



Publications 2009

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Preface

In 2009 the Department of Epidemiology of the Erasmus Medical Center celebrated its 40th anniversary. Founded in 1969 by Hans Valkenburg, on the initiative of the first dean of the Erasmus Medical School, Andries Querido, the department has grown into one of the cornerstones of the Erasmus Medical Center. At a successful symposium at this occasion, speakers from inside and outside of epidemiology referred to the remarkable re-emergence of epidemiology among the medical research disciplines. Webcasts of their presentations can be viewed on www.erasmus-epidemiology.nl or www.nihes.nl.

As will be clear from this publication report, 2009 was the year in which the avalanche of major results from the genome-wide association studies has lead to major publications, generally as part of large international collaborations. In particular the work in the CHARGE consortium, in which the Rotterdam Study collaborates with colleagues from Framingham, CHS, ARIC and AGES, has been very gratifying.

In 2009, 15 PhD students successfully defended their thesis and brief summaries of their work can be found in this report.

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



Albert Hofman
Chair Department of Epidemiology



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■ Mendel D.M.Haag

NSAIDs and cardiovascular drugs in neurodegenerative and cerebrovascular diseases

(Co)promotores: Breteler, prof.dr. MMB, Stricker, prof.dr. BHC

13 February 2009



On the basis of previously proposed risk factors and current knowledge of pathogenesis, we investigated nonsteroidal anti-inflammatory drugs (NSAIDs) and cardiovascular medication as determinants of neurodegenerative and cerebrovascular disease and of potential imaging markers of these disorders. The studies presented in this thesis are based on the prospective population-based Rotterdam

Study in persons of >55 years, living in a suburb of Rotterdam, The Netherlands. We had detailed information on prescription drug use from local automated pharmacy records from 1991 onwards. Our main findings included a lower risk of Alzheimer disease (AD) with long-term use of amyloid-b₄₂ lowering NSAIDs. However, we found an increased risk of stroke and TIA with use of COX₂- and non-selective NSAIDs. For cardiovascular mediation we showed that the protective effect of statins on AD was observed irrespective of their lipophilicity and that antihypertensive drugs may reduce dementia risk and progression of WMLs in persons below 75 years. Finally, antithrombotic drug use was related to a higher prevalence of cerebral microbleeds.

■ **Fan Liu**

Methodological approaches to study the genetics of dementia and cognitive function

*(Co) promotores: Van Duijn, prof.dr. CM, Oostra, prof.dr. BA, Aulchenko, dr. YS
18 February 2009*



Alzheimer's disease (AD) is the primary cause of dementia in Western societies. The genetic origin of late onset AD and cognitive function is largely unknown. In this thesis we presents an efficient pedigree splitting algorithm and associated software that can facilitate genome-wide linkage analysis in large pedigrees. Based on this method we identified a novel locus on chromosome 3q23 that is linked to late onset AD in a genome-wide linkage study. In candidate gene studies, we show that the E4 allele of the APOE gene leads to reduced memory performance and increased risk of cardiovascular disease through independent pathways. We also show that the SORL1 gene is not associated with AD or cognitive function. We confirmed a recent finding that genetic variants in the GAB2 gene are associated with AD in carriers of the E4 allele of the APOE gene.

■ **Edwin H.G. Oei**

Magnetic resonance imaging for traumatic knee injury

(Co)promotores: Hunink, prof.dr. MGM, Ginai, dr. AZ

4 March 2009



This thesis describes various aspects of magnetic resonance imaging (MRI) for traumatic knee injury. In a systematic review of the literature, it was confirmed that MRI has high diagnostic accuracy and that it is not influenced by MRI field strength.

In a randomized clinical trial in the hospital emergency department (n=189) we found that short dedicated extremity MRI in all patients in the acute stage after knee trauma is

not useful for therapeutic decision making and not cost-effective compared to radiography. MRI is, however, potentially cost-effective from societal perspective if used selectively in patients without radiographic abnormalities. In another study in primary care (n=134), the initial MRI after knee trauma was compared with follow-up MRI after one year, showing that some meniscal lesions heal, but that deterioration is likely if there is an associated anterior cruciate ligament rupture. Bone marrow edema on initial MRI was a significant predictor of osteoarthritis.

■ **Meike Vernooij**

Imaging of age-related brain changes. A population-based approach

(Co)promotores: Breteler, prof. dr. MMB, Krestin, prof.dr. GP.

