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University Medical Center Rotterdam

Publications 2014

Department of Epidemiology

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Contents

Preface

This publication report of the Department of Epidemiology at Erasmus for 2014 is again a testimony of the fruitful application of epidemiology and its methods to many clinical and public health questions.

In 2014 fifteen PhD students successfully defended their thesis: three in pediatric epidemiology (Marieke Bouwland-Both, Romy Gaillard, Agnes Sonnenschein-van der Vaart), two in psychiatric epidemiology (Maartje Basten, Marina Verlinden-Bondaruk), two in neuro-epidemiology (Jory Hoogendam, Ben Verhaaren), two in genetic epidemiology (Carla Ibrahim-Verbaas, Sara Willems), two in cardiovascular epidemiology (Mariana Selwaness, Germaine Verwoert), one in pulmonary epidemiology (Lies Lahousse), one in pharmaco epidemiology (Nico van Blijderveen), one in clinical epidemiology (Eline Bunnik) and one in collaboration with the Erasmus School of Economics (Niels Rietveld).

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 for their creativity, dedication and hard work.

Albert Hofman
Chair Department of Epidemiology

Highlights

Arking DE, Pulit SL, Crotti L, van der Harst P, Munroe PB, Koopmann TT, Sotoodehnia N, Rossin EJ, Morley M, Wang X, Johnson AD, Lundby A, Gudbjartsson DF, Noseworthy PA, Eijgelsheim M, Bradford Y, Tarasov KV, Dorr M, Muller-Nurasyid M, Lahtinen AM, Nolte IM, Smith AV, Bis JC, Isaacs A, Newhouse SJ, Evans DS, Post WS, Waggott D, Lyytikainen LP, Hicks AA, Eisele L, Ellinghaus D, Hayward C, Navarro P, Ulivi S, Tanaka T, Tester DJ, Chatel S, Gustafsson S, Kumari M, Morris RW, Naluai AT, Padmanabhan S, Kluttig A, Strohmer B, Panayiotou AG, Torres M, Knoflach M, Hubacek JA, Slowikowski K, Raychaudhuri S, Kumar RD, Harris TB, Launer LJ, Shuldiner AR, Alonso A, Bader JS, Ehret G, Huang H, Kao WH, Strait JB, Macfarlane PW, Brown M, Caulfield MJ, Samani NJ, Kronenberg F, Willeit J, Consortium CA, Consortium C, Smith JG, Greiser KH, Meyer Zu Schwabedissen H, Werdan K, Carella M, Zelante L, Heckbert SR, Psaty BM, Rotter JI, Kolcic I, Polasek O, Wright AF, Griffin M, Daly MJ, Dcct/Edic, Arnar DO, Holm H, Thorsteinsdottir U, e MC, Denny JC, Roden DM, Zuvich RL, Emilsson V, Plump AS, Larson MG, O'Donnell CJ, Yin X, Bobbo M, D'Adamo AP, Iorio A, Sinagra G, Carracedo A, Cummings SR, Nalls MA, Jula A, Kontula KK, Marjamaa A, Oikarinen L, Perola M, Porthan K, Erbel R, Hoffmann P, Jockel KH, Kalsch H, Nothen MM, Consortium H, den Hoed M, Loos RJ, Thelle DS, Gieger C, Meitinger T, Perz S, Peters A, Prucha H, Sinner MF, Waldenberger M, de Boer RA, Franke L, van der Vleuten PA, Beckmann BM, Martens E, Bardai A, Hofman N, Wilde AA, Behr ER, Dalageorgou C, Giudicessi JR, Medeiros-Domingo A, Barc J, Kyndt F, Probst V, Ghidoni A, Insolia R, Hamilton RM, Scherer SW, Brandimarto J, Margulies K, Moravec CE, Greco MF, Fuchsberger C, O'Connell JR, Lee WK, Watt GC, Campbell H, Wild SH, El Mokhtari NE, Frey N, Asselbergs FW, Mateo Leach I, Navis G, van den Berg MP, van Veldhuisen DJ, Kellis M, Krijthe BP, Franco OH, Hofman A, Kors JA, Uitterlinden AG, Witteman JC, Kedenko L, Lamina C, Oostra BA, Abecasis GR, Lakatta EG, Mulas A, Orru M, Schlessinger D, Uda M, Markus MR, Volker U, Snieder H, Spector TD, Arnlov J, Lind L, Sundstrom J, Syvanen AC, Kivimaki M, Kahonen M, Mononen N, Raitakari OT, Viikari JS, Adamkova V, Kiechl S, Brion M, Nicolaides AN, Paulweber B, Haerting J, Dominiczak AF, Nyberg F, Whincup PH, Hingorani AD, Schott JJ, Bezzina CR, Ingelsson E, Ferrucci L, Gasparini P, Wilson JF, Rudan I, Franke A, Muhleisen TW, Pramstaller PP, Lehtimaki TJ, Paterson AD, Parsa A, Liu Y, van Duijn CM, Siscovick DS, Gudnason V, Jamshidi Y, Salomaa V, Felix SB, Sanna S, Ritchie MD, Stricker BH, Stefansson K, Boyer LA, Cappola TP, Olsen JV, Lage K, Schwartz PJ, Kaab S, Chakravarti A, Ackerman MJ, Pfeufer A, de Bakker PI, Newton-Cheh C. **Genetic association study of QT interval highlights role for calcium signaling pathways in myocardial repolarization.**
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Dissertations Epidemiology 2014

