Maternal stress during pregnancy and neurodevelopmental outcomes of children during the first 2 years of life

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Aim: A growing body of literature documents associations between maternal stress in pregnancy and child development, but findings across studies are often inconsistent. The aim of this study was to estimate the association between exposure to different kinds of prenatal stress and child psychomotor development.

Methods: The study population consisted of 372 mother-child pairs from Polish Mother and Child Cohort. The analysis was restricted to the women who worked at least 1 month during pregnancy period. Maternal psychological stress during pregnancy was assessed based on: the Subjective Work Characteristics Questionnaire, Perceived Stress Scale and Social Readjustment Rating Scale. The level of satisfaction with family functioning and support was evaluated by APGAR Family Scale. Child psychomotor development was assessed at the 12th and 24th months of age by Bayley Scales of Infant and Toddler Development.

Results: Negative impact on child cognitive development at the age of two was observed for the Perceived Stress Scale ($\beta = -0.8; P = 0.01$) and the Social Readjustment Rating Scale ($\beta = -0.4; P = 0.03$) after adjusting for the variety of confounders. Occupational stress, as well as satisfaction with family functioning, was not significantly associated with child psychomotor development ($P > 0.05$).

Conclusions: The study supports the findings that prenatal exposure to maternal stress is significantly associated with decreased child cognitive functions. In order to further understand and quantify the effects of prenatal stress on child neurodevelopment further studies are needed. This will be important for developing interventions that provide more assistance to pregnant women, including emotional support or help to manage psychological stress.

Key words: child psychomotor development; family functioning; life events stress; life stress; occupational stress.

What is already known on this topic

1. A growing body of literature documents associations between maternal stress in pregnancy and child development, but findings across studies are often inconsistent.
2. The effects depend to a large extent on the kind of stressors, their objective intensity and duration, time of occurrence and mother’s subjective perception of a stressor-related threat.
3. Existing studies have focused on different aspects of stress covering general, occupational, pregnancy-related stress, daily hassles and relevant life events.

What this paper adds

1. The study indicated that child neurodevelopment is differentially affected by different kinds of maternal stressors.
2. Children prenatally exposed to maternal life stress had decreased cognitive functions.
3. Occupational stress and satisfaction with family functioning were not significantly associated with child psychomotor development.

Psychological stressors, a generic term that includes a wide range of different types of events, can be acute – resulting from external events, as well as chronic – such as daily hassles. Negative health effects of stress depend on many factors including its duration and/or magnitude.1 The following outcomes are associated with prenatal stress: congenital malformations, lower birthweight or shorter gestation, and neurodevelopmental as well as psychopathological outcomes.2–11

While there is general agreement that maternal stress is a risk factor for future child’s health, various factors contribute to the inconsistencies reported in epidemiological studies including differences in stress measurements, and the lack of consensus on the definition of maternal stress.6,12,13 Existing studies have focused on different aspects of stress covering general, occupational, pregnancy-related stress, daily hassles and relevant life...
events. Stress results from a perceived imbalance between acute and chronic stressors and individual resources including personality, social support and lifestyle, leading to the increased risk of maladaptive cognitive, emotional and behavioural responses. In addition, instruments used to assess stress of a general population might not be appropriate for the period of pregnancy.\textsuperscript{12,13} Other difficulties in the studies evaluating the impact of prenatal stress on child neurodevelopment are related to inadequate control for confounding factors and selection of appropriate tests for child development assessment.

