Erasmus MC
University Medical Center Rotterdam

Publications 2013

Department of Epidemiology

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Contents

Preface

The Department of Epidemiology at Erasmus saw in 2013 the continued harvest of results of genomics studies in the two Erasmus cohorts, Generation R and the Rotterdam Study. Many new genes linked to major diseases have been identified, including the TREM2 variant of Alzheimer's disease, Pls3 mutations in osteoporotic fractures and many new genes involved in myopia. We also published an article on two genetic variants associated with educational attainment, after so many years of fruitless searches for intelligence genes and the accompanying nature-nurture debate. Many of these observation are done in highly collaborative work in international consortia.

In 2013 fifteen PhD students successfully defended their thesis: four in pediatric epidemiology (Busra Durmus, Layla de Jonge, Rob Taal, Ralf van der Valk), two in clinical epidemiology (Bart Ferket, Raluca Mihaescu), two in genetic epidemiology (Linda Broer, Maksim Struchalin), two in psychiatric epidemiology (Karin Hek, Eszter Szekely), one in cardiovascular epidemiology (Maryam Kavousi), one in economics (Matthijs van der Loos), one in neuroepidemiology (Daniel Bos), one in respiratory epidemiology (Daan Loth), and one in pharmacoepidemiology (Bouwe Krijthe).

In 2013 Jacqueline Witteman left Erasmus MC after many years of work in particular in the Rotterdam Study. We thank her for her great contributions to cardiovascular epidemiology over the years and for her methodologic insights, and wish her much success in her new endeavers.

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

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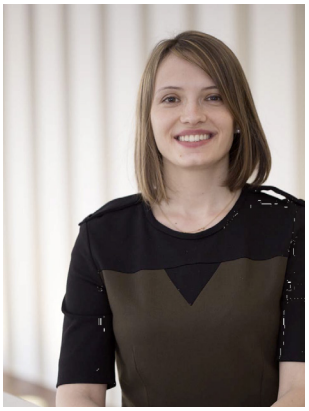
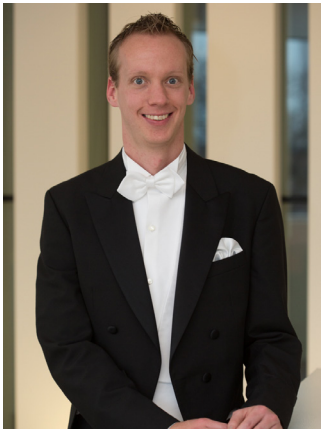
Dissertations Epidemiology 2013

Eszter Székely
Children's emotional functioning in the preschool period: emotion recognition, temperament, and their links with early risk factors, The Generation R Study
(Co)promotores: Tiemeier H, Verhulst FC, Herba CM
23 January 2013



Deficits in emotional functioning are present in many forms of psychopathology even before an individual is diagnosed with a psychiatric disorder. Therefore, identifying early predictors of normal and pathological emotional functioning can prove valuable for the development of effective preventive interventions. The general aim of my thesis was to provide greater insight into the relationship between young children's emotional functioning and a number of important early risk factors of psychopathology. Such risk factors include maternal depression and children's genetic makeup. All studies described in my thesis were conducted within the context of the Generation R Study, a large-scale population-based prospective child cohort from fetal life onward in Rotterdam, the Netherlands. The Generation R Study offers a unique opportunity to identify early environmental and genetic causes of normal and abnormal growth, development, and health. My thesis is based on a subsample of this cohort, consisting of approximately 1000 Dutch children and their parents, in whom more detailed observational measurements were available. Findings are discussed with a particular focus on two key aspects of young children's emotional functioning, temperament and the ability to accurately recognize emotional facial expressions.

Hendrik Robert Taal
Early growth, cardiovascular and renal development, The Generation R Study
(Co)promotores: van der Heijden AJ, Hofman A, Jaddoe VWV
20 March 2013

