



ORIGINAL ARTICLE

Maternal psychological distress during pregnancy and childhood cardio-metabolic risk factors



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Abstract *Background and aims:* Previous studies suggest that psychological distress during pregnancy may lead to fetal developmental adaptations, which programme cardio-metabolic disease of the offspring. We examined the associations of maternal overall psychological distress, depression and anxiety during pregnancy with cardio-metabolic risk factors in 10-year-old children and explore potential sex-specific differences.

Methods and results: In a population-based prospective cohort study among 4,088 mothers and their children, information about overall psychological distress, including depression and anxiety was obtained through the Brief Symptom Inventory during pregnancy. We measured child blood pressure and heart rate and insulin, glucose, serum lipids and C-reactive protein blood concentrations at 10 years. Analyses were performed in the total group and in boys and girls separately. Psychological distress during pregnancy was associated with higher childhood heart rate among boys only (differences 0.34 (95% Confidence Interval (CI) 0.18, 0.50) standard deviation scores (SDS), 0.22 (95% CI 0.06, 0.38) SDS, 0.33 (95% CI 0.19, 0.48) SDS, for overall psychological distress, depression and anxiety, respectively). Maternal anxiety during pregnancy was associated with higher childhood triglycerides among girls (difference 0.35 (95% CI 0.17, 0.53) SDS). Maternal psychological distress was not associated with childhood blood pressure, cholesterol, insulin, glucose and C-reactive protein concentrations.

Conclusions: Maternal psychological distress may influence their offspring heart rate and triglycerides concentrations. Further studies are needed to replicate these findings and assess the long-term cardio-metabolic consequences of maternal psychological distress.

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Introduction

Pregnancy is a period of great physiological and psychological transformations [1]. Psychological distress has been reported by 10–20% of women during pregnancy [2]. Maternal psychological distress may cause a suboptimal intrauterine environment leading to long-term consequences on growth and health of the offspring [3,4]. More specifically, intrauterine stress exposure may affect offspring cardio-metabolic development via dysregulation of the hypothalamic-pituitary-adrenal axis, increase of inflammatory responses and changes in the balance of the autonomic nervous system [5–7]. In addition, growing evidence suggested sex-specific differences in fetal programming in response to stress, which may result in sex-specific risks for later diseases [8,9]. We have previously reported that maternal psychological distress during pregnancy was not associated with offspring infant heart rate and early-childhood blood pressure [7,10]. Other studies reported inconsistent associations of distress during pregnancy with blood pressure and insulin resistance in children and adolescents [11–14]. To date, no studies have focused on the associations of maternal psychological distress during pregnancy with childhood lipids profile or inflammatory markers. Insight into the associations of maternal distress during pregnancy with childhood cardio-metabolic risk factors may help to develop future preventive strategies.

We examined, in a population-based prospective cohort study among 4,088 mothers and their children, the associations of maternal overall psychological distress, depression and anxiety during pregnancy with blood pressure, heart rate, lipids profile, glucose metabolism, and C-reactive protein concentrations in 10-year-old children. We explored whether the associations with cardio-metabolic risk factors differ for boys and girls.

Methods

Study design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until adulthood in Rotterdam, the Netherlands. The study was approved by the local Medical Ethics Committee of Erasmus MC (MEC 198.782/2001/31). Pregnant women were enrolled between 2002 and 2006. Written informed consent was obtained for all participants. In total, 8,879 mothers were enrolled during prenatal period [15]. We excluded pregnancies not leading to singleton live births ($N = 246$). Information about psychological distress during pregnancy was available in 6,548 of 8,633 mothers with singleton children. For 2,460 children, no information on any measurement of cardio-metabolic risk factors at 10 years was available. Thus, 4,088 mothers and children had information on psychological distress during pregnancy and at least one measurement of cardio-metabolic risk factors at 10 years. The specific population for analysis for

each outcome is shown in the flowchart (Fig. S1 in Supplementary Materials).

