or friends were involved in a traffic jam”. The score used in the analyses is a mean valence rating; the sum of the total (negative) valence was divided by the frequency of daily hassles. A higher score indicated more negativity.

Pregnancy-related daily hassles

Pregnancy-related daily hassles were measured using a Dutch translation of the Pregnancy Experience Scale (PES; DiPietro,
Ghera, Costigan, & Hawkins, 2004), consisting of 43 items (z = .87). Example items are “discussing baby names with your spouse”, and “preparing the nursery”. Participants had to rate the listed pregnancy-related experiences on two 5-point scales, indicating (1) the extent to which the experience was experienced as a hassle, and (2) the extent to which the experience was experienced as an uplift. A total score was calculated by dividing the sum of intensities of hassles by the sum of intensities of uplifts. A higher score indicated more negative emotional valence toward pregnancy.

Prenatal cortisol

Around week 37 of pregnancy (mean: 37 weeks, 0.8 d, SD: 9.4 d), mothers collected saliva samples by passive drooling into sterile containers with screw caps to determine cortisol concentrations. Five samples were collected at two consecutive days at awakening, 30 min after waking, and at 12:00, 16:00, and 21:00 h. Samples were stored in a freezer (−20 Celsius) until analysis. An in-house competitive radioimmunoassay was used to measure cortisol (Laboratory of Endocrinology, University Medical Center Utrecht, Utrecht, the Netherlands). Intra- and inter-assay variations were below 10%. Cortisol concentrations between days correlated strongly, therefore, mean cortisol concentrations over the 2 d were calculated (for more details see Beijers et al., 2010; Tollenaar, Beijers, Jansen, Riksen-Walraven, & de Weerth, 2011). The evening cortisol concentrations and cortisol decline over the day (wakening minus evening) were not correlated (r = −.11, p > .05), but were highly correlated with other cortisol measures: area under the curve (decline: r = .18; evening: r = .85), morning (decline: r = .83; evening: r = .45), and cortisol awakening response (decline: r = −.33; evening: r = −.10). The evening cortisol and the cortisol decline over the day were used in the analyses because of this pattern of correlations, together with the fact that this study is a follow up on the Beijers et al. (2010) study, in which these variables were also used as independent variables. Additional reasons are that higher evening cortisol and flattened diurnal cortisol rhythms have been related to many psychopathologies (Goodyer, Park, Netherton, & Herbert, 2001), and a flatter diurnal cortisol curve is often found in adults and children under chronic stress (Cicchetti, Rogosch, Gunnar, & Toth, 2010; Gunnar & Vazquez, 2001; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; Miller, Chen, & Zhou, 2007).

Statistical analyses

Multilevel modeling analyses using mixed models in SPSS version 22.0 (SPSS Inc., Chicago, IL) were conducted to test whether maternal reported PNS and prenatal cortisol concentrations were related to children’s health between 18 months and six years of life.

Next, scores higher than three SDs above the mean were defined as outliers and deleted (respiratory N = 11, digestive N = 10, general N = 9). All analyses were performed with and without outliers. The PES variable needed square root transformation to achieve normality. The residuals of the analyses with skin illnesses and antibiotic treatments violated the assumption of normality, even after transformation. Therefore, we conducted multiple hierarchical regression analyses with skin problems (sum of assessments at 30 till 72 months, covering the period of 18–72 months) and antibiotic treatments (sum of prescriptions from one to six years of age) as dependent variables.

Three multilevel analyses were conducted with respiratory, digestive, and general illnesses as dependent variables. At level 1 the illnesses were introduced, which were nested within the children in level 2. First, for each dependent variable the intraclass correlation was calculated to test whether multilevel analyses were appropriate. For respiratory illnesses, the intraclass correlation was 43%, meaning that 43% of the variance was associated with differences between infants. This indicates that a multilevel analysis was appropriate. The intraclass correlation for digestive illnesses was 26%, and for general illnesses 38%, also indicating that multilevel analyses were appropriate. Second, a build-up strategy was used by adding the variables to the model one by one. After adding a variable to the model, the −2 log likelihood ratio scale after least square estimation was examined. If the added variable significantly contributed to the model, it remained in the model. The variables were added as follows: linear time (random), quadratic time, confounders, maternal prenatal anxiety, and stress (PNS, maternal reports and cortisol concentrations), and interactions between time, and PNS predictors (using centered scores). The best fitting models are presented in the results section.

