



Publications 2010

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Preface

In 2010 the Department of Epidemiology of the Erasmus Medical Center celebrated the 20th anniversary of the Rotterdam Study. After 5 years of preparation, data-collection started in 1990 in this prospective cohort study, known in Dutch under the acronym ERGO (Erasmus Rotterdam Gezondheid Onderzoek). The Rotterdam Study began with 7,983 participants of 55 years and over. Two later recruitment phases increased the cohort to its current size of 14,926 persons aged 45 years or over. The Rotterdam Study is conducted in the Rotterdam district of Ommoord and it focuses on causes and consequences of major chronic diseases, including cardiovascular diseases (heart disease and stroke), neurological diseases (Alzheimer disease and Parkinson disease), endocrine diseases (diabetes mellitus, thyroid diseases), locomotor diseases (osteoporosis and fractures), ophthalmic diseases (macular degeneration, glaucoma and myopia), psychiatric diseases (depression, anxiety and sleep disorders), and, more recently, respiratory diseases, hepatic diseases, dermatological diseases, renal diseases and hearing disorders. Findings in the Rotterdam Study have been published in over 1,000 scientific articles and in over 100 PhD theses. Important assets of the study are its dedicated imaging facility with a 1.5T MRI scanner and the detailed genotyping of the full cohort. The latter enables the extensive gene-finding in genome-wide association studies in which the Rotterdam Study has been one of the pioneers and of which the results are seen in many articles in this publication report for 2010. The response rate in the Rotterdam Study has been very high throughout the 20 years of its existence and this reflects the strong dedication of both the nearly 15,000 participants and the many workers involved in the study.

In 2010, 6 PhD students successfully defended their thesis: Abbas Dehghan (cardiovascular epidemiology), Bettina Hansen (biostatistics), Dika Luijendijk (psychiatric epidemiology), Dennis Mook-Kanamori (pediatric epidemiology), Maaïke Schuur (genetic epidemiology) and Ineke van den Berg-de Lange (clinical epidemiology). Short summaries of their work can be found in this report.

It is as always a great pleasure to acknowledge the work of the many collaborators at Erasmus and elsewhere, and to thank all those involved in biostatistical and epidemiological studies at Erasmus for their creativity, dedication and hard work.

Albert Hofman,
Chair of Epidemiology

Emmanuel Lesaffre,
Chair of Biostatistics



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Highlights

- Abecasis GR, Boehnke M, Borecki IB, Deloukas P, Frayling TM, Groop LC, Haritunians T, Hunter DJ, Kaplan RC, North KE, O'Connell JR, Peltonen, et al. **Meta-analysis identifies 13 new loci associated with waist-hip ratio and reveals sexual dimorphism in the genetic basis of fat distribution.**
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■ Dika Luijendijk

Vascular heart and brain disease and incident late-life depression

(Co)promotores: Stricker prof.dr. BHCh, Tiemeier dr. H.

10 February 2010



The aim of this thesis was to assess the longitudinal relationship between vascular heart and brain disease and the risk of incident depression. New-onset depressions occurred frequently. This was due to the high incidence of episodes with clinically relevant depressive symptoms and to recurrence of depressive syndromes, including DSM-defined depression, in persons with a history of depression. There was no association between atrial fibrillation or use of beta-blockers in general and late-life depression. Heart failure was associated with an increased risk of incident depressive syndromes. The

substantial loss of daily functioning and high mortality rates as a result of heart failure, may explain this association. In addition, TIA was related to incident depression. The association between TIA and depression might confirm the vascular depression hypothesis. However, the relatively small number of post-TIA depressions calls for replication of the TIA-depression finding in other population-based cohorts, especially because none of the other measures of vascular brain disease that we studied such as the volume of retinal vessels, the volume of grey and white matter on MRI, or stroke on MRI showed an association with incident depression.

■ **Abbas Dehghan**

Novel risk factors for type II diabetes mellitus and coronary heart disease

(Co)promotores: Witteman prof.dr.JCM, Sijbrands prof.dr. EJG.

31 March 2010



Although several risk factors have been identified for type II diabetes and coronary heart disease (CHD), there is a need to search for further novel risk factors. In this thesis, C-reactive protein (CRP) and uric acid have been studied as such novel risk factors. Moreover, the advent of hypothesis free genome-wide association (GWA) studies provided the possibility to investigate the genetic structure of these two risk factors.

Our studies showed that high serum CRP and high uric acid levels are associated with increased risk of type II diabetes. We used population attributable risk (PAR) as a measure to assess the impact of these risk factors on the risk of disease. The estimates showed that nearly one third of the risk of type II diabetes and coronary heart disease could be attributed to high serum CRP or high serum uric acid level. We performed GWA studies on uric acid in the Rotterdam Study and the Framingham Heart Study and replicated our findings in the ARIC Study. The study identified three genetic loci that affects serum uric acid. To find the genes that play a role in regulation of serum CRP, we performed a meta-analysis of GWA scans in six studies comprising nearly 27,000 individuals and identified six genetic loci. This study highlighted the metabolic pathways in regulation of serum CRP. Finally, we identified four genetic loci that regulate fibrinogen levels in a meta-analysis of GWA studies in six studies comprising around 22,000 subjects.

