ERACOL| Research lines Erasmus University

2010-04-30

General information

Institution:	Erasmus University
City:	Rotterdam
Country:	The Netherlands

CONTENT

Epidemiology

1. research line 1:
Pharmaco-epidemiology
2. general description of the research line:
The focus is on intended effects of medications, and the effects of medication use under common circumstances in large populations. There are several drug-related research projects in the Rotterdam Study, a large prospective cohort study that is being conducted since 1990 to investigate cardiovascular, locomotor, neurological, and ophthalmological diseases.
3. specific subtopics within the research line:
Cardiovascular, locomotor, neurological, and ophthalmological diseases.
4. contact person for interested students/teaching staff:
Prof.dr. B. Stricker, email; b.stricker@erasmusmc.nl
5. Field of research (for example: epidemiology, public health, statistics, medicine):
Clinical Epidemiology, Epidemiology
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate

1. research line 2
Pharmacoepidemiology by using health care database in the Netherlands and across countries
2. general description of the research line:
In this research line we assess the use and effects of drug use. Since both drug use and outcomes (frequently adverse effects) are uncommon, large populations are required. This can be achieved by using data from electronic health care data, that are available in most countries. In Europe we use data from many countries by using common data models, for the estimation of risk and relative risk.
3. specific subtopics within the research line:
Safety assessment of drugs in general Safety of drugs in pediatrics Safety of vaccinations Occurrence of rare diseases and predictors of these diseases Use of medical record data for epidemiological research Drug safety signal generation from electronic health care data
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Epidemiology
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master Doctorate Post-doctorate Teaching staff

1. research line 3:

Assessment of Diagnostic Imaging Tests and Minimal Invasive Therapies

2. general description of the research line:

This program focuses on the assessment of medical imaging technology, both diagnostic imaging and minimal invasive (image-guided) therapies. The clinical problems studied are mainly related to cardiovascular disease (CVD) and include imaging for suspected coronary artery disease, imaging of carotid artery disease, imaging and treatment of peripheral arterial disease, screening of asymptomatic individuals to identify and treat those with high CVD risk, screening and treatment of abdominal aortic aneurysms. Neuroimaging is another clinical area of interest in particular imaging for head injury and brain tumors. The studies performed include systematic reviews and meta-analyses, prediction rules, decision modeling, randomized controlled trials, and cost-effectiveness analyses. The goal is to assess the added value of imaging, to determine the appropriate indications for specific imaging technologies, and to estimate prognosis on the basis of imaging findings.

3. specific subtopics within the research line:

- Cardiovascular disease (CVD):
  - Imaging for suspected coronary artery disease,
  - imaging of carotid artery disease,
  - imaging and treatment of peripheral arterial disease,
  - screening of asymptomatic individuals to identify and treat those with high CVD risk,
  - screening and treatment of abdominal aortic aneurysms.
- Neuroimaging
  - imaging for head injury
  - brain tumors

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Clinical Epidemiology

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

All levels

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1. research line 4:

Neuroepidemiology

2. general description of the research line:

The research program of the Neuroepidemiology group focuses on the etiology and early detection of major age-related cerebrovascular and neurodegenerative disorders, including Alzheimer disease, other dementing disorders, Parkinson's disease and stroke. We aim to identify preclinical biomarkers (imaging, genetic, blood-based) for cerebrovascular and neurodegenerative disorders, to identify people at risk (risk profiling) for cerebrovascular or neurodegenerative disorders, and to find modifiable and genetic risk factors for those disorders. The research is mostly embedded in the Rotterdam Study and the Rotterdam Scan Study. The Rotterdam Study is a prospective population-based study of frequency and causes of age-related disorders that includes 15,000 persons and is ongoing since 1990. The Rotterdam Scan Study started as a population-based MRI study of determinants and clinical consequences of degenerative and cerebrovascular brain changes in over 1,000 persons in 1995. In 2005, we expanded the Rotterdam Scan Study into a large new prospective population based neuroimaging study, embedded in the Rotterdam Study, which will include over 8,000 elderly who will be repeatedly scanned, and which forms the core of a multidisciplinary research program involving neuroepidemiologists, neuroradiologists, MR physicists, neuroscientists, neurologists, and image processers.

3. specific subtopics within the research line:

1. Identification of preclinical biomarkers (imaging, genomic, proteomic) for cerebrovascular and neurodegenerative disorders
2. Risk prediction of Alzheimer disease, cognitive decline, stroke
3. Risk factors (etiologic research) for Alzheimer disease, cognitive decline, Parkinson disease, and stroke
4. Causes and consequences of degenerative and vascular brain changes as assessed through structural MRI
5. The importance of resting state networks in cognitive decline and dementia

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Epidemiology

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Doctorate; post-doctorate; teaching staff

1. research line 5:

Fetal and early postnatal origins of cardiovascular disease, type 2 diabetes and obesity

2. general description of the research line:

This research is embedded in The Generation R Study and focused on environmental and genetic exposures related to fetal and postnatal growth, early cardiovascular development, insulin resistance en obesity. We also study risk factors of pregnancy complications in mother and child, such as preeclampsia and preterm birth. Research is performed in closed collaboration between the departments of Pediatrics, Epidemiology, Obstetrics, Pediatric Cardiology and Pediatric Nephrology.
Examples of research topic are:

- Development of growth curves
- Maternal life style habits in relation to pregnancy complications
- Genetics of fetal and postnatal growth
- Maternal and childhood nutrition in relation to cardiovascular and metabolic development
- Biomarkers of preeclampsia and pregnancy induced hypertension

Researchers are actively participating in one of the research projects, actively participate in the research Group (data collection, scientific meetings) and write papers that will be submitted for publication.

3. specific subtopics within the research line:

- Nutritional and life style related determinants of fetal and postnatal growth;
- Genome wide association studies related to fetal and early postnatal growth and development;
- Cardiovascular riks factor development in early childhood;
- Obesity and body composition in early childhood;

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Epidemiology, Pediatrics

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Masters '/ doctorate / post-doctorate

1. research line 6:

Vascular-related pregnancy disorders and maternal risk of cardiovascular disease in later life: The Generation R study

2. general description of the research line:

Goals: This study is designed to investigate whether vascular-related pregnancy complications are associated with specific maternal cardiovascular risk profiles 5 years after pregnancy, and to identify lifestyle factors that underlie these associations. The ability to identify young women at increased risk for future cardiovascular disease, through pregnancy complications, may enable unique programs of secondary prevention.

Background: Several epidemiological studies suggest associations between vascular-related pregnancy complications, comprising preeclampsia, pregnancy-induced hypertension (PIH), HELLP-syndrome, and intrauterine growth retardation (IUGR), and increased maternal risk of cardiovascular disease (CVD) later in life. In this respect, it has been put forward that common risk factors, such as chronic hypertension, increased total cholesterol, decreased insulin sensitivity and obesity, predispose to both vascular-related pregnancy disorders, as well as CVD. Moreover, both vascular-related pregnancy complications and chronic vascular diseases have pathognomic features of atherosclerosis, endothelial dysfunction, and smooth muscle cell proliferation in common. In this respect, it has been shown that women with a history of vascular-related pregnancy disorders, and no signs of clinical disease after pregnancy, may exhibit the phenotype of metabolic syndrome or impaired endothelial function after pregnancy. Apparently, exposure of women with this phenotype to the additional cardiovascular challenges of pregnancy, induces transient clinical disease that subsides after pregnancy but is likely to re-emerge later in life as CVD. It has not bee studied whether lifestyle habits, including nutrition and smoking, are able to influence the interaction between cardiovascular stress during pregnancy and the hypothesized predisposition to vascular and metabolic disease.
In the proposed study we want to test the hypothesis that it is the maternal constitution that underlies both vascular-related pregnancy disorders as well as future maternal CVD (rather than that vascular-related pregnancy disorders are a cause of CVD), and that life style habits are able to affect this constitution.

