Eur J Epidemiol (2012) 27:739–756
DOI 10.1007/s10654-012-9735-1

STUDY UPDATE

The Generation R Study: design and cohort update 2012

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Received: 12 June 2012 / Accepted: 20 September 2012 / Published online: 20 October 2012

Abstract The Generation R Study is a population-based prospective cohort study from fetal life until adulthood. The study is designed to identify early environmental and genetic causes and causal pathways leading to normal and abnormal growth, development and health during fetal life, childhood and adulthood. The study focuses on six areas of research: (1) maternal health; (2) growth and physical development; (3) behavioural and cognitive development; (4) respiratory health and allergies; (5) diseases in childhood; and (6) health and healthcare for children and their parents. Main exposures of interest include environmental, endocrine, genetic and epigenetic, lifestyle related, nutritional and socio-demographic determinants. In total, n = 9,778 mothers with a delivery date from April 2002 until January 2006 were enrolled in the study. Response at baseline was 61 %, and general follow-up rates until the age of 6 years exceed 80 %. Data collection in mothers, fathers and children include questionnaires, detailed physical and ultrasound examinations, behavioural observations, and biological samples. A genome and epigenome wide association screen is available in the participating children. From the age of 5 years, regular detailed hands-on assessments are performed in a dedicated research center including advanced imaging facilities such as Magnetic Resonance Imaging. Eventually, results forthcoming from the Generation R Study contribute to the development of strategies for optimizing health and healthcare for pregnant women and children.

Keywords Cohort · Pregnancy · Child · Fetal

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Introduction

The Generation R Study is a population-based prospective cohort study from fetal life until young adulthood. The study is designed to identify early environmental and genetic causes, and causal pathways leading to normal and abnormal growth, development and health during fetal life, childhood and adulthood. The background has been described in detail previously [1–3]. Specific interest is in the effects of fetal and early childhood conditions on health and disease in later life [4–7]. The study focuses on six areas of research: (1) maternal health; (2) growth and physical development; (3) behavioural and cognitive development; (4) respiratory health and allergies; (5) diseases in childhood; and (6) health and healthcare for children and their parents. Main exposures of interest include environmental, endocrine, genetic and epigenetic, lifestyle related, nutritional and socio-demographic determinants.

The main outcomes and exposures are presented in Tables 1 and 2. Main outcomes studied in the Generation R Study are new or well known risk factors in childhood or adulthood for cardiovascular disease, type 2 diabetes, obesity, asthma, neurological diseases and psychopathology. Many studies focused on these risk factors have been recently published in the *European Journal of Epidemiology* [8–98]. Results forthcoming from the Generation R Study should contribute to the development of strategies for optimizing health and healthcare for pregnant women and children.

Table 1 Main outcomes per research area

Maternal health
Cardiovascular health
Pregnancy complications
Risk factors for osteoporosis
Risk factors for type 2 diabetes
Growth and physical development
Body composition and obesity
Bone development
Childhood growth patterns
Fetal growth patterns and organ development
Physical characteristics and appearance
Risk factors for cardiovascular disease
Risk factors for type 2 diabetes
Behavioral and cognitive development
Attachment
Behavioral and emotional problems
Brain development
Child psychopathology
Compliance and moral development
Family interaction, parenting and child attachment
Neuromotor development
Neuropsychology—executive function
Stress reactivity
Verbal and nonverbal cognitive development
Respiratory health and allergies
Airways and lung structure
Allergy
Asthma
Eczema
Lung function
Diseases in childhood
Celiac disease
Constipation
Febrile seizures
Infectious diseases and immune system
Myopia
Health and healthcare
Social and ethnic health inequalities
Quality of life
Health care utilization
Effectiveness of screening programmes

Study area

The Generation R Study is conducted in Rotterdam, the second largest city in the Netherlands. Rotterdam is situated in the Western part of the Netherlands on almost 80 km south from Amsterdam, the capital of the Netherlands. The total population consists of about 600,000 inhabitants of almost 150 different ethnicities. The study area is well defined by postal codes and covers more than half of the cities inhabitants (almost 350,000 inhabitants) [99]. The largest ethnic groups in this population are the Dutch (56 %), Surinamese (9 %), Turkish (7 %), Moroccan (6 %), Dutch Antillean (3 %) and Cape Verdian (3 %) groups [100]. The percentages of the non-Dutch groups are higher in younger age groups.