Two multiple hierarchical regression analyses were performed, with skin problems and antibiotic use as dependent variables. Log10 transformations were used to fulfill the assumption of normality. No outliers were detected in these transformed variables. For each dependent variable two models were analyzed. In the first model all possible confounders and prenatal predictors were added. In the second model, to eliminate irrelevant variables and increase power, only variables that explained at least 1% of the variance in the first model were included (part correlation ≥ .10). The final models, with confounders in step 1, and prenatal predictors in step 2, are presented in these results (see also Beijers et al., 2010).

Confounders

The following confounders were included: maternal educational level, prenatal smoking, prenatal alcohol use, birth weight, infant biological sex, attendance of center based childcare, and duration of breastfeeding. Attendance to center-based childcare at 12 months and 30 months (57.5 and 60.9%, respectively) were strongly correlated (r = .78, p < .001). Therefore, only attendance to center-based childcare at 30 months was included. Number of siblings was measured at each time point and included as a repeated measure variable in the multilevel analyses. In the hierarchical regression analyses, birth order (first born or not) was included. To control for postnatal state anxiety, the STAI was included as a confounder at each time point in the multilevel analyses. In the hierarchical regression analyses, a mean score of the postnatal STAI measures was included (significant correlations over time; r’s > .303, p < .001) to avoid multicollinearity.
Main analyses

The final multilevel models with respiratory, digestive, and general illnesses are summarized in Table 4. For all illnesses, a main effect of time shows that respiratory \( \chi^2 (406.54) = -5.46, p < .001 \), digestive \( \chi^2 (419.52) = -3.61, p < .001 \), and general illnesses \( \chi^2 (380.33) = -4.30, p < .001 \) decline over age. With respect to respiratory illnesses, the analyses showed that higher levels of fear of bearing a handicapped child \( \chi^2 (497.198) = 3.69, p < .05 \) and higher levels of prenatal state anxiety \( \chi^2 (497.91) = 2.63, p < .01 \) were significantly related to more child respiratory illnesses. These main effects are moderated by time. The interaction effect of fear of bearing a handicapped child with time shows that the higher the fear, the higher the number of respiratory illnesses in early life, with the association disappearing over time. As indicated by the region of significance the association is significant until 38.3 months \( \chi^2 (382.66) = -2.23, p < .05 \), see Figure 1. The interaction effect of general anxiety with time is similar; the higher the general anxiety during late pregnancy, the higher
Note. Spearman correlations were used for all correlations with the PES, skin problems and antibiotic use (because of non-normality). All other correlations are Pearson correlations.

Table 3. Correlations between maternal PNS variables and children’s health variables for the period between 18 and 72 months of age.