Design: The study is embedded in the **Generation R Study**, a population-based prospective cohort study from early pregnancy onwards in Rotterdam (Jaddoe et al, Eur J Epidemiol 2006). In total, 8,880 pregnant women prenatally enrolled. During pregnancy, detailed information on vascular-related pregnancy disorders and determinants has been collected by physical and ultrasound examinations and questionnaires in early (gestational age < 18 weeks), mid- (gestational age 18 – 25 weeks) and late pregnancy (gestational age ≥ 25 weeks), and from medical records at delivery. Maternal and paediatric follow-up measurements are being performed 5 years after pregnancy. In total, about 7000 women will participate in the measurements, that are scheduled from 2008 until 2010.

3. specific subtopics within the research line:

By assessing the following research questions we aim to develop a strategy of post-pregnancy non-invasive health risk assessment in women who have experienced a vascular-related complicated pregnancy.
1.) Which pregnancy-related vascular complications are associated with maternal cardiovascular risk profiles, including arterial stiffness, intima-media thickness (IMT), left ventricular mass and retinal microvasculature, 5 years after pregnancy.
2.) Which maternal life style habits during pregnancy, such as nutrition and smoking, are associated with vascular-related pregnancy disorders.

3.) Can these lifestyle habits during pregnancy be related to the specific maternal cardiovascular risk profiles 5 years after pregnancy.

The following maternal cardiovascular parameters, 5 years after the index pregnancy are being measured: Maternal arterial stiffness measured as aortic-femoral pulse wave velocity using a non-invasive, validated device (Complior®); IMT measured following standardised protocols for the right and left carotid arteries; Left cardiac structures and function measured by two-dimensional echo-cardiography and M-mode, including intracardiac dimensions, left ventricular systolic and

diastolic function (E-, A-waves, pulmonary flow) and left ventricular mass (Philips iE33); Blood pressure measured by a validated automatic device (Omron 907®). Microvascular structures are assessed by Digital retinal photographs centred on the optic disc, from both eyes, taken by use of a non-mydriatic retinal camera (Topcon Optical Company).

Information on preeclampsia, PIH, HELLP syndrome and IUGR has been retrieved from medical records. Maternal blood pressure has been measured by a validated automatic device (Omron 907®) in early, mid- and late pregnancy. Placental blood flow patterns include uterine and umbilical artery flow patterns measured in mid- and late pregnancy by Doppler (Baschat et al, Clin Obstet Gynecol 2003). Fetal growth was measured by ultrasound in early, mid- and late pregnancy (Verburg et al, Ultrasound Obstet Gynecol 2007). Maternal nutrition and smoking in pregnancy were measured by food frequency questionnaires (early pregnancy) and by questionnaire in early, mid- and late pregnancy, respectively. Biochemical markers of nutritional status (folate, vitamin B12 and homocysteine) have been measured in stored blood samples that have been collected in early, mid- and late pregnancy. Genetic variants were selected based on their role in the pathogenesis of CVD and pregnancy-related pregnancy disorders and include the VEGF-, MTHFR-, and glutathione-S-transferase polymorfisms. Other variants will be selected from the current genome wide analysis studies.

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Epidemiology, public health, medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

All levels

1. research line 7:

Periconception gene-environment factors, embryogenesis and adverse pregnancy outcome. The Predict study.

2. general description of the research line:

The genes of the child and placenta are derived from the gametes of both parents. Therefore, the genetic background together with the environmental exposures of the parents such as nutrition, lifestyle, occupational exposures, medication and chronic disease determine the quality of the gametes, fertilisation and subsequent pregnancy outcome. The environment of the embryo and fetus is determined by the maternal body. Genes of the conceptus and maternal environmental exposures are implicated in the embryogenesis and placentation in early pregnancy as well as the fetal programming, growth and development in the second and third pregnancy trimester.
Focus: Our research is focussed on the *periconception* period and first 10 weeks of pregnancy. The phenotypes of interest are subfertility, embryonic growth and morphogenesis, congenital malformations, miscarriage, pre-eclampsia, and intrauterine growth restriction.
Study Design: To investigate this topic, we are conducting a hospital based *periconception* cohort study (The Predict Study). In this cohort study couples are followed from the preconception period onwards until 1 year after delivery, with a focus on the preconception period and first 10 weeks of pregnancy.
Measurements of embryonic growth: In the first 10 weeks of pregnancy we perform weekly three-dimensional (3D) ultrasound examinations of the embryo and developing placenta. The 3D ultrasound datasets are transferred to the I-Space VR system and analyzed using V-Scope software. This program creates a 'hologram' of the ultrasound image and allows depth perception and detailed embryonic measurements (not possible by routine ultrasound). Serial (automated) measurements are conducted, using segmentation-algorithms and a tracing-tool, of the crown rump length and volumes of the total embryo, the yolk sac and ventricles of the embryonic brain.
Determinants: (Preconception) questionnaires: constitutional characteristics, nutrition, lifestyle, occupation exposures. Biomarkers in semen, ovarian follicular fluid (IVF), maternal and paternal blood (and DNA) and cord blood. Tissues: chorionic villous samples, amniotic fluid, umbilical cord and placental tissue.
All materials and isolated DNA are available for sophisticated (nutri)genomics, in particular epigenetic and proteomic techniques.
Relevance: The importance of this collaborative research of the department of Obstetrics and Gynaecology is that the identification of modifiable risk factors and underlying epigenetic mechanisms contribute to the understanding of the etiology of abnormal pregnancy outcomes and such knowledge can be used in future preconception care of subfertile, normal and high risk couples. Furthermore interventions of (secondary) prevention may be developed, improving reproductive performance by epigenetic reprogramming.
Research activities: Depending on the level of the candidate, applicants will participate in all phases of the studies; the designing of the study, the recruitment and clinical data sampling, the performing of measurements and the data analysis. Final aim is the (supervision of) writing of full papers and a thesis.

3. specific subtopics within the research line:

Main research themes:
1. Subfertility
2. Congenital malformations
3. Adverse pregnancy course and outcome

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Epidemiology, public health, statistics, medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

undergraduate, master, doctorate, post-doctorate

1. research line 8:

Psychiatric Epidemiology: Behavoural and cognitive research in young children: The Generation R Study

2. general description of the research line:

Whereas most somatic disorders are quite rare, behavioural and learning disorders in children are frequent. About one in ten children will develop a mental health disorder and many more have behavioural or cognitive problems that are a burden to child, families and society.
Behavioural problems can be caused by social factors (e.g. bullying or poverty), psychological factors (e.g. bad parenting or poor emotion recognition) and biological factors (e.g. genetic variation or altered stress hormones). Aetiological research has demonstrated that many child psychiatric disorders are neurodevelopmental in origin, i.e. they have their onset early in life and affect the functioning of the nervous system. Furthermore, child psychiatric research has been leading the field of gene-environment interaction studies.
This understanding has guided the behavioural and cognitive research in Generation R. We are thus investigating the importance of fetal development for behaviour and cognition later in life, and have assessed neurodevelopment with brain-ultrasound, neurological examinations, and will soon start MRI imaging. Moreover, we are conducting genome wide analyses and candidate studies to detect genetic risk factors and vulnerabilities. Together with several EUR and external partners we have introduced many innovative child assessments, which are unique to large-scale behaviour studies. These include the Strange Situation Procedure, HOME environment assessment, executive function, parent-child interaction tasks or tasks of moral development.