11 March 2009



Despite all research efforts on safety and efficacy of drugs, not every drug is safe and beneficial for every patient. In this thesis we explore the effect of interaction of common variants in the ABCB1 and NOS1AP genes with drugs on drug response and adverse effects of drugs.

We found that the ABCB1 1236-2677-3435 TTT-haplotype allele is associated with higher digoxin serum concentrations and with a two-fold increased risk of SCD in digoxin users. In a cohort of mefloquine users, the same haplotype allele increases the risk of neuro-psychiatric adverse events of mefloquine by 2.5 times.

Common variants in the NOS1AP gene are associated with an increased QTc-interval. Digoxin users carrying the NOS1AP minor allele showed increased QT-shortening to digoxin and an increased risk of SCD. Also, the minor allele was associated with increased QTc prolongation in users of triamterene or verapamil. Finally, the NOS1AP minor allele is associated with the glucose lowering effect of and risk of mortality to sulfonylurea.

■ **Mohammad Arfan Ikram**

Determinants and outcomes of structural brain changes

(Co)promotores: Breteler, prof.dr. MMB

25 March 2009



Arfan Ikram's research project focused on environmental and genetic determinants of clinical and subclinical neurological diseases. He used data from the Rotterdam Study, which has state-of-the-art MR imaging data as well as genome-wide genotyping data in a large subset of participants. In the first part of his thesis he investigated determinants of brain atrophy and cerebral small vessel disease on MRI. He found that vascular risk factors are strongly associated with especially white matter atrophy and cerebral small vessel disease. In the second part he showed that brain atrophy on MRI predicts dementia in a typical pattern that closely resembles pathologic studies. Moreover, brain atrophy and cerebral small vessel disease also affect risk of death, especially death due to a cardiovascular cause. Finally, in the last part he focused on neuro-genetics and investigated two novel genes in relation with stroke and dementia.

■ **Jan Heeringa**

Epidemiology of atrial fibrillation in the general population.

(Co)promotores: Witteman, prof.dr. JCM, Hofman, prof.dr. A

17 June 2009



The prevalence and incidence of atrial fibrillation, a common disease in the elderly, were measured in the population-based Rotterdam Study, resulting in the first West European figures in the general population on this disease that is characterized by an impaired quality of life and an increased morbidity and mortality. Jan Heeringa investigated further the associations of several new risk factors with atrial fibrillation. Subclinical

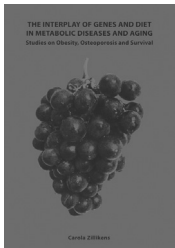
atherosclerosis, cigarette smoking and high-normal thyroid function were associated with risk of atrial fibrillation. Intake of very long-chain n-3 fatty acids was not associated with risk of atrial fibrillation. Atrial fibrillation is complicated by an increased risk of stroke. Therefore, markers of a prothrombotic state were measured in participants with atrial fibrillation and controls in sinus rhythm. No differences were found between the two groups with respect to the levels of markers of a prothrombotic state. Neither were levels of prothrombotic markers different between the two groups with respect to stroke outcome, mortality or cardiovascular mortality.

In this thesis heart failure, all-cause and cause-specific mortality and stroke were investigated as potential consequences of atrial fibrillation. Despite the considerable improvements in the treatment of cardiovascular diseases in the recent decades, atrial fibrillation in the general population is still associated with a 100% increased risk of heart failure, a 60% increased risk of all-cause mortality and a 200% increased risk of stroke.

■ **Carola Zillikens**

The interplay of genes and diet in metabolic diseases and aging. Studies on obesity, Osteoporosis and survival

*(Co) promotores: Uitterlinden, prof.dr. AG, Van Duijn, prof.dr. CM, Oostra, prof.dr. BA
7 October 2009*



In this thesis, epidemiological, genetic and nutritional studies are presented on the metabolic diseases obesity and osteoporosis, and on survival. In the epidemiological studies the relationship is investigated between body fat distribution and bone mineral density, and a relation is described between the intake of dietary B vitamins and bone mineral density and fractures. The genetic studies use two main approaches to disentangle the genetic background of these conditions, namely 1) a family-based design for the estimation of trait heritability, and 2) the association design with both the candidate gene and genome wide association (GWA) approach. In the heritability study evidence for the existence of sex-specific genetic effects on body composition is presented. Using the candidate gene approach we show how variants in the SIRT1 gene influence BMI, the risk of obesity and longitudinal BMI-changes. Within the context of large-scale collaborative genome-wide association studies we identified NRXN3 as a novel locus influencing waist circumference and 20 loci influencing BMD variation. Furthermore, results are described of investigations on gene-diet interactions on body mass index and survival at the SIRT1 locus.

