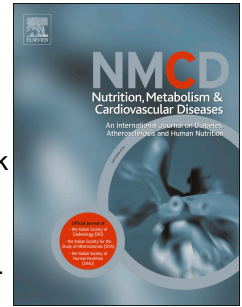# Accepted Manuscript

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

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1 Original article

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3 **childhood cardio-metabolic risk factors**

4

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26   **ABSTRACT**

27   **Background and Aims:** Previous studies suggest that psychological distress during

28   pregnancy may lead to fetal developmental adaptations, which programme cardio-metabolic

29   disease of the offspring. We examined the associations of maternal overall psychological

30   distress, depression and anxiety during pregnancy with cardio-metabolic risk factors in 10-

31   year-old children and explore potential sex-specific differences.

32   **Methods and results:** In a population-based prospective cohort study among 4,088 mothers

33   and their children, information about overall psychological distress, including depression and

34   anxiety was obtained through the Brief Symptom Inventory during pregnancy. We measured

35   child blood pressure and heart rate and insulin, glucose, serum lipids and C-reactive protein

36   blood concentrations at 10 years. Analyses were performed in the total group and in boys and

37   girls separately. Psychological distress during pregnancy was associated with higher

38   childhood heart rate among boys only (differences 0.34 (95% Confidence Interval (CI) 0.18,

39   0.50) standard deviation scores (SDS), 0.22 (95% CI 0.06, 0.38) SDS, 0.33 (95% CI 0.19,

40   0.48) SDS, for overall psychological distress, depression and anxiety, respectively). Maternal

41   anxiety during pregnancy was associated with higher childhood triglycerides among girls

42   (difference 0.35 (95% CI 0.17, 0.53) SDS). Maternal psychological distress was not

43   associated with childhood blood pressure, cholesterol, insulin, glucose and C-reactive protein

44   concentrations.

45   **Conclusions:** Maternal psychological distress may influence their offspring heart rate and

46   triglycerides concentrations. Further studies are needed to replicate these findings and assess

47   the long-term cardio-metabolic consequences of maternal psychological distress.

48   **Keywords:** psychological distress, pregnancy, cardio-metabolic risk, children, heart rate,

49   blood pressure, cholesterol

50

51 **INTRODUCTION**

52 Pregnancy is a period of great physiological and psychological transformations.(1)

53 Psychological distress has been reported by 10-20% of women during pregnancy.(2) Maternal

54 psychological distress may cause a suboptimal intrauterine environment leading to long-term

55 consequences on growth and health of the offspring.(3, 4) More specifically, intrauterine

56 stress exposure may affect offspring cardio-metabolic development via dysregulation of the

57 hypothalamic-pituitary-adrenal axis, increase of inflammatory responses and changes in the

58 balance of the autonomic nervous system.(5-7) In addition, growing evidence suggested sex-

59 specific differences in fetal programming in response to stress, which may result in sex-

60 specific risks for later diseases.(8, 9) We have previously reported that maternal psychological

61 distress during pregnancy was not associated with offspring infant heart rate and early-

62 childhood blood pressure.(7, 10) Other studies reported inconsistent associations of distress

63 during pregnancy with blood pressure and insulin resistance in children and adolescents.(11-

64 14) To date, no studies have focused on the associations of maternal psychological distress

65 during pregnancy with childhood lipids profile or inflammatory markers. Insight into the

66 associations of maternal distress during pregnancy with childhood cardio-metabolic risk

67 factors may help to develop future preventive strategies.

68 We examined, in a population-based prospective cohort study among 4,088 mothers

69 and their children, the associations of maternal overall psychological distress, depression and

70 anxiety during pregnancy with blood pressure, heart rate, lipids profile, glucose metabolism,

71 and C-reactive protein concentrations in 10-year-old children. We explored whether the

72 associations with cardio-metabolic risk factors differ for boys and girls.

73

74 **METHODS**

75

Study design

77 This study was embedded in the Generation R Study, a population-based prospective cohort

78 study from fetal life until adulthood in Rotterdam, the Netherlands. The study was approved

79 by the local Medical Ethics Committee of Erasmus MC (MEC 198.782/2001/31). Pregnant

80 women were enrolled between 2002 and 2006. Written informed consent was obtained for all

81 participants. In total, 8,879 mothers were enrolled during prenatal period.(15) We excluded

82 pregnancies not leading to singleton live births (N = 246). Information about psychological

83 distress during pregnancy was available in 6,548 of 8,633 mothers with singleton children.