<table>
<thead>
<tr>
<th>PNS questionnaires (N = 174)</th>
<th>STAI</th>
<th>APL</th>
<th>PRAQ-R birth</th>
<th>PRAQ-R handicapped</th>
<th>PES</th>
<th>Cortisol decline</th>
<th>Cortisol evening</th>
</tr>
</thead>
<tbody>
<tr>
<td>STAI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRAQ-Rbirth</td>
<td>.30**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRAQ-Rhandicapped</td>
<td>.30**</td>
<td>.09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-natal maternal cortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol decline (N = 148)</td>
<td>.02</td>
<td>.01</td>
<td>.03</td>
<td>-.17</td>
<td>.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol evening (N = 154)</td>
<td>-.02</td>
<td>-.05</td>
<td>.08</td>
<td>-.07</td>
<td>-.21**</td>
<td>-11</td>
<td></td>
</tr>
<tr>
<td>Cortisol AUCground (N = 140)</td>
<td>-.02</td>
<td>-.02</td>
<td>.07</td>
<td>-.03</td>
<td>-.09</td>
<td>.18**</td>
<td>.85**</td>
</tr>
<tr>
<td>CAR (N = 147)</td>
<td>-.01</td>
<td>-.18**</td>
<td>-.02</td>
<td>-.02</td>
<td>-.12</td>
<td>-33**</td>
<td>-.10</td>
</tr>
<tr>
<td>Child health variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory 30 months</td>
<td>-.20**</td>
<td>.15</td>
<td>.05</td>
<td>.16**</td>
<td>.14</td>
<td>-.06</td>
<td>-.04</td>
</tr>
<tr>
<td>Respiratory 48 months</td>
<td>.36**</td>
<td>.24**</td>
<td>.14</td>
<td>.27**</td>
<td>.14</td>
<td>-.07</td>
<td>-.12</td>
</tr>
<tr>
<td>Respiratory 60 months</td>
<td>.13</td>
<td>.02</td>
<td>.02</td>
<td>.01</td>
<td>.16**</td>
<td>.11</td>
<td>-.06</td>
</tr>
<tr>
<td>Respiratory 72 months</td>
<td>.01</td>
<td>-.08</td>
<td>.05</td>
<td>.10</td>
<td>.06</td>
<td>.01</td>
<td>.03</td>
</tr>
<tr>
<td>Digestive 30 months</td>
<td>.13</td>
<td>-.00</td>
<td>.08</td>
<td>.13</td>
<td>-.13</td>
<td>.20**</td>
<td>.27**</td>
</tr>
<tr>
<td>Digestive 48 months</td>
<td>.11</td>
<td>.09</td>
<td>.13</td>
<td>.09</td>
<td>.02</td>
<td>.05</td>
<td>.02</td>
</tr>
<tr>
<td>Digestive 60 months</td>
<td>.17**</td>
<td>.17**</td>
<td>-.02</td>
<td>.07</td>
<td>.01</td>
<td>-.04</td>
<td>-.07</td>
</tr>
<tr>
<td>Digestive 72 months</td>
<td>-.04</td>
<td>-.06</td>
<td>.01</td>
<td>-.04</td>
<td>-.02</td>
<td>-.05</td>
<td>-.03</td>
</tr>
<tr>
<td>General 30 months</td>
<td>.14</td>
<td>.07</td>
<td>.02</td>
<td>.01</td>
<td>.08</td>
<td>.03</td>
<td>.04</td>
</tr>
<tr>
<td>General 48 months</td>
<td>.27**</td>
<td>.16**</td>
<td>.13</td>
<td>.09</td>
<td>.14</td>
<td>.03</td>
<td>-.02</td>
</tr>
<tr>
<td>General 60 months</td>
<td>.10</td>
<td>.15</td>
<td>.09</td>
<td>.04</td>
<td>.14</td>
<td>.11</td>
<td>-.05</td>
</tr>
<tr>
<td>General 72 months</td>
<td>.02</td>
<td>-.02</td>
<td>.01</td>
<td>.04</td>
<td>.07</td>
<td>.12</td>
<td>.12</td>
</tr>
<tr>
<td>Skin, total 6 years</td>
<td>-.02</td>
<td>.03</td>
<td>.09</td>
<td>.01</td>
<td>-.01</td>
<td>-.04</td>
<td>-.12</td>
</tr>
<tr>
<td>Antibiotic use, total 6 years (N = 130)</td>
<td>-.09</td>
<td>.14</td>
<td>-.19**</td>
<td>.07</td>
<td>-.08</td>
<td>-.09</td>
<td>-.06</td>
</tr>
</tbody>
</table>

*p<.05.
**p<.01.
STAI: state anxiety; APL: daily hassles; PRAQ-Rbirth: fear of giving birth; PRAQ-Rhandicapped: fear of bearing a handicapped child; PES: pregnancy specific daily hassles

Note. The presented results contain dependent variables without outliers. The number of respiratory illnesses in early life. This association remains significant for a longer period of time, namely till 45.2 months of age, as indicated by the region of significance (χ²(380.75) = −3.09, p < .01, see Figure 2).