This study intends to address the above-mentioned criticalities in human studies. To this aim, we estimated the association between different kinds of maternal stress during pregnancy and child psychomotor development in a prospective mother-child cohort. Prospective cohort study design enables longitudinal assessment of a variety of stressors that may influence a child’s neurodevelopment. Additionally, the analysis includes several potential confounding factors and a well-standardised test evaluating neurodevelopmental effects in young children.\textsuperscript{14}

**Methods**

**Study design and population**

The mother-child pairs included in this study were part of the Polish Mother and Child Cohort (REPRO\_PL) – a multicentre prospective cohort established in 2007 with the aim to evaluate environmental factors contributing to the pregnancy outcomes, children’s health and neurodevelopment.\textsuperscript{15,16} Briefly, in REPRO\_PL women were recruited if they fulfilled the following inclusion criteria: single pregnancy up to 12 weeks of gestation, no assisted conception, no pregnancy complications and no chronic diseases as specified in the study protocol.\textsuperscript{17} The whole cohort comprises 1700 mother-child pairs followed-up from pregnancy period up to 2 years of age (with the ongoing stage of the study focused on children at age of 7).

The participants were interviewed once in each trimester of pregnancy to collect and update socio-demographic data, medical and reproductive history, information about environmental, occupational and life-style factors. Children were assessed for their exposure, health status and neurodevelopment at 1 and 2 years of age.\textsuperscript{18,19}

Taking into account financial and organisational feasibility of the study, the present assessment is restricted to subpopulation from the Lodz district (central Poland). This article is intended to assess the impact of prenatal stress on child neurodevelopment, considering: occupational stress, perceived levels of stress in the daily life, family functioning and occurrence of stressful life events. Therefore, the analysis was restricted to the population of mothers working at least 1 month during pregnancy (464 out of 547; 85\% of the population). Complete data on stress during pregnancy were available for 377 of the 464 women who indicated being employed during pregnancy.

The study was approved by the Ethical Committee of the Nofer Institute of Occupational Medicine, Lodz, Poland.

**Assessment of maternal stress during pregnancy**

Between the 20th and the 24th week of gestation the study participants completed three self-administered questionnaires to measure occupational stress, life stress and family functioning. A fourth questionnaire measuring life events stress was completed between the 30th and 34th week of gestation.

There is quite a large number of instruments for stress measurement based on different theoretical approaches and focusing on different aspects of stress phenomenon. The decision about the selection of the tests/scales for stress measurements for this study was determined by scientific (proven to be sensitive in studies on relationship between stress and health outcomes), pragmatic (adopted and psychometrically verified in Polish conditions) and economical (easy to fill in with the simple standardised answer scale) reasons.

Occupational stress was assessed using the Subjective Work Characteristics Questionnaire (SWCQ) by Dudek \textit{et al.}\textsuperscript{20} This widely used scale for diagnosis of occupational stress in Poland consists of 55 items describing potential occupational stressors. The subjects were asked to state if a given characteristic is present in their work position and how stressful they find it to be. Each item had the following answers: (i) a given psychosocial factor is not present; (ii) it is present but it is neither irritating nor disturbing; (iii) it is irritating or disturbing from time to time; (iv) it is quite often irritating or disturbing; and (v) it is irritating all the time. The general indicator of the level of stress was the sum of points marked by each woman. In the present analysis an additional indicator of occupational stress – the number of stressful work characteristics as pointed out by each subject – was used.

Life stress was assessed by means of the Perceived Stress Scale (PSS, a 10-item scale) which measures an individual’s level of perceived stress in the past month.\textsuperscript{21} The items are designed in such a way to tap into unpredictable, uncontrollable and overloaded the respondents find their lives. The response options for each item indicate the frequency with which it occurs from 0 – never to 4 – very often. The results were the sum of points. The higher the score obtained by the respondents, the higher the level of their global stress.

Satisfaction with family functioning and support was assessed using Polish adaptation of the APGAR Family Scale by Smilkstein.\textsuperscript{22,23} The scale consists of seven statements related to help, acceptance or support from the family. The women indicated the frequency of experiencing positive behaviour from their family on a 3-point scale, from 3 almost never to 1 very often. The higher the overall score, the lower the level of support experienced from the family.