84 For 2,460 children, no information on any measurement of cardio-metabolic risk factors at 10

85 years was available. Thus, 4,088 mothers and children had information on psychological

86 distress during pregnancy and at least one measurement of cardio-metabolic risk factors at 10

87 years. The specific population for analysis for each outcome is shown in the flowchart.

88 (**Figure S1** in Supplementary Materials).

89

Psychological distress during pregnancy

91 Information on maternal psychological distress was obtained through the Brief Symptom

92 Inventory (BSI) that was mailed to participants and returned at around 20 weeks of gestation.

93 The BSI is a validated self-report questionnaire with 53 items, describing the

94 psychopathologic problems and complaints that mothers may have experienced in the

95 preceding 7 days.(16) These items include a broad spectrum of psychological symptoms,

96 divided in 9 dimensions (anxiety, depression, hostility, phobic anxiety, interpersonal

97 sensitivity, obsessive-compulsiveness, paranoid ideation, psychoticism, somatization). We

98 used the overall psychological distress scale (Global Severity Index) and 2 symptom scales

99 (depression and anxiety) to define psychological distress. We chose these subscales because

100 depression and anxiety are widely used as indicators of psychological distress during

101 pregnancy.(1) To indicate the extent of the symptoms, the items were rated on a 5-point

102 unidimensional scale ranging from '0' (not at all) to '4' (extremely). A total score was

103 provided for each symptom scale by summing the item scores and dividing the results by the

104 number of reported symptoms. Then, the symptoms were dichotomized (into "yes" or "no"

105 categories) by using the following cutoffs derived from a psychiatric outpatient sample of

106 Dutch women: 0.71 for overall psychological symptoms scale; 0.80 for depression scale and

107 0.71 for anxiety scale.(17, 18)

108

109 **Cardio-metabolic risk factors at 10 years**

110 As previously described, children around the age of 10 years were invited to visit our research

111 center at Erasmus MC-Sophia Children's Hospital.(19) Blood pressure and heart rate were

112 measured at the right brachial artery four times with one minute intervals, using the validated

113 automatic sphygmanometer Datascope Accutor Plus (Paramus, NJ).(20) We calculated the

114 mean value for systolic and diastolic blood pressure and heart rate using the last three

115 measurements of each participant. Non-fasting blood samples were collected to determine

116 serum concentrations of glucose, insulin, total cholesterol, high-density lipoprotein (HDL)-

117 cholesterol and triglycerides. Glucose, total cholesterol, HDL-cholesterol and triglycerides

118 concentrations were measured using the c702 module on the Cobas 8000 analyzer. Insulin

119 was measured with electrochemiluminescence immunoassay (ECLIA) on the E411 module

120 (Roche, Almere, the Netherlands).(21) Low-density lipoprotein (LDL)–cholesterol was

121 calculated according to the Friedewald formula.(22)

122

123 **Covariates**

124   We obtained information on maternal age, ethnicity, educational level, marital status, body

125   mass index before pregnancy, smoking habits and alcohol consumption during pregnancy, and

126   folic acid supplement use, by questionnaire. Information on maternal selective serotonin

127   reuptake inhibitors (SSRIs) use in pregnancy was obtained by questionnaires and prescription

128   records from pharmacies.(23) Information on child sex, gestational age at birth and birth

129   weight were available from medical records. We calculated body mass index (kg/m^2) at 10

130   years from height and weight, both measured without shoes and heavy clothing.

131

132   **Statistical analysis**

133   We compared subject characteristics between women with and without psychological distress

134   using Pearson's chi-square tests, independent sample t-tests and Mann-Whitney tests. Similar

135   statistical tests were performed to compare characteristics between participants and non-

136   participants. We used linear and logistic regression models to assess the associations of

137   maternal overall psychological distress, depression and anxiety with childhood cardio-

138   metabolic risk factors. We included covariates in the models if they were associated with

139   maternal psychological distress and childhood cardio-metabolic risk factors in our study and

140   if they changed the effect estimates substantially (>10%) for at least one outcome. Thus, all

141   models were adjusted for maternal age, ethnicity, educational level, marital status, body mass

142   index before pregnancy, alcohol consumption, smoking, folic acid and selective serotonin

143   reuptake inhibitors use during pregnancy. Child body mass index at 10 years might be in the