Agnes Sonnenschein – van der Voort
Fetal and infant origins of childhood asthma – The Generation R Study
(Co)promotores: de Jongste JC, Jaddoe VWV, Duijts L
15 January 2014

Asthma symptoms are common in childhood and are responsible for a large proportion of the morbidity in childhood. Studies on early growth and childhood asthma suggest that, at birth, younger gestational age is an important risk factor for the development of asthma symptoms. Fetal growth seems to have an influence on lung structure growth, whereas infant growth seems to influence the development of asthma symptoms. Also, fetal environmental exposures, including maternal psychological distress, obesity and gestational weight gain, and C-reactive protein influence the risk of developing childhood asthma in which immunomodulatory and inflammatory factors seem to play an important role. Infant exposures including breastfeeding duration and exclusiveness or exposure to air pollution affects the development of asthma symptoms, potentially as a result of infectious mechanisms or irritative agents.
Ultimately, by identification of early life exposures related to the development of asthma throughout childhood, we hope to develop preventive strategies focused on pregnant women and young children to improve respiratory health during childhood.

Ben Verhaaren
Determinants of subclinical vascular brain disease in aging
(Co)promotores: Hofman A, van der Lugt A, Ikram MA, Vernooij MW
16 April 2014

We are at the dawn of a large epidemic of dementia and stroke that will have a major impact on our society. At the time of diagnosis we may already be too late, as in both dementia and stroke irreversible brain damage is already present, for which at present no treatment is available. Advances in research have shown that for both diseases, signs of disease may already be detectable in the brain years or even decades in advance. These subtle signs generally go unnoticed and therefore are often called subclinical brain disease. In particular vascular pathology, such as the presence of white matter lesions, has been shown to already manifest in the middle-aged and was found to increase the risk of both dementia and stroke. Subclinical brain disease can be visualized with magnetic resonance imaging (MRI) in vivo and has proved to be highly prevalent in the aging population. Yet, their exact etiology remains to be elucidated. Developments in genetics and imaging have greatly increased the potential to identify novel determinants of neurodegenerative disease and cerebrovascular disease and to investigate their role in subclinical brain disease in the general population.

Carla Ibrahim-Verbaas
A genetic epidemiological study of dementia and cognitive function
(Co)promotores: van Duijn CM, van Swieten JC, Amin N
10 June 2014

Dementia is a chronic, progressive syndrome of cognitive deterioration, more than can be expected based on normal ageing. Alzheimer's disease is the most common form of dementia of older age, and it affects one in three women and one in six men, and therefore has a great impact on healthcare systems. The main symptoms comprise dysfunction in short term memory, language and loss of visuospatial ability. There is and important association with accumulation of amyloid ß and Tau proteins in the brain, and a central role of these accumulations in the pathogenesis of the disease, among others through inflammatory processes and apoptosis, has been assumed. Loss of function and loss of tissue are found in the hippocampus and temporoparietal regions. The heritability of Alzheimer's disease is estimated to be around 60-74%, but the genetic variations driving this heritability are still largely unknown. Rare mutations are known in a few genes (APP, PSEN1, PSEN2) which cause a familial form of Alzheimer's disease, but only variants in the APOE gene have in themselves, as far as we know, a large influence on the incidence of AD in the general population.