Study design

Overview

The study is a population-based prospective cohort study from fetal life onwards. Mothers with an expected delivery date between April 2002 and January 2006 were eligible. Extensive assessments are performed in mothers, fathers and children. Measurements during pregnancy were conducted in two well-equipped research centers in the study area, with a close collaboration with midwives and hospitals, and planned in early pregnancy (gestational

Table 2 Main determinants

Endocrine determinants
Childhood cortisol levels
Maternal and fetal thyroid hormone levels
Environmental determinants
Air pollution during pregnancy and childhood (PM^{10}, NO^2)
Bisphenol A, pesticides, phthalates
Housing conditions
Home environment
Genetic and epigenetic determinants
Genetic variants (genome wide, candidate gene)
DNA methylation (genome wide, candidate gene)
Lifestyle related determinants
Parental alcohol consumption
Parental anthropometrics and obesity
Parental smoking
Parental working conditions
Nutritional determinants
Breastfeeding
Maternal nutrition (products, patterns)
Infant and childhood nutrition (timing, products, patterns)
Folic acid supplement use
Nutritional biomarkers (folate, homocystein, Vitamin B12, Vitamin D)
Social-demographic determinants
Parental education, employment status and household income
Parental marital status
Parental psychopathology
Ethnicity

age <18 weeks), mid-pregnancy (gestational age 18–25 weeks) and late pregnancy (gestational age >25 weeks). These measurements are generally considered as first, second and third trimester measurements. The fathers were assessed once during pregnancy of their partner. The specific timing of these measurements depended on the gestational age at enrolment [2]. The children form a prenatally recruited birth-cohort that will be followed until young adulthood. In the preschool period, which in the Netherlands refers to the period from birth to the age of 4 years, data collection was performed by a home-visit at the age of 3 months, and by repeated questionnaires and routine child health centres visits. Additional detailed measurements of fetal and postnatal growth and development have been conducted in a randomly selected subgroup of Dutch children and their parents at a gestational age of 32 weeks and postnatally at the ages of 1.5, 6, 14, 24, 36 and 48 months in a dedicated research center. From the age of 5 years onwards, regular detailed hands-on assessments are performed on all children in a dedicated research center that includes advanced imaging facilities.

Study cohort

Eligibility, enrolment and response

Eligible mothers were those who were resident in the study area at their delivery date and had a delivery date from April 2002 until January 2006. We aimed to enrol mothers in early pregnancy (gestational age <18 weeks) but enrolment was allowed until birth of their child. Midwives and obstetricians informed eligible mothers about the study at their first prenatal visit in routine care, handed out the information package and asked these mothers to make an appointment for their first ultrasound examination. The study staff contacted these mothers by phone for additional information about the study and in person at the ultrasound examination to obtain informed consent. Mothers who could not be approached in pregnancy were approached in the first months after birth of their child when newborns visited the routine child health centers [2]. The fathers were not approached directly by the study staff but the mothers were informed about the importance of involvement of the fathers in the study.

In total, 9,778 mothers were enrolled in the study (Fig. 1). Of these mothers, 91 % (n = 8,879) was enrolled in pregnancy. Partners from mothers enrolled in pregnancy were invited to participate. In total, 71 % (n = 6,347) of all fathers was enrolled. Of all participating mothers, data are available from early pregnancy in 72 % (n = 7,069), mid-pregnancy in 16 % (n = 1,594), late pregnancy in 2 % (n = 216) and from birth of their child in 9 % (n = 899). Of all pregnant women who were enrolled, 94 (n = 8,356), 6 (n = 515) and 0.1 % (n = 8) were first, second and third pregnancies in the study, respectively. A total of 1,232 pregnant women and their children were enrolled in the subgroup of Dutch children for additional detailed studies until the age of 4 years. Estimation of the precise number of eligible pregnant women in the study area is difficult since there is no satisfactory registry of pregnancies. Therefore, it was not attempted to identify overall response rates based on pregnant women, but the response rate was based on the number of children at is birth 61 %. Ethnicity and education of participating mothers and partners was defined according the classification of Statistics Netherlands [100–104]. The largest ethnic groups were the Dutch, Surinamese, Turkish and Moroccan groups. Both household income and highest followed educational level in mothers and fathers in the study cohort suggest a selection towards a higher socioeconomic status than in the whole study area [104]. This pattern is similar as in other large scale cohort studies [105].