Psychological distress during pregnancy

Information on maternal psychological distress was obtained through the Brief Symptom Inventory (BSI) that was mailed to participants and returned at around 20 weeks of gestation. The BSI is a validated self-report questionnaire with 53 items, describing the psychopathologic problems and complaints that mothers may have experienced in the preceding 7 days [16]. These items include a broad spectrum of psychological symptoms, divided in 9 dimensions (anxiety, depression, hostility, phobic anxiety, interpersonal sensitivity, obsessive-compulsiveness, paranoid ideation, psychoticism, somatization). We used the overall psychological distress scale (Global Severity Index) and 2 symptom scales (depression and anxiety) to define psychological distress. We chose these subscales because depression and anxiety are widely used as indicators of psychological distress during pregnancy [1]. To indicate the extent of the symptoms, the items were rated on a 5-point unidimensional scale ranging from '0' (not at all) to '4' (extremely). A total score was provided for each symptom scale by summing the item scores and dividing the results by the number of reported symptoms. Then, the symptoms were dichotomized (into "yes" or "no" categories) by using the following cutoffs derived from a psychiatric outpatient sample of Dutch women: 0.71 for overall psychological symptoms scale; 0.80 for depression scale and 0.71 for anxiety scale [17,18].

Cardio-metabolic risk factors at 10 years

As previously described, children around the age of 10 years were invited to visit our research center at Erasmus MC-Sophia Children's Hospital [19]. Blood pressure and heart rate were measured at the right brachial artery four times with one minute intervals, using the validated automatic sphygmomanometer Datascope Accutor Plus (Paramus, NJ) [20]. We calculated the mean value for systolic and diastolic blood pressure and heart rate using the last three measurements of each participant. Non-fasting blood samples were collected to determine serum concentrations of glucose, insulin, total cholesterol, high-density lipoprotein (HDL)-cholesterol and triglycerides. Glucose, total cholesterol, HDL-cholesterol and triglycerides concentrations were measured using the c702 module on the Cobas 8000 analyzer. Insulin was measured with electrochemiluminescence immunoassay (ECLIA) on the E411 module (Roche, Almere, the Netherlands) [21]. Low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald formula [22].

Covariates

We obtained information on maternal age, ethnicity, educational level, marital status, body mass index before

pregnancy, smoking habits and alcohol consumption during pregnancy, and folic acid supplement use, by questionnaire. Information on maternal selective serotonin reuptake inhibitors (SSRIs) use in pregnancy was obtained by questionnaires and prescription records from pharmacies [23]. Information on child sex, gestational age at birth and birth weight were available from medical records. We calculated body mass index (kg/m^2) at 10 years from height and weight, both measured without shoes and heavy clothing.

Statistical analysis

We compared subject characteristics between women with and without psychological distress using Pearson's chi-square tests, independent sample t-tests and Mann–Whitney tests. Similar statistical tests were performed to compare characteristics between participants and non-participants. We used linear and logistic regression models to assess the associations of maternal overall psychological distress, depression and anxiety with childhood cardio-metabolic risk factors. We included covariates in the models if they were associated with maternal psychological distress and childhood cardio-metabolic risk factors in our study and if they changed the effect estimates substantially ($>10\%$) for at least one outcome. Thus, all models were adjusted for maternal age, ethnicity, educational level, marital status, body mass index before pregnancy, alcohol consumption, smoking, folic acid and selective serotonin reuptake inhibitors use during pregnancy. Child body mass index at 10 years might be in the causal pathway of the associations of maternal overall psychological distress with childhood cardio-metabolic risk factors. We assessed whether these associations were independent of child body mass index, by additionally adjusting our models for this covariate. The distributions of insulin and triglycerides were skewed and natural logged transformed. Since C-reactive protein was not normally distributed and the log-transformation did not yield an acceptable distribution, we categorized C-reactive protein concentrations into <3 mg/l (normal levels) or ≥ 3 mg/l (high levels) in line with previous studies [24]. To enable comparison of effect sizes of different outcome measures, we constructed standard deviation scores (SDS) ($(\text{observed value} - \text{mean})/\text{SD}$). Analyses were performed for the total group and for boys and girls, separately. We found statistically significant sex interactions for the associations of maternal psychological distress with child heart rate and diastolic blood pressure. We did not observe statistical interactions for maternal ethnicity, child's gestational age at birth, birth weight and body mass index at 10 years. To enable interpretation of statistical significance level, we presented p -values < 0.05 and p -values < 0.01 . Missing data in covariates (ranging from 0 to 21%) were multiple-imputed using Markov chain Monte Carlo approach. Five imputed datasets were created and analyzed together. All statistical analyses were performed using the Statistical Package of Social Sciences version 24.0 for Windows (SPSS IBM, Chicago, IL, USA).

