Cardio-metabolic risk in children prenatally exposed to maternal psychosocial stress
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2 | General methods

Adapted from

Cardio-metabolic risk in 5-year-old children prenatally exposed to maternal psychosocial stress: the ABCD study

The data used for the research in this thesis was collected within the Amsterdam Born Children and their Development (ABCD) study, a large prospective, multi-ethnic birth cohort situated in the Netherlands. Chapter 9 is the only exception: data from another population-based birth cohort, the Avon Longitudinal Study of Parents and Children (ALSPAC, coordinated by the University of Bristol, U.K) was used for those analyses. Both cohorts were founded to detect and analyze early life factors that are associated with later health and health differences. In this chapter, the focus will mainly be on the ABCD study, because most research in this thesis is conducted using ABCD data.

**STUDY POPULATION**

![Diagram of the ABCD Study cohort process]

*Figure 1* Procedure of the ABCD Study cohort
The progression of the ABCD study cohort is also presented in a flowchart (figure 1). During phase one of the ABCD study (January 2003 - March 2004) all pregnant women from Amsterdam visiting an obstetric care provider were asked to fill out a questionnaire. Of 12,373 women, 8,266 (67%) did so, at a median of 16 weeks gestation (inter-quartile range 14-18 weeks). A group of 4,389 (53%) participants also donated a blood sample for biomarker analysis, at a median of 13 weeks’ gestation (inter-quartile range 12-14 weeks).

A total of 6,735 (81%) women gave permission for follow-up. Three months after birth another questionnaire was sent out and 5,131 (76%) women returned it. In the following years, growth data of the children were collected from Youth Health Care centers.

When the first children turned five, the third phase of the study started (2008-2010). The addresses of 6,161 mothers were retrieved from the Youth Health Care registry; attrition in this follow-up number was largely due to untraceable changes in address or migration. The mothers received a questionnaire, including an informed consent sheet for the age five health check. Two weeks before the health check, mothers received a notifying letter and an additional self-administered food frequency questionnaire (FFQ). The health check itself consisted of a finger puncture and various health measurements, for which separate consents are signed.

**Maternal Psychosocial Stress**

All the following maternal psychosocial stress instruments were included in the pregnancy questionnaire.

**Depressive symptoms**

Depressive symptoms were assessed using the validated Dutch version of the 20-item Center for Epidemiological Studies Depression Scale (CES-D) \(^{23}\). It evaluates the frequency of depressive symptoms experienced over the preceding week. Each item is scored on a four-point scale (0=rarely or none of the time, 1=some or a little of the time, 2=occasionally or a moderate amount of the time and 3=most or all of the time), resulting in a total score ranging from zero to sixty. Internal consistency (Cronbach’s Alpha) of the CES-D scale was 0.90.

**Anxiety**

General anxiety was assessed using the Dutch version \(^4\) of the State-Trait Anxiety Inventory (STAI) \(^5\). The 20 items regarding state-anxiety (transient or temporarily experienced anxiety) were included in the questionnaire, with each item scored on a 4-point scale (0=rarely or none of the time, 1=some or a little of the time, 2=occasionally or a moderate amount of the time and 3=most or all of the time). Cronbach’s Alpha of the scale was 0.94.
Pregnancy-related anxiety
Pregnancy-related anxiety was assessed using an abbreviated 10-item version \(^6\) of the Pregnancy Related Anxieties Questionnaire (PRAQ) \(^7\). Each item is scored on a four-point scale (0=definitely not true, 1=not true, 2=true and 3=very true). Three aspects that can be distinguished are ‘fear of giving birth’, ‘fear of bearing a physically or mentally handicapped child’ and ‘concern about one’s appearance’. Cronbach’s Alphas of the scales were 0.77, 0.86 and 0.77 respectively.

Parenting stress
To assess parenting stress a Dutch adaptation \(^8\) of the 20-item Parenting Daily Hassles (PDH) scale was used \(^9\). The parents rated the occurrence of typical everyday events in parenting and parent-child interactions on a four-point scale (0=never or rarely, 1=sometimes, 2=a lot and 3=constantly). Internal consistency (Cronbach’s Alpha) of the scale was 0.85.

Work stress/Job strain
To assess job strain, a Dutch version of the Job Content Questionnaire was used \(^10,11\). It consists of 2 subscales: job demands and job control. The job demands subscale consists of 25 four-point scale items focusing on work pace, mental workload and physical workload. The job control subscale consists of 11 four-point scale items (Cronbach’s alpha 0.85 and 0.92, respectively). Job strain is a combination of high job demands and low control. Women in the category ‘low job strain’ had reported low job demand with moderate or high job control. ‘High job strain’, consisted of women who reported high job demand with low or moderate job control. All other women fell into the ‘moderate job strain’ category.