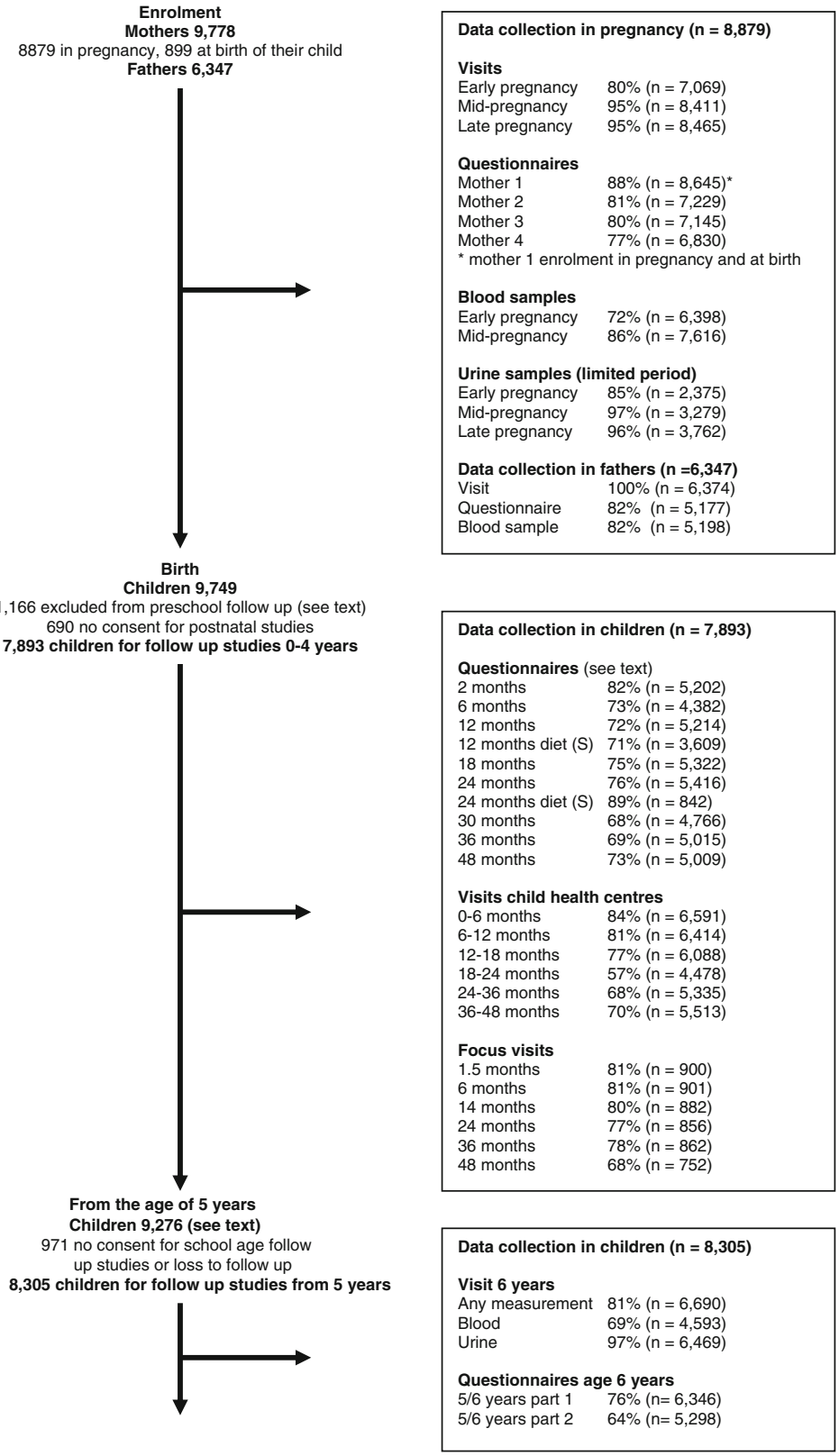

Fig. 1 Enrolment and measurements in the Generation R Study

Follow-up studies

As described above, 9,778 mothers were enrolled in the study and gave birth to 9,749 known live born children. During the preschool period (0–4 years), the logistics of the postnatal follow-up studies were embedded in the municipal routine child care system and restricted to only part of the study area due to logistical constraints. In total 1,166 children lived outside this definite study area at birth and were therefore not approached for the postnatal follow-up studies during the preschool period. Of the remaining 8,583 children, 690 (8 %) parents did not give consent for the preschool period studies, leaving 7,893 children for the preschool period follow-up studies.