■ **Matthijs Becker**

Individualizing pharmacotherapy. Genetic factors and co-prescribed drugs affecting pharmacotherapy

(Co) promotores: Stricker, prof.dr. BHCh, Vulto, prof.dr. AG, Visser, dr. LE

4 November 2009



Drug therapy may result in adverse drug reactions or in ineffective therapy. Adverse drug reactions are partly avoidable if we can predict which patients will not respond to drug therapy or will develop adverse drug reactions. In this thesis we studied the effect of drug-drug interactions and genetic variation. The response to drug therapy is better predictable if not only the individual factors are taken into account, but also the interaction between these factors. We identified, for example, genetic variation in two drug transporters associated with the response to the antidiabetic drug metformin. The predictability of the response to metformin increased substantially if also the interaction between both polymorphisms was included. Similarly, the effect of drug-drug interactions will partly be explained by genetic variation. Our results can be used to individualize pharmacotherapy and avoid adverse drug reactions and ineffective therapy. We emphasize the importance of interaction between factors.

■ **Stefania Boccia**

Genetic determinants of gastric cancer

(Co) promotores: Van Duijn, prof.dr. CM, Ricciardi, prof.dr. W

18 November 2009



Gastric cancer is the fourth most common cancer and the second most frequent cause of cancer deaths. Beside the major role of *Helicobacter pylori* in its aetiology, lifestyle habits, environmental risk factors and the genetic background might explain the individual variation in gastric cancer susceptibility. The objective of the work described in this thesis was dual: to investigate the association of candidate genes and gastric

cancer risk by selecting genes that, given their function, should have a high probability to be involved in gastric cancer;

to assess the cumulative evidence on the most extensively studied gene polymorphisms in association with gastric cancer risk through meta-analyses and pooled analysis of the scientific literature.

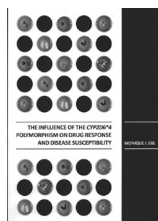
The study subjects were selected according to a case-control study design and enrolled in Rome (Università Cattolica del Sacro Cuore, Hospital "A. Gemelli").

Results show that gastric cancer risk is increased by the inheritance of the variant alleles of the metabolic genes *SULT1A1* and *CYP2E1* *6, *GSTT1* null variant, especially if combined with the *NAT2* slow acetylator status, and a combination of *p53* exon 4 and intron 6 variant alleles protects from gastric. Meta-analyses showed that the c2 variant allele of the phase I enzyme *CYP2E1**2 affect the risk of gastric cancer, especially by interacting with a key phase II enzyme as *GSTM1*, and that the phase II enzyme *GSTT1* confer an increased risk of gastric cancer if combined with *GSTM1* null. Pooled analysis confirmed the role of folate in gastric carcinogenesis, as individuals with the homozygous *MTHFR* C677T variant genotype are at increased risk of gastric cancer especially if carrying a low folate status.

■ Monique Bijl

The influence of the CYP2D6*4 polymorphism on drug response and disease susceptibility

(Co)promotores: Stricker, prof.dr. BHch, Vulto, prof.dr. AG, Visser, dr. LE, Van Gelder, dr. T
20 November 2009



Patients differ in their response to drugs. On average only 40% of all patients will benefit from a particular drug. Some patients will experience adverse drug reactions, while others will not. Although variability in drug response can be explained by age, gender, renal and liver function, underlying disease or drug interactions, genetic factors also contribute to differences in drug response. CYP2D6 is responsible for the metabolism

of approximately 25% of all drugs metabolized by the cytochrome P450 system. Approximately 5-10% of the Caucasian population completely lacks CYP2D6 enzyme activity, and is therefore at increased risk of suffering from adverse drug reactions or ineffectiveness.

Since cytochrome P450 enzymes metabolize not only drugs but also endogenous substances such as hormones, environmental chemicals and toxins, one might expect that variability in enzyme activity could result in an altered susceptibility to certain diseases.

Therefore, the aim of this thesis was to study the influence of genetic variation in the CYP2D6 gene on drug response and disease susceptibility from an epidemiological perspective. The studies described in this thesis are embedded in the Rotterdam Study, a population-based cohort study among 7983 inhabitants of Ommoord, a district in Rotterdam, aged 55 years or over.