3. specific subtopics within the research line:

The topics and possible themes for research in Generation R cover a wide area; selected but prototypical questions addressed in the coming years include:
- Do low thyroid hormone or vitamin levels in pregnant women cause cognitive problems in the offspring? (Neurodevelopmental research)
- Does father-child interaction matter in respect to the emotion development of the child? (Med Psychology)
- What do teacher, father and 5-year child self report add to maternal report of behavioural problems? (Methods)
- Do daycare, bullying in kindergarten, television watching or unstructured parenting affect certain children predisposed to behavioural problems? (Social Psychiatry)
- Are altered cortisol secretion patterns cause or consequence of behavioural problems? (Psychobiology)
- Does prenatal cannabis exposure affect the brain development? (Psy. Imaging)
- Can we identify the genetic basis of child resilience to family adversity (Psy.Genetics)

4. contact person for interested students/teaching staff:

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5. Field of research:

Epidemiology with close links to psychiatry and public health

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Undergraduate, master, doctorate

1. research line 9:

Psychiatric Epidemiology

2. general description of the research line:

Often, psychiatric epidemiology is restricted to measuring the prevalence of mental illness in society. Descriptive studies are important for social policy and to generate hypotheses, but if one studies only the sick, the opportunities to understand mental illness are very limited. Modern psychiatric epidemiology shows how the frequency of psychiatric problems varies in groups identified by education, genetic variation, brain morphology or temperament. This approach has become the main scientific foundation of psychiatry.
The Psychiatric Epidemiology in Rotterdam is analytical epidemiology of common psychiatric problems in childhood and late adult life. All ongoing projects are conducted in large populations-based cohorts, in particular the Generation R Study and the Rotterdam Study

3. specific subtopics within the research line:

The focus of psychiatric research in the elderly has been on determinants and consequences of depressive disorders but anxiety disorders, sleep disturbances and complicated grief are also being studied. A particular research interest has been vascular depression assessed with different measures of atherosclerosis, arterial stiffness and cerebral blood flow. In ongoing projects, diurnal patterns of cortisol secretion, sleep fragmentation, genetic variations and brain morphology are studied. Current data collection also includes a dexamethasone suppression test to measure hypothalamic-pituitary-adrenal axis activity in all participants, which is unique in a large population-based study.
We currently have vacancies in depression, sleep and grief research. Contact us or attachment for details

4. contact person for interested students/teaching staff:

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5. Field of research:

Epidemiology with close links to psychiatry and public health

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

doctorate

Attachment:

Complicated Grief in Older Adults

Research group:
Rachel Newson (post doc, supervisor), Henning Tiemeier (associate professor, supervisor), Albert Hofman (Department Head, promoter/mentor)
Department of Epidemiology, Erasmus Medical Centre

The Department of Epidemiology at Erasmus Medical Center, Rotterdam, is a renowned research and training center. The institute is particularly well recognized for its large population-based studies of determinants of disease. A relatively new focus of the Department is research on healthy aging and common psychiatric problems. This research will be conducted largely in the Rotterdam Study, a prospective cohort study that started in 1990 in a suburb of Rotterdam, among 10,994, men and women aged 55 and over.

Background
Death of a loved one is the most common adverse event of older age. Although it is a disrupting event, after a delimited period of grief, the majority of adults recover. However, an estimated 15% of bereaved people continue to grieve for an extended period and begin to exhibit symptoms of a state known as complicated grief.1 This is distinct from normal grief as the person cannot accept the death and instead experiences disbelief and preoccupations with the deceased. Sufferers exhibit additional symptoms such as intense yearning and searching, distressing memories and difficulties to move on.2 Whilst complicated grief does share some symptoms with depression, anxiety and post-traumatic stress disorder, it largely exhibits distinct symptoms not attributable to other disorders.3 A set of consensus criteria have been developed for

complicated grief. However, complicated grief has not been recognised as a disorder in classification systems such as the Diagnostic and Statistical Manual of Mental Disorders and the International Classification of Diseases.4

Although there is an abundance of research on normal grief in older adults, there is little research on complicated grief. It is thought to affect a large number of older adults. However, the real figure is unclear, with reports ranging from 10-40%. Further, it is known that there is some overlap with mental health problems, but the overlap with physical health is unclear. Understanding the extent of complicated grief, particularly in a Dutch population, and co-morbid disorders is important to estimate the burden and social significance. It is also essential to understand what makes people vulnerable to complicated grief to determine who is at risk. Gender and relation to deceased are related to complicated grief. However, it is beneficial to examine additional factors, such as features of loss, cognition and mental and physical health. Finally, it is presumed that complicated grief impacts on the lives of older adults, which has been shown for quality of life and daily functioning. However, these studies examined younger adults in small studies and only examined short-term effects. These outcomes need to be examined a large representative sample of older adults and the long-term effects should be assessed to determine if it a temporary or lasting problem. Complicated grief is a large public health problem and affects the quality of life of the sufferer. Therefore, complicated grief is a significant problem for older adults, but poorly understood, so that further research is required.5

Research Objective
The objective of this PhD project will therefore be to enhance knowledge of complicated grief in older adults. The project will be based within The Rotterdam Study (more details on the Rotterdam Study can be found elsewhere).6 In brief, in 1990-1993 7,983 adults aged 55 and over were invited to participate in a research study on chronic diseases of ageing. Data is collected during intermittent examination rounds and continuously from medical and specialist records. During this time psychiatric measures were introduced which allow us to study psychiatric diseases of ageing. Thus we are able to examine complicated grief in older adults, other psychiatric disorders of ageing and associated factors in a cross-sectional and longitudinal context. This study is highly unique in grief research which to date has largely relied on small scale cross-sectional studies.
Research Studies
There are several lines of enquiry that could be conducted within this PhD project which fits within a broader research project which may include, but are not limited to, the following:

- identify the prevalence of complicated grief in an older Dutch population so that a comprehension of the scope of the problem of complicated grief can be attained,
- differentiate complicated grief from other psychiatric disorders such as anxiety, depression and sleep disorders the place of complicated grief amongst psychiatric disorders can be understood.
- explore factors that make people more vulnerable to experiencing complicated grief. For example: background, lifestyle, socioeconomic status, physical and mental health, personal factors). This could be evaluated at two stages in the grief process: pre-loss risk factors and post-loss risk factors. This enables the identification of who is at risk.
- identify the acute (short-term) and chronic (long-term) consequences of complicated grief. This could be done in many areas:

a).Psycho-social: emotional well-being (happiness, quality of life, personal factors), mental well-being (depression, anxiety, sleep), social and functional ability (disability, daily activity, social support)
b).Cognitive: cognitive capacity (memory, executive function, cognitive decline)
c).Medical: health indicators (blood pressure, heart function), diseases (cardiovascular disease, cancer, stroke)

Collaboration
This project will involve working with other researchers who are working on this topic and other psychiatric disorders of ageing in the Rotterdam Study. Further, this project is conducted in collaboration with Utrecht University where a preventative intervention is planned for older adults at risk of complicated grief.

Key References
1. Glass RM. Is grief a disease? Sometimes. JAMA. 2005;293:2658-2659.
2. Prigerson HG, Maciejewski PK, Reynolds CF, et al. Inventory of Complicated Grief: a scale to measure maladaptive symptoms of loss. Psychiatry Research. 1995;29:65-79.
3. Dillen L, Fontaine JR, Verhofstadt-Denève L. Confirming the distinctiveness of complicated grief from depression and anxiety among adolescents. Death Studies. 2009;33:437-461.
4. Prigerson HG, Horowitz MJ, Jacobs SC, et al. Prolonged Grief Disorder: Psychometric Validation of Criteria Proposed for DSM-V and ICD-11. PLoS Medicine. 2009;6:e1000121.
5. Workman S. Prolonged Grief Disorder: A Problem for the Past, the Present, and the Future. PLoS Medicine 2009;6:e1000122.
6. Hofman A, Breteler MM, van Duijn CM, et al. The Rotterdam Study: 2010 objectives and design update. European Journal of Epidemiology. 2009;24:553-572.