From the age of 5 years onwards (school age period), we invited all 9,276 children from the original cohort of 9,749 children to participate in follow-up studies. This invitation was independent of their home address and participation in the preschool period. Of the 473 children who were not invited, 52 children died during follow-up, 106 children had withdrawn during follow-up and 315 children were lost to follow-up during the preschool period. In total, 8,305 children (90 % of those who were invited (n = 9,276) and 85 % of the original cohort (n = 9,749)) still participate in the study from the age of 5 years, of whom n = 6,690 visited the research center at the median age of 6.0 years.

Measurements

Data collection during pregnancy

Physical examinations were planned at each visit in early pregnancy, mid-pregnancy and late pregnancy and included height, weight and blood pressure measurements of both parents (Fig. 1). Since there was a wide range of gestational age at each visit, these measurements are used in the analyses as gestational age-adjusted measurements.

Mothers received four postal questionnaires and father received one postal questionnaire during pregnancy (Table 3). Topics in these questionnaires were:

- Mother 1: medical and family history, previous pregnancies, quality of life, life style habits, housing conditions, ethnicity, and educational level;
- Mother 2: diet, including macronutrients and micronutrients;
- Mother 3: current pregnancy, quality of life, life style habits, and psychopathology;
- Mother 4: current pregnancy, quality of life, life style habits, working conditions, household income, and self-esteem;
- Father: medical history, family history, life style habits, educational level, and psychopathology.

Table 3 Assessments in mothers, fathers and their children during pregnancy

	Early pregnancy	Mid-pregnancy	Late pregnancy	Birth
Mother				
Physical examination	+	+	+	
Questionnaire	+	+	+	
Interview psychopathology			S	
Fetal growth ultrasound exam	+	+	+	
Fetal organ ultrasound exam			S	
Blood sample	+	+		
Urine sample	+	+	+	
Father				
Physical examination	+			
Questionnaire		+		
Psychiatric interview			S	
Blood sample	+			
Child				
Physical examination				+
Cord blood				+

Early pregnancy: gestational age < 18 weeks; mid-pregnancy: gestational age 18–25 weeks; late pregnancy: gestational age > 25 weeks

+, Assessment in whole cohort; S, assessment only in subgroup

Blood samples were collected in early (mother, father) and mid-pregnancy (mother) and at birth (child). Procedures for collection, processing and storage of biological samples have been described previously in detail [104]. Maternal and cord blood samples have been used for measuring dietary biomarkers (folate, homocystein, total vitamin B12, free vitamin B12) levels; angiogenesis biomarkers (soluble fms-like tyrosine kinase-1 (sFlft-1), Placental growth factor (PlGF)); thyroid hormone levels (thyroid-stimulating hormone (TSH), free thyroxine (FT4)) and thyroid antibody levels, and inflammation markers (high-sensitivity C-reactive protein (hs CRP) [106–111]. Urine samples of mothers have been collected from February 2004 until November 2005 and are stored for future measurements. Urine samples have been used for measurement of *Chlamydia trachomatis*, cannabis, pesticides, bisphenol A, and phthalates levels [112–116].

Fetal ultrasound examinations were performed at each prenatal visit. These ultrasound examinations were used for both establishing gestational age and assessing fetal growth patterns. These methods have previously been described in detail [117, 118]. Longitudinal curves of all fetal growth measurements (head circumference, biparietal diameter,

Table 4 Assessments in mothers, fathers and children during the preschool period

	Age (months)												
	2	3	4	6	11	12	14	18	24	30	36	45	48
Child													
Questionnaire (parent)	+			+		+		+	+	+	+		+
Physical examination	+	+	+	+	+		+		+		+	+	
Brain ultrasound	S												
Cardiac and renal ultrasound				S					S				
Blood pressure									S				
Airway inflammation				S					S				
Behavioural observation							S				S		S
Bacterial carriage	S			S			S		S		S		
Blood sample				S			S		S				
Mother specific													
Questionnaire		+		+							+		S
Interaction with child							S				S		
Father specific													
Questionnaire											+		
Interaction with child													S

Topic in questionnaires are given in Table 5

+, Assessment in whole cohort; S, assessment only in subgroup

abdominal circumference and femur length) were created resulting in standard deviation scores for all of these specific growth measurements. Placental haemodynamics including resistance indices of the uterine and umbilical arteries have been measured in second and third trimester [119]. Detailed measurements of fetal brain, lung, heart and kidney development have been assessed in the subcohort [120–122].

