



Publications 2012

Department of Epidemiology

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Preface

It is a pleasure to present this 2012 publication report of the Department of Epidemiology of the Erasmus Medical Center. 2012 has been a very productive year, in no small measure due to the many articles reporting genomics studies, in particular of genome-wide association studies. These studies are based on the three Erasmus Population Cohorts, the Rotterdam Study, Generation R and the ERF study, which have been highly successful elements of various international consortia.

In 2012 13 PhD students successfully defended their thesis. They worked in cardiovascular epidemiology (Suzette Elias-Smale), in clinical epidemiology (Tessa Genders, Nathalie Grootenboer), in genetic epidemiology (Ayse Demirkan), neuro-epidemiology (Vincent Koppelmans, Marielle Poels, Renske Wieberdink), pediatric epidemiology (Edith van den Hooven), pharmaco-epidemiology (Eline Rodenburg, Rikje Ruiter) and psychiatric epidemiology (Tamara van Batenbrug-Eddes, Fleur Velders, Stefan Walter).

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 epidemiological studies at Erasmus for their creativity, dedication and hard work.

Albert Hofman,
Chairman

Highlights

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Dissertations Epidemiology 2012

Suzette Elias-Smale

Coronary artery calcification and cardiovascular risk prediction

(Co)promotors: Witteman, JC / van der Lugt A

18 January 2012



The keystone of adequate cardiovascular disease prevention is accurate risk prediction. The main purpose of the research described in my thesis was to explore the value of calcification of the thoracic aorta and carotid arteries, as assessed by Computed Tomography scan, for their ability to improve of cardiovascular risk prediction beyond traditional risk factors in the general population. Most studies were conducted within the Rotterdam Study. My clinically most important work includes a large study with almost 10 years of follow-up showing that addition of

coronary calcium to traditional cardiovascular risk factors leads to an accurate and substantial reclassification between coronary heart disease (CHD) risk categories, especially in persons at intermediate risk (absolute 10-year CHD risk of 10-20%). Over 50 percent of both men and women in the intermediate risk group were reclassified into the high (>20%) or low risk (<10%) category.

Stefan Walter

Determinants of healthy ageing: studies of disability and survival among the elderly

(Co)promotors: Mackenbach JP, Hofman A, Tiemeier HW

18 January 2012



Slowing ageing, i.e. postponing the disease onset, promises gains in quality of life. This thesis investigates risk factors that influence ageing. With data from up to 25.000 individuals, we were unable to identify genetic markers of ageing. Interestingly, cellular maintenance, cellular death, and in particular neural plasticity in the brain, feasibly responsible for coordinating downstream physiological changes in the human body, could be responsible for ageing. Obesity, physical inactivity, and positive affect influence ageing. While adiposity is associated with higher disease

incidence, it might protect from death initially at the price of increases in time spent with disabilities. As for physical activity, a conscious decision to do sports is needed to achieve compression of morbidity. The non-significant genetic findings are still very informative if seen in relation to other mortality risk indicators. While an individual's present health is the best predictor of instantaneous mortality risk, socio-economic position and lifestyle give insights into the health risks that turn into powerful predictors of future mortality. And underneath it all is the genetic layout. In conclusion, genes are important predisposing factors of our individual health and life span, but our actions largely determine whether this predisposition is a friend or a foe.

Mariëlle Poels

Population imaging of cerebral small vessel disease

(Co)promotors: Breteler MMB / van der Lugt A / Vernooij MW

19 January 2012



In order to develop prevention strategies for dementia and stroke, it is crucial to explore the early presymptomatic phases of these diseases. Cerebral small vessel disease – i.e., pathologic alterations in the small penetrating arteries and arterioles of the brain – occupies an important position within the spectrum of presymptomatic brain pathology as it has been associated with both dementia and stroke. In this thesis – conducted as part of the Rotterdam Scan Study - we gained new insights into the pathophysiology of small vessel disease in the aging brain. This was accomplished by (i) examining cerebral microbleeds as new imaging marker of small vessel disease; (ii) identifying new

vascular risk factors for cerebral small vessel disease; and (iii) exploring how these vascular risk factors and imaging markers of cerebral small vessel disease relate to clinical outcomes. In addition, the prevalence, determinants and clinical course of incidental findings in the Rotterdam Scan Study were examined.