Results

Subject characteristics

Participants characteristics are presented in Table 1. Of all pregnant women, 8.5%, 8.6% and 9.5% experienced overall psychological distress, depression and anxiety, respectively. Women with psychological distress during pregnancy were more often younger, non-European, lower educated, without partner and were more likely to be smokers compared to women without psychological distress (p -values < 0.05). Non-response analyses showed that mothers of children with follow-up data available were slightly older, more often European, higher educated and reported less clinical psychological distress during pregnancy compared to mothers of children without follow-up data available (p -values < 0.05) (Table S1 in Supplementary Materials).

Maternal psychological distress and childhood blood pressure and heart rate

In the unadjusted models, maternal overall psychological distress, depression and anxiety during pregnancy were associated with higher childhood blood pressure in the total group and among boys (p -values < 0.05). Maternal overall distress and anxiety were also associated with higher childhood systolic and diastolic blood pressure, respectively among girls (p -values < 0.05). All maternal psychological distress scales were associated with higher childhood heart rate among boys and girls (p -values < 0.05) (Table S2 in Supplementary Materials). After adjustment for potential confounders, no associations were observed between maternal overall psychological distress, depression and anxiety and childhood blood pressure in boys and girls. All maternal psychological distress scales remained associated with higher childhood heart rate only among boys (differences 0.34 (95% Confidence Interval (CI) 0.18, 0.50) SDS, 0.22 (95% CI 0.06, 0.38) SDS, 0.33 (95% CI 0.19, 0.48) SDS for overall distress, depression and anxiety, respectively) (Table 2). After additional adjustment for child body mass index, similar associations of maternal psychological distress scales with childhood blood pressure and heart rate were observed (Table S3 in Supplementary Materials).

Maternal psychological distress and childhood lipids profile

In the unadjusted models, no associations were observed of any maternal psychological distress scales with total cholesterol concentrations. Overall psychological distress and depression were associated with lower HDL-cholesterol concentrations among boys, whereas anxiety was associated with lower HDL-cholesterol and higher triglycerides concentrations among girls (p -values < 0.05) (Table S4 in Supplementary Materials). After adjustment for potential confounders, only maternal anxiety remained associated with higher childhood triglycerides among girls (difference 0.35 (95% CI 0.17, 0.53) SDS) (Table 3). Similar