1. research line 10:

Child Psychiatric Research (Added 2010-04-10)

2. general description of the research line:

Whereas most somatic disorders are quite rare, behavioural and learning disorders in children are frequent. About one in ten children will develop a mental health disorder and many more have behavioural or cognitive problems that are a burden to child, families and society. Behavioural problems can be caused by social factors (e.g. bullying or poverty), psychological factors (e.g. bad parenting or poor emotion recognition) and biological factors (e.g. genetic variation or altered stress hormones). Aetiological research has demonstrated that many child psychiatric disorders are neurodevelopmental in origin, i.e. they have their onset early in life and affect the functioning of the nervous system. Furthermore, child psychiatric research has been leading the field of gene-environment interaction studies.

3. specific subtopics within the research line:

The epidemiological approach has guided the behavioural and cognitive research in Generation R. We are investigating the importance of fetal development for behaviour and cognition later in life, and have assessed neurodevelopment with brain-ultrasound, neurological examinations, and have started MRI imaging. Moreover, we are conducting genome wide analyses and candidate studies to detect genetic risk factors and vulnerabilities. Together with several EUR and external partners we have introduced many innovative child assessments, which are unique to large-scale behaviour studies.
See attachment for specific project

4. contact person for interested students/teaching staff:

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5. Field of research:

Neuro-imaging in a Birth Cohort with links to Epidemiology and Psychiatry

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Doctorate

Attachment:
Altered Pathways: A study of abnormal neural connectivity in children at risk for severe psychopathology

Research Group: Tonya White (Assistant Professor, supervisor), Henning Tiemeier (Associate Professor, supervisor), Frank Verhulst (Department Head, promotor)
Department of child and adolescent psychiatry

The Department of Child and Adolescent Psychiatry at Erasmus Medical Centre, Rotterdam is a renowned research and training centre. The department is well known for large, epidemiology-based studies of child development and the emergence of psychiatric disorders. The department is one of the key members participating in the Generation R Study, a large-population based longitudinal study of approximately 10.000. The children were recruited while their mothers were in the early stages of pregnancy and are currently between four and seven years of age. Children are currently being evaluated using measures of behaviour, cognition, and the application of neuroimaging techniques.

Background: Many of the major psychiatric disorders begin when people are young. Disorders such as schizophrenia, in which people have hallucinations and delusions, and bipolar affective disorder, in which people experience depression and mania, commonly develop during adolescence and interfere with many important aspects of life. Research over the past several decades have supported the theory that these major psychiatric disorders are not caused by focal brain abnormalities, but rather by impairments in the multiple neural networks involved in higher-order brain functions1, 2. The connections between brain regions that normally develop, may be altered by the illness. This may cause abnormal connections to develop.
We are now able to test the connections between brain regions using brain imaging techniques. One common method is known as functional magnetic resonance imaging (fMRI). Interestingly, recent evidence from fMRI has suggested that there are common abnormalities in two major areas of the brain. These two regions are the limbic system (which is the emotional part of the brain) and the prefrontal cortex (which is the problem solving part of the brain). Cognitive problems are present in both schizophrenia and bipolar affective disorder. 3,4.

This raises the question whether common neural pathways are associated with cognitive deficits in different psychiatric disorders. Since cognitive deficits are highly predictive of functional outcome5, understanding the common neurobiological substrates across psychiatric disorders will be crucial for developing early interventions and treatments. Most directed research to date focuses on a specific psychiatric disorder (i.e. schizophrenia or bipolar affective disorder) in adults, and only after the onset of the illness. There are no studies to date that evaluate abnormal brain connectivity in at-risk populations. Yet, this is the time when the emerging brain differences are most likely to be found. Is it possible that the emergence of severe psychiatric disorders involves a common impairment in maturation that prevents the optimization of brain function?

Research Objective: The primary aim of this proposal is to study the development of brain connectivity in a group of children at high behavioural risk for the development of severe psychiatric disorders. The participants will be recruited through the Generation R study, a prospective population-based study of nearly 10.000 children and their mothers6. The high-risk subjects in this research will be chosen on the basis of the parent-reported psychopathology. This will be defined by parent-reported measures of aggression, depression/anxiety, and inattention/hyperactivity. The combination of these three behaviors on a parent report form, known as the Child Behavior Checklist, is well-described. Interestingly, while these symptoms do not predict the outcome of a specific psychiatric diagnosis, it predicts ongoing psychosocial impairment7,8 . Impairment refers to problems with school, getting or keeping a job, romantic relationships and friendships, and even the ability to take care of common activities of daily life (shopping, balancing a check book, cooking). Since impairment has been shown to be tied to cognitive deficits, it may be that there are common cognitive deficits that are a result of common problems in the connections between brain regions. A better understanding of the common cognitive problems, may help improve the outcome for children and adolescents, irrespective of their final diagnosis.

Higher-order cognitive processes include the ability to problem solve and to link together different ideas or concepts.. Working memory (WkM), or short term memory, is considered an important building block for higher-order cognitive processes9. Thus, as a part of this study the participants will perform both a verbal working memory task and a spatial working memory task (Sternberg 1966)). These tasks will be performed during a functional magnetic resonance imaging session.

The MRI experiments will be performed in the Erasmus MC Radiology Department on a 3 Tesla General Electric Scanner. A high-resolution T1 FLASH image with 0.9 mm isotropic voxels will be obtained prior to the functional imaging sequence. A gradient-echo blood oxygen level dependent (BOLD) sequence will be acquired with a TE of 30 ms, TR of 2.0 sec., Flip Angle of 90 degrees, a FOV of 220 mm, and a slice thickness of 4 mm covering the entire brain.

Research Studies: There are several lines of enquiry that can be conducted within this PhD project that mesh with overarching goals of the neuroimaging group. These inquiries include, but are not limited to, the following:
(1) Since higher-order cognitive processes mature through childhood and into early adulthood, these high-risk children will also begin to show cognitive problems during these ages.
(2) Differences in working memory performance in these children who are at-risk for developing a psychiatric disorder will have altered brain connections between the limbic system and the prefrontal cortex 4,10,11.

Hypothesis: We hypothesize that abnormalities involving these brain networks explain the common cognitive deficits in individuals with severe psychiatric disorders.

Collaboration: This study will be conducted within the Generation R study and the Pediatric Neuroimaging Group at Erasmus Medical Centre. Specific imaging processing techniques may be performed in collaboration with the Department of Bioinformatics at Erasmus Medical Centre and with the Department of Electrical and Computer Engineering at the University of New Mexico.

Key References

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1. research line 11:

Clinical and public health genomics

2. general description of the research line:

Translating genomic information into medical care and public health is currently one of the main challenges in public health genomics. Genomic profiling, testing multiple genes simultaneously, is anticipated to improve prediction of risks of complex diseases and thereby lead to personalized prevention and treatment strategies. But how predictive is our DNA? Can we identify individuals at high risk of disease on the basis of genetic profiling? And when will genetic profiling be useful; are interventions available that need to be targeted?
These questions are the core topics of research group on clinical and public health genomics.
Examples of our projects include:

- Empirical evaluations of genetic risk prediction for various diseases, for example type 2 diabetes, coronary heart disease and age-related macular degeneration. For these analyses, we mostly use data from the Rotterdam study, a large-scale population-based cohort study among individuals aged 55+, the Erasmus Rucphen Family study, and data available from large international consortia.
- Methodology development. There still is much debate about which metrics best assess the predictive performance and the clinical impact of genetic risk prediction. We contribute to the development of new metrics, e.g. by investigating the usability and added information value of newly proposed metrics in relation to existing measures.
- Evaluations of commercially available tests. While it is widely acknowledged that genetic prediction of disease is not useful at this stage, many companies are already offering genome wide scans on the basis of which they predict risk of many disorders. Using the same approaches in the empirical evaluations, we scientifically investigate the predictive performance and usefulness of commercially available tests.