Furthermore, a larger maternal cortisol decline over the day was related to more child digestive illnesses (χ²(477.94) = 3.10, p < .01). The interaction effect between cortisol decline and time indicates that the larger the maternal cortisol decline over the day, the higher the number of digestive illnesses in early life. This association is significant until the age of 37.3 months, as indicated by the region of significance (χ²(391.51) = −2.87, p < .01, see Figure 3).

Lastly, the multilevel results for general illnesses show that a lower educational level (χ²(135.75) = −3.31, p < .01) and higher maternal postnatal anxiety (χ²(135.92) = 3.39, p < .01) were related to more child general illnesses. PNS was not related to general illnesses.

The final multiple regression models with antibiotic use and skin problems as dependent variables are presented in Table 5. Regarding antibiotic use, model 2 (including the pre-natal predictors), was significant (F(8,113) = 2.88, p < .006), and shows that higher prenatal maternal daily hassles were related to more child antibiotic prescriptions between one and six years of age (β = .24, p < .05). Regarding skin problems, both models were non-significant (p > .05) indicating that PNS was not related to skin problems.

### Discussion

The results of this study show a positive relation between PNS in late pregnancy and child respiratory and digestive
illnesses until toddlerhood, but not at later ages, and antibiotic use between age one and six. Hence, these results extend part of the previous results of the Beijers et al. (2010) study on the links between PNS and illnesses and health symptoms in the first year of life. More precisely, more maternal prenatal general and pregnancy-specific anxiety symptoms were related to more respiratory illnesses. Additionally, interaction effects with time show that the higher the general anxiety and the higher the fear of bearing a handicapped child during late pregnancy, the higher the initial number of illnesses during early life until toddlerhood, and disappearing over time. Furthermore, a larger decline of maternal cortisol during the day was related to more digestive illnesses, until around three years of age. Lastly, higher levels of prenatal daily hassles were positively related to antibiotic use between one and six years of age. In contrast with the study of Beijers

![Interaction effect prenatal PRAQfear handicapped child /C3 time on children's respiratory illnesses. Note: children's illnesses in the preceding year were assessed at 30, 48, 60, and 72 months, reflecting the period between 18 and 72 months. Slope for high STAI: p < .001, slope for mean STAI p < .01 and low STAI p > .05. Region of significance: < 38.30 months.](image1)

![Interaction effect prenatal STAI /C3 time on children’s respiratory illnesses. Note: children’s illnesses in the preceding year were assessed at 30, 48, 60, and 72 months, reflecting the period between 18 and 72 months. Slope for high STAI: p < .01, slope for mean STAI p < .05 and low STAI p > .05. Region of significance: < 45.15 months.](image2)
et al. (2010), PNS was not related to general and skin illnesses.

The positive relation between prenatal anxiety symptoms and the child’s respiratory illnesses is in line with previous studies on maternal prenatal stress and child wheezing and respiratory illnesses, as described in a recent meta-analysis of van de Loo et al. (2016). This relation may be explained by effects of the mother’s anxiety on the development of the offspring’s immune system. Immune development starts during early fetal life and is vulnerable to environmental factors in utero and after birth (Goenka & Kollmann, 2015; Marques et al., 2010). First, an anxious mother’s own immune functioning may be affected, directly influencing the developing fetal immunity through a reduced transplacental transfer of passive immunity. In rats, this transfer of passive immunity occurs especially in late pregnancy (Merlot, Couret, & Otten, 2008). Note, however, that rodent and human pregnancies are not on the same timelines (Holladay & Smialowicz, 2000). For example, in humans the fetal immune system mainly develops in utero, whereas in rats the immune development mainly occurs during late pregnancy and the postnatal period. This suggests that a late pregnancy rat fetus is in a similar developmental state as a mid-pregnancy human fetus and emphasizes the importance of taking also early and mid-pregnancy into account (Merlot et al., 2008). Secondly, the functioning of the placenta might be affected by PNS. To protect the fetus from extremely high concentrations of maternal cortisol during pregnancy, the 11βHSD2 enzyme in the placenta has a protective barrier function, inactivating most of the maternal cortisol into cortisone. However, this barrier function appears to function less optimally in anxious mothers, resulting in the fetus being exposed to more cortisol during pregnancy (O’Donnell et al., 2012). This occurs especially in late pregnancy (O’Donnell et al., 2012; Seth et al., 2015). As glucocorticoids can have an immune-suppressive effect on immune function parameters (Marques et al., 2010), this can result in a suppressed immune response in the infant. Finally, the infant intestinal microbiota, that plays an important role in the development of immunity, may be involved (Dimmitt et al., 2010). Maternal microbes,
transferred from the mother to the infant during and after birth, are the first colonizers of the infant gut (Gosalbes et al., 2013; Tannock, Fuller, Smith, & Hall, 1990). Prenatal anxiety symptoms may negatively affect the composition of the mother’s own microbiota (Sekirov, Russel, Antunes, & Finlay, 2010), hence affecting the microbiota she passes on to her child. In support of this hypothesis, a study in Rhesus monkeys showed that infants from mothers who experienced stress during pregnancy had altered intestinal microbiota and more diarrheic symptoms than infants from mothers who were not stressed (Bailey, Lubach, & Coe, 2004). Furthermore, we recently reported links between maternal PNS and the composition of the infant intestinal microbiota, and how children with this altered composition had more health problems in the first months of life (Zijlmans et al., 2015). For other potential mechanisms linking prenatal anxiety and infant health see the review by Beijers, Buitelaar, and de Weerth (2014).