Table 1 Characteristics of mothers and their children.^a

Maternal characteristics	Total group (N = 4,088)	Overall psychological distress (N = 352)	No overall psychological distress (N = 3,736)	P-value ^b
Age at intake, mean (SD), years	30.9 (4.8)	28.1 (5.8)	31.2 (4.6)	<0.001
Ethnicity, N (%)				<0.001
European	2,767 (68.2)	104 (30.4)	2,663 (71.7)	
Non-European	1,288 (31.8)	238 (69.6)	1,050 (28.3)	
Education, N (%)				<0.001
Primary school	255 (6.4)	56 (17.6)	199 (5.5)	
Secondary school	1,628 (41.1)	195 (61.1)	1,433 (39.4)	
High education	2,076 (52.4)	68 (21.3)	2,008 (55.2)	
Marital status, N (%)				<0.001
Married/living together	3,502 (89.2)	236 (71.3)	3,266 (90.8)	
No partner	425 (10.8)	95 (28.7)	330 (9.2)	
Pre-pregnancy body mass index, median (95% range) kg/m ²	22.6 (18.1, 34.3)	23.2 (17.9, 36.1)	22.5 (18.1, 34.0)	<0.05
Alcohol consumption, N (%)				<0.001
Yes	2,219 (59.9)	137 (44.6)	2,082 (61.3)	
No	1,486 (40.1)	170 (55.4)	1,316 (38.7)	
Smoking, N (%)				<0.001
Yes	901 (24.0)	132 (41.9)	769 (22.4)	
No	2,847 (76.0)	183 (58.1)	2,664 (77.6)	
Folic acid supplement use, N (%)				<0.001
No	650 (20.1)	108 (44.8)	542 (18.2)	
Start during first 10 weeks	1,030 (31.9)	84 (34.9)	946 (31.7)	
Preconceptional use	1,546 (47.9)	49 (20.3)	1,497 (50.2)	
Exposed to SSRIs, N (%)				<0.001
Yes	43 (1.1)	12 (3.7)	31 (0.9)	
No	3,823 (98.9)	314 (96.3)	3,509 (99.1)	
Child characteristics				
Sex, N (%)				0.06
Boys	1,987 (48.6)	188 (53.4)	1,799 (48.2)	
Girls	2,101 (51.4)	164 (46.6)	1,937 (51.8)	
Gestational age at birth, N (%)				<0.05
Preterm (<37 weeks)	178 (4.4)	23 (6.5)	155 (4.1)	
Term (≥37 weeks)	3,910 (95.6)	329 (93.5)	3,581 (95.9)	
Birth weight ^c , N (%)				<0.05
Small for gestational age	405 (9.9)	48 (13.7)	357 (9.6)	
Appropriate for gestational age	3,270 (80.1)	277 (78.9)	2,993 (80.2)	
Large for gestational age	409 (10.0)	26 (7.4)	383 (10.3)	
Age at visit, mean (SD), years	9.8 (0.3)	9.8 (0.4)	9.8 (0.3)	<0.05
Body mass index, median (95% range), kg/m ²	16.9 (14.0, 24.5)	17.8 (13.9, 27.7)	16.9 (14.0, 24.0)	<0.001
Systolic blood pressure, mean (SD), mmHg	103.1 (8.0)	104.8 (8.9)	102.9 (7.9)	<0.001
Diastolic blood pressure, mean (SD), mmHg	58.5 (6.4)	59.7 (7.0)	58.4 (6.4)	<0.001
Heart rate, mean (SD), beats/minute	73.5 (10.0)	76.7 (10.7)	73.2 (9.9)	<0.001
Insulin, median (95% range), pmol/L	172.9 (35.2, 642.6)	206.8 (40.7, 824.6)	170.2 (34.6, 637.5)	<0.05
Glucose, mean (SD), mmol/L	5.2 (0.9)	5.2 (0.9)	5.2 (0.9)	0.77
Total-cholesterol, mean (SD), mmol/L	4.3 (0.7)	4.3 (0.7)	4.3 (0.7)	0.53
HDL-cholesterol, mean (SD), mmol/L	1.5 (0.3)	1.4 (0.3)	1.5 (0.3)	<0.05
LDL-cholesterol, mean (SD), mmol/L	2.3 (0.6)	2.3 (0.6)	2.3 (0.6)	0.96
Triglycerides, median (95% range), mmol/L	1.0 (0.4, 2.6)	1.0 (0.4, 3.0)	1.0 (0.4, 2.5)	0.32
C-reactive protein, median (95% range), mg/L	0.3 (0.3, 5.2)	0.3 (0.3, 12.4)	0.3 (0.3, 4.9)	<0.001

^a Values are means (standard deviation), medians (95% range) or numbers of subjects (valid %).

^b P-values for differences in subject characteristics between groups were calculated performing independent sample t-tests for normally distributed continuous variables, Mann–Whitney test for not normally distributed continuous variables and chi-square tests for categorical variables.

^c Sex- and gestational age-adjusted birth weight SDS were created based on a North-European reference chart. Small and large size for gestational age at birth were defined as sex- and gestational age-adjusted birth weight below the 10th percentile and above the 90th percentile, respectively.

associations were observed after further adjustment for body mass index at 10 years (Table S5 in Supplementary Materials). No associations were observed of any maternal psychological distress scale with childhood LDL-cholesterol (Table S6 in Supplementary Materials).

Maternal psychological distress and childhood glucose metabolism and inflammatory factors

Maternal overall psychological distress, depression and anxiety during pregnancy were associated with higher

childhood insulin concentrations in the total group (p -values <0.05). Maternal depression was associated with higher childhood insulin concentrations among boys and girls, whereas anxiety was associated with higher childhood insulin concentrations among girls only (p -values <0.05). No associations were observed for childhood glucose concentrations. All maternal psychological distress scales were associated with an increased risk of high C-reactive protein concentrations among girls only (p -values <0.05) (Table S7 in Supplementary Materials). The associations were no longer significant after adjustment for potential confounders (Table 4) and further adjustment for body mass index at 10 years (Table S8 in Supplementary Materials).