Tanneke Rikje Ruiter

Pharmaco-epidemiology as a tool in pharmacovigilance: studying cancer as adverse drug reaction

(Co)promotors: Stricker BHCh, Uitterlinden AG, Visser LE

1 February 2012



The aim of this thesis was to gain more insight with regard to the occurrence of cancer as potential adverse drug reaction of medicines by performing pharmaco-epidemiological studies. Numerous articles have been published analyzing a possible relationship between use of hypoglycemic agents and the risk of cancer. In this thesis, a decreased risk of cancer in general for use of metformin was described. Furthermore, an increased risk of breast cancer for use of insulin glargine was presented. With regard to the risk of breast cancer, the association with use of NSAIDs was described as well. For breast cancer survival in tamoxifen users,

the effect of CYP2C19*2 genotype was assessed. Last, we describe the association between use of high-ceiling diuretics, which are known for their photosensitizing abilities, and the risk of basal cell carcinoma. When properly designed, to avoid potential bias and confounding, and if tentatively interpreted, observational pharmaco-epidemiological studies can be of important additive value to assess the incidence of cancer as adverse drug reaction. Within an aging population, an increasing number of drugs is used chronically, therefore, the limited knowledge of cancer as potential adverse drug reaction is a deficit. Hence, more efforts should be made to study cancer as potential adverse drug reaction.

Renske Wieberdink

Determinants of cerebral infarction and intracerebral hemorrhage, The Rotterdam Study

(Co)promotors: Breteler MMB / Koudstaal PJ / Ikram MA

1 maart 2012



Stroke is a frequent disorder in elderly people. Despite improvements in primary prevention, the burden of stroke remains high and is predicted to even increase in the near future due to aging of the population. Therefore, additional targets for primary prevention are urgently needed. Most previous epidemiological studies have not specifically studied the two main subtypes of stroke, i.e., cerebral infarction and intracerebral hemorrhage, whereas differences in etiology between these subtypes suggest that they may have different risk profiles. Therefore, primary prevention may benefit from the identification of

subtype-specific determinants.

The main goals of my thesis were: (1) to study temporal trends in stroke incidence rates and conventional stroke risk factors in the Netherlands during the past twenty years; (2) to identify new risk indicators for stroke and more specifically for cerebral infarction and intracerebral hemorrhage. The studies described in this thesis were based on data from the large population based Rotterdam Study.

Edith H. van den Hooven

Air pollution exposure and pregnancy complications. The Generation R Study

(Co)promotors: Hofman A, Steegers EAP, Jaddoe VWV, Pierik FH

19 April 2012



The objectives of this thesis were to examine the associations of air pollution exposure during pregnancy with the risks of maternal and neonatal complications, and to examine the mechanisms that underlie these associations. All studies in the thesis were embedded in the Generation R Study, a population-based prospective cohort study from early pregnancy onward in Rotterdam, involving 8880 pregnant women. Maternal exposures to PM₁₀ and NO₂ for different prenatal periods were assessed at the home addresses, using advanced dispersion modelling techniques and continuous monitoring data. Our findings demonstrate that higher exposure to air pollution is associated with elevated C-reactive protein levels in maternal blood and fetal cord blood, suggesting an inflammatory response. We also observed in-

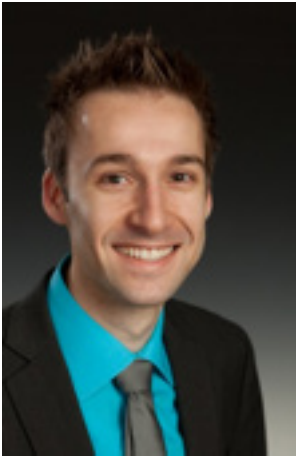
dications that air pollution exposure may affect placental growth and function, measured by placental weight and angiogenic growth factors, but the evidence is insufficient to identify this pathway as playing a major role in the associations of air pollution with pregnancy complications. Furthermore, higher PM₁₀ and NO₂ exposure levels were associated with increased systolic blood pressure levels in the different trimesters of pregnancy, but not with diastolic blood pressure. Also, higher PM₁₀ exposure was associated with an increased risk of gestational hypertension. Finally, we observed indications for fetal growth restriction in different periods in pregnancy, and higher PM₁₀ exposure was associated with increased risks of preterm birth and small size for gestational age at birth. To conclude, our findings demonstrate that air pollution exposure during pregnancy may adversely affect various aspects of maternal and fetal health, including fetal growth, inflammatory markers, maternal blood pressure, and the risks of gestational hypertension and preterm birth. This indicates that pregnant women and their unborn children may be more susceptible to the impact of air pollution. Future studies are needed to confirm our findings and to (further) elucidate the underlying mechanisms.

