

The Rotterdam Study: 2012 objectives and design update

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Abstract The Rotterdam Study is a prospective cohort study ongoing since 1990 in the city of Rotterdam in The Netherlands. The study targets cardiovascular, endocrine, hepatic, neurological, ophthalmic, psychiatric, dermatological, oncological, and respiratory diseases. As of 2008, 14,926 subjects aged 45 years or over comprise the Rotterdam Study cohort. The findings of the Rotterdam Study have been presented in over a 1,000 research articles and reports (see www.erasmus-epidemiology.nl/rotterdamstudy). This article gives the rationale of the study and its design. It also presents a summary of the major findings and an update of the objectives and methods.

Keywords Biomarkers · Cardiovascular diseases · Cohort study · Dermatological diseases · Endocrine diseases · Epidemiologic methods · Genetic epidemiology · Liver diseases · Neurological diseases · Oncology · Ophthalmic diseases · Pharmacoepidemiology · Renal diseases · Psychiatric diseases · Respiratory diseases

Introduction

The Rotterdam Study was designed in the mid-1980s as a response to the demographic changes that were leading to an increase of the proportion of elderly people in most populations [1]. It was clear that this would produce a

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strong rise in elderly people living with diseases, as most diseases cluster at the end of life, and that to discover the causes of diseases in the elderly one would have to study risk factors of those diseases [2]. A major approach to finding causes is the prospective follow-up study, which has proven quite effective in finding causes of heart disease and cancer.

The design of the Rotterdam Study

The design of the Rotterdam Study is that of a prospective cohort study among, initially, 7,983 persons living in the well-defined Ommoord district in the city of Rotterdam in The Netherlands (78% of 10,215 invitees). They were all 55 years of age or over and the oldest participant at the start was 106 years [3]. The study started with a pilot phase in the second half of 1989. From January 1990 onwards participants were recruited for the Rotterdam Study.

Figure 1 gives a diagram of the various cycles in the study. In 2000, 3,011 participants (out of 4,472 invitees) who had become 55 years of age or moved into the study district since the start of the study were added to the cohort. In 2006, a further extension of the cohort was initiated in which 3,932 subjects were included, aged 45–54 years, out of 6,057 invited, living in the Ommoord district. By the end of 2008, the Rotterdam Study therefore comprised 14,926 subjects aged 45 years or over [4, 5]. The overall response figure for all three cycles at baseline was 72.0% (14,926 of 20,744).

The participants were all examined in some detail at baseline. They were interviewed at home (2 h) and then had an extensive set of examinations (a total of 5 h) in a specially built research facility in the centre of their district. These examinations focussed on possible causes of invalidating diseases in the elderly in a clinically state-of-the-art manner, as far as the circumstances allowed. The emphasis was put on imaging (of heart, blood vessels, eyes,

