Erasmus MC
University Medical Center Rotterdam

Publications 2011

Department of Biostatistics
Department of Epidemiology

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Department of Biostatistics
Erasmus Medical Center
PO Box 2040
3000 CA Rotterdam, The Netherlands
Tel +31 10 7044514, fax +31 10 7043014
e-mail: *Secretariat.Biostatistics@ErasmusMC.nl*
www.erasmusmc.nl/biostatistiek

Department of Epidemiology
Erasmus Medical Center
PO Box 2040
3000 CA Rotterdam, The Netherlands
Tel +31 10 7043488, fax +31 10 7044657
e-mail: *secretariat.epi@erasmusmc.nl*
www.erasmus-epidemiology.nl

Preface

The year 2011 saw the start of ErasmusAGE as a new center in the Department of Epidemiology for the life-course study of various aspects of population ageing. ErasmusAGE will investigate important life-style determinants of health and disease across generations, will make use of data collected in the two Erasmus cohorts, the Rotterdam Study and Generation R, and will summarize existing evidence in state-of-the-art meta-analyses. ErasmusAge will collaborate for these purposes with many groups within and outside the Erasmus Medical Center. The center is led by Dr Oscar Franco, our newly appointed professor of preventive medicine, and the head of both ErasmusAGE and the cardiovascular epidemiology group.

In 2011 nine PhD students successfully defended their thesis: Najaf Amin (genetic epidemiology), Lamise Ay (pediatric epidemiology), Rachel Bakker (pediatric epidemiology), Renske de Boer (neuro-epidemiology), Marieke Dekker (psychiatric epidemiology), Mark Eijgelsheim (pharmaco-epidemiology), Wishal Ramdas (ophthalmic epidemiology), Elisabeth Schrijvers (neuro-epidemiology) and Martina Teichert (pharmaco-epidemiology).

It is as always a great pleasure to acknowledge the work of 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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Dissertations Epidemiology 2011

Lamise Ay
Body Composistion in Early Childhood
(Co)promotores: Hokken-Koelenga ACS, Hofman A, Jaddoe VWV
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The *developmental origins of health and disease* hypothesis poses that an adverse fetal environment leads to increased fatmass and insulin resistance.Within the Generation R Study, we investigated paternal, fetal and postnatal characteristics. We found that maternal anthropometrics were associated with fetal growth and adverse birth outcomes. Also, it was postulated that catch-up-in-weight leads to an unfavourable metabolic profile. (4-8) We found that catch-up within 6 weeks after birth was associated with an increased fatmass at 6 months. Obesity in childhood is associated with morbidity in adulthood. We found that subcutaneous fatmass tends to track in the first 2 years of life. Genetic variants may contribute to disease in adult life. We found that glucocorticoid-gene- haplotypes were not associated with body composition in early infancy, or the risk of overweight in preschool children. However, catch-up-in-weight in the first 6 weeks of life may modulate genetic susceptibility. Finally, we found that growth characteristics are positively associated with bone mass. Remaining in the lowest weight tertile at 6 months considerably increases the risk of low bone- mineral-density at 6 months. Catch-up-in-weight during the first 6 weeks of life decreases this risk.

Martina Teichert
Pharamacogenetic Aspects and Drug Interactions in Anticoagulation Therapy with Coumarins
(Co)promotores: Stricker BHCh, De Smet PAGM, Visser LE
18 February 2011

In this thesis pharmacogentic aspects and drug interactions with acenocoumarol and phenprocoumon were described. We studied the effects of variant alleles in the vitamin K epoxide reductase complex (*VKORC1*) and the cytochrome P450 isoform 2C9 (*CYP2C9*) genes on anticoagulation therapy with acenocoumarol during the initial treatment period. Each VKORC1variant allele significantly increased the risk of severe overanticoagulation by 85% after the initial standard dosage scheme. In a GWAS we described that inter personal dosage variation in acenocoumarol maintenance dosage mainly depends on polymorphisms in the *VKORC1* (28%) and *CYP2C9* (6%) genes. A model with age, sex, body mass index, target INR and one polymorphism within each of the *VKORC1*, *CYP2C9*, *CYP4F2* and *CYP2C18* genes explained 48.8% of variation in acenocoumarol maintenance dosage. For phenprocoumon we confirmed in another GWAS earlier findings that phenprocoumon maintenance dosage mainly depended on polymorphisms in the *VKORC1* gene. For interactions of acenocoumarol with proton pump inhibitors, co-medication with esomeprazole was significantly associated with a double risk of overanticoagulation and lansoprazole increased this risk by 50%. For combinations of acenocoumarol with selective serotonin reuptake inhibitors, fluvoxamine and venlafaxine more than doubled the risk for over anticoagulation.