Discussion

In this population-based prospective cohort study, the associations of maternal psychological distress with childhood cardio-metabolic outcomes are largely explained by socio-economic and family-based factors. Maternal psychological distress, depression and anxiety during pregnancy were, independent of potential confounders, associated with higher childhood heart rate among boys. Maternal anxiety was also associated with higher triglycerides among girls. Maternal psychological distress was not associated with childhood blood pressure, cholesterol, insulin, glucose and C-reactive protein concentrations.

Interpretation of main findings

Maternal psychological distress during pregnancy may lead to fetal developmental adaptations, which programme cardio-metabolic disease of the offspring [2]. Previous studies suggested an association between maternal distress during pregnancy and a higher risk of hypertension, insulin resistance, and type 2 diabetes in adolescence and adulthood, but not in childhood [10–14,25]. Next to blood pressure, increased heart rate has been recognized as a risk factor for cardiovascular morbidity and mortality [26]. Previous studies reported that maternal stress during pregnancy is associated with higher fetal heart rate [27,28]. We have previously described a positive association of maternal distress after pregnancy with infant heart rate, but no association was present for distress during pregnancy [7]. This latter study was performed in a subgroup of the current cohort. To our knowledge, no studies on the association between maternal psychological distress during pregnancy and lipids profile or inflammatory markers in childhood have been performed.

In the current study, the associations of maternal psychological distress, depression and anxiety with offspring blood pressure, cholesterol, insulin, glucose, or C-reactive protein concentrations seem to be explained by family based socio-demographic factors. However, independent of these factors, maternal overall psychological distress, depression and anxiety during pregnancy

were associated with higher childhood heart rate at 10 years in boys, but not in girls. It has been proposed that fetal sex-specific placental responsiveness to maternal stress may result in increased risk for later diseases in boys. The higher growth rates of male fetuses may increase their vulnerability and subsequently place them at increased risk of adverse outcomes throughout the life course [8]. In the current study, we also observed that maternal anxiety, but not overall psychological distress and depression during pregnancy, was associated with higher triglycerides among girls. This suggests that the mechanisms relating maternal stress during pregnancy with childhood triglycerides may relate to specific psychological symptoms and be sex-specific. We cannot exclude the possibility of these results being a chance finding. We considered Bonferroni correction for multiple testing too strict since our outcomes are correlated [29]. However, the observed associations remained significant when considering a p -value of 0.017 ($0.05/3$ groups of outcomes). Altogether, our findings suggest that maternal psychological distress during pregnancy seems to have a small but persistent influence on cardio-metabolic profile during childhood.

We performed a model additionally adjusted for child body mass index, which might be in the causal pathway of the associations. Since the main results were similar with and without adjustment for child body mass index, the observed associations of maternal psychological distress with childhood heart rate and triglycerides concentrations seem to be independent of childhood adiposity. Fetal programming mechanisms might partly explain these associations. Fetal exposure to increased glucocorticoids levels due to adaptations of the maternal hypothalamic–pituitary–adrenal axis is the most well-known mechanism through which maternal psychological distress may influence the offspring cardio-metabolic outcomes [4,5]. Another mechanism is the programming of the fetal autonomic nervous system, specifically changes in the balance of sympathetic and parasympathetic nervous system, by maternal psychological stress [7]. An elevated sympathetic nervous system activity established in utero may affect fetal and childhood heart rate and subsequently may lead to cardiovascular diseases later in life. Further research is needed to identify the causality, the underlying mechanisms and to allow a better understanding of the sex-specific responses. Although the observed associations are small and without clinical relevance on individual level, the results may be important from a developmental perspective since cardio-metabolic risk factors tend to track into adulthood. Further studies are needed to replicate our findings and to assess the long-term cardio-metabolic consequences of maternal psychological distress.

Strengths and limitations

Strengths of this study were the prospective design, the large sample size and the detailed data available on childhood cardio-metabolic risk factors. This study also has

Table 2 Associations of maternal psychological distress scales with childhood blood pressure and heart rate at 10 years for the total group and stratified for boys and girls.