Vincent Koppelmans

Late effects of adjuvant chemotherapy on brain function and structure

(Co)promotors: Breteler MMB / Schagen SB

20 April 2012



Adjuvant chemotherapy is widely used in the treatment of breast cancer and can induce cognitive problems up to years after treatment. Not much is known about the potential long-term cognitive effects of chemotherapy. Therefore, we compared cognitive functioning and brain structure of almost 200 former breast cancer patients to that of women from the Rotterdam Study who were never diagnosed with cancer. Breast cancer patients had completed adjuvant CMF (Cyclofosfamide-Methotrexat-5-Fluorouracil) chemotherapy on average 21 years ago. Study results showed that the chemotherapy-exposed breast

cancer survivors performed generally worse than reference subjects from the Rotterdam Study on measures of verbal memory, psychomotor speed, executive functioning and processing speed, and reported memory problems more often. Neuroimaging revealed that on average the chemotherapy-exposed breast cancer survivors had smaller brain volumes than women from the reference population. This global difference was driven by smaller gray matter volume. No group differences were observed in microstructural white matter integrity or cerebral perfusion. However, independent of age, white matter integrity deteriorated with accumulating time since treatment. These results suggest that brain structural alterations may underlie long-term cognitive dysfunction following chemotherapy. From a patient's perspective, physicians should be aware of the potential long-term cognitive effects of adjuvant chemotherapy.

Tessa Genders

Diagnostic imaging strategies for patients with suspected coronary artery disease

(Co)promotors: Hunink MGM, Nieman K

29 June 2012



Our aim was to optimize the diagnostic work-up for patients with chest pain who are suspected of having coronary artery disease (CAD). We showed that stress perfusion magnetic resonance imaging compares favorably to single-photon emission computed tomography in terms of diagnostic performance and demonstrated that the coronary CT calcium score has predictive value beyond existing cardiovascular risk factors for diagnosing CAD. Coronary CT angiography was demonstrated to be cost-effective as triage test prior to catheter-based coronary angiography if the pre-test probability was below 40%. CT coronary calcium scoring with

or without subsequent coronary CT angiography was less expensive and equally effective compared to standard-of-care. The pre-test probability of CAD is traditionally estimated based on the Diamond & Forrester method or the Duke Clinical Score. We demonstrated that these prediction models systematically overestimate the probability of CAD and updated the models based on contemporary data. An online calculator was developed providing more accurate estimates.

Elaine M. Rodenburg

Sex differences in cardiovascular drug response

(Co) promoters: Stricker BHCh, Uitterlinden AG, Visser LE

19 September 2012



Drug response is not similar in men and women. The aim of this thesis was to study sex differences in risk of adverse drug reactions (ADRs). Sex differences were studied in hospital admissions attributed to ADRs. Major differences were observed for cardiovascular drugs. Admissions due to diuretics were in second place and showed a more than four times higher risk in women than in men and mainly concerned hyponatremia and hypokalemia. In the population of the Rotterdam Study, it was shown that age, body mass index, certain drug-drug interactions and SNPs within the genetic region encoding the organic anion transporters, influenced the

risk of hyponatremia. The risk of thiazide-induced hypokalemia was significantly higher in men than in women. Both thiazides solely and thiazides in combination with a potassium-sparing agent, showed an increased risk of hypokalemia. From the IPCI-data, it was shown that extra safety measurements to prevent hyponatremia and hypokalemia in subjects at risk were not performed as frequently as recommended by the 'Dutch HARM-Wrestling Task Force'. In addition, sex differences were studied in genetic effects on myocardial infarction (MI) and also these associations were modified by sex.