Mark Eijgelsheim
Genetic Determinants of Heart Rythm and Conduction Disorders
(Co)promotores: Stricker BHCh, Uiterlinden AG
9 March 2011

Sudden cardiac death (SCD) has a genetic risk component and identifying the genetic pathways contributing to SCD risk can lead to knowledge of novel mechanistic pathways underlying ventricular arrhythmogenesis and aid in risk stratification. Important reasons to study the quantitative traits that underlie the common disorder of interest are heterogeneity, together with the assumption that common genetic complex disorders, such as SCD, have a normally distributed genetic liability conferred by Mendelian inherited genes and thus the trait would be normally distributed as a quantitative trait. For SCD, several of such endophenotypical risk factors measured on electrocardiographic recordings (ECG) are available, namely: 1) the QT interval, 2) the QRS duration and 3) the RR interval.
The main objectives of this thesis were: 1) refining the NOS1AP – QT interval association signal and assessing the relation with SCD, 2) to identify, by means of genome wide association studies, the genetic variants underlying the genetically determined variation within quantitative endo- phenotypes of SCD, 3) to develop methodology to enhance our ability to do so and, finally, 4) to perform hypothesis driven gene-drug interaction studies. Studies described in this thesis were conducted within the Rotterdam Study, a population based cohort study, often in collaboration with other studies in larger consortia.

Najaf Amin
A Genetic Epidemiological Study of Behavioral Traits
(Co)promotores: van Duijn CM, Oostra BA
23 March 2011

In my thesis I have made an effort to unfold the genetics of complex human behavioral traits that are known to affect social, somatic and psychological health. I have studied a variety of traits including personality, attention-deficit hyperactivity disorder (ADHD), sleep and coffee/caffeine use. All are common or quantitative traits and also known to be significantly heritable. I have used various gene-mapping techniques including genetic linkage and association and more advanced molecular and statistical analysis including copy number variation, gene expression and genomic imprinting analysis to find genetic variants associated with these traits. Using these methods I discovered novel loci (genes) implicated in the traits studied. I linked ADHD to chromosome 18q21-22 and personality traits of conscientiousness and neuroticism to chromosomes 20p13 and 21q22 respectively. Leading large international collaborations of genome-wide association studies I discovered association of genetic variants in *CYP1A1/CYP1A2*-locus and *NRCAM*-gene with coffee-intake and of variants in the genes *ABCC9* and *RBFOX3* with sleep duration and sleep onset latency. We found the expression of *CYP1A1* in lymphoblastoid cell lines to be down-regulated after being treated with caffeine and by performing a knock down of the homologues of *ABCC9* in flies, we confirmed the association with sleep duration.

Rachel Bakker
Maternal Lifestyle and Pregnancy Complications
(Co)promotores: Hofman A, Steegers EAP
9 December 2010

In Western countries, the most common adverse maternal lifestyle habits during pregnancy include smoking, alcohol consumption, and caffeine intake. Although not directly lifestyle related, maternal age is also considered as a modifiable risk factor for pregnancy complications. These adverse maternal lifestyle habits may influence cardiovascular adaptations during pregnancy, and subsequently increase the risk of hypertensive disorders during pregnancy. Maternal cardiovascular adaptations might also be involved in the pathway leading to an adverse fetal environment and subsequently neonatal complications because of impaired placental perfusion that may lead to limited oxygen and nutrient supply to the fetus.The main objectives of the studies presented in this thesis are to examine the associations of maternal lifestyle habits with hypertensive complications during pregnancy, and with fetal growth and the risks of neonatal complications. In conclusion, the associations of maternal lifestyle habits with fetal and hypertensive complications seem to be within the normal and physiological ranges. The findings also suggest that specific exposures in different periods of fetal life have differential consequences for fetal development. Although the findings might be of important public health relevance, they should be interpreted carefully because of the observational design. Future studies should be focused on identification of the underlying mechanisms.

Renske de Boer
Automatic Analysis of Brain Tissue and Structural Connectivity in MRI
(Co)promotores: Niessen WJ, Breteler MMB, Vrooman HA
17 June 2011

Studies of the brain using magnetic resonance imaging (MRI) can provide insights in physiology and pathology that can eventually aid clinical diagnosis and therapy monitoring. MRI data acquired in these studies can be difficult and laborious to interpret and analyze by human observers. Moreover, both inter- and intra-observer variability can hamper the reproducibility of the analysis. These studies do, therefore, require accurate and reproducible quantitative image analysis techniques to optimally benefit from the valuable information contained in the MRI data. In this thesis, we focus on quantitative analysis techniques for brain MRI data.The first part of this thesis is about automatic brain tissue and white matter lesion (WML) segmentation. We propose a method for automatic WML segmentation and optimize a previously proposed automatic brain tissue segmentation method, in combination with the WML segmentation method. We evaluate the accuracy and reproducibility of this segmentation framework and other methods.In the second part of this thesis we propose a framework for analysis of structural brain connectivity in large groups of subjects. We establish structural connectivity based on diffusion MRI data and summarize it in brain networks. We investigate the information contained in these networks and the reproducibility of the framework.