The obstetric records of mothers have been looked up in the hospitals and mid-wife practices to collect information about pregnancy outcomes. Specialists in the relevant field code items in these records [123] (Table 4).

Data collection during the preschool period

At the age of 3 months, home visits were performed to assess neuromotor development using an adapted version of Touwen's Neurodevelopmental examination and to perform a home environment assessment [124, 125]. Information about growth (length (height), weight, head circumference) was collected at each visit to the routine child health centres in the study area using standardized procedures [126] (Table 4).

During the preschool period, parents received 8 questionnaires. One questionnaire was specifically for fathers. Items included in these questionnaires and their references are demonstrated in Table 5 [127–179]. Response rates based on the number of send questionnaires are shown in Fig. 1. Not all children received each questionnaire due to logistical constraints and implementation of questionnaires after the first group of children reached a certain age. Thus, although response rates may be similar, the absolute number of completed questionnaires differs between different ages. Response rates presented in Fig. 1 are based on the number of send questionnaires.

During the preschool period, children participating in the subgroup have been invited six times to a dedicated research center. Measurements at these visits included physical examinations (height, weight, head circumference, skinfold thickness and waist—hip ratio, Touwen's Neurodevelopmental Examination) and ultrasound examinations (brain, cardiac and kidney structures) [180–184]. Dual X Energy Absorptiometry (DXA) scanning and Fractional exhaled Nitric Oxide (FeNO) measurements have been performed in a smaller subgroup [185, 186]. Blood pressure was measured at the age of 24 months [187]. Observations of parent–child interaction and behaviour, such as executive function, heart rate variability, infant-parent attachment, moral development, and compliance with mother and child have been repeatedly performed and with father and child once [188–192]. Biological materials have been collected if parents gave consent [193–196].

Data collection during the school period

From the age of 5 years onwards, we invite all participating children to a well-equipped and dedicated research center in the Erasmus Medical Center—Sophia Children's Hospital every 3 years (age 6 years visit completed, age

Table 5 Themes in questionnaires until the age of 9 years

Main themes	2 months	6 months	12 months	18 months	24 months	30 months	36 months[e]	48 months	5 years[f]	9 years[g]
Parental questionnaire										
Mother/father										
General health										
Quality of life [127]	+	+								
Pregnancy and complications	+								+	
Life events							+			
Medical history										+
Lifestyle [128]									+	+
Social and demographic factors										
Housing and living conditions[a]	+	+			+			+	+	+
Work and working conditions		+							+	
Educational level and household income					+		+		+	+
Family activities and social support [129, 130]		+								+
Mental health and stress										
Parenting [131, 132]				+			+		+	
Depressive symptoms [133]	+									+
Psychopathology [134]	+	+					+			
Family functioning [135]									+	+
Child										
Diet and physical activity										
Diet[b] [136, 137]	+	+	+		+/S				+	
Eating behaviour [138–140]					+			+	+	+
Television, computer, physical activity [142, 143]					+		+	+	+	+
Day-care, School		+	+				+		+	+
Childhood health and diseases										
Quality of life [144–147]					+		+		+	+
Fever and infectious diseases [148]	+	+	+		+		+	+	+	+
Asthma related symptoms and eczema [149–152]		+	+		+		+	+	+	+
Accidents [153, 154]		+		+	+				+	+
Seizures	+	+	+		+		+	+	+	
Abdominal pain, stool pattern [155]					+		+	+	+	+
Doctors visit	+	+			+		+	+	+	+
Teeth and dental care									+	
Physical characteristics									+	
Hearing [156]										+
Eyes										+

Table 5 continued

Main themes	2 months	6 months	12 months	18 months	24 months	30 months	36 months[e]	48 months	5 years[f]	9 years[g]
Behaviour and cognition										
Sleeping, crying and soothing [157, 158]	+	+	+		+		+			+
Temperament [159–161]	+								+	
Motor development [162]		+	+	+	+			+		
Behaviour and emotional problems [163–166][d]		+		+			+		+	+
Pain perception [167–169]					+		+		+	
Language development [170]				+		+				+
Non verbal cognition [171]					+	+				
Executive function [172]								+		
Prosocial behaviour [173]									+	
Autistic traits [174–176]									+	
Bullying									+	
Child questionnaire										
Friendships [177]										+
Eating and sleeping behaviour										+
Television watching and physical activity [142, 143, 178, 179]										+
Behaviour [177]										+
Self-perception										+
Lifestyle										+