As mentioned before, the positive relation between prenatal anxiety symptoms and child respiratory illnesses continued until toddlerhood, and later disappeared. As can be seen in Table 2, respiratory illnesses and symptoms are reported more frequently than digestive and general illnesses. The relatively frequent occurrence of respiratory complaints may make them an especially good marker for studying subtle differences in immune functioning in healthy children. Possibly, children from mothers with high levels of prenatal anxiety are born with an immature and less well-functioning immune system, making them especially vulnerable for pathogens in their environment during early years. The fact that the association between prenatal anxiety and respiratory complaints disappears after toddler age, may be a consequence of the general decline in respiratory illnesses over time. This decrease in respiratory symptoms and complaints may make it difficult to discern variance explained by PNS in later childhood years. Alternatively, the disappearance of the association could be explained by the variations in health data collection methods at the different ages: pencil and paper and internet-based assessment versus in-person assessments.

The finding that pregnant mothers with a steeper cortisol decline over the day during late pregnancy had children with more digestive illnesses is difficult to explain. Previous studies showed that a flatter diurnal cortisol curve is often related to chronic stress in children, adolescents, and adults (Cicchetti et al., 2010; Gunnar & Vazquez, 2001; Heim et al., 2008; Miller et al., 2007). Therefore, we had hypothesized that a flatter cortisol decline would represent higher maternal stress and anxiety levels, and that this in turn would be related to more health problems in children. Previous studies on the relation between prenatal maternal cortisol decline and child outcomes support this hypothesis (Zijlmans et al., 2015). For example, one study found that mothers with a flatter daily cortisol decline in late pregnancy gave birth to infants with lower birth weight (D’Anna Hernandez et al., 2012). In the previous study on this population (Beijers et al., 2010), a relation was found between a flatter maternal late pregnancy slope and more infant respiratory illnesses in the first year, making the present results all the more intriguing. One possible explanation for our present findings is that in our sample the cortisol decline was positively correlated with the total cortisol concentrations during the day ($r = .18, p < .05$; Area Under Curve with respect to the ground). This could potentially explain our findings, as maternal cortisol concentrations can cross the placenta and in turn affect HPA axis development, possibly increasing basal and cortisol reactivity concentrations after birth (Tollenaar et al., 2011). This in turn could affect gut immune cells, motility, permeability, and barrier function, which could influence the composition and function of the gut microbiota (Cryan & Dinan, 2012; Kelly et al., 2015; Moloney et al., 2016). This is supported by studies showing a relation between HPA axis and functional gastrointestinal disorders, such as Irritable Bowel Syndrome, or IBS (Borre, Moloney, Clarke, Dinan, & Cryan, 2014; Carabotti, Scirocco, Maselli, & Severi, 2015; O’Mahony, Dinan, & Cryan, 2017). Another mechanism that could explain the relation between prenatal maternal cortisol concentrations and child digestive illnesses is the transfer of maternal cortisol postnatally, via breastmilk, resulting in higher infant cortisol concentrations, and again, the above-mentioned negative effects on the gut, and microbiota (Zijlmans et al., 2015). However, since other prenatal maternal cortisol measures were not related to digestive illnesses and given the paucity of earlier research and especially research reaching into middle childhood, it is not yet possible to draw firm conclusions. More extended longitudinal studies on the development of child health in the light of maternal prenatal cortisol physiology are needed to increase our understanding on the subject. Studies involving large birth cohorts would be especially helpful in this context.