Elisabeth Schrijvers
Biomarkers and Risk Factors of Dementia
(Co)promotores: Breteler MMB, Koudstaal PJ
30 September 2011

Dementia is a devastating disease that is common in elderly people. Although many risk factors of dementia have been identified in the past decades, the exact mechanisms that lead to dementia are still unclear. When the clinical diagnosis of dementia is made, the actual neuropathological processes that have lead to dementia have already been ongoing for many years. Biomarkers that can detect these processes before a clinical diagnosis can be made are needed to identify persons that will develop dementia, to gain more insight in the pathogenesis of dementia and ultimately to help find new therapeutic agents that may alter or stop the disease. The primary aim of this thesis was to search for non-invasive biomarkers and explore risk factors of dementia. Furthermore, one chapter describes a reduction in age-adjusted incidence rates of dementia between 1990 and 2005 and two chapters focus on methodological issues in biomarker research and dementia risk prediction.

Marieke Dekker

Pre-receptor regulation of cortisol in Hypothalamic-Pituitary-Adrenal axis functioning and metabolism

(Co)promotores: Lamberts SWJ, Tiemeier H

12 October 2011

The general aims of this thesis were to evaluate the effects of free cortisol, as measured by salivary cortisol, and the effects of pre-receptor regulation of cortisol by 11ß-hydroxysteroid dehydrogenase type 1 (11ß-HSD1) on hypothalamic-pituitary-adrenal (HPA) axis regulation and metabolism. We found that 11ß-HSD1 is expressed at the two main feedback sites of the HPA axis in humans: the anterior pituitary and the paraventricular nucleus (PVN) of the hypothalamus. In the PVN, 11ß-HSD1 colocalizes with vasopressin-, oxytocin- and corticotropin-relaesing hormone-producing cells. These results suggest that 11ß-HSD1 is implicated in HPA axis-regulation. The expression of 11ß-HSD1 was studied using (fluorescence) immunocytochemistry, and was performed at the Netherlands Institute for Neuroscience in Amsterdam. Next, we evaluated the effects of common genetic variation in the 11ß-HSD1 gene (HSD11B1) on HPA axis functioning and the metabolic syndrome using a tagging SNP approach. For this study we used data of the Rotterdam Study. We found that one of the selected SNPs, rs11119328, was associated with increased HPA axis activity. Carriers of this polymorphism also had an increased risk of incident depression. SNPs in HSD11B1 were not associated with the metabolic syndrome. Lastly, we found that total cortisol exposure while awake is associated with an increased number of atherosclerotic plaques.

Wishal D. Ramdas
Epidemiologic and genetic insights into open-angle glaucoma
(Co)promotores: Vingerling JR, van Duijn CM, Jansonius NM
9 November 2011

Glaucoma is the leading cause of irreversible blindness worldwide. The number of people suffering from open-angle glaucoma (glaucoma) is expected to increase. After decades of research only a few risk factors have been identified for glaucoma: high age, African descent, elevated intraocular pressure, myopia, and a positive family history of glaucoma – the latter indicating a genetic background. To date three genes have been found, but these mutations explain only a few percent of glaucoma in the general population.Our study was the first revealing consistent associations between common genetic variants and glaucoma. Meanwhile our results have been replicated by several other international researchgroups. We identified a total of 11 genes playing a role in glaucoma. Participants carrying a large number of these variants seemed to have a 2-3-fold higher risk compared to participants carrying only a few of these variants. These findings provide new insights into the pathophysiology of glaucoma, but also into new opportunities for diagnosis and treatment for glaucoma. Beside the identification of new genes this thesis evaluated potential environmental riskfactors. In women with overweight the current method of measurement of intraocular pressure often leads to false-positive high readings. In daily praxis an ophthalmologist should pay extra attention when measuring intraocular pressure in overweight women. Next to lifestyle-related factors we found statistic evidence for nutrition influencing the risk of developing glaucoma. Participants with high dietary intake of magnesium had a higher risk for developing glaucoma. A low dietary intake of vitamin A and B1 reduced the risk for developing glaucoma.

Epidemiology of diseases

Main participants

Albert Hofman
Arfan Ikram
Caroline Klaver
Henning Tiemeier
Meike Vernooij
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 Rotterdan 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 neurodegenrative 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, Parkinsons's disease, white matter lesions.

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Basic epidemiologic research

Main participants

Cornelia van Duijn
Vincent Jaddoe
André Uitterlinden

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 wether 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, osteoarthrosis.

International scientific publications

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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.

International scientific publications

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Department of Biostatistics

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 trail research, correlated data, repeated measurements, survival analysis.

International scientific publications

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