Overall, we have provided in this thesis more evidence that pharmacogenetics could contribute to the quality and safety of pharmacotherapy. Pharmacogenetic testing should be part of overall quality improvement in healthcare for a number of drugs (e.g. tamoxifen). However, we should keep in mind that not all variation in drug response is explained by pharmacogenetics. Accurate interpretation of data is necessary and pharmacists could play a role in this.

■ **Carmelo Gabriele**

Respiratory morbidity and exhaled nitric oxide in the first 2 years of life. The Generation R Study

(Co)promotores: De Jongste, prof.dr. JC, Hofman, prof.dr. A

25 November 2009



Exhaled nitric oxide (FeNO) is a marker of eosinophilic bronchial inflammation in asthma. To date no standardized method to measure FeNO in infants is available.

In the current thesis, we showed that the measurement of exhaled nitric oxide (FeNO) in infants is feasible and highly reproducible. We also found that smoke exposure was associated with FeNO values, with an effect dependent on the

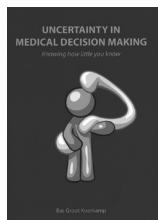
timing and intensity of the exposure. Also, we showed that FeNO measurements with uncontrolled flow could differentiate infants with various airway diseases. The occurrence and the severity of respiratory symptoms were associated with FeNO, suggesting that FeNO could be a useful marker of eosinophilic bronchial inflammation in infants at increased risk of developing asthma. Furthermore, we evaluated the prevalence of respiratory symptoms in ethnically different infants living in the same urban area and we found that, compared to Dutch, Antillean and Turkish infants had increased risk of lower respiratory symptoms, whereas Moroccan ethnicity was associated with reduced risk of lower respiratory symptoms during the first 2 years of life.

■ **Bas Groot Koerkamp**

Uncertainty in medical decision making. Knowing how little you know

(Co)promotores: Hunink, prof.dr. MGM, Stijnen, prof.dr. T, Weinstein, prof.dr. MC

1 December 2009



Making decisions about the care of individual patients is fundamental to health care. In daily practice, most medical decisions are based on experience and judgment. Medical decision making was developed because of concerns about human judgment, practice variation, and the proliferation of diagnostic and treatment options. The aim of medical decision making is to perform a complete formal assessment of every aspect that is relevant for a decision. This assessment includes patient preferences, rare events, and health care costs, all of which are typically ignored within the evidence-based medicine framework. Considerable uncertainty about the optimal intervention typically remains after evaluating all available evidence. However, a decision between the interventions has to be made, regardless of the extent of uncertainty. Evaluation of uncertainty is particularly relevant to determine whether more quantitative research is justified. A future study could reduce decision uncertainty which is expected to benefit future patients, reduce health care costs, or both. Value of information (VOI) analysis was introduced to estimate the expected benefit of a future study. Moreover, VOI analysis can guide the design of a study by identifying key parameters as well as the optimal sample size. This dissertation concerns the analysis and presentation of uncertainty in medical decision making with a focus on VOI analysis.

■ Miranda Geelhoed

Early influences on cardiovascular and renal development. The Generation R Study
(Co)promotores: Hofman, prof.dr. A, Van der Heijden, prof.dr. AJ, Jaddoe, dr. VWV.
11 december 2009



Many lines of evidence indicate an important role of early life events in influencing later susceptibility to cardiovascular disease. Adverse environmental exposures in fetal and early postnatal life lead to adaptations that permanently program the fetus' structure, physiology and metabolism, leading to both low birth weight and cardiovascular disease in adulthood.

We designed a prospective cohort study from early fetal life until the age of two years to identify mechanisms underlying the associations between low birth weight and cardiovascular disease. Main interest was in cardiovascular and renal development. We concluded that genetic variations in the IGF1 gene, INS VNTR gene and the glucocorticoid receptor gene may be involved in growth and development in early life.

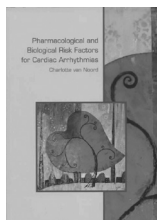
Our findings suggest that maternal smoking during pregnancy affects kidney development in fetal life. Furthermore, fetal arterial resistance adaptations may be involved in the pathways leading from maternal smoking during pregnancy to both low birth weight and cardiovascular developmental changes in childhood in the offspring. Maternal height and pre-pregnancy weight were positively associated with kidney volume at the age of 2 years. In addition, small size at birth and haemodynamic variations in fetal life, including resistance indices of the umbilical and uterine arteries and cardiac output, have consequences for postnatal cardiac size and function. Finally, maternal weight gain until late pregnancy was associated with an increased growth of left ventricular mass from 6 weeks to 6 months, suggesting that maternal health status during pregnancy may have permanent consequences for left ventricular mass in their children.