3. specific subtopics within the research line:

Genetic risk prediction of disease, evaluation of genetic tests

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Genetic epidemiology

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Doctorate (PhD student)

1. research line 12:
Genetic epidemiology
2. general description of the research line:
In the past decade, genetic epidemiologic research has developed rapidly from small-scale family studies using a few genetic markers to large-scale population-based studies using millions of markers. This development has been instrumental for the discovery of genes involved in major diseases in the population, but has put a continuing quest for new methodology and tools. Our research on gene discovery is conducted in empirical family-based and population-based studies. These are the Rotterdam study (adults 55 years and older), the Erasmus Rucphen Family study (three generation families) and Generation R (children followed from prenatally onwards, and their parents). These studies have well-collected data on all major common diseases, including cardiovascular, neurological, neurogeriatric, ophthalmologic and metabolic phenotypes. The genetic epidemiology group is involved in many international consortia that collaborate in the conduct of genome-wide association studies. Students are welcome to join in any of these projects.
3. specific subtopics within the research line:
Gene discovery, extended family study, Rotterdam study, genome-wide association studies
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Genetic epidemiology
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Doctorate (PhD student)

1. research line 13:

Genetics of musculoskeletal disorders (Added 2010-04-20)

2. general description of the research line:

The current wave of genome-wide association studies (GWAS) has been successful identifying common variants convincingly associated with numerous complex quantitative trait and diseases. However, functional implications of the large majority of these loci remain largely unexplored. The aim of this project is to pursue functionsl and genetic-epidemiological follow-up studies of the loci identified by meta-analysis of GWAS, specifically those associated with musculoskeletal traits and diseases within the collaborative setting of the:
- GEFOS (http://www.gefos.org)
- EAGLE consortia http://wiki.genepi.org.au/display/EAGLE/EAGLE

Within the setting of the GEFOS consortium we have identified 20 BMD loci in the first-round of GWAS meta-analysis *Nature Genetics* **41**, 1199 - 1206 (2009) while the second-round currently underway is targeting ~60 additional loci for BMD and dozens more for associated musculoskeletal traits. Functional evaluation of genetic factors and pathways will be assessed using gene expression and sequencing complemented by subsequent extended analysis of GWAS and pleitropy with other musculoskeletal traits in adults and children.

3. specific subtopics within the research line:

- Functional evaluation of discovered loci using:
  - gene expression
  - sequencing
  - pathway analysis
- Genome-wide association studies of:
  - Bone strength and hip geometry, mechanosensitivity and lean mass in adults
- BMD, bone geometry and lean mass in children

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Endocrine Epidemiology, Genetic Epidemiology, Human Genetics, Bioinformatics

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Master, Doctorate

Biostatistics

1. research line 1:
Bayesian approaches to the analysis of multivariate longitudinal growth curve data
2. general description of the research line:
Growth curve data are longitudinal data that often show a monotonic character. The aim is to describe in a flexible manner the growth pattern of a multivariate outcome (several measures taken at the same time and of a possibly different nature, i.e. continuous and categorical) as a function of covariates (phenotypic or genotypic) using Bayesian methods.
3. specific subtopics within the research line:
Model development, checking and diagnostics Development of efficient software
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Biostatistics
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate, post-doctorate, teaching-staff

1. research line 2:
Bayesian methods for variable selection in GWA studies
2. general description of the research line:
Genome wide association studies search for the relationship between a vast number of genes and phenotypes. A popular approach is to perform numerous significance tests and then to correct for multiple testing. An alternative approach is to select the genes in a Bayesian manner using specific prior distributions, which is the topic of interest here.
3. specific subtopics within the research line:
Research in the most appropriate prior distributions Developing efficient computational procedures
4. contact person for interested students/teaching staff:
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Biostatistics
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate, post-doctorate, teaching-staff

1. research line 3:
Joint Modeling of Longitudinal & Time-to-Event Data
2. general description of the research line:
Investigate associations between longitudinally measured markets and time-to-event outcomes. Standard applications of this framework are found in fields like HIV research (longitudinal CD4 cell count measurements & time-to-death), Cancer trials (e.g., longitudinal PSA levels & time-to-death or relapse), Transplantation studies (longitudinal marker levels & time-to-transplantation or death (competing risks)), and many similar fields.
3. specific subtopics within the research line:
Development of new estimation approaches, Dynamic Predictions & Discrimination, Development of Software under maximum likelihood and Bayesian approaches.
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Biostatistics
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate, post-doctorate, teaching-staff

1. research line 4:
Multivariate Longitudinal Data Analysis with Missing Data
2. general description of the research line:
Often in longitudinal studies we are interested in the joint analysis of several longitudinally measured outcomes. Moreover, almost all longitudinal studies suffer from missing data. In this project we aim to develop statistical methodology for the joint analysis of many longitudinal outcomes while appropriately taking into account missingness.
3. specific subtopics within the research line:
Development of new estimation approaches, Development of Software.
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Biostatistics
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate, post-doctorate, teaching-staff

Public Health

1. research line 1:
Occupational and environmental health
2. general description of the research line:
Occupational and environmental exposure may have hazardous effects for population health, eg cancer, musculoskeletal disorders, reproductive disorders, and respiratory disorders. Our studies consist of detailed assessment of exposure to risk factors at the workplace and in the general environment, evaluation of exposure-response relationships, estimates of the proportion of disease that can be attributed to a particular exposure, and evaluation of the effects of primary preventive interventions.
3. specific subtopics within the research line:
* exposure assessment and modeling strategies * evaluation of exposure-response relationships * health impact assessment of potential interventions
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Public health
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate

1. research line 2:

Socio-economic inequalities in health

2. general description of the research line:

Some population groups are healthier than others. People with lower education, social class or income more often suffer ill health and die at a younger age. Socio-economic inequalities in health persist over time, and there is evidence for a widening of these health inequalities in many countries. Other important disparities in health are those between men and women, between different ethnic groups, and between people with a different marital status. Our research aims to explain inequalities in health and support policies to reduce inequalities in health in both the Netherlands and abroad.

3. specific subtopics within the research line:

- comparative studies of socio-economic inequalities in health between different countries and populations within countries
- the role of environmental characteristics in the explanation of socio-economic inequalities in health-related behaviour.
- the effects of policies and interventions in reducing inequalities in health.

4. contact person for interested students/teaching staff:

Dr Frank van Lenthe, associate professor
Department of Public Health

5. Field of research (for example: epidemiology, public health, statistics, medicine):

Public health

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Master, doctorate

1. research line 3:

Screening

2. general description of the research line:

The development and improvement of screening tests for the detection of asymptomatic disease will continue to lead to an increased use of such tests in hospitals, physician' practices, organized screening programs and individuals. Early detection of diseases may lead to considerable improvement in survival or quality of life. However, early detection also means a longer period of life during which a person is aware of having the disease, and false-positive test results will induce unnecessary diagnostic interventions.
Our research quantifies the health benefits, unfavourable side-effects, impact on quality of life, and the cost consequences of introducing screening. This may lead to advice to introduce, or not introduce, screening for a specific disease, or to introduce it in a specific way, e.g., for selective groups of the population only.
Recent Examples of public health research that have impact in practice. Our section is partly responsible for the continuing follow-up of the European Study of Screening for Prostate Cancer. As many of the tumours that are detected by prostate cancer screening have a relatively benign character (indolent cancers), the question is when is treatment necessary, and when can treatment be replaced by active surveillance or watchful waiting. A model was developed to predict indolent cancer, based on characteristics that are available before surgery. This model may help to distinguish the indolent cancers from the aggressive ones for which immediate treatment is the best option.
In 2006, implementation trials have started in the Netherlands for colorectal cancer screening. We will use the simulation model Miscan to conduct a cost-effectiveness analysis that will support decision makers in their choice concerning various screen tests and screening frequencies.
Recently, a new test has been developed to identify the DNA of developing cancer in a person's stool. This test is considered for reimbursement by the Centers for Medicare & Medicaid Services in the USA. We were asked to determine the costs at which this test is a cost-effective alternative to currently recommended tests in the USA. We helped develop an interactive website to assist policymakers. The site provides a modeling tool that projects future trends in colorectal cancer mortality and evaluates how alternative cancer control strategies may affect future mortality trends.