+ = Assessment in whole cohort. S = assessment only in subgroup

[a] Housing conditions include information about family structure (environmental) smoking and pets

[b] Diet questionnaires included in 2, 6 and 12 months questionnaire. Additional food frequency questionnaires at 12 months for all Dutch speaking children and at 24 months for all focus cohort children

[c] Screening 10 items questionnaire on seizures. Screen positives receive additional questionnaire and are being asked for their medical records

[d] Infant Behaviour Questionnaire at the age of 6 months, Child Behaviour Checklist thereafter

[e] For parenting, psychopathology and child behaviour additional questionnaire for fathers

[f] Diet and part of behaviour and cognition additional at the age of 8 years

[g] For medical history,lifestyle, depressive symptoms, psychopathology, family activities, behaviour and emotional problems additional questionnaire for fathers

9 years visit ongoing, and age 12 and 15 years visits planned). Currently, the total visit takes about 3 hours and all measurements are grouped in thematic 20–30 min blocks. Clinically relevant results are discussed with the parents and, if needed, children or mothers are referred to their general practitioner, paediatrician or other relevant health care provider.

At each age, we collect data with questionnaires dealing with the growth, health and physical and mental development of the children. Also we collect information on childhood diet and behaviour (Table 5). These questionnaires are being sent to the primary caregiver. From the age of 9 years, children also receive their own questionnaires.

The measurements at the research center are focused on several health outcomes including asthma, bacterial carriage, behaviour and cognition, body composition, bone health, eye and tooth development, immune status, heart and vascular development, hearing and language development, kidney growth and function, obesity, and physical appearance. Cardiovascular, metabolic and bone measurements are also conducted in mothers (Table 6).

We use various advanced imaging techniques including ultrasound and Doppler (GE LOGIQ E9, Milwaukee, WI, USA) for measuring thoracic and abdominal structures, Dual X Absorptiometry for measuring body composition and bone mineral density (iDXA scanner, GE Healthcare, Madison, WI), and 3.0 Tesla Magnetic Resonance Imaging (MRI) (Discovery MR750, GE Healthcare, Milwaukee, WI, USA) for brain imaging in subgroups of the study. Children in our study are scanned using standard imaging and positioning protocols. They are wearing light clothing without metal objects while undergoing the body scanning. Thus far, Magnetic Resonance Imaging (MRI) has been used for brain imaging in subgroups of the study using a hospital-based 3.0 Tesla MRI scanner (GE Healthcare, Milwaukee, WI, USA) [197]. We use a mock scanner, in which the children can practice to lie within the MRI scanner in a friendly way and get used to the scanner procedures. The scanner is operated by trained research technicians and all imaging data are collected according to standardized imaging protocols. Changes or updates in hardware have been avoided. Changes or updates in software configuration are minimized and regular checks with phantoms are performed to secure validity of cross-subject and cross-scan comparisons. Imaging is performed without administration of contrast agents. All imaging data are stored on a securely backed-up research picture archiving system, using programmed scripts to check for completeness of the data received. The current scanning protocol includes a 3D T1-weighted sequence, 2D PD-weighted sequence, diffusion tensor imaging (DTI), and resting state functional MRI. Total scanning time amounts to approximately 35 min. We

Table 6 Assessments in mothers and children at visits at the age of 5 and 9 years

	6 years	9 years
Mother		
General		
Cognition	+	
Interaction with child		+
Life events		+
Maternal health		
Anthropometrics and blood pressure	+	+
Arterial stiffness	+	
Body composition (DXA)	+	+
Intima media thickness		+
Physical appearance	+	+
Ultrasound heart	+	
Eyes; retinal vasculature, refraction	+	
Biological samples		
Blood and urine sample	+	+
Glucose		+
Hair sample	+	
Child		
Behaviour and cognition		
Behaviour and behavioural observation	+	+
Cognition	+	+
Language development	+	+
Pain perception	+	
Cardiovascular and metabolic development		
Anthropometrics and blood pressure	+	+
Arterial stiffness	+	
Body composition (DXA)	+	+
Intima-media thickness		+
Ultrasound abdominal fat	+	
Ultrasound heart	+	+
Ultrasound kidney	+	
Physical appearance	+	+
Eyes, ears and mouth		
Eyes; visual acuity, retinal picture, refraction	+	+
Dental and face development	+	+
Hearing		+
Taste experience	+	
Lungs		
Airway inflammation	+	
Lung function	+	+
Biological samples		
Bacterial carriage	+	+
Blood and urine sample	+	+
Faeces		+
Hair	+	
Saliva	+	+