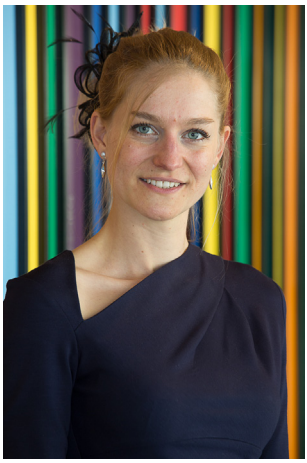


Recent studies suggest that an adverse intra-uterine environment leads to fetal growth retardation and adaptations in renal and cardiovascular development. In this thesis we investigated genetic determinants of early growth and consequences of growth patterns in early life. We showed that early postnatal growth affected the risk of being overweight in later life, depending on the birth weight for gestational age. We also identified genetic variants associated with birth weight, head circumference in infancy and obesity in childhood. Furthermore, we investigated which factors, both during pregnancy and in early life, influence the cardiovascular development . We found that intra-uterine growth, gestational age, birth weight, smoking during pregnancy and early postnatal growth are important factors in determining blood pressure and cardiovascular and renal development, as well as their function in later life.The results described in this thesis support the hypothesis that both environmental factors during pregnancy and in early life, as well as genetic factors are important in developing obesity and chronic diseases at later age.

Ralf van der Valk
Exhaled nitric oxide and asthma in childhood
(Co)promotores: de Jongste JC, Hofman A, Jaddoe VWV
12 April 2013

Asthma is a frequent chronic disorder in childhood. Childhood asthma exists in various forms, influenced by genetic and environmental factors. We focussed on a biomarker for a subtype of asthma. FeNO is a non-invasive biomarker of a distinct type of airway inflammation, and is associated with asthma and allergy. We interpreted daily fluctuations in FeNO, and focussed on genetic and environmental risk-factors of asthma and FeNO. We found that FeNO was differentially associated with five distinct types of wheezing, only in allergic children. FeNO-guided asthma management was suggested to improve asthma control and reduce asthma attacks. Our study revealed changes in daily FeNO prior to asthma attacks and described correlations between daily FeNO and symptoms. Whether changes in daily FeNO can be used to prevent loss of asthma control should be further explored. We identified genetic regions influencing FeNO and highlighted that both shared and distinct genetic factors affect FeNO and childhood asthma. We showed that an important genetic factor of childhood asthma is associated with symptoms in preschool children, and this association is modified by smoke exposure already during fetal life. Whether our results can be used for development of novel diagnostic and/or therapeutic approaches remains to be explored.

Layla de Jonge
Early growth and cardiovascular development in childhood, The Generation R Study
(Co)promotores: Hofman A, Helbing WA, Jaddoe VWV
18 April 2013



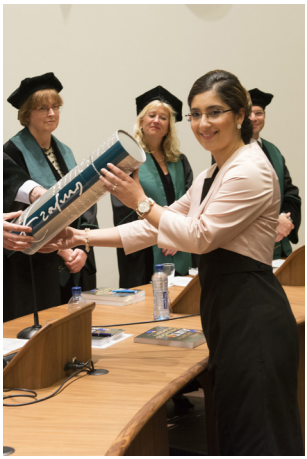
It has been hypothesized that the association between early growth and the susceptibility to cardiovascular disease in later life might partly be explained by suboptimal cardiovascular adaptations in response to impaired growth and an adverse environment. Therefore, this thesis focused on the effects of fetal and childhood growth patterns and their determinants on cardiovascular outcomes in childhood and adulthood.

Most studies were embedded in The Generation R Study, a population based prospective cohort study from fetal life until young adulthood. We observed that fetal and infant growth characteristics are associated with cardiovascular structural and functional development in childhood. Results from this study also suggest that specific exposures in fetal life and early childhood, such as infant nutrition, may have consequences for cardiovascular structures and function. In the Nurses' Health Study II, an ongoing prospective cohort study of female nurses in USA, we concluded that the positive associations of both maternal and paternal smoking during pregnancy with the risk of hypertension and Diabetes Type II in their adult daughters, were largely attenuated after adjustment for body weight throughout life. Further research is needed to explore the underlying mechanisms and long-term clinical importance of our findings.

Karin Hek
Anxiety disorders and depression in older adults
(Co)promotores:Mulder CL, Tiemeier HW
24 April 2013

Anxiety disorders and depression are common complex disorders with unknown etiology. In this thesis comorbidity, health services use, cortisol, atherosclerosis and genetic factors were studied in relation to anxiety disorders and, or depression to help unravel their etiology. These studies were set in the Rotterdam Study, a population-based cohort of older adults.
We identified a genetic vulnerability jointly explaining both variance in anxiety and depression. This may explain the high life-time comorbidity of anxiety disorders and depression. In addition, we identified genetic factors, a variant in the PCLO gene and a region on chromosome 5, and a biological factor, cortisol, that may be involved in the etiology of anxiety disorders and, or depression.
From the findings in this thesis we recommend for future studies to always account for the comorbidity between anxiety disorders and depression, as comorbidity is inherent to these disorders. In addition, we encourage genetic epidemiologists in the field to continue working on the genetics of anxiety disorders and depression. Evolution in methods, phenotype definition and collaboration will lead to genetic successes for anxiety disorders and depression.