Eline Bunnik
Up close and personal, Ethical issues in genomic testing
(Co)promotores: Janssens ACJW, Schermer MHN
10 June 2014

Genomically speaking, human beings are much alike: they differ from one another less than 1%. Still, there are a few million differences between most people – after all, DNA contains about three billion base-pairs. These differences largely determine how we look (different), how we speak, eat and move our bodies, how we think, love and vote, and how we remain healthy or fall ill. By using new technologies to look into our genomes, we can gain insight into our strengths and weaknesses. Such insight may benefit us: our genomes can be tested for genetic susceptibilities to diseases, which we may then try to avoid by changing our lifestyles or through early medical interventions. But we can also be harmed by such insight: not everyone will want to know their Achilles' heels, in particular when these Achilles' heels concern diseases for which there are no preventive of therapeutic options. Our genomes are up close and personal. But given that the genomic looking glass is rather new to us, we may not yet know what to do with in, or how to use it responsibly.

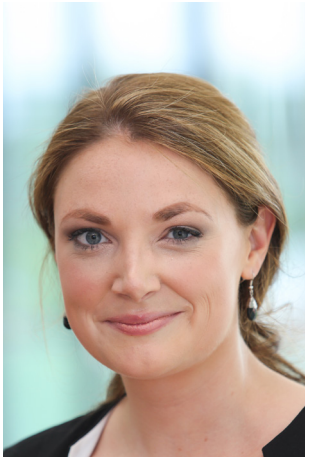
Germaine Verwoert
Arterial hemodynamics in aging populations
(Co)promotores: Sijbrands EJG, van Duijn CM, Mattace-Raso FUS
11 June 2014

Cardiovascular disease is the number one leading cause of morbidity worldwide. A large proportion of cardiovascular diseases can be prevented by addressing risk factors and early assessment of target organ damage. The leading cardiovascular risk factor is raised blood pressure, however this relationship is more complex than only the two extremes, systolic and diastolic blood pressure. The pulsatile component of blood pressure plays a role in predicting cardiovascular diseases.

Jory Hoogendam
The role of brain aging in cognition and motor function
(Co)promotores: Hofman A, van der Lugt A, Ikram MA, van der Geest JN
25 June 201

Aging is accompanied by loss of brain tissue, which can be quantified using magnetic resonance imaging. Brain changes can already be visible in absence of clinical disease of the brain. Still, even when no clinical disease is apparent, decline in brain functions can cause considerable discomfort in daily activities. Cognition and motor function are important brain functions that are affected by aging. Both functions are controlled by the cerebrum and cerebellum. However, most research has concentrated on either the role of cerebrum or cerebellum, and has taken place outside the scope of population-based imaging studies in community-dwelling elderly. The aim of the research reported in this thesis was to describe age effects on multiple aspects of cognition and motor function and to further explore the relation between cerebral and cerebellar volumes with cognition and motor function in a population of middle-aged and elderly persons.

Romy Gaillard
Cardiovascular health in pregnant women and their children – The Generation R Study
(Co)promotores: Jaddoe VWV, Steegers EAP
25 June 2014



Cardiovascular health and disease in pregnant women and their children is important for clinically relevant, adverse short-term and long-term health outcomes. Studies presented in this thesis were designed to identify maternal, placental and fetal factors and critical developmental periods during pregnancy associated with cardiovascular health outcomes in mothers and children. We observed that nulliparous women had a higher risk of gestational hypertensive disorders, and delivering preterm and small size for gestational age infants. Children of nulliparous mothers also had higher risks of childhood overweight and an adverse metabolic profile. Maternal prepregnancy obesity and excessive gestational weight gain, especially in early pregnancy, were associated with increased risks of maternal pregnancy complications, childhood obesity and clustering of cardiovascular risk factors. Higher third trimester feto-placental vascular resistance, but not utero-placental vascular resistance, was associated with slower fetal growth rates and cardiovascular adaptations in childhood. We found that first trimester fetal growth might be a critical period for cardiovascular and metabolic function in later life. In conclusion, findings from this thesis suggest that maternal, placental and fetal influences are associated with maternal and childhood cardiovascular health outcomes. Early pregnancy seems to be a critical period for health outcomes in pregnant women and their children.