expect to have a dedicated 3.0 Tesla MRI scanner (MR 750w, GE Healthcare, Milwaukee, WI, USA) in the Generation R research center and start with brain, lung, cardiovascular, and body fat scanning in the full cohort at age 9 years early 2013.

DNA and genome and epigenome biobank

DNA from both parents and children (cord blood) has been extracted and is used for several genotype studies. Genetic data have been generated by taqman analyses and a genome wide association scan (GWAS) using the Illumina 670 K platform in the children [3]. For genotyping, we used the infrastructure of the Genetic Laboratory of the Department of Internal Medicine (www.glimdna.org) that was also used for creation of the GWAS datasets of the Rotterdam Study, a prospective cohort study among more than 10,000 adults [198, 199]. The GWAS dataset underwent a stringent QC process, which has been described in detail previously [3]. Most GWAS analyses are strongly embedded in the Early Growth Genetics (EGG) Consortium and Early Genetics and Longitudinal Epidemiology (EAGLE) Consortium, in which several birth cohort studies combine their GWAS efforts focused on multiple outcomes in fetal life, childhood and adolescence [199–204]. These efforts have already led to successful identification of various common genetic variants related to birth weight, infant head circumference, childhood obesity and atopic dermatitis. DNA from parents is used for genotyping for candidate gene or replication studies. Recently, we started with measuring DNA methylation on a genome wide level in cord blood samples using the Illumina 450 K Infinium BeadChip, which contains 485,553 methylation sites at a single nucleotide resolution. The Illumina 450 K BeadChip provides a very good genomic coverage and requires low amounts of DNA making it ideal for use in large cohorts. We plan to measure DNA methylation at different ages to identify specific critical windows and to relate DNA methylation with expression markers and clinical outcomes.

Ethical issues

The general design, all research aims and the specific measurements in the Generation R Study have been approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam. New measurements will only be embedded in the study after approval of the Medical Ethical Committee. Participants are asked for their written informed consent for the four consecutive phases of the study (prenatally, birth to 4 years, 4–12 years, and from 12 years onwards). At the start of each phase, mothers and their partners receive written and oral information about the study. Even with consent of the parents, when the child is not willing to participate actively, no measurements are performed.

Follow-up and retention strategies

Thus far, loss to follow-up seems to be limited and is lower than 10 %. Major efforts are made to keep the children and parents involved in the study and to minimize loss to follow-up. Several strategies have been implemented and are currently part of the study design:

- Addresses: new addresses of participants, which are known by the municipal health service are forwarded to the study staff;
- Newsletters: participants receive two to four newsletters per year, in which several results of the study are presented and explained, questions of participants are answered and new research initiatives are presented;
- Presents and discounts: all children who visit our research center receive small presents. Also, discount offers are regularly presented in the newsletter;
- Transport costs: all costs for transport and parking related to visits to the research center are paid by Generation R;
- Reminders for questionnaires: when the questionnaire has not been returned within 3 weeks, a kind reminder letter is send to the parents. After 6 weeks, when the questionnaire has still not been returned, the parents receive a phone call. If necessary, help for completing the questionnaire is offered and the importance of filling in the questionnaire is explained once more during this phone call;
- Individual feedback: if clinically relevant, all results of hands-on measurements are discussed with the parents at the visit. If necessary, follow-up appointments with the general practitioner or pediatrician are planned;
- Support for ethnic minorities: all study materials such as questionnaires, newsletters, website, and information folders are available in three languages (Dutch, English, and Turkish). Furthermore, staff from different ethnic minorities is available and able to verbally translate these materials into Arabic, French and Portuguese. With this, the study staff is able to communicate to all participants.
- Care-cases: children and parents who showed low response rates for different measurements, showed difficulties in completing questionnaires or require additional explanation or support are considered as care-cases. Care–cases have a more individual based

approach and are pro-actively contacted by one dedicated member of the study staff.
- Home visits: We bring a visit to children and parents who cannot be contacted by phone or letter. Most visits are planned in the evenings to have higher chances that both parents and children are at home;

New methods for contacting participants, including use of internet and e-mail, are currently explored in subgroups [80].