Tamara van Batenburg-Eddes

Causes and consequences of infant neuromotor development

(Co)promotors: Tiemeier H, Verhulst FC

27 September 2012



The studies in this thesis aimed to extend existing knowledge on the prenatal and early neurodevelopmental basis of behavioural and cognitive problems. To evaluate the maturity of infants' central nervous system, neuromotor development was assessed when infants were between 9 and 15 weeks old. The studies were conducted as part of the Generation R Study, a prospective population-based cohort study from fetal life onwards in Rotterdam, the Netherlands. The results suggest that a shorter gestational duration and a smaller foetal size - both within the normal range - increased the risk of a less optimal neuromotor development. Furthermore, our results suggest that

subtle deviances from normal neuromotor development may be markers of subsequent behavioral or emotional problems and cognitive delays. Further research with a longer follow-up is necessary to determine whether these behavioral and emotional problems and cognitive delays due to less optimal infant neuromotor development will persist or attenuate over time.

Fleur Velders

**Genes, parental psychiatric symptoms and child emotional problems,
nurture versus nature: there and back again**

(Co)promotors: Tiemeier H, Verhulst FC

31 October 2012



The high comorbidity and the likelihood of a long-term vulnerability for mental health problems underscores the importance of a better understanding of the etiology of childhood disorders. To increase this understanding, the papers in this thesis report on the effects of common genetic variation, parental psychiatric symptoms, and gene-environment interaction during pregnancy and early childhood on the risk of emotional and behavioural problems in children. These hypotheses were tested in the Generation R Study, a population-based cohort from fetal life onwards. With respect to gene-environment interaction during pregnancy, our findings suggest that variation

in genes (Glucocorticoid receptor gene, serotonin transporter gene) associated with the regulation of the hypothalamic- pituitary-adrenal axis moderate the association between prenatal psychiatric symptoms of the mother and the risk of child emotional problems, child cortisol levels and children's basic ability to process emotions. These findings implicate that programming processes during pregnancy may affect child functioning later in life, which underscores the importance of the prenatal environment.

Nathalie Grootenboer

Gender differences in presentation of disease and clinical outcome after vascular surgery

(Co)promotors: Hunink MGM, van Sambeek MRHM

7 November 2012



We wrote this thesis because cardiovascular disease was long considered a male disease, however for women too, cardiovascular disease is the leading cause of death. Due to the underrepresentation of women in studies, treatment guidelines are based on a predominately male population and it is debatable whether these guidelines can simply be applied to women. We studied abdominal aortic aneurysms and carotid artery stenoses by means of reviews, systematic reviews and analyses of the largest registries in this field. We demonstrated women to have higher mortality rates following both elective open aneurysm repair and elective endovascular aneurysm repair

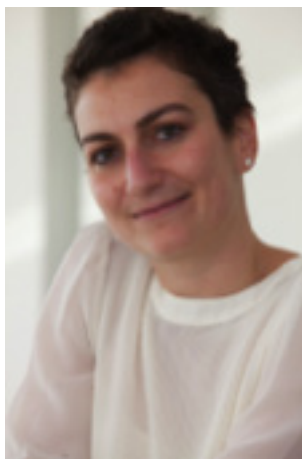
(EVAR), and to have higher complication rates and re-intervention rates than men after EVAR. We believe that increasing awareness of gender differences in cardiovascular disease and putting gender-specific guidelines into place will lead to better health care on the whole, not only for women but for men too.

Ayşe Demirkan

A genetic epidemiologic study of lipids and depressive symptoms

(Co)promotors: van Duijn CM, Oostra BA, Isaacs A

14 November 2012



We wrote this thesis because cardiovascular disease was long considered a male disease, however for women too, cardiovascular disease is the leading cause of death. Due to the underrepresentation of women in studies, treatment guidelines are based on a predominately male population and it is debatable whether these guidelines can simply be applied to women. We studied abdominal aortic aneurysms and carotid artery stenoses by means of reviews, systematic reviews and analyses of the largest registries in this field. We demonstrated women to have higher mortality rates following both elective open aneurysm repair and elec-

tive endovascular aneurysm repair (EVAR), and to have higher complication rates and re-intervention rates than men after EVAR. We believe that increasing awareness of gender differences in cardiovascular disease and putting gender-specific guidelines into place will lead to better health care on the whole, not only for women but for men too.

Epidemiology of diseases

Main participants

Albert Hofman
Oscar Franco
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 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.

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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.

International scientific publications

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Clinical Epidemiology

Main participants

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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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