Life events as stress factors were measured by a modified version of the Social Readjustment Rating Scale (SRRS).\textsuperscript{24} Not only was the presence of critical life events during pregnancy measured but its impact on women’s emotional well-being was also assessed. Thus, we obtained two indices of stress: a sum impact scores assigned to the pointed life events and an individual perception of stress related to indicated events, which was the sum of the scores calculated from the answers to the question ‘To what extent did the event have impact on your emotional well-being?’ ranging from ‘no’ to ‘extreme impact’ (0–3).

**Child neurodevelopment assessment**

Bayley Scales of Infant and Toddler Development (3rd edition) was used to assess children’s neurodevelopment at around 12 and at 24 months of age.\textsuperscript{14,19} The detailed concerning regarding child psychomotor assessment has been published elsewhere.\textsuperscript{16–19}
We excluded data from five children, since their Bayley test outcomes were of poor quality because of pathologies or less-than-optimal cooperation of the child. Finally, based on availability of the data on prenatal stress exposure and psychomotor development test results, the analysis was performed for 372 children (337 children were examined at 12 months of age, 184 had the examination repeated at 24 months and 35 were examined only at 24 months of age).

### Confounding variables

The evaluated covariates that were identified from the literature were as follows: parental age and education; marital status, place of residence, socioeconomic status (SES) and their changes over the study period; child gender; major pregnancy complications which appeared after inclusion into the study; type of delivery; gestational age and birth outcomes; breastfeeding; number of siblings; day care attendance; active/passive smoking and alcohol consumption during pregnancy; child environmental tobacco smoke (ETS) exposure after birth; child health status and hospitalisations. Socio-demographic data and information about alcohol consumption during pregnancy were obtained based on questionnaires. SES of the family was measured based on the following question: ‘What is the financial status of your family?’ Women who declared that they have sufficient money for current expenses and that it is possible for them to put a substantial sum aside were allocated into the high income category. Those who indicated sufficient money for current expenses, with possibility to put aside some money were allocated into the medium and those who declared insufficient money for current expenses into the low income category. The information about the alcohol consumption during pregnancy was obtained by questionnaire. The mothers were asked about the types of alcoholic drinks (beer, wine and spirit) and frequency of their drinking (with possible answers: (i) never; (ii) less than once per month; (iii) 1–3 times per month; (iv) 1–3 times per week; (v) 4–5 times per week; and (vi) everyday). Taking into account percentages of drinkers, in the current assessment the women were divided into two categories: (i) no alcohol consumption during pregnancy if for each category of alcoholic drinks the frequency was indicated as (i) or (ii) and (2) alcohol consumption during pregnancy if for any of each category of alcoholic drinks the frequency was indicated as (iii) to (vi). Prenatal exposure to tobacco constituents was assessed based on cotinine level in saliva and child ETS exposure after birth based on cotinine level in urine. The biomarker levels were measured using LC-MS/MS-ESI+. As the cotinine levels in each trimester of pregnancy were highly correlated (the first/second and the second/third trimester: \( r = 0.8 \); the first/third trimester: \( r = 0.7; P < 0.001 \)) the samples from the first trimester were included in analyses. The cotinine levels were log transformed. Child health status was assessed by means of frequency of respiratory diseases and otitis media.

### Statistical analysis

First, univariate analysis was performed to assess the effect of each potential confounding variable on the Bayley test results. The following confounders \((P \leq 0.1)\) were identified to be included in the multivariate model: child gender \((P \leq 0.08)\), parental age \((P \leq 0.03)\) and education \((P \leq 0.08)\), prenatal stress exposure \((P \leq 0.05)\), child ETS exposure \((P < 0.06)\), child health status \((P < 0.1)\) and, in the case of cognitive development, marital status \((P < 0.03)\), changes of marital status during pregnancy and after delivery \((P = 0.09)\) and day care attendance \((P < 0.08)\). As some confounders, namely mother and father’s age as well as mother and father’s education were highly correlated, sensitivity analysis was performed and finally only maternal age and education were selected in the final model. The second stage of the analysis focused on the evaluation of the impact of prenatal stress exposure on child psychomotor performance at 1 and 2 years of age. In the first model, confounding effects of the examiner who administered the test were taken into account. The second model was conducted with additional adjustment for potential confounders. Statistical significance was specified as \(P < 0.05\). The analysis was performed using the R software.