144   causal pathway of the associations of maternal overall psychological distress with childhood

145   cardio-metabolic risk factors. We assessed whether these associations were independent of

146   child body mass index, by additionally adjusting our models for this covariate. The

147   distributions of insulin and triglycerides were skewed and natural logged transformed. Since

148   C-reactive protein was not normally distributed and the log-transformation did not yield an

149   acceptable distribution, we categorized C-reactive protein concentrations into <3 mg/l

150   (normal levels) or ≥3 mg/l (high levels) in line with previous studies.(24) To enable

151   comparison of effect sizes of different outcome measures, we constructed standard deviation

152   scores (SDS) ((observed value – mean) / SD). Analyses were performed for the total group

153   and for boys and girls, separately. We found statistically significant sex interactions for the

154   associations of maternal psychological distress with child heart rate and diastolic blood

155   pressure. We did not observe statistical interactions for maternal ethnicity, child's gestational

156   age at birth, birth weight and body mass index at 10 years. To enable interpretation of

157   statistical significance level, we presented p-values<0.05 and p-values<0.01. Missing data in

158   covariates (ranging from 0 to 21%) were multiple-imputed using Markov chain Monte Carlo

159   approach. Five imputed datasets were created and analyzed together. All statistical analyses

160   were performed using the Statistical Package of Social Sciences version 24.0 for Windows

161   (SPSS IBM, Chicago, IL, USA).

162

163   **RESULTS**

164

165   **Subject characteristics**

166   Participants characteristics are presented in **Table 1**. Of all pregnant women, 8.5%, 8.6% and

167   9.5% experienced overall psychological distress, depression and anxiety, respectively.

168   Women with psychological distress during pregnancy were more often younger, non-

169   European, lower educated, without partner and were more likely to be smokers compared to

170   women without psychological distress (p-values<0.05). Non-response analyses showed that

171   mothers of children with follow-up data available were slightly older, more often European,

172   higher educated and reported less clinical psychological distress during pregnancy compared

173   to mothers of children without follow-up data available (p-values<0.05) (**Table S1** in

174   Supplementary Materials).

175

176   **Maternal psychological distress and childhood blood pressure and heart rate**

177   In the unadjusted models, maternal overall psychological distress, depression and anxiety

178   during pregnancy were associated with higher childhood blood pressure in the total group and

179   among boys (p-values<0.05). Maternal overall distress and anxiety were also associated with

180   higher childhood systolic and diastolic blood pressure, respectively among girls (p-

181   values<0.05). All maternal psychological distress scales were associated with higher

182   childhood heart rate among boys and girls (p-values<0.05) (**Table S2** in Supplementary

183   Materials). After adjustment for potential confounders, no associations were observed

184   between maternal overall psychological distress, depression and anxiety and childhood blood

185   pressure in boys and girls. All maternal psychological distress scales remained associated with

186   higher childhood heart rate only among boys (differences 0.34 (95% Confidence Interval (CI)

187   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

188   distress, depression and anxiety, respectively) (**Table 2**). After additional adjustment for child

189   body mass index, similar associations of maternal psychological distress scales with

190   childhood blood pressure and heart rate were observed (**Table S3** in Supplementary

191   Materials).

192

193   **Maternal psychological distress and childhood lipids profile** In the unadjusted models, no

194   associations were observed of any maternal psychological distress scales with total cholesterol

195   concentrations. Overall psychological distress and depression were associated with lower

196   HDL-cholesterol concentrations among boys, whereas anxiety was associated with lower

197   HDL-cholesterol and higher triglycerides concentrations among girls (p-values<0.05) (**Table**

198 **S4** in Supplementary Materials). After adjustment for potential confounders, only maternal

199 anxiety remained associated with higher childhood triglycerides among girls (difference 0.35

200 (95% CI 0.17, 0.53) SDS) (**Table 3**). Similar associations were observed after further

201 adjustment for body mass index at 10 years (**Table S5** in Supplementary Materials). No

202 associations were observed of any maternal psychological distress scale with childhood LDL-

203 cholesterol (**Table S6** in Supplementary Materials).

204

205 **Maternal psychological distress and childhood glucose metabolism and inflammatory**

206 **factors**

207 Maternal overall psychological distress, depression and anxiety during pregnancy were

208 associated with higher childhood insulin concentrations in the total group (p-values<0.05).