Niels Rietveld
Essays on the Intersection of Economics and Biology
(Co)promotores: Thurik AR, Koellinger PD, Groenen PJF, Hofman A
2 October 2014

Economists have always been adept at integrating ideas and concepts from other scientific fields into their own research agenda. My thesis adopts a perspective in which individual economic choices and outcomes are connected to individual biological characteristics. I find that genetic variants explain an important part of the population variance in educational attainment, cognitive function, subjective well-being and entrepreneurship. Moreover, specific genetic variants associated with educational attainment, cognitive function and entrepreneurship are identified. I also find that entrepreneurs are generally healthier than wage-workers, and that the selection of comparatively healthier individuals into entrepreneurship accounts for the positive cross-sectional association. Finally, my thesis provides empirical evidence that dyslectic and left-handed individuals are not more likely to be(come) entrepreneurs than non-dyslectic and right-handed individuals. Although the full breakthrough of biological economics still remains, the expected value of research on the intersection of economics and biology is argued to be high. It is reasonable to assume that the interest in biological economics will only grow in the coming years. My thesis shows how a collaborative confrontation between economics and biology within an interdisciplinary team yields high quality research.

Mariana Selwaness
Magnetic resonance imaging of carotid atherosclerosis: a population-based approach
(Co) promotores: van der Lugt A, Franco OH, Wentzel JJ, Vernooij MW
21 October 2014

Atherosclerotic plaques located in the carotid arteries are the main cause of stroke. Current treatment strategies that target atherosclerosis are insufficient to early identify the individual who is at risk of stroke and the incidence of cerebrovascular events remains dramatically high. Recent advances in the prevention of stroke include discrimination of different plaque components and recognition of the vulnerable atherosclerotic plaque, which could consist of an intraplaque haemorrhage. Intraplaque haemorrhage is assumed to be caused by rupture or leakage of plaque neovasculature, and, stimulates the progression and destabilization of the plaque. Magnetic resonance imaging (MRI) is able to discriminate between the different atherosclerotic plaque components and it can accurately detect intraplaque haemorrhage in atherosclerotic plaques of the carotid artery. Knowledge about factors that influence carotid atherosclerotic plaque composition may eventually contribute to stroke prevention.into economics.

Maartje Basten
Poor self-regulation in young children
(Co)promotores: Verhulst FC, Hudziak JJ, Tiemeier H
6 November 2014

Child psychiatry continues to struggle how to describe children with severe emotional and behavioral problems. One of the recently developed methods to decribe these children is the Child Behavior Checklist Dysregulation profile (CBCL-DP). CBCL-DP is characterized by high scores on three syndrome scales of the CBCL: Anxious/Depressed, Attention Problems, and Aggressive Behavior. These three scales reflect poor regulation of emotions, attention, and behavior. Studies in school-age children and adolecents have shown that children with this profile show high levels of impairment and are at high risk for suicidality and psychopathology in adulthood. Little is known about the CBCL-DP in young children. The aim of this thesis was to examine whether a CBCL-DP could be identified in 5- to 7-year-old children. Additionally, we examined determinants and correlates of the CBCL-DP in young children and studied the stability of dysregulated behavior across the preschool period.

Lies Lahousse
Epidemiology of comorbidities in chronic obstructive pulmonary disease
(Co)promotores: Brusselle GG, Stricker BH
11 November 2014

COPD is a common respiratory disease among elderly caused by long term exposure to irritants such as cigarette smoke and characterized by prolonged cough, excessive mucus production and shortness of breath. In addition to the chronic inflammatory response in the lungs, systemic effects and comorbidities are frequently present and determine the quality of life and prognosis in patients with COPD. To reach a better prevention and treatment of comorbidities in COPD, the main objective of this thesis was to identify and explore (novel) comorbid conditions of COPD in the general population (the Rotterdam Study).

A key finding of this thesis was the identification of vascular dysfunction in patients with COPD. Carotid artery wall thickening was more prevalent in COPD patients, especially vulnerable lipid core plaques which place them at high risk for stroke. In addition, COPD was associated with microbleeds in the brains which reflect underlying vascular abnormalities and may partially explain the cognitive and functional decline in patients with COPD. Furthermore, we found that systemic inflammation predicts poorer survival in patients with COPD and may contribute to the cardiovascular comorbidities. In conclusion, this thesis demonstrated that COPD goes beyond the lungs and that patients with COPD need comprehensive care.