■ **Maaïke Schuur**

Genetic Determinants of Cognitive Function and Age-Related Brain Changes

(Co)promotores: Van Duijn prof.dr. CM, Oostra prof.dr. BA

12 May 2010



The thesis describes our research on genetic determinants of cognitive function and age-related brain changes. We studied outcomes that are highly heritable as endophenotypes for Alzheimer's disease, including cognitive function, A β plasma levels and age-related brain changes as visible on magnetic resonance imaging (MRI). To explore new susceptibility regions for cognitive functioning without prior assumptions

of pathways involved, we conducted genome-wide searches on cognitive tests. In these studies we found significant linkage to cognitive functioning on chromosomes 1p13.1, 12q24.33, 19q13.43, 20p13, 21q22.13 and 21q22.3 in the Erasmus Rucphen Family (ERF) Study [1]. Fine-mapping showed significant associations to chromosome 1 and 21 in ERF, and the latter region was replicated in the Rotterdam Study, a large outbred population-based cohort [2]. In a large meta-analysis of different genome-wide association studies performed in the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium [3] we found association of the cognitive test, TMT-B, and a marker on chromosome 18, located between two interesting candidate genes. We further examined the role of candidate genes involved in blood pressure regulation and in amyloid metabolism in relation to age-related brain changes. The angiotensin gene was associated to A β ₄₂ levels. We also found associations of APOE with lacunar infarcts and SORL1 with microbleeds and hippocampal volume. Interestingly, SORL1 also emerged in our genome-wide association meta-analyses of cognitive function. The genes that we identified in these studies may provide further insights into the pathways involved in the normal variation of cognition and age-related brain changes.

■ **Dennis Mook**

Genetic and Enviromental Influences on Early Growth

(Co)promotores: Hofman prof.dr. A, Steegers prof.dr. EAP

24 November 2010



Dennis Mook-Kanamori completed his Ph.D. in 2010 at the Departments of Epidemiology and Pediatrics. His main focus was on genetic and environmental influences on early growth. Most of his research was performed in the Generation R Study, a population-based birth cohort study. His main finding was that the maternal characteristics, such as age at pregnancy, and lifestyle factors, such as smoking and folic acid intake, influence the growth of fetus in the first 10 weeks of pregnancy. This is often before mothers have entered routine obstetric care. His conclusion was that mothers and healthcare providers need to be aware that some modifiable maternal factors can influence the health of the unborn child in the first weeks of pregnancy. In another study and in collaboration with a large international consortium (the Early Growth Genetics Consortium), Dennis identified two new genes that are associated with birth weight and fetal growth, one of which is known to be also associated with type 2 diabetes. He concluded that this gene may play a role in the previously identified relationship between low birth weight and an increased risk of type 2 diabetes in adulthood.

■ **Ineke van den Berg-de Lange**

The Contribution of Acupuncture and Moxibustion to Healthcare an Evidence-based Approach

(Co)promotores: Hunink prof.dr. MGM, Duvekot dr. JJ

9 December 2010



To provide more evidence-based results of traditional Chinese Medicine (TCM) applied to Western medicine, we studied TCM in integrated healthcare. The studies in this thesis represent a range of scientific approaches to elucidate possible beneficial effects of acupuncture, as rooted in traditional Chinese medicine. Three fields of TCM were studied in different epidemiological ways. First, we studied the quality of life in a cohort of patients seeking treatment for musculoskeletal complaints at a general acupuncture practice. Second, next to a review of the literature on the attributive effect of acupuncture in inflammatory diseases, we presented a case-control study investigating whether a specified menstrual condition described in TCM as related to CRPS1, could be associated with the risk of developing CRPS1. The results suggest that specific menstrual disorders are associated with the development of CRPS1. The TCM questionnaire used in this study could contribute to the early recognition and diagnosis of female CRPS1 patients Third, we considered the induced version of breech presentation, for which an acupuncture-like treatment can be performed using a single prescribed point. For safety issues we first described the natural history of singleton breech presentation in the Generation R study and determined the prognostic value of ultrasound performed at 20 and 30 weeks of gestation in predicting nonvertex delivery. Then, we investigated if acupuncture should be recommended as an effective and cost-effective addition to the standard care in treating women with a fetus in breech position. Using meta-analysis, decision modeling, and cost-effectiveness analysis.



Epidemiology of diseases

Main participants

Albert Hofman
Arfan Ikram
Caroline Klaver
Henning Tiemeier
Hans Vingerling
Jacqueline Witteman

General objectives

This program includes scientific research in cardiovascular epidemiology, neuro-epidemiology and ophthalmic epidemiology.

Cardiovascular epidemiologic research focuses on the determinants of atherosclerosis and coronary heart disease in the elderly and on cardiovascular diseases in women.