209 Maternal depression was associated with higher childhood insulin concentrations among boys

210 and girls, whereas anxiety was associated with higher childhood insulin concentrations among

211 girls only (p-values<0.05). No associations were observed for childhood glucose

212 concentrations. All maternal psychological distress scales were associated with an increased

213 risk of high C-reactive protein concentrations among girls only (p-values<0.05). (**Table S7** in

214 Supplementary Materials). The associations were no longer significant after adjustment for

215 potential confounders (**Table 4**) and further adjustment for body mass index at 10 years

216 (**Table S8** in Supplementary Materials).

217

218 **DISCUSSION**

219 In this population-based prospective cohort study, the associations of maternal psychological

220 distress with childhood cardio-metabolic outcomes are largely explained by socio-economic

221 and family-based factors. Maternal psychological distress, depression and anxiety during

222 pregnancy were, independent of potential confounders, associated with higher childhood heart

223 rate among boys. Maternal anxiety was also associated with higher triglycerides among girls.

224 Maternal psychological distress was not associated with childhood blood pressure,

225 cholesterol, insulin, glucose and C-reactive protein concentrations.

226

227 **Interpretation of main findings**

228 Maternal psychological distress during pregnancy may lead to fetal developmental

229 adaptations, which programme cardio-metabolic disease of the offspring. (2) Previous studies

230 suggested an association between maternal distress during pregnancy and a higher risk of

231 hypertension, insulin resistance, and type 2 diabetes in adolescence and adulthood, but not in

232 childhood.(10-14, 25) Next to blood pressure, increased heart rate has been recognized as a

233 risk factor for cardiovascular morbidity and mortality.(26) Previous studies reported that

234 maternal stress during pregnancy is associated with higher fetal heart rate.(27, 28) We have

235 previously described a positive association of maternal distress after pregnancy with infant

236 heart rate, but no association was present for distress during pregnancy.(7) This latter study

237 was performed in a subgroup of the current cohort. To our knowledge, no studies on the

238 association between maternal psychological distress during pregnancy and lipids profile or

239 inflammatory markers in childhood have been performed.

240   In the current study, the associations of maternal psychological distress, depression

241 and anxiety with offspring blood pressure, cholesterol, insulin, glucose, or C-reactive protein

242 concentrations seem to be explained by family based socio-demographic factors. However,

243 independent of these factors, maternal overall psychological distress, depression and anxiety

244 during pregnancy were associated with higher childhood heart rate at 10 years in boys, but not

245 in girls. It has been proposed that fetal sex-specific placental responsiveness to maternal stress

246 may result in increased risk for later diseases in boys. The higher growth rates of male fetuses

247 may increase their vulnerability and subsequently place them at increased risk of adverse

248 outcomes throughout the life course.(8) In the current study, we also observed that maternal

249 anxiety, but not overall psychological distress and depression during pregnancy, was

250 associated with higher triglycerides among girls. This suggests that the mechanisms relating

251 maternal stress during pregnancy with childhood triglycerides may relate to specific

252 psychological symptoms and be sex-specific. We cannot exclude the possibility of these

253 results being a chance finding. We considered Bonferroni correction for multiple testing too

254 strict since our outcomes are correlated.(29) However, the observed associations remained

255 significant when considering a p-value of 0.017 (0.05/3 groups of outcomes). Altogether, our

256 findings suggest that maternal psychological distress during pregnancy seems to have a small

257 but persistent influence on cardio-metabolic profile during childhood.

258   We performed a model additionally adjusted for child body mass index, which might

259 be in the causal pathway of the associations. Since the main results were similar with and

260 without adjustment for child body mass index, the observed associations of maternal

261 psychological distress with childhood heart rate and triglycerides concentrations seem to be

262 independent of childhood adiposity. Fetal programming mechanisms might partly explain

263 these associations. Fetal exposure to increased glucocorticoids levels due to adaptations of the

264 maternal hypothalamic–pituitary–adrenal axis is the most well-known mechanism through

265 which maternal psychological distress may influence the offspring cardio-metabolic

266 outcomes.(4, 5) Another mechanism is the programming of the fetal autonomic nervous

267 system, specifically changes in the balance of sympathetic and parasympathetic nervous

268 system, by maternal psychological stress.(7) An elevated sympathetic nervous system activity

269 established in utero may affect fetal and childhood heart rate and subsequently may lead to

270 cardiovascular diseases later in life. Further research is needed to identify the causality, the

271 underlying mechanisms and to allow a better understanding of the sex-specific responses.