### Results

#### Child and parental characteristics

Demographic and exposure characteristics of mothers and children are summarised in Table 1. About 51% of the children were girls. On average, the children were born at the 39th week of gestation \((\pm 1.5 \text{ week})\) with the mean birthweight of 3370 g \((\pm 478 \text{ g})\). About 58% of the children did not have siblings and 7% of mothers indicated child day care attendance at one and 23% at 2 years of age. The mean maternal and paternal age was 31 \((\pm 4.3)\) and 33 \((\pm 5.6)\) years, respectively. Most of the mothers and 43% of the fathers had a university degree. About 9% of the women indicated alcohol consumption and 10% were classified as active smokers during pregnancy.

The mean composite scores for psychomotor development were average or high average at 1- and 2-year-old assessments (Table 2). About 39% of the children were hospitalised at least once and 54% of them were ill at least once within the 2-year period.

#### Characteristics of the maternal stress and family functioning during pregnancy

Occupational stress measured by the SWCQ with the mean of 93 points (range 57–180) and the mean number of stressful psychosocial factors at work equal 22 (range 2–50) can be interpreted as moderate (Table 2). The level of stress measured by PSS (mean 18, range 2–34) was also medium. The mean for SRRS, which was 101 (range 40–435), indicated a low level of stress in life and low probability of developing a stress-related disorder. The demographic and neurodevelopmental characteristics stratified by prenatal stress are included in Table S1 (Supporting Information).

The mean APGAR Family score was 10 points (range 7–19), which indicates high satisfaction with family support and functioning.

#### Maternal stress, family functioning and child neurodevelopment

Table 3 presents the associations between prenatal stress and child psychomotor development (adjusted for examiner). Life
stress assessed by PSS was negatively associated with child cognitive development at the age of two \((\beta = -0.7; P = 0.01)\). The same pattern was observed when considering life events \((\beta = -0.3; P = 0.04)\). No association was observed between occupational stress and the analysed domains of child development.

Mother’s satisfaction with family functioning and support during pregnancy was not significantly associated with the child’s psychomotor development.

The final model confirmed the results observed in Model 1 - (Table 4). Negative impact on child cognitive development at the age of two was observed for PSS \((\beta = -0.8; P = 0.01)\) and SRRS \((\beta = -0.4; P = 0.03)\).

**Discussion**

A number of studies report that prenatal stressors influence brain development. The effects depend to a large extent on the kind of stressors, their objective intensity and duration, time of occurrence and mother’s subjective perception of a stressor related threat.11 We show here that child neurodevelopment is differentially affected by different kinds of maternal stressors. In this study prenatal exposure to maternal stress measured by the PSS and SRRS was associated with decreased cognitive functions at 2 years of age. Occupational stress and satisfaction with family functioning were not significantly associated with the child’s psychomotor development.

It is worth noting that we did not find any associations between prenatal stress and children’s development at the age of one. Moreover, stress-related effects occurred only for cognitive development. Our results might be partly attributable to the characteristics of Bayley Scales at the age of 12 and 24 months. Cognitive development in the first year of life is measured mainly by observation of the child and obviously by non-verbal tasks. At the age of 2 years, tasks become more complex and the attention is
paid to exploration activities and adaptation to new situations. Moreover, according to Piaget’s theory, our study covered the first two stages of child cognitive development: sensorimotor stage (0–24 months of age) and early phase of pre-operational stage (between the ages of two and seven).26–28 Some of the toddlers in our study at the time of the second measurement might have already been at the beginning of pre-operational stage characterised by dynamic language and further cognitive development. Thus, our results support the concept that maternal stress does not appear to be significant for coordination of sensation through reflexive behaviours and primary circular reactions, visual-motor coordination but seems to be an important factor for development of cognitive schemata, mental operations and insight.