The age five health check
Blood glucose, insulin sensitivity and lipid profile
As a part of the health check, capillary blood was collected in the morning. We used an ambulatory collection kit (Demecal kit: LabAnywhere, Haarlem, The Netherlands) \(^12\) to determine fasting plasma glucose, C-peptide, total cholesterol, high density lipoprotein cholesterol and triglycerides. From these measurements, insulin sensitivity (using the HOMA-IR method \(^13\)) could be derived.

Body composition
During the health check measurements, the children were only wearing their underwear bottoms. Height was determined to the nearest millimeter using a Leicester portable height measure (Seca, Hamburg, Germany) and weight to the nearest 100 gram using a Marsden MS-4102 weighing scale (Oxfordshire, United Kingdom). Then waist circumference was measured to the nearest millimeter midway between the costal border and iliac crest, using a Seca measuring tape, and the children lied down for two bioelectrical impedance analysis (BIA) measurements using the Bodystat 1500 MDD system (Bodystat Inc., Douglas, United Kingdom). From these measurements, outcome variables Body Mass Index (kg/m\(^2\)) and fat percentage could be derived \(^14,15\).

Autonomic nervous system activity and blood pressure
To measure nervous system effect at the health check we used an ambulatory device, the VU University Ambulatory Monitoring System (VU-AMS; Amsterdam, the Netherlands). Relia-
bility and validity aspects and recording methodology of the VU-AMS have been described previously \textsuperscript{16}. The system records three lead electro cardiograms (ECG) and four lead impedance cardiograms (ICG) (Ultratrace Diagnostic ECG with wet gel; ConMed Corporation, Utica, New York, United States of America). Blood pressure is measured by the Omron 705 IT (Omron Healthcare Inc., Bannockburn, IL, USA) with an age appropriate small cuff (arm circumference 17-22 cm). The following procedure of VU-AMS and blood pressure measurement is illustrated in figure 2.

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\textbf{Figure 2} VU-AMS and blood pressure measurement procedure on a time axis

First, the child lied down in a supine position. During the first minute, one test blood pressure measurement was performed. Then the first official VU-AMS recording period was marked: the child lied in rest for four minutes. The second recording period consisted of lying down while blood pressure was measured twice. Then the child was seated and acclimatized for one minute, followed by four minutes of sitting in rest (recording period 3). Finally, during the fourth recording period, blood pressure was measured twice.

As derivatives of parasympathetic nervous system activity, two time domain indices of heart rate variability in the respiratory frequency range, also called respiratory sinus arrhythmia (RSA), were obtained \textsuperscript{17}. The first one is the root-mean-square-of-successive-differences (RMSSD) of the inter beat intervals. This RMSSD was calculated automatically from the R-peaks in the ECG. The second RSA measure is the peak valley estimation (pvRSA) which was obtained automatically by subtracting the shortest inter beat interval during heart rate acceleration in the inspirational phase from the longest inter beat interval during deceleration in the expirational phase.

As a derivate of sympathetic nervous system activity, pre-ejection period (PEP) was used. PEP is the time interval between the onset of ventricular depolarization (the Q wave onset in the ECG) and the opening of the aortic valves (B-point in ICG) and is considered to be an adequate surrogate measure for sympathetic nervous system activity \textsuperscript{16}. It was scored manually in large-scale ensemble averages of the impedance cardiograms \textsuperscript{18}.

\textbf{Covariates}
Maternal characteristics considered potential confounders are age, pre-pregnancy BMI (kg/m\textsuperscript{2}), educational level, ethnicity, smoking, alcohol consumption and parity, all available from the pregnancy questionnaire, and thus all self-reported. Missing values on maternal weight (9.5\%) and height (3.4\%) were imputed by means of a random imputation method using linear regression \textsuperscript{19}, which accounted for the differences between the ethnic groups. Educational level was included as years of education after primary school, as a proxy of socioeconomic status. Ethnicity was based on the mother’s country of birth (definition of
ethnicity by the Dutch Central Bureau of Statistics; CBS). Smoking, alcohol consumption and parity were usually dichotomized.

Maternal hypertension is also considered a potential confounder (no/pre-existent/pregnancy-induced), which was available by combining data from the pregnancy questionnaire and Dutch Perinatal Registration (PRN). Pre-existent hypertension was defined by either an indication in the PRN or self-reported high blood pressure and/or use of medication before the 20th week of pregnancy. Pregnancy-induced hypertension was defined by either an indication of pregnancy related hypertension/eclampsia/pre-eclampsia in the PRN or self-reported high blood pressure and/or use of medication after the 20th week of pregnancy. This classification was in accordance with the guidelines of the International Society for the Study of Hypertension in Pregnancy.20

Gestational duration and birthweight were available from the Youth Health Care Registration and PRN systems. Gestational duration was based on ultrasound by the obstetric care provider or, when unavailable (<10%), on the first day of the last menstrual period. Birthweight was standardized for gender, gestational duration and parity using reference values from the PRN.21 When the outcome measures were not sex-specific, sex of the child was also added as a potential confounder, and additionally explored as an effect modifier.
REferences