3. specific subtopics within the research line:

Ongoing projects:
Evaluation of the nation-wide breast cancer screening programme in the Netherlands
Prospective cohort study of MRI-screening for women at high risk for breast cancer and cost-effectiveness
Full information for informed participation in breast and cervical cancer screening
National evaluation of cervical cancer screening in the Netherlands
Quality of life evaluation in cervical cancer screening
Cost-effectiveness of HPV-vaccination in the Netherlands
Prevention of cervical cancer by vaccinations against human papillomavirus (HPV); parental intention and uptake of HPV-vaccinations inadolescents
Dutch-Belgian randomised controlled lung cancer multi-slice CT screening trial
Smoking cessation in lung cancer screening
Genetic screening policy model for colorectal cancer
Effects and cost-effectiveness of colorectal cancer screening with different fecal occult blood tests
Quality of life and informed decision making in lung cancer screening
European Randomized Study for Screening on Prostate Cancer (ERSPC)
Implementation of compliance improvement methods in amblyopia prevention
A new programme for prenatal screening for Down's syndrome in the Netherlands: informed participation and non-participation
Screening on child abuse at emergency departments, implementation of an optimal protocol
CISNET: Colorectal Micro-simulation modelling
CISNET: Modeling breast cancer incidence and mortality in the USA; the spectrum of disparities
CISNET: A trial-based Miscan model for prostate cancer screening
CISNET: Surveillance of Lung Cancer Trends in the U.S. with MISCAN.

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Public Health
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, Doctorate, Post-doctorate

1. research line 4:
The impact of social and economic policies on health and health inequalities: An international perspective
2. general description of the research line:
This research line strives to understand how social and economic forces shape the distribution of health across countries with different welfare state policies and institutions. The relationship between socioeconomic status and health is embedded in an institutional and policy context, which can only be understood through a cross-national comparative perspective. Research within this line will focus on two major objectives: The first objective is to examine the impact of historical social, economic and labour policies on health and health inequalities across high and middle income countries. Second, it will focus on the integration of innovative epidemiological and econometric methodologiles and approaches for causal inference in social epidemiology, adopting an international perspective. Research will be based on rigorous analysis of quanitiative international survey data for high- and middle-income countries, which will be linked to macro-level data on national policies and institutions.
3. specific subtopics within the research line:
- International comparative research on health and health inequalities - Econometric and epidemiological methods for causal inference in social epidemiology - The impact of economic, social and labor policies on health and health inequalities
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Epidemiology and Public Health
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Master, doctorate, post-doctorate and teaching staff level

1. research line 5:
Prognostic research
2. general description of the research line:
Prognostic studies are increasingly published in the medical literature. They hold the promise of individualized medicine. Special interest in our group is in prognosis and predictive modeling. We frequently use regression analysis for prediction of the presence of disease (diagnosis) or the outcome of a disease process (prognosis) given patient and/or care characteristics. Recent interest is expanding from development and validation of prediction models to assessment of impact in clinical practice. The research is done in close collaboration with various clinical groups in and ouside Erasmus MC. Methodological background is reflected in a text book by Prof Steyerberg: http://www.clinicalpredictionmodels.org
3. specific subtopics within the research line:
We study a wide scope of medical problems, including patients with various cancers (e.g. bladder, prostate, colorectal), cardiovascular disease, neurological disorders, surgical interventions, and acute diseases (e.g children presenting at the emergency department, patients with brain injury), and fertility problems (e.g. who is benefiting from IVF?).
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Clinical epidemiology / biostatistics
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
master, doctorate, post-doctorate/teaching staff

1. research line 6:
Cancer Surveillance (added April 30, 2010)
2. general description of the research line:
Our research and teaching focuses on exploring and elucidating the various cancer epidemics in the Netherlands and internationally with respect to risk and outcome (incidence, mortality, survival, quality of life, quality of care). There is a focus on behaviour related cancers such as skin cancer and multiple primary cancers, but we also look at effects of socio-economic status, etc. We thereby provide added value to the precious data of the long standing south Netherlands (Eindhoven) Cancer Registry that is also part of the Netherlands Cancer Registry and the European Network of Cancer Registries, both in operation since 1989. Since relatively recently, we also make model-based scenario exercises to explore possibilities for the prevention of cancer across Europe. This modelling is explicitly based on the large variation in carcinogenic exposures and incidence of cancer in the various countries and also takes socio-economic status into account.
3. specific subtopics within the research line:
– Cancer Incidence – Cancer mortality – Cancer survival – Quality of life of cancer survivors – Quality of care for cancer patients – Multiple cancers – Skin cancer – International comparisons – Modelling / effects of changes in risk factors
4. contact person for interested students/teaching staff:
Dr. Esther de Vries: e.devries@erasmusmc.nl or Prof.dr. Jan Willem Coebergh: j.coebergh@erasmusmc.nl
5. Field of research (for example: epidemiology, public health, statistics, medicine):
Public Health and Epidemiology
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
All levels

Clinical Research

1. research line 1:
Cardiology
2. general description of the research line:
Research lines of the Cardiovascular Research School Erasmus University Rotterdam (COEUR) has six different research themes that can be summarized as follows: 1. Cardiovascular Biology and Pharmacology Molecular basis, pathophysiology and therapy of obstructive coronary artery disease, cardiacand coronary remodelling and heart failure 2. Vascular Medicine Hemostasis and Stroke The clinical complement to the previous theme. Cardiovascular genetics, blood pressure regulation and vascular medicine, thrombotic and bleeding disorders, acute and chronic cardiovasculardisease 3. Image-guided Cardiovascular Medicine Fundamental and clinical research of novel diagnostic imaging modalities 4. Surgical- Interventional and Device Therapy of Cardiovascular Disease Clinical application and implementation of new diagnostic and therapeutic techniques. Local drug delivery cell therapy vascular interventions and other device therapy 5. Congenital Heart Disease Small but important theme focussing on major structural congenital cardiac abnormalities and their management 6. Neurovascular and Cardiovascular Clinical Epidemiology Risk modelling rational, predictive thinking and implementation of appropriate diagnostic and therapeutic measures across a wide range of clinical cardiovascular syndromes and procedures.
3. specific subtopics within the research line:
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Medicine, Clinical Epidemiology
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
Undergraduate, Master, doctorate, post-doctorate, teaching/staff

1. research line 2:

Treatment failure in breast cancer

2. general description of the research line:

Summary

One of the major problems in the treatment of cancer is recurrence of disease and therapy resistance. To improve treatment strategies, mechanisms involved in tumor progression and therapy failure are investigated worldwide.
Recently, we observed that endocrine therapy resistance in breast cancer was associated with high mRNA levels of Enhancer of Zeste Homolog 2 (**EZH2**), a histone H3 methyl-transferase, and low levels of Seven in Absentia Homolog 2 (**SIAH2**), an ubiquitin E3 ligase, whereby both genes have been shown to interact with **VAV** oncogenes.

Knockdown experiments in the breast cancer cell line MCF7 with siRNAs against EZH2 and SIAH2 showed that both genes influence the response to the estrogen receptor modulator ICI 164,384. Since SIAH2 degrades histone deacetylases (HDACs), and EZH2 together with HDACs participate in gene silencing by polycomb repressive complexes, we hypothesize that therapy failure in breast cancer is associated with gene silencing in a subset of patients, see attached PDF.