Data management and privacy protection

Data collected by measurements in the research centers are directly entered onto written forms and into the electronic database. Data collected by questionnaires are scanned and manually entered into an electronic database by a commercial bureau. Random samples of all questionnaires are double checked by study staff members to monitor the quality of this manual data entry process. The percentage of mistakes is kept as low as possible and does not exceed 3 % per questionnaire. Open text fields are entered into the electronic database exactly as they are filled in on the questionnaires. In a secondary stage, these open text fields are cleaned and coded by a specialist in the relevant field. All measurements are centrally checked by examination of the data including their ranges, distributions, means, standard deviations, outliers and logical errors. Data outliers and missing values are checked on the original forms. The data of one specific measurement are only distributed for analyses after data collection and preparation is completed for that measurement for the whole cohort. Datasets needed for answering specific research questions are centrally built from different databases. All information in these datasets that enables identification of a particular participant (including identification number used for the logistics of the study, names and dates) is excluded before distribution to the researchers. The datasets for researchers include subject unique identification numbers that enable feedback about one subject to the data manager but do not enable identification of that particular subject.

Table 7 Effects sizes in standard deviation that can minimally be detected according to the prevalence of the exposure

Proportion exposed (%)	Whole cohort (n = 7,000)	Focus cohort (n = 700)
50	0.067	0.212
25	0.077	0.276
10	0.112	0.353
5	0.154	0.486
1	0.337	1.064

The presented effect sizes are detectable proportions of the standard deviation with a type I error of 5 % and a type II error of 20 % (power 80 %)

Statistical power

Due to expected missing values and loss to follow-up, most analyses in the study are not based on data in all subjects. Therefore, power calculations demonstrated in Tables 7 and 8 are based on 7,000 subjects in the whole cohort and 700 subjects in the subgroup. The presented power calculations are rather conservative since most studies will assess the effects of continuously instead of dichotomous measured exposures and studies may be focused on outcomes collected in more than only 1 year. Furthermore, the Generation R Study has a large number of measurements repeated over time, which may increase the accuracy of measuring the true underlying value and may thereby increase the statistical power for these measurements.

Collaboration

The Generation R Study is conducted by several research groups from the Erasmus Medical Center in close collaboration with the Erasmus University Rotterdam and the Municipal Health Service Rotterdam area. Since the data collection is still ongoing and growing, the number of collaborating research groups in and outside the Netherlands is expected to increase. Various research project are performed as part of ongoing European or world wide

Table 8 Relative risks that can minimally be detected according to the prevalence of the exposure

Proportion exposed (%)	Incidence (1 year) of outcome of interest					
	Whole cohort (n = 7,000)			Focus cohort (n = 700)		
	10 %	5 %	1 %	10 %	5 %	1 %
50	1.23	1.33	1.83	1.83	2.28	4.94
25	1.26	1.38	1.94	1.96	2.46	5.41
10	1.39	1.56	2.42	2.48	3.26	7.92
5	1.55	1.80	3.09	3.20	4.39	11.74
1	2.36	3.04	6.83	7.75	11.61	37.55

The presented effect sizes are detectable relative risks with a type I error of 5 % and a type II error of 20 % (power 80 %)

collaboration projects. The study has an open policy in regard to collaboration with other research groups. Request for collaboration should primarily be pointed to Vincent Jaddoe (v.jaddoe@erasmusmc.nl). These requests are discussed in the Generation R Study Management Team regarding their study aims, overlap with ongoing studies, logistic consequences and financial contributions. After approval of the project by the Generation R Study Management Team and the Medical Ethical Committee of the Erasmus Medical Center, the collaborative research project is embedded in one of the research areas supervised by the corresponding principal investigator.

Acknowledgments The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. We thank Marjolein Kooijman, Claudia Kruithof, Natalia Loekabino, Patricia Maeijer, Ronald van den Nieuwenhof, and Karien Toebes for their study coordination. The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport. Vincent Jaddoe received an additional grant from the Netherlands Organization for Health Research and Development (ZonMw 907.00303, ZonMw 916.10159).

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