No relation was found between PNS and skin illnesses between 18 months and six years of life, while Beijers et al. (2010) did find a relation between PNS and skin illnesses during the first postnatal year. In line with these findings, an epidemiological study that also focused on the first six years of life, showed a relation between stress-related maternal factors during pregnancy and an increased risk for childhood eczema up to the age of 2 years but not later (Sausenthaler et al., 2009). Additionally, the lack of associations in this study may be explained by the general decrease of eczema, one of the most frequently reported skin illnesses in our sample, over time (Nivel, 2013).

A positive relation was found for postnatal anxiety and general illnesses. This secondary finding could be explained in at least three manners. First, anxious mothers may detect and report more general illnesses in their children because they are more focused on their child’s well-being and notice more subtle health changes. Second, anxious mothers may be less capable of buffering their children from environmental stressors and may even provoke stress in their children, which in turn may lead to immunosuppression and more general illnesses in the children. And third, children who are often ill may provoke anxiety in mothers. The general illnesses measured in our study consisted mainly of fever and ear infections. A study by Lagerlov, Helseth, and Holager (2003) in preschool children showed that fever often results in anxious feelings in caregivers. Parents feel an increased responsibility for the child and the burden of parenting.
A strong point of this research is the longitudinal design, in which illnesses were measured every year, covering the period from 18 months to age six. Also, in addition to diagnosed illnesses (e.g. eczema and asthma) we recorded subtle health complaints (e.g. coughing and fever), which may be a better representation of the general functioning of the immune system. Such health complaints are also of societal relevance as they often result in parents staying at home from work to care for the child. This is particularly the case with fever, which is part of the category general illnesses in our study. Children suffering from fever are not allowed to go to daycare or school. Furthermore, mothers do not often delegate the care of a sick child to others and, therefore, mostly stay at home to care for their child during illness (Lagerlov et al., 2003). Finally, in the analyses, we controlled for postnatal anxiety during all measurement points, and PNS and child’s health were measured using different methods (questionnaires and cortisol) and different sources (mothers and general practitioners).

Our research also has some limitations. The assessment of subtle health complaints made us necessarily dependent on maternal reports, which may be subjective. However, we also found a positive relation between PNS and antibiotic use, supporting the relation between PNS and child health by medication prescribed by general practitioners. Furthermore, mothers from our sample are highly educated which could affect the generalizability of the study. For future studies, we would recommend to shorten the reporting period of health complaints from one year to monthly or bimonthly reporting. Also, other potential confounders or mediators, such as maternal postnatal stress (epi)genetics, immune parameters, and diet that could influence the relation between prenatal stress and child health are important to include in future studies. Finally, to obtain more insight in potentially sensitive gestational periods in which the fetus is more susceptible to maternal cortisol concentrations and lower psychological wellbeing, we recommend to study the impact of fetal exposure to maternal PNS during all trimesters of pregnancy.

To conclude, this research showed that prenatal anxiety symptoms and cortisol are related to children’s respiratory and digestive illnesses in early life, until around the age of three years. Furthermore, higher prenatal anxiety was related to more child antibiotic use between one and six years of age. Programming effects of PNS may lie behind these apparently persistent relations. Although replication studies are warranted before firm conclusions can be drawn, these findings point in the direction of possible effects of PNS persisting beyond the first year of life and into toddlerhood, but disappearing at older ages.

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References


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