This project will help to identify breast cancer patients who are at **high risk for tumor progression and endocrine therapy failure.** Furthermore, the effect of EZH2 and SIAH2 interaction with VAV on gene silencing and therapy failure will be investigated. These results can be translated into novel diagnostic and treatment strategies in breast cancer.

Objectives

Gene/protein (in)activation can be regulated by methylation, ubiquitination, (de)acetylation or phosphorylation. The main objective is to determine the role of the "**silenceosome**" in relation with endocrine therapy failure in breast cancer.

We will investigate which genes are silenced in relation with therapy response in both clinical samples and in cell lines with special emphasis on DNA and histone methylation, mRNA and miRNA expression.
Based on our previous studies, we will study the downstream effects of two key genes, i.e. EZH2 and SIAH2, both interacting with VAV oncogenes.

We hypothesize that the methyltransferase gene EZH2 and the estrogen regulated gene SIAH2, an "in vivo" HDAC degrader, influence gene silencing.

3. specific subtopics within the research line:

Plan of investigation and research topics

The aim is to determine the "silenceosome" in breast cancer in relation with endocrine therapy failure by addressing the following questions:

1. Can EZH2 and SIAH2 protein expression levels be used to stratify breast patients at high risk to develop metastatic disease and endocrine therapy resistance?
2. What are the functional effects of the EZH2 and SIAH2 interaction with VAV3, and do these interactions affect (sub)cellular localization, gene silencing and response to endocrine therapy?
3. Which genes and proteins in breast cancer patients are silenced by EZH2 and SIAH2 and are associated with endocrine therapy failure?
4. Are these EZH2 and SIAH2 silenced genes and proteins functionally involved in endocrine therapy response?

Models and methodology

The Department of Medical Oncology has a collection of well defined breast and ovarian cancer cell lines. Whole genome expression data are available and will be used for this project. We selected cell lines expressing EZH2, SIAH2 and VAV3. We have started with transient silencing experiments using siRNA oligoduplexes, and this is followed by on stable knockdowns using shRNAs in order to evaluate long-term effects in selected test models.

Standard procedures will be applied for ChIP, co-immunoprecipitation, siRNA/shRNA experiments, immunocytochemistry, (confocal) microscopy and western blotting. All expertise and technologies are currently available at our and neighbouring departments.
Our department of Medical Oncology has a track record in high-throughput analyses. ChIP and MeDIP protocols for are currently developed and experiments are amongst others facilitated by the Erasmus Center for Biomics.

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Translational medical research

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Master, doctorate, post-doc

1. research line 3:

Contrast-enhanced ultrasound for assessment of vasa vasorum

2. general description of the research line:

Dr. A.F.L. Schinkel and Prof. Dr. E.J.G. Sijbrands

Atherosclerosis is a progressive chronic inflammatory disease that may be complicated by cardiovascular events. Early identification of atherosclerosis is important to begin treatment at a far more manageable point in the disease cycle. The formation of microvessels in the vessel wall and plaque (vasa vasorum) could be used as an early sign of atherosclerosis and plaque vulnerability. Contrast-enhanced ultrasound imaging is perhaps the most promising imaging modality for detecting vasa vasorum, because of its high spatial and temporal resolution. Contrast-enhanced ultrasound is safe, and the repeatability of recording and cost provide an incentive to develop approaches using this modality. The aims of this study are:

- To study the feasibility and optimize the current contrast-enhanced ultrasound methods and technology in order to develop reliable imaging of vasa vasorum;
- To investigate the role of increased neovascularization (vasa vasorum) within the arterial wall. A particularly novel approach, because if arterial wall neovascularization precedes overt symptoms of atherosclerosis and, importantly, precedes observed increases in intima-media thickness, vasa vasorum may be an early predictor of cardiovascular events.

3. specific subtopics within the research line:

- Quantification of contrast-enhanced ultrasound imaging of vasa vasorum.
- Studies on neovascularization in type 2 diabetes and familial hypercholesterolemia.

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Physics, epidemiology & medicine.

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.D., who aspires after a career in internal medicine (vascular medicine) or cardiology.

1. research line 4:

Very long-term prognostic value of myocardial stress imaging

2. general description of the research line:

Dr. A.F.L. Schinkel and Prof. Dr. E.J.G. Sijbrands

With the rapidly changing lifestyle, cardiovascular mortality has emerged: coronary artery disease has become the most common cause of death today increasing the need for risk stratification of patients with suspected or known coronary artery disease. Myocardial stress imaging (stress myocardial perfusion imaging and/or stress echocardiography) provides useful information for risk stratification and determination of optimal clinical management: who will benefit from further invasive strategies and who do not require further invasive evaluation? Multiple studies have reported good prognostic value of myocardial stress imaging after short- to intermediate follow-up. Currently, information on the long-term to very long-term (>10 years) prognostic value of myocardial stress imaging is very limited. Moreover, the "warranty" period of a normal myocardial stress study is not clear. The aims of this study are:

- To determine the long-term to very long-term (>10 years) prognostic value of myocardial stress imaging;
- To determine the clinical value and optimal time intervals of periodic stress testing in patients with known or suspected coronary artery disease.

3. specific subtopics within the research line:

- Diagnostic trial
- Prognostic modeling

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Epidemiology & medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.D., who aspires after a career in internal medicine (vascular medicine), cardiology, or nuclear medicine.

1. research line 5:

Lipids in cardiovascular disease

2. general description of the research line:

Dr. M.T. Mulder and Prof. Dr. E.J.G. Sijbrands
Hypercholesterolemia is an established risk factor for cardiovascular disease (CVD) even in type 2 diabetes. The atherogenic and cardioprotective properties and impaired cognition have been attributed to specific lipoproteins. However, this resembles a strongly simplified interpretation. The size, the specific lipid and protein composition, and functional properties of the lipoproteins obviously determine the atherogenicity. Therefore, our aim is to analyze the composition of plasma lipoproteins in detail. The composition of the lipoproteins will be related to their functionality by examination the delivery to and removal of lipids from cells in culture. Lipoprotein profiles of patients with inherited lipid disorders and patients with cognitive impairment will be determined and the functionality of lipoproteins with different compositions will be tested with a number of different cultured cells. The data will lead to insight into high risk plasma lipoprotein profiles associated with CVD, and the underlying molecular alterations. This may reveal novel possibilities for the development of therapeutic strategies for CVD.

3. specific subtopics within the research line:

- Biomarkers
- Cohort studies

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Biochemistry, epidemiology & medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.Sc. in biomedical sciences, molecular life sciences, biochemistry, or a related one. Preferably the candidate has experience with molecular biology techniques and cell culture, animal models, lipids and lipid analyses.

1. research line 6:

Lipids in the pathogenesis of Alzheimer's disease

2. general description of the research line:

Dr. M.T. Mulder and Prof. Dr. E.J.G. Sijbrands
Aberrations in cerebral cholesterol homeostasis can lead to severe neurological diseases and have been linked to Alzheimer's disease. Recent findings strengthen the link between brain cholesterol metabolism and factors involved in synaptic plasticity, a process essential for learning and memory functions, as well as regeneration, which are affected in Alzheimer's disease. We obtained evidence that enhancing cholesterol turnover in the brain enhances memory functions in an Alzheimer-model.
Many proteins involved in peripheral cholesterol metabolism are also present in the brain, although brain cholesterol metabolism is very different from that in the remainder of the body. The aim of this project is to obtain insights into the regulation of cerebral cholesterol homeostasis and the aberrations herein during the progression of Alzheimer's disease, focusing on cholesterol trafficking between astrocytes and neurons, and the secretion of cholesterol from the brain into the circulation. A better understanding of the regulation of cerebral cholesterol homeostasis will provide possibilities to modulate the key steps involved and may lead to the development of therapies for the prevention as well as treatment of neurodegenerative diseases such as Alzheimer's disease.