Busra Durmus
Early growth and childhood adiposity, The Generation R Study
(Co)promotores: Hofman A, van der Heijden AJ, Jaddoe VWV
8 May 2013



The key objective for this thesis was to examine the associations of several exposures in utero en in early postnatal life, and repeatedly measured fetal and infant growth characteristics with body fat distribution and cardiometabolic outcomes in childhood. The results described in chapter 3 suggest that specific fetal and early postnatal growth patterns influence body fat distribution and the risk of overweight in childhood. The results described in chapter 4 suggest that weight, height and BMI of parents are related to childhood growth and the risk of overweight. Parental smoking appears to increase the risk of overweight and an adverse body fat distribution in childhood. Finally, the results described in chapter 5 suggest that breastfeeding and the timing of introduction of solid foods in the first year of life do not strongly influence growth and body fat distribution and the risk of overweight in childhood.

Maksim V. Struchalin
Approaches to dissect the complex genetic architecture of common traits
(Co)promotores: van Duijn CM, Oostra BA, Karssen LC
22 May 2013

Genome-wide association studies (GWAS) have substantially improved our understanding of the complex genetic architecture of many common traits. For the last decade, more than a thousand genetic variants were discovered using GWAS. The fast development of the field necessitated the improvement of existing instruments as well as the develoment of new ones. This thesis discusses methodology, software tools and new approaches facilitating the study of the complex genetic architecture of common traits.

Bouwe P. Krijthe
Risk factors for atrial fibrillation
(Co)promotores: Stricker BHC, Witteman JC, Heeringa J
31 May 2013

Atrial fibrillation is a common cardiac arrhythmia in the elderly. It has serious consequences for the health of affected individuals and is a substantial burden for the health care system. The thesis had several objectives. The first objective was to project the number of individuals with atrial fibrillation in the Netherlands and the European Union. By combining data on atrial fibrillation from the population-based Rotterdam Study with population projections from the statistical bureau of the European Union, Eurostat, we project that from 2010 to 2060, the number of adults aged 55 years and over with atrial fibrillation will more than double in the Netherlands and in the European Union. The second objective was to identify novel risk factors for atrial fibrillation. We report on the association between clinically unrecognized myocardial infarction and the risk of atrial fibrillation. Also we report on the association between serum dehydroepiandrosterone sulphate levels, serum potassium levels, use of non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation. Furthermore, by combining data from several studies, we found six novel genetic regions associated with the risk of atrial fibrillation. Finally, we found that a simple risk model including variables routinely collected in a primary care setting is useful to predict the future risk of atrial fibrillation.

Matthijs van der Loos
Molecular genetics and hormones, new frontiers in entrepreneurship research
(Co) promotores: Thurik AR, Groenen PJF, Hofman A, Koellinger PD
20 June 2013

Recent studies suggest that entrepreneurship is partly heritable, but are unable to pinpoint the specific genes involved. This thesis presents results from novel research aiming to identify genes associated with entrepreneurship using genetic data on the molecular level. In addition, the relationship between testosterone and entrepreneurship is examined since genes may exert their influence through this hormone. The thesis starts by reviewing candidate gene studies that test a pre-specified set of genes for association, but which often fail to replicate. An example within the setting of entrepreneurship research is provided to illustrate this last point. Next, the genome-wide association study (GWAS) design is presented that scans the entire genome for associations. However, due to multiple testing, GWAS requires very large sample sizes to establish robust associations and we perform a simulation study to estimate the minimum sample size needed for a GWAS on entrepreneurship. The following part reports evidence that entrepreneurship is partly heritable and around half of the heritability is accounted for by actual molecular genetic data. However, a GWAS on entrepreneurship does not identify robustly associated genes and prediction exercises show that it is currently impossible to predict entrepreneurship solely from molecular genetic data. In the final part, we show that, in contrast to earlier findings, testosterone is not associated with entrepreneurship. Taken as a whole, the results suggest that entrepreneurship is likely to be influenced by hundreds if not thousands of genes with a very small effect size each, implying that very large sample sizes will be needed in future research to discover associated genes. Most importantly, this thesis may serve as a practical guide for studying the molecular genetics of other economic variables. In conclusion, this thesis helps to build the foundations for a novel research field that integrates molecular genetics into economics.

