The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward

Henning Tiemeier, M.D., Ph.D., Fleur P. Velders, M.D., Eszter Szekely, M.Sc., Sabine J. Roza, M.D., Ph.D., Gwen Dieleman, M.D., Vincent W.V. Jaddoe, M.D., Ph.D., Andre G. Uitterlinden, Ph.D., Tonya J.H. White, M.D., Ph.D., Marian J. Bakermans-Kranenburg, Ph.D., Albert Hofman, M.D., Ph.D., Marinus H. Van IJzendoorn, M.D., Ph.D., James J. Hudziak, M.D., Frank C. Verhulst, M.D., Ph.D.

Objective: First, we give an overview of child psychiatric research in the Generation R Study, a population-based cohort from fetal life forward. Second, we examine within Generation R whether the functional polymorphism (5-HTTLPR) in the promoter of the serotonin transporter gene interacts with prenatal maternal chronic difficulties, prenatal maternal anxiety or postnatal maternal anxiety to influence child emotional development. **Method:** A total of 2,136 northern European children were genotyped for 5-HTTLPR and rs25531. Mothers reported chronic difficulties and anxiety symptoms at 20 weeks' pregnancy and when the child was 3 years old. Child emotion recognition was observed at 3 years, and child emotional problems were assessed with the CBCL/1½–5 at 5 years. **Results:** There were consistent main effects of maternal difficulties and anxiety on child emotional problems, but no main effect of 5-HTTLPR. Moreover, children with the s allele were at increased risk for emotional problems if their mothers reported prenatal anxiety symptoms ($\beta = 2.02$, $p < .001$) or postnatal anxiety symptoms ($\beta = 1.64$, $p < 0.001$). Also, in children of mothers with prenatal anxiety symptoms, the s allele was associated with less accurate emotion-matching ($\beta = -0.11$, $p = .004$). **Conclusions:** This population-based study shows that vulnerability due to 5-HTTLPR is not specific for certain adverse exposures or severe events, but suggests that the small effects of gene–environment interaction on emotional development become manifest early in life. J. Am. Acad. Child Adolesc. Psychiatry, 2012;51(11):1119–1135. **Key Words:** Generation R, 5-HTTLPR, maternal anxiety, gene–environment interaction, emotional problems

The Generation R Study ("R" for Rotterdam) is a longitudinal, population-based cohort in which children are followed up from fetal life forward. There have been multiple timepoints of data collection on this cohort, with data at age 5 years most recently completed. The aim of Generation R Study is to identify early environmental and genetic determinants of growth, development, and health. Generation R focuses on a wide range of issues relating to physical development, childhood diseases, use of healthcare, and behavior and cognition (described in detail by Jaddoe *et al.*).[1] This review provides a brief summary of child behavioral, emotional, and cognitive research within Generation R. Key issues to be addressed include the following: an overview of the design and data collection; presentation and discussion of key results relating to intrauterine, environmental, and genetic determinants of neurodevelopment and child mental health; and a brief consideration of the advan-


This article will be discussed in an editorial by Drs. James J. Hudziak and Douglas K. Novins in an upcoming issue.


Supplemental material cited in this article is available online.

tages and limitations of the Generation R data collection project.

DESIGN AND DATA COLLECTION

Cohort

The initial cohort comprised 9,778 pregnant women with a delivery date between April 2002 and January 2006, living in Rotterdam, the Netherlands. The population of Rotterdam consists of about 600,000 inhabitants of almost 150 different ethnicities. To recruit pregnant women, the researchers collaborated closely with midwives, who provide routine antenatal care in the Netherlands. These 9,778 mothers gave birth to 9,745 live-born children (Figure 1). Of all mothers, 8,880 were assessed during pregnancy, together with 6,347 (71%) partners (Figure 1, enrollment). The response rate was estimated at 61% based on birth rates. The largest groups according to national origin are Dutch (59%), Surinamese (9%), Turkish (9%), and Moroccan (6%) (Figure 1, box 1).

In a subgroup of 1,106 pregnant women and their children, we conducted very detailed hands-on assessments during six visits to the research center up to age 4 years (Figure 1, box 3). This group was of Dutch national origin to exclude confounding or effect modification by ethnicity.

Sample Retention

In January 2012, the 6-year examination wave was completed, in which 6,694 children together with a parent were assessed, and also 594 children participated by questionnaire only. In total, for 8,306 children, parents gave consent, and children participated at least with health care data; 1,493 children have been lost to follow-up.

Assessments

The following data sources have been used during the course of the study: biological measures (ultrasonography of fetal growth and circulation, parental blood and urine samples, child cord and 6-year blood samples, brain imaging); observational assessments (e.g., of home environment, motor development, executive function, parent–child interaction and attachment styles, cognition, and IQ); parental questionnaires (see Table S1, available online, for psychosocial measures, child behavioral and emotional problems, and other variables); teacher questionnaires at 6 years; records of child health care centers; and child interviews on behavioral and emotional problems (Berkeley Puppet Interview at 6 years).

MAIN RESULTS OF THE GENERATION R STUDY

Here we present selected results and sketch future plans; for detailed information, we refer readers to the Generation R publications, as referenced below.

Intrauterine Environment

The repeated fetal ultrasounds combined with detailed pregnancy questionnaires offer Generation R researchers unique opportunities (Figure 1, box 2). We studied trajectories of fetal head growth to test whether maternal exposures during pregnancy impact on early neurodevelopment. Maternal depression,[2] anxiety, smoking during pregnancy,[3] maternal serotonin-specific reuptake inhibitor (SSRI) use,[4] and cannabis exposure[5] all negatively affected fetal head growth. In particular, maternal nicotine, SSRI, and cannabis use during pregnancy had relatively strong effects. Furthermore, we addressed the association between intrauterine growth trajectories and child development. We found support for a relation of intrauterine head growth with observed motor development but not with behavioral or emotional problems of infants and preschool children.[6,7] These studies add to the literature relating variations in birth weight,[8] an end-point measure of fetal growth, to child behavior. We also identified specific prenatal determinants and mechanisms behind common emotional and behavioral problems. Cannabis exposure during prenatal life increased the risk of externalizing problems in girls.[9] Furthermore, subclinical maternal hypothyroxinemia early in pregnancy was a consistent risk factor for poor cognitive functioning and emotional problems.[10] Similarly, folate deficiency and lack of folate supplementation were associated with emotional problems in 3-year old children.[11]

Future plans: We intend to relate prenatal risk factors and variations in head growth to specific child psychiatric problems such as autistic traits and structural brain imaging parameters. For example, we will test, in children with and without autistic traits, whether neurodevelopmental differences in cerebellar volume emerge during prenatal development.

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