Difference (95% CI) in standard deviation scores									
Maternal psychological distress scales	Systolic blood pressure			Diastolic blood pressure			Heart rate		
	Total group (n = 4,011)	Boys (n = 1,945)	Girls (n = 2,066)	Total group (n = 4,011)	Boys (n = 1,946)	Girls (n = 2,065)	Total group (n = 3,954)	Boys (n = 1,918)	Girls (n = 2,036)
Overall distress									
No stress	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Stress	0.09 (-0.03, 0.20)	0.12 (-0.03, 0.28)	0.06 (-0.11, 0.23)	0.07 (-0.04, 0.19)	0.11 (-0.05, 0.27)	0.03 (-0.14, 0.20)	0.23 (0.12, 0.35)**	0.34 (0.18, 0.50)**	0.14 (-0.03, 0.31)
Depression									
No depression	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Depression	0.01 (-0.10, 0.13)	0.02 (-0.14, 0.18)	0.01 (-0.16, 0.18)	0.05 (-0.07, 0.16)	0.06 (-0.10, 0.23)	0.04 (-0.13, 0.20)	0.17 (0.06, 0.29)**	0.22 (0.06, 0.38)**	0.15 (-0.02, 0.32)
Anxiety									
No anxiety	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Anxiety	0.09 (-0.02, 0.19)	0.14 (-0.01, 0.28)	0.05 (-0.11, 0.20)	0.09 (-0.01, 0.20)	0.07 (-0.08, 0.22)	0.12 (-0.03, 0.27)	0.21 (0.10, 0.31)**	0.33 (0.19, 0.48)**	0.09 (-0.06, 0.25)

Values are linear regression coefficients (95% confidence intervals) and reflect the change in childhood blood pressure and heart rate in standard deviation scores for maternal overall distress, depression and anxiety, compared to the reference group. Models are adjusted for maternal age, ethnicity, educational level, marital status, body mass index before pregnancy, alcohol consumption, smoking during pregnancy, folic acid and selective serotonin reuptake inhibitors use. *p < 0.05. **p < 0.01.

limitations. We used all data available for each specific analysis in order to optimize statistical power. The analyses for childhood lipids profile, glucose metabolism and C-reactive protein may have lower statistical power due to lower sample sizes. Mothers of children with and without follow-up data were different regarding the socioeconomic background and prevalence of psychological distress. We cannot exclude the possibility of selection bias. We relied on a self-report questionnaire of maternal psychological distress, which might lead to misclassification bias, due to underreporting of psychological symptoms, and subsequently to underestimation of observed effects [30]. The

use of non-fasting blood samples of childhood cardio-metabolic profile may have resulted in misclassification and thus may have led to underestimation of the observed associations. However, previous studies in adults have shown that non-fasting blood lipids levels can accurately predict increased risks of cardiovascular events later in life [31,32] and that semi-fasted insulin resistance is moderately correlated with fasting values [33]. Finally, although we have adjusted for many sociodemographic and lifestyle variables known to influence the associations, residual confounding might still be an issue due to the observational design of the study.

Table 3 Associations of maternal psychological distress scales with childhood lipids profile at 10 years, total group and stratified for boys and girls.

Difference (95% CI) in standard deviation scores									
Maternal psychological distress scales	Total Cholesterol			HDL Cholesterol			Triglycerides		
	Total group (n = 2,879)	Boys (n = 1,397)	Girls (n = 1,482)	Total group (n = 2,879)	Boys (n = 1,397)	Girls (n = 1,482)	Total group (n = 2,873)	Boys (n = 1,398)	Girls (n = 1,475)
Overall distress									
No stress	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Stress	-0.06 (-0.20, 0.08)	-0.05 (-0.24, 0.14)	-0.01 (-0.22, 0.20)	-0.09 (-0.23, 0.05)	-0.19 (-0.39, 0.00)	0.03 (-0.17, 0.24)	0.02 (-0.13, 0.16)	0.01 (-0.19, 0.21)	0.02 (-0.18, 0.22)
Depression									
No depression	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Depression	-0.04 (-0.18, 0.10)	-0.14 (-0.34, 0.06)	0.12 (-0.09, 0.33)	-0.06 (-0.20, 0.09)	-0.17 (-0.38, 0.03)	0.08 (-0.13, 0.28)	0.04 (-0.11, 0.18)	0.02 (-0.19, 0.23)	0.06 (-0.14, 0.26)
Anxiety									
No anxiety	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Anxiety	-0.01 (-0.14, 0.12)	0.03 (-0.15, 0.21)	-0.02 (-0.21, 0.18)	-0.09 (-0.22, 0.05)	-0.02 (-0.21, 0.17)	-0.15 (-0.33, 0.04)	0.17 (0.04, 0.30)*	0.01 (-0.18, 0.20)	0.35 (0.17, 0.53)**