272 Although the observed associations are small and without clinical relevance on individual

273   level, the results may be important from a developmental perspective since cardio-metabolic

274   risk factors tend to track into adulthood. Further studies are needed to replicate our findings

275   and to assess the long-term cardio-metabolic consequences of maternal psychological distress.

276

277   **Strengths and limitations**

278   Strengths of this study were the prospective design, the large sample size and the detailed data

279   available on childhood cardio-metabolic risk factors. This study also has limitations. We used

280   all data available for each specific analysis in order to optimize statistical power. The analyses

281   for childhood lipids profile, glucose metabolism and C-reactive protein may have lower

282   statistical power due to lower sample sizes. Mothers of children with and without follow-up

283   data were different regarding the socioeconomic background and prevalence of psychological

284   distress. We cannot exclude the possibility of selection bias. We relied on a self-report

285   questionnaire of maternal psychological distress, which might lead to misclassification bias,

286   due to underreporting of psychological symptoms, and subsequently to underestimation of

287   observed effects.(30) The use of non-fasting blood samples of childhood cardio-metabolic

288   profile may have resulted in misclassification and thus may have led to underestimation of the

289   observed associations. However, previous studies in adults have shown that non-fasting blood

290   lipids levels can accurately predict increased risks of cardiovascular events later in life (31,

291   32) and that semi-fasted insulin resistance is moderately correlated with fasting values.(33)

292   Finally, although we have adjusted for many sociodemographic and lifestyle variables known

293   to influence the associations, residual confounding might still be an issue due to the

294   observational design of the study.

295

296   **Conclusions**

297 The associations of maternal psychological distress with childhood cardio-metabolic

298 outcomes are largely explained by socio-economic family factors. Maternal psychological

299 distress may, independently of these factors, influence offspring heart rate and triglycerides

300 concentrations. Promoting a healthy mental state during pregnancy may improve child cardio-

301 metabolic health.

302

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305 general practitioners, hospitals, midwives and pharmacies in Rotterdam.

306

307 **Conflict of Interest**

308 The authors declare no conflicts of interest.

309

310 **Author's contributions**

311 CS, FV, VJ and SS designed and conducted the study. CS and FV analyzed the data. CS, FV

312 and SS wrote the manuscript. VJ and SS contributed to the interpretation of the data and gave

313 input at all stages of the study. CS and SS had primary responsibility for final content. HM, JF

314 and VJ advised and reviewed the manuscript. All authors read and approved the final version

315 of the manuscript.

316

317 **Sources of support**

REFERENCES

1.   Woods SM, Melville JL, Guo Y, Fan MY, Gavin A. Psychosocial stress during pregnancy. Am J Obstet Gynecol. 2010;202(1):61 e1-7.

2.   Vehmeijer F, Guxens M, Duijts L, Marroun HE. Maternal psychological distress during pregnancy and childhood health outcomes: a narrative review. J Dev Orig Health Dis. 2018.

3.   Lewis AJ, Austin E, Galbally M. Prenatal maternal mental health and fetal growth restriction: a systematic review. J Dev Orig Health Dis. 2016;7(4):416-28.

4.   Hompes T, Vrieze E, Fieuws S, Simons A, Jaspers L, Van Bussel J, et al. The influence of maternal cortisol and emotional state during pregnancy on fetal intrauterine growth. Pediatr Res. 2012;72(3):305-15.

5.   Cottrell EC, Seckl JR. Prenatal stress, glucocorticoids and the programming of adult disease. Front Behav Neurosci. 2009;3:19.

6.   Garfield L, Mathews HL, Witek Janusek L. Inflammatory and Epigenetic Pathways for Perinatal Depression. Biol Res Nurs. 2016;18(3):331-43.

7.   Dierckx B, Tulen JH, van den Berg MP, Tharner A, Jaddoe VW, Moll HA, et al. Maternal psychopathology influences infant heart rate variability: Generation R Study. Psychosom Med. 2009;71(3):313-21.

8.   Cheong JN, Wlodek ME, Moritz KM, Cuffe JS. Programming of maternal and offspring disease: impact of growth restriction, fetal sex and transmission across generations. J Physiol. 2016;594(17):4727-40.

9.   Park H, Sundaram R, Gilman SE, Bell G, Louis GMB, Yeung EH. Timing of Maternal Depression and Sex-Specific Child Growth, the Upstate KIDS Study. Obesity (Silver Spring). 2018;26(1):160-6.