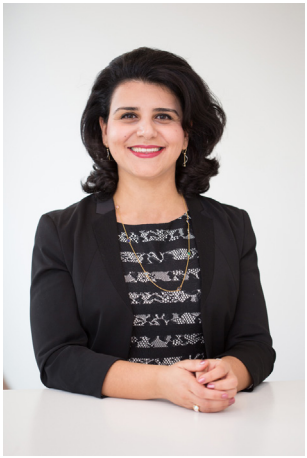
Raluca Mihaescu
Genetic risk prediction for common diseases. Methodology and applications.
(Co)promotores: Janssens ACJW, Hunink MGM
27 September 2013

This thesis describes methodological and empirical studies of genetic risk prediction of common diseases. The methodological studies involved the evaluation of traditional and new methods of model performance, the evaluation of rare variants for risk prediction of common diseases, the assessment of simulations strategies for replication of empirical data, and the evaluation of reporting in empirical risk prediction studies. The empirical studies involved the evaluation of direct-to-consumer (DTC) genetic tests, the external validation of genetic risk prediction models across European samples, and the evaluation of differences in prediction performance in published genetic risk prediction models. Both simulated and empirical data were used to conduct these studies. By means of simulation, a population distribution of genetic variants was created starting from the effect size and frequency of individual variants and assuming that genetic variants are inherited independently and that their joint effects follow a multiplicative risk model. The empirical data came from the Rotterdam study, a prospective, population-based, cohort study among 7,983 inhabitants of a Rotterdam suburb, designed to investigate determinants of chronic diseases; and from a community-based cohort i.e., the combination of Atherosclerosis Risk in Communities Study, Cardiovascular Health Study and Framingham Heart Study.

Bart Ferket
Personalized medical decision making for prevention of a first cardiovascular event
(Co)promotores: Hunink MGM, Steyerberg EW
2 October 2013

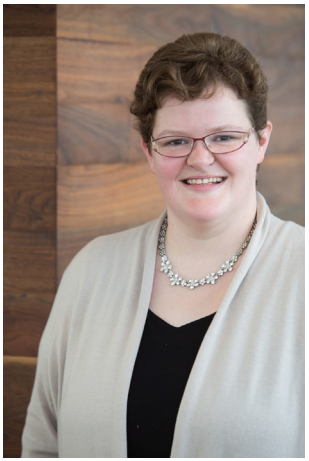
The objective of this thesis was to improve personalized primary prevention of cardiovascular disease (CVD). Based on systematic reviews of clinical practice guidelines it was concluded that the current recommended practice to prevent first CVD events consists of risk-based decision-making using fixed risk thresholds. The CT calcium score was considered to be the most useful imaging marker.
To improve personalized decision making on cholesterol lowering with statin therapy, the Rotterdam Ischemic heart disease and Stroke Computer simulation (RISC) model was used to calculate treatment benefits taking into account the life expectancy of the individual. Expected benefits with statin therapy were found to be discordant with decision making based on European guidelines. Finally, the added predictive value of four promising novel risk markers beyond traditional CVD risk scores was assessed for the U.S. general population. Among the four novel risk markers, the CT calcium score improved the predictive performance, whereas the other three novel markers did not. This thesis showed how personalized decision-making on primary prevention of CVD can be refined by taking into account the individual's life expectancy and by including cardiovascular imaging.

Maryam Kavousi
Subclinical measures of atherosclerosis genetics and cardiovascular risk prediction
(Co)promotores: Hofman A, Franco Duran O
8 October 2013



My thesis expands the knowledge on three measures of subclinical atherosclerosis burden; Coronary artery calcium, carotid intima-media thickness, and ankle-brachial index. The genome-wide association studies in my thesis identify several new genetic loci associated with these three subclinical measures of atherosclerosis. Interestingly, several of the identified loci are also associated with coronary artery disease. The suggested common etiology for subclinical and clinically apparent cardiovascular disease might ultimately propose new strategies for prediction, prevention, and treatment of cardiovascular disease. My prediction studies demonstrate a substantial gain in coronary heart disease risk prediction, above the traditional cardiovascular risk factors, provided by coronary artery calcium. My findings suggest use of coronary artery calcium as a supplemental tool for refining coronary heart disease risk prediction, but not for heart failure or stroke. My cardiovascular risk prediction studies also indicate that among women it is relevant to (1) assess a woman's risk for developing various components of cardiovascular disease, and not coronary heart disease only; (2) consider the risk factor burden in the context of longer time horizons, than 10 years; and (3) assess subclinical atherosclerosis burden to identify women that are at low short-term but high long-term risk for cardiovascular disease that would benefit from more intensive prevention.