Our findings are consistent with those of Zhu et al. (2014) who reported that stressful life events predicted a lower mental development but had no impact on psychomotor development index of 16- to 18-month-old children.12 Also in the study of Quebec women who were pregnant during a severe ice storm, the level of objective stress the mother experienced was related to poorer intellectual and language abilities in 2-year-old toddlers.29 High amounts of daily hassles in early pregnancy were associated with lower development in the study by Huizink et al.30

The methods used for assessment of exposure and outcome of interest play important role in the studies evaluating the association between maternal stress and child neurodevelopment. Firstly, tools for assessment of infants and toddlers neurodevelopment are less reliable and more situation-sensitive than the methods used for older children, which may lead to a bigger measurement error. Secondly, the way of stress exposure measurement may be crucial.31,32 The recently published review of psychometric instruments to assess stress during pregnancy indicated that, among the four different tests for measuring disturbances of daily hassles, PSS is the best instrument, for its excellent reliability data in pregnant samples and its high validity data in non-pregnant samples.13 Limitation of the PSS is that the scores obtained by the respondents reflect life stress intensity only in the preceding month. Of the five different instruments to measure life events as a stress factor, Prenatal Life Events Scale was identified by the authors as the best available.13 In our study, we selected SRRS with the adaptation of asking respondents to report how undesirable or negative a given event was. As concerns measurement of occupational stress, the advantage of SWCQ is the availability of the norms for the Polish population. In our study low/medium level of stress was indicated by 79% of the respondents. It needs to be pointed that in Poland <20% of women continue working until late pregnancy.33 Therefore, a relatively small proportion of pregnant women was exposed to occupational stress during entire pregnancy. Taking this into account, it seems that the working condition is of less importance than the other sources of stress during pregnancy period. In our analysis, prenatal perceived family support was not associated with any of the measured scores of child psychomotor development. It is noteworthy that the mean score obtained by the respondents in our study indicated that they were generally pleased with family support.

This study has several strengths. First, the prospective study design with well assessed exposure is the main advantage of this analysis. Prenatal exposure to maternal stress was determined taking into account different sources of stress. Second, a series of detailed questionnaires allow for a reliable assessment of

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Table 2  Characteristics of the exposure and outcome variables

| Variables                                      | n  | Mean | SD  | Median | Min | Max  |
|------------------------------------------------|----|------|-----|--------|-----|------|
| Subjective Work Characteristics Questionnaire |    |      |     |        |     |      |
| Sum in points (potential range: 55–275)       | 372| 93.1 | 23.9| 89.0   | 57.0| 180.0|
| Number of psychosocial factors at work (potential range: 0–55) | 372| 21.6 | 9.4 | 21.0   | 2.0 | 50.0 |
| APGAR Family Scale                            |    |      |     |        |     |      |
| Sum in points (potential range: 7–21)         | 372| 9.7  | 2.4 | 9.0    | 7.0 | 19.0 |
| Perceived Stress Scale                        |    |      |     |        |     |      |
| Sum in points (potential range: 0–40)         | 372| 17.5 | 5.6 | 17.0   | 2.0 | 34.0 |
| Social Readjustment Rating Scale              |    |      |     |        |     |      |
| Sum of wages (potential range: 40–1398)       | 367| 100.7| 78.8| 78.0   | 40  | 435.0|
| Subjective stress related to events (sum of scores) (potential range: 0–120) | 367| 4    | 5   | 2      | 0   | 26   |
| Composite score for 1-year-old children, n = 337 |    |      |     |        |     |      |
| Cognitive                                     |    | 107.2| 10.5| 110.0  | 80.0| 145.0|
| Language                                      |    | 108.7| 13.6| 109.0  | 68.0| 141.0|
| Motor                                         |    | 105.8| 14.0| 107.0  | 73.0| 151.0|
| Composite score for 2-year-old children, n = 219 |    |      |     |        |     |      |
| Cognitive                                     |    | 113.0| 16.3| 110.0  | 80.0| 145.0|
| Language                                      |    | 102.5| 13.0| 100.0  | 74.0| 144.0|
| Motor                                         |    | 112.3| 14.3| 110.0  | 73.0| 154.0|