The research is based on the Rotterdam Study and addresses inflammation markers and hemostasis as determinants of cardiovascular diseases in the elderly, and the effect of menopause, endogenous hormones and hormone replacement therapy in women.

Neuro-epidemiologic research focuses on the etiology of neurodegenerative and cerebrovascular diseases, including dementia and Alzheimer's, Parkinson's disease, stroke and cerebral white matter lesions. The research emphasizes the role of vascular factors in the etiology of these diseases, with use of state of art neuro-imaging techniques.

Ophthalmic epidemiologic research focuses on determinants of macula degeneration and glaucoma. The emphasis is on the putative role of genetic factors and vascular factors in etiology of these diseases.

Keywords

Atherosclerosis, Alzheimer's disease, cardiovascular disorders, dementia, depression, glaucoma, macular degeneration, Parkinson's disease, white matter lesions.



International scientific publications

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Basic epidemiologic research

Main participants

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General objectives

This program includes research in the fields of genetic epidemiology, endocrinologic epidemiology and developmental epidemiology. *Genetic epidemiologic research* aims at quantifying the population risk of disorders associated with genetic risk factors and at identifying new genetic factors involved in complex genetic disorders. The work in *endocrinologic epidemiology* focuses on the question whether circulating hormone levels are associated with incident diseases of the elderly and with parameters of frailty. The emphasis is on determinants of locomotor diseases (osteoporosis, osteoarthritis) and on sex hormones and thyroid hormones as determinants of disease. Research in *developmental epidemiology* focuses on in-utero and early life determinants of diseases. It comprises work in reproductive epidemiology, and it is largely based on the Generation R cohort study.

Keywords

Alzheimer's disease, endocrinologic epidemiology, genetic epidemiology, sex hormones, thyroid hormones, Parkinson's disease, pediatric epidemiology, osteoporosis, osteoarthritis.



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Curr Biol. 2010;20:R970-971.

Clinical Epidemiology

Main participants

Myriam Hunink

Cecile Janssens

Bruno Stricker

General objectives

This program comprises three parts: clinical epidemiology in collaboration with radiology, biostatistics and pharmaco-epidemiology. The *clinical epidemiology* group collaborates with the department of radiology in a joint research program for the Assessment of Radiological Technology (ART program). This program's research focuses on the assessment of diagnostic imaging and image-guided therapy, with an emphasis on cardiovascular disease and trauma imaging. Methodological research in the ART program focuses on developing the methods for evaluating diagnostic imaging procedures and stochastic modeling. *Pharmaco-epidemiologic* research focuses on unintended effects of medications, and the effects of medication use under common circumstances in large populations.

Keywords

Clinical epidemiology, diagnostic procedures, imaging techniques, pharmaco-epidemiology, prognostic factors, radiology, research methods.



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- **Bettina E. Hansen**

Statistical models of treatment effects in chronic hepatitis B and C

(Co)promotores: H.L.A. Janssen

19 november 2010



Treatment options for both chronic hepatitis B and C are expanding and there is a growing demand for individual first-line treatment recommendation. This can only be achieved by studying the effects of treatment in detail. Which patients benefit from treatment, in whom should treatment be stopped and what are the early and long-term effects of treatment?

This research focuses on development and application of statistical models to analyse the treatment effects in chronic hepatitis B and C. With advanced statistical models the results of clinical studies of treatment of chronic hepatitis B and C are analysed, achieving more insight into how the individual patient reacts to treatment. Prediction models of response to therapy of baseline factors are designed and several dynamic prediction models to update this prediction during treatment are explored. The studies especially focus on an early identification of patient who does not respond to therapy.



Department of Biostatistics 2010

Main participants:

Paul Eilers

Wim Hop

Emmanuel Lesaffre

Dimitris Rizopoulos

General objectives

The research of the department of Biostatistics can be classified under the heading of 'statistical modeling' especially for complex data structures. In more detail this implies the development of new statistical models for correlated data (repeated measures, growth curve analysis, spatial data analysis), survival analysis, genomics and proteomics, chemometrics, demographic data and meta-analysis. Frequentist as well as Bayesian methods are employed. Several aspects that complicate the analysis such as missing data, measurement error, misclassification, etc are also under investigation. New statistical developments are translated into the development of novel statistical software in order to translate theory into practice. The department collaborates with the various clinical and epidemiological departments of Erasmus MC to set up joint research and provide high level statistical support using state-of-the-art statistical techniques. Finally, the department also participates in clinical trial research from a statistical as well as from a clinical view point.

Keywords

Bayesian methods, biostatistics, clinical trial research, correlated data, repeated measurements, survival analysis



International scientific publications

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Pediatric Nephrology, 25(2), 289-298.
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Abstracts in book

- Commandeur J, van Montfort CAGM.
State space methods for latent trajectory and parameter estimation.
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Book editors

- van Montfort CAGM, Oud JHL, Satorra A (Eds.)
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