Linda Broer
(Genetic) Epidemiology of ageing
(Co)promotores: van Duijn CM, Oostra BA, Isaacs A
9 October 2013



Longevity (here defined as reaching age of 90+) is a complex phenotype with moderate heritability (20 to 40%). Factors thought to be involved in longevity are IGF-1 signaling, stress response and telomere length. We aimed to identify genetic factors associated with longevity in the unknown biological pathways, the stress response and telomere length. Using a traditional GWAS approach, we failed to identify new variants associated with longevity. With a burden test of exome sequence data we identified one region on chromosome 12 to be associated with longevity. This region remains to be confirmed. We next studied the association of Heat Shock Proteins (HSPs), main mediators of the stress response, with Alzheimer's disease (AD), Parkinson's disease (PD) and all-cause mortality. We did not find any significant associations of HSPs with PD. For AD we discovered two HSPs in the discovery phase, while only PDFN2 replicated in two independent cohorts. Additionally we found significant evidence for the association of HSF2 with all-cause mortality. Finally, we focused on telomere length. Telomere length showed a high heritability (~70%), with a significant maternal component. We also observed that the variation in telomere length in the population decreases with age, hinting at a survivor effect. Finally, we found significant associations between telomere length and leptin, height and several blood metabolites. The identified blood metabolites point to the association of telomere length with homocysteine, thyroid and lipid metabolism.

Daan W. Loth
Epidemiology of lung function and chronic obstructive pulmonary disease
(Co)promotores: Stricker BHC, Brusselle G, Leufkens HGM
30 October 2013

The main objectives of this thesis were, 1) to explore the epidemiology of (ab) normal spirometric measurements in elderly, 2) to identify genetic determinants for lung function, smoking susceptibility, lung function decline and COPD, 3) to assess the effects of drugs on lung function or disease progression and to elucidate the genetic- and environmental modifiers of drug response. We calculated reference values for three spirometry measures; Forced Expiratory Volume in 1 second (FEV1), Forced Vital Capacity (FVC) and the ratio of FEV1 over FVC. In chapter 2.2 we studied the relationship between pulmonary and cardiovascular function. We described the results of three "standard" genome-wide association analyses across two large consortia (CHARGE and SpiroMeta) for: 1) FEV1 and FEV1/FVC, 2) FVC and 3) COPD. Furthermore, did a gene-environment interaction of cigarette smoke exposure on FEV1 and FEV1/FVC. Lastly in this series, we evaluated the interaction between genes and time on FEV1. Lastly, we investigated the effect of cardiovascular medication (-blockers and statins) on pulmonary function and mortality. Use of -blockers was associated with a lower FEV1 and FVC and statins reduce mortality in COPD patients.

Daniel Bos
Atherosclerotic calcification: Determinants and clinical neurological consequences.
(Co)promotores: van der Lugt A, Hofman A, Vernooij MW, Ikram MA
11 December 2013

Atherosclerosis is a frequently occurring vascular disease in middle-aged and older persons. Its major clinical consequences are myocardial infarctions and stroke. Specifically with regard to brain health, increasing evidence points in the direction of a much broader range of consequences of atherosclerosis, besides solely clinical stroke. Moreover, an emerging topic of interest is the location of atherosclerosis. Although atherosclerosis may occur systemically across the arterial system, its burden may vary considerably across different vessel beds. Both the origin as well as the contribution to subsequent disease of these differences needs further elucidation. In my research I focused on these topics. Using CT examinations of almost 2500 participants from the Rotterdam Study, I measured the atherosclerotic calcification volume in the coronary arteries, the aortic arch, the extracranial carotid artery and the intracranial carotid artery. Additionally, these participants underwent extensive examinations on cardiovascular risk factors, cognitive performance, genetics and they were followed for the occurrence of stroke and dementia. Briefly, I found differences in the etiology of atherosclerosis in the different vessel beds. Moreover, I found that atherosclerosis is an important risk factor for subclinical brain damage, such as white matter lesions and subtle cognitive deterioration. Atherosclerosis also contributes to the development of dementia, especially Alzheimer's disease. Finally, I found that intracranial atherosclerosis is a major risk factor for stroke in the western population and deserves significantly more attention in current clinical practice.

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
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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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