348 10.   Taal HR, de Jonge LL, Tiemeier H, van Osch-Gevers L, Hofman A, Verhulst FC, et al.

349 Parental psychological distress during pregnancy and childhood cardiovascular development.

350 The Generation R Study. Early Hum Dev. 2013;89(8):547-53.

351 11.   van Dijk AE, van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. The association

352 between prenatal psychosocial stress and blood pressure in the child at age 5-7 years. PLoS One.

353 2012;7(8):e43548.

354 12.   Dancause KN, Veru F, Andersen RE, Laplante DP, King S. Prenatal stress due to a

355 natural disaster predicts insulin secretion in adolescence. Early Hum Dev. 2013;89(9):773-6.

356 13.   Virk J, Li J, Vestergaard M, Obel C, Kristensen JK, Olsen J. Prenatal exposure to

357 bereavement and type-2 diabetes: a Danish longitudinal population based study. PLoS One.

358 2012;7(8):e43508.

359 14.   van Dijk AE, van Eijsden M, Stronks K, Gemke RJ, Vrijkotte TG. No associations of

360 prenatal maternal psychosocial stress with fasting glucose metabolism in offspring at 5-6 years

361 of age. J Dev Orig Health Dis. 2014;5(5):361-9.

362 15.   Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IMH, et al. The

363 Generation R Study: design and cohort update 2017. Eur J Epidemiol. 2016;31(12):1243-64.

364 16.   J B. Reliability and validity of the Brief Symptom Inventory. J Consult Clin Psychol.

365 1991;3(3(3):433):433.

366 17.   De Beurs E. Brief Symptom Inventory. Handleiding Leiden, The The Netherlands PITS

367 BV. 2004.

368 18.   De Beurs E. Brief Symptom Inventory. Handleiding Addendum. Leiden, The

369 Netherlands. PITS BV. 2009.

370   19.   Jaddoe VW, Bakker R, van Duijn CM, van der Heijden AJ, Lindemans J, Mackenbach

371   JP, et al. The Generation R Study Biobank: a resource for epidemiological studies in children

372   and their parents. Eur J Epidemiol. 2007;22(12):917-23.

373   20.   Wong SN, Tz Sung RY, Leung LC. Validation of three oscillometric blood pressure

374   devices against auscultatory mercury sphygmomanometer in children. Blood Press Monit.

375   2006;11(5):281-91.

376   21.   Kruithof CJ, Kooijman MN, van Duijn CM, Franco OH, de Jongste JC, Klaver CC, et al.

377   The Generation R Study: Biobank update 2015. Eur J Epidemiol. 2014;29(12):911-27.

378   22.   Onyenekwu CP HM, Smit F, Matsha TE, Erasmus RT. Comparison of LDL-cholesterol

379   estimate using the Friedewald formula and the newly proposed de Cordova formula with a

380   directly measured LDL-cholesterol in a healthy South African population. Ann Clin Biochem.

381   2014;51(Pt 6):672-9.

382   23.   El Marroun H, White TJ, van der Knaap NJ, Homberg JR, Fernandez G, Schoemaker

383   NK, et al. Prenatal exposure to selective serotonin reuptake inhibitors and social responsiveness

384   symptoms of autism: population-based study of young children. Br J Psychiatry. 2014;205(2):95-

385   102.

386   24.   Toemen L, Gishti O, Vogelezang S, Gaillard R, Hofman A, Franco OH, et al. Cross-

387   sectional population associations between detailed adiposity measures and C-reactive protein

388   levels at age 6 years: the Generation R Study. Int J Obes (Lond). 2015;39(7):1101-8.

389   25.   Edwards CR, Benediktsson R, Lindsay RS, Seckl JR. Dysfunction of placental

390   glucocorticoid barrier: link between fetal environment and adult hypertension? Lancet.

391   1993;341(8841):355-7.

392   26.   Palatini P. Role of elevated heart rate in the development of cardiovascular disease in

393   hypertension. Hypertension. 2011;58(5):745-50.

394   27.   Monk C, Fifer WP, Myers MM, Sloan RP, Trien L, Hurtado A. Maternal stress responses

395   and anxiety during pregnancy: effects on fetal heart rate. Dev Psychobiol. 2000;36(1):67-77.