3. specific subtopics within the research line:

- In vitro work
- In vivo animal studies
- Cohort study

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Biochemistry, molecular biology & medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.Sc. Biomedical Sciences, Molecular Life Sciences, Biochemistry, or a related one. Preferably the candidate has experience with molecular biology techniques.

1. research line 7:

Lipids and early detection of high Alzheimer's disease risk

2. general description of the research line:

Dr. M.T. Mulder, Prof. E.W. Steyerberg, and Prof. Dr. E.J.G. Sijbrands
In order to prevent Alzheimer's disease (AD) early diagnosis is required. Best would be to identify a marker in biological fluids such as blood that are indicative of the process that will lead to neurodegeneration and not a marker indicative of the already ongoing neurodegenerative process itself. A number of proteins in plasma, including amyloid and tau, may be suitable candidates. However, it is generally recognized that an altered cerebral cholesterol metabolism is linked to progression of AD. The alterations in cholesterol metabolism may not be restricted to the brain. In line AD subjects display lower high-density lipoprotein (HDL)-cholesterol, and higher low-density lipoprotein (LDL)-cholesterol levels. The aim of the present study is to determine the alterations in the lipid and protein composition of specific subfractions of lipoproteins can be found in AD patients in the preclinical stage, during mild cognitive impairment and in the advanced stage. This proteomics approach aims to identify biomarkers for the risk estimation of AD in an early stage.

3. specific subtopics within the research line:

- Biomarkers
- Prognostic modeling

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Biochemistry, epidemiology & medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.D. or M.Sc. degree in biomedical sciences, molecular life sciences, biochemistry, or a related one. Preferably the candidate has experience with molecular biology techniques and is interested in prognostic modeling.

1. research line 8:

Improved oral glucose tolerance test

2. general description of the research line:

Dr. F.W.M. de Rooij and Prof. Dr. E.J.G. Sijbrands

There is mounting evidence that dysfunction of the insulin secreting beta-cells strongly contributes to the susceptibility to type 2 diabetes (T2D). In this clinical project, we investigate an improved biochemical phenotype for beta-cell function after glucose intake to identify high-risk T2D persons at an early stage. We performed a successful pilot phase in T2D high-risk families showing that we are able to differentiate between insulin stored in beta-cell granula and freshly produced insulin. Moreover, we have detected potentially novel mechanisms underlying T2D in families of Asian origin. The aims of the project are to:

- evaluate the efficacy of the 13C-Leucine oral glucose tolerance test (OGTT);
- evaluate the sustainability of the mass spectrometry (MS) based techniques of the 13C Leucine OGTT by comparing retrieved beta-cell marker measurements with immunoassay based measurements;
- explore characteristic phenotypes for insulin biosynthesis and secretion;
- to use these phenotypes for gene hunting in high-risk families and populations.

3. specific subtopics within the research line:

- Biochemistry & molecular biology
- Linkage analyses
- Genetic association studies

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Molecular biology & genetic epidemiology

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.Sc. in biomedical sciences, molecular life sciences, biochemistry, or a related one. Preferably the candidate has experience with molecular biology techniques and mass spectrometry.

1. research line 9:

Mechanisms of premature coronary artery disease in families without apparent risk factors

2. general description of the research line:

Dr. A.F.L. Schinkel, Prof. Dr. E.J.G. Sijbrands, Prof. C. van Duijn
Atherosclerosis is a major cause of cardiovascular morbidity in the general population. In certain patients premature coronary artery disease (CAD) occurs without the presence of known risk factors (without primary lipid disorders, type 2 diabetes, etc.). The first grade asymptomatic relatives can therefore not be identified as high risk patients for cardiac events at young age. Although premature CAD shows clear familial aggregation, first degree relatives remain mostly without any preventive care. In our general population, we found a strong association between coronary calcification and myocardial infarction. The novel high-speed multislize coronary computed tomography angiography (CTA) enables noninvasive imaging of stenoses and soft plaques in a protocol with a total radiation exposure of approximately 1.0 mSv. The project is linked to similar studies in familial hypercholesterolemia and type 2 diabetes. The aims of the present project are:

- to determine the if the Calcium score and CTA enable identification of severe risk in asymptomatic relatives in 25 families with premature CAD without known cause;
- to test the relationship between biobank data and Calcium score or soft plaques;
- to perform linkage analysis.

3. specific subtopics within the research line:

- Imaging
- Linkage analyses
- Genetic association studies

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Genetic epidemiology & medicine

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

Requested Ph.D. profile: M.D., who aspires after a career in internal medicine (vascular medicine), cardiology, or radiology.

Health Policy and Management

1. research line 1:
Competition and regulation in health care
2. general description of the research line:
Dutch health care is undergoing transition to a managed competition model. Why is fundamental research so important? The Netherlands is the first country in the world that is implementing the managed competition model in health care. In theory this is an elegant model, but it's hard to implement in practice and knowledge about some fundamental issues is lacking. The implementation of the Health Insurance Act in 2006 was a major achievement, as it created a system of universal affordable health insurance. The key question now is whether insurers will become cost-conscious purchasers of care on behalf of their insured consumers.
3. specific subtopics within the research line:
Care system Insurance Market Patient's perspective
4. contact person for interested students/teaching staff:
Dr. S. Meeuwsen Erasmus University Rotterdam, institute of Health Policy and Management Email: meeuwsen@bmg.eur.nl
5. Field of research (for example: epidemiology, public health, statistics, medicine):
Public Health, health care market
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
All levels, depends on specific research question

1. research line 2:

Quality and efficiency in health care

2. general description of the research line:

The past 20 years have seen great progress in economic evaluation – or health technology assessment (HTA). This is now by far the largest research area within health economics. Not only has there been more activity and have methods considerably improved, the studies have also gained a firm place in policy and practice. For instance, cost-effectiveness studies of new innovative medicines have become mandatory for reimbursement in a majority of OECD-countries. The research focuses on scientific work and policy advice such as support on various submissions for reimbursement of major innovative drugs as well as recommendations on various aspects of the new health insurance package in the Netherlands, including the conditional reimbursement policy regarding expensive hospital drugs.

3. specific subtopics within the research line:

Methodology and application of economic evaluation
Basic health care package and guidelines
Outcomes research: (cost-)effectiveness of (medical) technologies in daily practice
Health and income

4. contact person for interested students/teaching staff:

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5. Field of research (for example: epidemiology, public health, statistics, medicine):

Public Health, Economics

6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)

All levels, depends on specific research question

1. research line 3:
Health care management
2. general description of the research line:
The research focuses at improving internal operations management and innovative processes in health care -organisations via integrated care management, logistics, quality management and human resource management. Good management is gaining importance because the system reforms challenge health care institutions to become more enterprising. And then, competition forces them to perform as best as possible. But still, the media frequently report on hospitals or nursing homes where things have gone wrong, business-wise. So it would seem that health care institutions need more insight into their own operations in terms of quality, effectiveness and efficiency. Quality in this sense is a wide concept – encompassing goals and performance related to care practices, professionalism, organisational logistics and social aspects. The research findings are useful to optimize an organisation's governance structure, performance and operations management. Furthermore it is interesting to investigate how health care organisations will be able to meet the increasing demands of patients or clients, seeing that at the same time they are under social pressure to keep costs within bounds. To answer this question we need to know how effective care delivery is and what the options are to reorganise care.
3. specific subtopics within the research line:
Business economics & HRM Integrated health care management & logistics Quality and safety Marketing, acquisition and strategy
4. contact person for interested students/teaching staff:
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5. Field of research (for example: epidemiology, public health, statistics, medicine):
Public Health, management
6. for which levels the research line is applicable (undergraduate, master, doctorate, post-doctorate/teaching staff)
All levels, depends on specific research question