Marieke Bouwland - Both
Periconception epidemiological and epigenetic studies
(Co)promotores: Steegers RPM, Jaddoe VWV
25 November 2014

Adverse birth outcomes are major contributors to short and long term morbidity and mortality. Evidence is accumulating that the course and outcome of pregnancy is not only important for the health of the mother and child, but can also be considered a predictor of future adult health and disease. Pregnancy complications are thought to originate in the periconception period. In this thesis we showed that the diet of the mother has an effect on fetal growth in early pregnancy. Moreover, an increase of biomarkers involved in placentation was associated with growth as early as the first trimester. This difference persisted throughout pregnancy, until the age of 6 years. Identifying women who are at risk for adverse birth outcomes in the periconception period may have potential for screening and early intervention trials. Changes in DNA methylation have been postulated to be one of the mechanisms underlying the effects of a suboptimal intrauterine environment on pregnancy course and outcome. We showed that changes in DNA methylation, caused by maternal smoking, are associated with an increased risk of adverse birth outcomes, including the risk of being born small for gestational age and the risk of a neural tube defect, and altered postnatal weight growth. These observations emphasize the importance of periconception care and are suggestive of links between a suboptimal intrauterine environment by epigenetic reprogramming

Marina Verlinden - Bondaruk
Population-based studies of bullying in young children
(Co)promotores: Tiemeier H, Verhulst FC, Veenstra R, Jansen PW
2 December 2014

The studies described in this thesis focus on bullying involvement in early elementary schools. Studying the nature and characteristics of bullying at a young age can help us to better understand factors which may increase a child's risk of bullying or victimization. In this thesis the topic of bullying was examined from a population-based perspective; children's risk of bullying or victimization was studied prospectively using varying methodologies and designs. The presented studies focused specifically on the assessment of bullying at a young age using both survey among teachers and a computerized peer nomination measure among children. The peer nomination measure used in these studies provided a unique insight into peer relations in a school class by mapping, for instance, who is bullied by whom in a class, or who is usually accepted or rejected by the peers. Information regarding various characteristics of children and their families were derived primarily from parental questionnaires or observational measures obtained at the assessment center. In addition to the socioeconomic and demographic characteristics of children who were affected by bullying, we examined risk factors such as: child behavioral problems at preschool age, executive function and media exposure. Important methodological advantages of the presented studies include their entrenchment in a large birth cohort and the use of repeated measures of child behavior. The findings of this thesis and potential applications, as well as the major challenges of research in this field, are discussed.

Nico van Blijderveen
Drug-induced kidney Injury and safe pharmacotherapy in elderly
(Co)promotores: Stricker BH, Sturkenboom, MCJM
9 December 2014

Preservation of kidney function, often represented by the estimated glomerular filtration rate, is important because a decreased renal function is associated with an increased risk of morbidity and mortality. Despite this, drug-induced nephrotoxicity has been shown to be a main determinant of preventable medication-related hospital admission.

Sara Willems
From gene discovery to understanding and predicting cardiometabolic disease
(Co)promotores: van Duijn CM, Isaacs A
18 December 2014

An increasing portion of cardiovascular diseases (CVDs) can be prevented by addressing the modifiable risk factors, including type 2 diabetes (T2D) and dyslipidemia. In my thesis I aimed to improve our understanding of the etiology of T2D and dyslipidemia and to investigate the extent to which genetic risk factors combined can improve their prediction. Main findings are the identification of a low-frequency variant associated with FG and T2D in GLP1R, a gene encoding a direct drug target for T2D and the finding that both rare non-synonymous and common non-coding variants with putative function in and near the IGF1 gene may have a role in insulin biology. Further, while the currently identified common T2D associated genetic variants do not yet improve prediction of T2D compared to clinical prediction models, this thesis provides evidence that genetic risk scores for lipid levels play a large role in determining who develops dyslipidemia through old age. These findings and several efforts that are underway may bring us closer to translation of complex disease genetics in clinical practice. Ultimately this may reduce the prevalence of the CVD risk factors T2D and dyslipidemia and thus the burden of morbidity.

Epidemiology of diseases

Main participants
Oscar Franco
Albert Hofman
Arfan Ikram
Caroline Klaver
Henning Tiemeier
Meike Vernooij

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
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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 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
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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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