Values are linear regression coefficients (95% confidence intervals) and reflect the change in childhood lipids profile in standard deviation scores for maternal overall distress, depression and anxiety, compared to the reference group. Models are adjusted for maternal age, ethnicity, educational level, marital status, body mass index before pregnancy, alcohol consumption, smoking during pregnancy, folic acid and selective serotonin reuptake inhibitors use. *p < 0.05. **p < 0.01.

Table 4 Associations of maternal psychological distress scales with childhood glucose metabolism and inflammatory factors at 10 years, total group and stratified for boys and girls.

Maternal psychological distress scales	Difference (95% CI) in standard deviation scores ^a						Odds Ratio (95% CI) ^b		
	Insulin			Glucose			C-reactive protein (≥ 3 mg/l)		
	Total group (n = 2,878)	Boys (n = 1,395)	Girls (n = 1,483)	Total group (n = 2,878)	Boys (n = 1,397)	Girls (n = 1,481)	Total group (n = 2,882)	Boys (n = 1,399)	Girls (n = 1,483)
Overall distress									
No stress	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Stress	0.03 (-0.11, 0.17)	0.06 (-0.13, 0.26)	0.02 (-0.19, 0.23)	-0.00 (-0.14, 0.14)	0.05 (-0.15, 0.24)	-0.08 (-0.29, 0.14)	1.25 (0.76, 2.07)	1.26 (0.57, 2.79)	1.33 (0.68, 2.58)
Depression									
No depression	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Depression	0.08 (-0.07, 0.22)	0.11 (-0.09, 0.31)	0.05 (-0.15, 0.26)	-0.02 (-0.17, 0.12)	0.06 (-0.14, 0.26)	-0.13 (-0.34, 0.08)	1.09 (0.64, 1.85)	0.80 (0.32, 2.01)	1.38 (0.71, 2.69)
Anxiety									
No anxiety	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Anxiety	0.06 (-0.08, 0.19)	0.05 (-0.14, 0.23)	0.09 (-0.10, 0.28)	0.04 (-0.09, 0.17)	0.13 (-0.05, 0.32)	-0.06 (-0.25, 0.13)	1.15 (0.69, 1.90)	0.77 (0.32, 1.89)	1.54 (0.83, 2.87)

Models are adjusted for maternal age, ethnicity, educational level, marital status, body mass index before pregnancy, alcohol consumption, smoking during pregnancy, folic acid and selective serotonin reuptake inhibitors use. * $p < 0.05$. ** $p < 0.01$.

^a Values are linear regression coefficients (95% confidence intervals) and reflect the change in childhood glucose metabolism in standard deviation scores for maternal overall distress, depression and anxiety, compared to the reference group.

^b Values are odds ratios (95% confidence intervals) and represent the risk of childhood high C-reactive protein at 10 years for maternal overall distress, depression and anxiety compared to the reference group.

Conclusions

The associations of maternal psychological distress with childhood cardio-metabolic outcomes are largely explained by socio-economic family factors. Maternal psychological distress may, independently of these factors, influence offspring heart rate and triglycerides concentrations. Promoting a healthy mental state during pregnancy may improve child cardio-metabolic health.

Conflicts of interest

The authors declare no conflicts of interest.

Author's contributions

CS, FV, VJ and SS designed and conducted the study. CS and FV analyzed the data. CS, FV and SS wrote the manuscript. VJ and SS contributed to the interpretation of the data and gave input at all stages of the study. CS and SS had primary responsibility for final content. HM, JF and VJ advised and reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.numecd.2019.02.008>.

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