TITLE OF PROPOSED RESEARCH PROJECT

Developmental origin of non-communicable disease intermediate risk factors: disentangling genetic factors from early life residential exposure in a large twin cohort

ABOUT THE SUPERVISORS

Promotor

Professor Maurice Zeegers has broad experience in big data, precision medicine, complex genetics, epidemiology, systematic reviewing and health promotion. He is head of the department of Complex Genetics and head of Maastricht University's Care and Public Health Research Institute, CAPHRI.

Co-promotor

Dr. Marij Gielen is assistant professor at Complex Genetics & Epidemiology at UM. Her main interest is prenatal programming of non-communicable diseases (NCD) with specific interest in the role of (epi)genetic factors. She collaborates with the East Flanders Prospective Twin Survey (EFPTS) and is the Study Manager of the MEFAB study and the TELOMAAS initiative.

ABOUT THE RESEARCH GROUP

The studentship will be embedded within the department of Complex Genetics. It is a small research group that aims to create knowledge to help people live a longer, healthier and happier life. Much of their research is based on disentangling the genetic and environmental risk factors of chronic complex diseases. Their research results are being used for the prevention of chronic disease, to improve patient care, to inform legal court decisions, on the market place and to improve the scientific process itself. Their core expertise is in the field of (genetic) epidemiology but it is continuous reaching outward into adjacent disciplines such as analytics, genomics and forensic medicine to lead new innovations and leave a legacy in public health. (http://www.ccge.nl)

ABOUT THE EAST FLANDERS PROSPECTIVE TWIN SURVEY (EFPTS)

The East Flanders Prospective Twin Survey (EFPTS) is the most fantastic twin register worldwide with at present >10.000 twin pairs being registered. The EFPTS is an ongoing registry of multiple births in the province of East Flanders, Belgium with unique features:

1. Founded in 1964 and prospective population based with at present > 10.000 twin pairs registered
2. Ascertainment at birth
3. Recording of basic perinatal data
4. Establishment of chorion type and zygosity
5. Since 1969 storage of placental biopsies in a biobank
6. Possibility of long term follow-up.

Chorion type and zygosity

The term zygosity reflects the number of fertilized ova. Monozygotic (MZ) twins are derived from a single one, whereas dizygotic (DZ) twins are derived from two separate ova. DZ twins always have two chorionic (DC=dichorionic) membranes and two placentas. In contrast, for MZ twins the chorion type and number of placentas depend on the moment of splitting of the fertilized ovum. Early splitting leads to each twin having its own fetal membranes (MZ DC twins) and two separate placentas as in DZ twins. Intermediate splitting leads to a single placenta and single chorionic membrane (MZ monochorionic (MC) twins). Late splitting results in one amniotic membrane for both twins. Altogether, taking zygosity, chorion type and number of placentas into account instead of the traditional distinction between MZ and DZ twins facilitates the study of prenatal programming in more detail with a focus on the early environment.

Twins in research

When differentiating between prenatal genetic, environmental and epigenetic programming, a twin design has several advantages above other study designs:

1 By comparing MZ (genetically identical) with DZ (on average 50% of shared genes) twin pairs, genetic factors can be distinguished from environmental factors and their interaction can be tested.
2 Discrimination by the moment of splitting of a fertilized ovum, makes it possible to unravel the influence of the early prenatal environment.
3 A further discrimination is possible by taking into account the environment at conception, namely ART vs natural conceived twins. Since MZ twins have the same genetic background, MZ twins are an ideal population to study environmental influences.
4 MZ twins are simply the best human model to investigate the epigenetic programming to health outcome, because genetic variation is ruled out.

Barker twins

Prenatal growth is determined by genetic factors and shaped by the intrauterine environment. Prenatal growth as expressed in birth weight has been shown to have a major impact on later health. This has been termed the developmental origins of adult health hypothesis (DOHaD a.k.a. Barker hypothesis). The "Barker subset" consists of 424 young adult twin pairs without major congenital malformations, who were born between July 1964 and May 1982, who participated in the prenatal programming study.
The twins visited the research center in 1997-1999. Measurements of body composition, blood pressure and ambulatory blood pressure, lung function were performed, and structured questionnaires about health and risk factors for NCDs, including intoxications (medication, alcohol and tobacco use), work, education, physical activity were filled in according to standardized procedures. Blood and urine samples were collected to determine carbohydrate and lipid metabolism and renal function. Placental telomere length is measured.

ABOUT THE PROJECT

Background

Early life exposures to surrounding greenness and traffic have been recently implicated as potential drivers of the obesity and asthma epidemics. Recently we made two key observations in a large twin sample of the EFPTS indicating that residential exposure plays a role in later health: in utero exposure to air pollution does not only result in suboptimal fetal growth, but also is residential surrounding greenness in early life associated with higher blood pressure at adult age. Air pollution is associated with shorter placental telomeres and is identified as a risk factor for small for gestational age. This may explain a significant proportion of air pollution-related adverse health outcomes starting from early life, since shortened telomeres accelerate the progression of many diseases. However, new research is warranted to extend the impact of early life on later health.
Modelling genetic and environmental exposure leads to a better estimate of their role in growth during gestation. Results potentially support preventive strategies to optimize birth weight, for example via placental function, to target later health, since environmental factors seem to play a more important role than genetic factors.

Key objective

To examine in depth the impact of genetic and early life residential exposure to NCD intermediate risk factors at young age in a large twin cohort.

Research questions

do differences in residential exposure contribute to the explanation of differences in

- cardiometabolic risk factors (obesity, blood pressure, glucose and lipid metabolism)?
- respiratory and allergy related outcomes (asthma, wheezing, rhinitis and eczema; lung function)?

and

- is further differentiation between the contribution of different environmental factors e.g. air pollution, water quality, noise disturbance, or green spaces possible?
- is further differentiation between different time frames in early life possible (moment of splitting of MZ twins; prenatal vs postnatal residential exposure) in the contribution to cardiometabolic risk factors and allergy related outcomes.

- Do the associations differ between MZ DC, MZ MC and DZ twins?
- Is placental telomere length an intermediate factor in the association between early life residential exposures?

Methods/Technologies

A geographic information system (GIS) is designed to relate spatial or geographic data by using location as key index variable. Residential addresses will be geocoded and GIS functions will be used to measure physical environment. The GIS analyses are carried out using ArcGIS software (Esri Nederland).

The measurement of traffic related air pollution and green spaces will be based upon our previously used analytic approach. Traffic related air pollution will be estimated by calculating the distances to the nearest major road with traffic counts available and traffic density. Semi-natural, forested, agricultural, residential and industrial area in a 5000 m radius from the residential address will be estimated based on Corine land cover 2000 (European Environment Agency; Corine: "coordination of information on the environment"). In addition, Normalized Difference Vegetation Index (NDVI), another indicator of greenness based on land surface reflectance of visible (red) and near-infrared parts of the spectrum is estimated.

We plan to use data provided by TNO Institute of Applied Geo-science for the measurement of groundwater quality and the GIS instrument URBIS provided by TNO for noise disturbance.

Expected results

This PhD projects aims to provide definite answers on the association between environmental exposure and health throughout the life course in order to provide strong evidence base for policy strategies to enable residential areas in cities and protect child health. Successful termination of this project will result in a PhD thesis and at least four to six WI-1 publications.