■ **Charlotte van Noord**

Pharmacological and biological risk factors for cardiac arrhythmias

(Co)promotores: Stricker, prof.dr. BHCh, Witteman, prof.dr. JCM, Sturkenboom, prof.dr. MCJM, Straus, dr. SMJM.

11 december 2009



Sudden death is among the most common causes of death in developed countries. The majority of sudden cardiac deaths (SCD) are caused by acute ventricular arrhythmia. This thesis focused on the effect of certain drugs and endocrine factors on SCD.

We demonstrated that current use of non-cardiovascular hERG (human ether a go-go related gene)-encoded potassium channels inhibiting drugs is associated with an increased risk of SCD. In addition, we demonstrated that drugs with a high hERG-channels inhibiting capacity had a higher risk of SCD than patients using drugs with a low potassium channels inhibiting capacity.

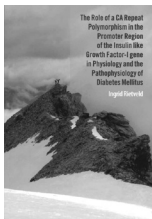
Furthermore, we showed that high levels of thyroid hormones are associated with repolarization disturbances. In addition, we demonstrated in two independent studies that use of antithyroid drugs was associated with a threefold increased risk of SCD. Although this might be due to antithyroid drug use itself, it could be more readily explained by underlying hyperthyroidism, since increased thyroid hormone levels are associated with repolarization disturbances and treated patients who developed SCD still had low TSH levels shortly before death. This suggests that hyperthyroidism may be a risk factor for SCD.

■ Ingrid Rietveld

The role of a CA repeat polymorphism in the promotor region of the insulin like growth factor-I gene in physiology and the pathophysiology of diabetes mellitus

(Co)promotores: Lamberts, prof.dr. SWJ, Van Duijn, prof.dr. CM, Janssen, dr. JAMJL.

16 december 2009



Insulin like growth factor-1 (IGF-I) is a polypeptide which most important function is mediating physiological growth. A CAn polymorphism in the promoter region of the IGF-I gene has been identified, varying between 10 and 24 CA repeats. In the Caucasian population, the most common allele comprises 19 CA repeats. In this thesis, we investigated the role of this CAn polymorphism on physiologic endpoints, but also its relation with diabetes mellitus type 2 and its complications. The well known inverse relation between age and total IGF-I levels and IGFBP3 levels was only observed in homozygous carriers of the CA19 allele, suggesting that the expression of this polymorphism is GH dependent. In another study we studied the relation between the number of alleles and IGF-I levels and body height. Homozygous carriers of the CA20 alleles had similar IGF-I serum levels and equal body height as homozygous carriers of the CA19 allele. A clear optimum was observed for these genotypes in IGF-I serum levels and body height.

Hereafter, we studied the relation between the CAn polymorphism and insulin sensitivity and beta cell function. Persons who were non-carriers of the CA19 and CA20 alleles had a diminished beta cell function and were more at risk to develop diabetes mellitus. Furthermore, non-carriers of the CA19 and CA20 alleles had an increased risk of incident diabetic retinopathy and were more susceptible to the progression of retinopathy. Finally, these non-carriers had a higher risk of micro-albuminuria and survival was worse after myocardial infarction.



Epidemiology of diseases

Main participants

Monique Breteler

Albert Hofman

Henning Tiemeier

Hans Vingerling

Jacqueline Witteman

General objectives

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

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

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

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

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

Keywords

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



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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.



Publications first author

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.



Publications first author

International scientific publications

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Department of Biostatistics

Publications first author

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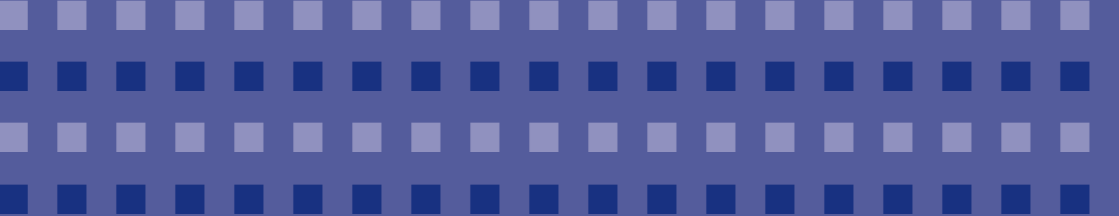
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