396   28.   Allister L, Lester BM, Carr S, Liu J. The effects of maternal depression on fetal heart rate

397   response to vibroacoustic stimulation. Dev Neuropsychol. 2001;20(3):639-51.

398   29.   Bland JM, Altman DG. Multiple significance tests: the Bonferroni method. BMJ.

399   1995;310(6973):170.

400   30.   Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EA, et al.

401   Maternal psychological distress and fetal growth trajectories: the Generation R Study. Psychol

402   Med. 2010;40(4):633-43.

403   31.   Freiberg JJ, Tybjaerg-Hansen A, Jensen JS, Nordestgaard BG. Nonfasting triglycerides

404   and risk of ischemic stroke in the general population. JAMA. 2008;300(18):2142-52.

405   32.   Bansal S, Buring JE, Rifai N, Mora S, Sacks FM, Ridker PM. Fasting compared with

406   nonfasting triglycerides and risk of cardiovascular events in women. JAMA. 2007;298(3):309-

407   16.

408   33.   Hancox RJ, Landhuis CE. Correlation between measures of insulin resistance in fasting

409   and non-fasting blood. Diabetol Metab Syndr. 2011;3(1):23.

410

411

Table 1. Characteristics of mothers and their children[1]

Maternal characteristics	Total group (N= 4,088)	Overall psychological distress (N= 352)	No overall psychological distress (N= 3,736)	P-value[2]
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/m²	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[3], 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/m²	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

[1] Values are means (standard deviation), medians (95% range) or numbers of subjects (valid %).

[2] 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.

[3] 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.

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.

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

Maternal psychological distress scales	Difference (95% CI) in standard deviation scores								
	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	-0.05	-0.01	-0.09	-0.19	0.03	0.02	0.01	0.02
	(-0.20, 0.08)	(-0.24, 0.14)	(-0.22, 0.20)	(-0.23, 0.05)	(-0.39, 0.00)	(-0.17, 0.24)	(-0.13, 0.16)	(-0.19, 0.21)	(-0.18, 0.22)
Depression									
No depression	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Depression	-0.04	-0.14	0.12	-0.06	-0.17	0.08	0.04	0.02	0.06
	(-0.18, 0.10)	(-0.34, 0.06)	(-0.09, 0.33)	(-0.20, 0.09)	(-0.38, 0.03)	(-0.13, 0.28)	(-0.11, 0.18)	(-0.19, 0.23)	(-0.14, 0.26)
Anxiety									
No anxiety	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Anxiety	-0.01	0.03	-0.02	-0.09	-0.02	-0.15	0.17	0.01	0.35
	(-0.14, 0.12)	(-0.15, 0.21)	(-0.21, 0.18)	(-0.22, 0.05)	(-0.21, 0.17)	(-0.33, 0.04)	(0.04, 0.30)*	(-0.18, 0.20)	(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.

	Difference (95% CI) in standard deviation scores[1]						Odds Ratio (95% CI)[2]		
Maternal psychological distress scales	**Insulin**			**Glucose**			**C-reactive protein (≥ 3mg/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	0.06	0.02	-0.00	0.05	-0.08	1.25	1.26	1.33
	(-0.11, 0.17)	(-0.13, 0.26)	(-0.19, 0.23)	(-0.14, 0.14)	(-0.15, 0.24)	(-0.29, 0.14)	(0.76, 2.07)	(0.57, 2.79)	(0.68, 2.58)
Depression									
No depression	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Depression	0.08	0.11	0.05	-0.02	0.06	-0.13	1.09	0.80	1.38
	(-0.07, 0.22)	(-0.09, 0.31)	(-0.15, 0.26)	(-0.17, 0.12)	(-0.14, 0.26)	(-0.34, 0.08)	(0.64, 1.85)	(0.32, 2.01)	(0.71, 2.69)
Anxiety									
No anxiety	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Anxiety	0.06	0.05	0.09	0.04	0.13	-0.06	1.15	0.77	1.54
	(-0.08, 0.19)	(-0.14, 0.23)	(-0.10, 0.28)	(-0.09, 0.17)	(-0.05, 0.32)	(-0.25, 0.13)	(0.69, 1.90)	(0.32, 1.89)	(0.83, 2.87)

[1] 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.

[2] 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.

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.

Highlights

- Psychological distress was associated with higher childhood heart rate among boys.

- Maternal anxiety was associated with higher childhood triglycerides among girls.

- Promoting a healthy mental state during pregnancy may improve children health.