Max, maximum; Min, minimum; SD, standard deviation.
Table 3  Association between prenatal stress exposure and child cognitive, language and motor development – Adjusted for examiner

|                          | 1-year-old children | 2-year-old children |
|--------------------------|---------------------|---------------------|
|                          | Cognitive           | Language            | Motor               | Cognitive           | Language            | Motor               |
| Subjective Work Characteristics Questionnaire | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Number of psychosocial factors at work | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| APGAR Family Scale       | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Perceived Stress Scale   | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Social Readjustment Rating Scale | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum of impact scores     | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Subjective stress related to events | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |

*\( P \leq 0.05. \) \( \text{\#} n = 337. \) \( \text{\#} n = 219. \) \( \text{\#} n = 332. \) \( \text{\#} n = 214. \) CI, confidence interval.

Table 4  Association between prenatal stress exposure and child cognitive, language and motor development – Multivariate model

|                          | 1-year-old children | 2-year-old children |
|--------------------------|---------------------|---------------------|
|                          | Cognitive           | Language            | Motor               | Cognitive           | Language            | Motor               |
| Subjective Work Characteristics Questionnaire | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Number of psychosocial factors at work | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| APGAR Family Scale       | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Perceived Stress Scale   | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum in points            | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Social Readjustment Rating Scale | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Sum of impact scores     | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |
| Subjective stress related to events | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) | \( \beta \) (95% CI) |

*\( P \leq 0.05. \) Model adjusted for: Examiner, child gender, maternal age, maternal education, cotinine level in maternal saliva during pregnancy, cotinine level in child urine, child health status and for cognitive development additionally marital status, changes in marital status during the study period and child day care attendance. CI, confidence interval.
confounding variables. By restricting our population to healthy women, we were able to eliminate additional confounding factors. Finally, in this analysis we assessed multiple aspects of child development.

Limitations of the study also need to be considered. Firstly, although we have measured different aspects of stress, we did not cover maternal anxiety, depression and stress related to pregnancy and performing parental roles, which can also be related to child neurodevelopment. Secondly, we cannot exclude the possibility that confounding by unmeasured risk factors (e.g. maternal IQ, quality of mother-child relationship and home environment, maternal stress after child birth) produced associations between exposure of interest and child development. In addition, the questionnaires measuring stress were applied during the second and third trimesters of pregnancy so the exact time of exposure allowing for assessment of critical window was not possible.

Conclusion

Our study found associations between prenatal exposure to maternal stress and child decreased cognitive functions. In order to further understand and quantify the effects of prenatal stress on child neurodevelopment further studies are needed. The future studies should be based on prospective study design with assessment of all potential sources and aspects of stress. An important issue is related to selection of the appropriate instruments for the assessment of specific stress with possible inclusion of physiological measures. Identification of periods of increased vulnerability during pregnancy, using repeated measurements, on child psychomotor development is also recommended. In addition, a crucial aspect which needs to be addressed is related to adequate controlling for confounders. Further follow-up studies are also needed to explore the long-term outcomes of prenatal stress. Lastly, investigation of the effectiveness of interventions that provide more assistance to pregnant women, such as emotional support or help to manage psychological stress through positive emotion-focused or problem-focused coping, could be essential.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:

Table S1. Demographic and neurodevelopmental characteristics stratified by prenatal stress.