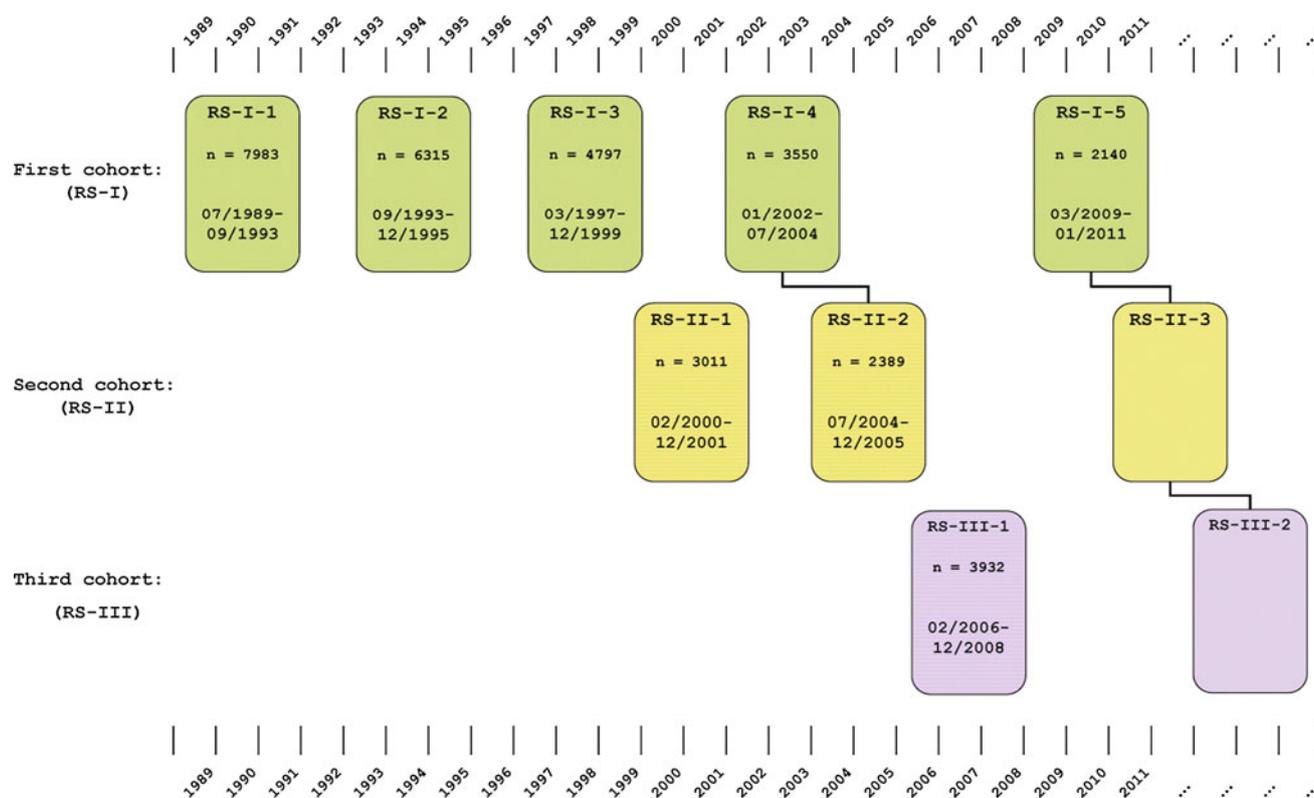


Fig. 1 Diagram of examination cycles of the Rotterdam Study (RS). RS-I-1 refers to the baseline examination of the original cohort (pilot phase 07/1989–12/1989; cohort recruitment 01/1990–09/1993). RS-I-2, RS-I-3, RS-I-4, and RS-I-5 refer to re-examination of the original cohort members. RS-II-1 refers to the extension of the cohort with persons in the study district that became 55 years since the start of the study or those of 55 years or over that migrated into the study district. RS-II-2 refers to re-examination of the extension cohort. RS-III-1

refers to the baseline examination of all persons aged 45 years and over living in the study district that had not been examined (i.e., mainly comprising those aged 45–60 years). RS-II-3 and RS-III-2 refer to ongoing and future re-examinations. Examination RS-I-4 and RS-II-2 were conducted as one project and feature an identical research program. Similarly, examinations RS-I-5, RS-II-3, and RS-III-2 will share the same project items

skeleton and later brain) and on collecting bodily fluids that enabled further in-depth molecular and genetic analyses. These examinations were repeated every 3–4 years in characteristics that could change over time. And so there were examination cycles from 1990 to 1993, from 1993 to 1995, from 1997 to 1999, from 2000 to 2001, from 2002 to 2004, from 2004 to 2005, from 2006 to 2008, and from 2009 to January 2011 (Fig. 1). In February 2011 the third examination cycle for the second cohort (RS-II-3) was started.

The participants in the Rotterdam Study are followed for a variety of diseases that are frequent in the elderly (and many are also in the not so elderly): coronary heart disease, heart failure and stroke, Parkinson disease, Alzheimer disease and other dementias, depression and anxiety disorders, macular degeneration and glaucoma, respiratory diseases, liver diseases, diabetes mellitus, osteoporosis, dermatological diseases and cancer. The Rotterdam Study has been approved by the institutional review board (Medical Ethics Committee) of the Erasmus Medical Center and by the review board of The Netherlands Ministry of Health, Welfare and Sports. The approval has been renewed every 5 years, as well as with the introduction of major new elements in the study (e.g., MRI investigations).

In the remainder of this article the objectives and major findings will be presented with an update of the research methods for cardiovascular diseases, dermatological diseases, endocrine diseases, liver diseases, neurological diseases, ophthalmic diseases, psychiatric diseases, respiratory diseases, as well as for genetic and biomarker studies and for pharmaco-epidemiologic studies. For relevant recent EJE references see [6–32].

Cardiovascular diseases

Objectives

Research on the epidemiology of cardiovascular disease focuses on the etiology and prediction of coronary heart disease and on cardiovascular conditions at older age, like heart failure and atrial fibrillation. Putative risk factors include three groups, endocrine factors, factors involved in hemostasis, inflammation and endothelial function, and genetic risk factors. A major focus is on non-invasive assessment of atherosclerosis to improve prediction of coronary heart disease, including measurement of coronary calcium with electron-beam and multi-detection CT and carotid plaque characterization by high-resolution MRI. Cerebrovascular diseases, including stroke, are also investigated in the Rotterdam Study. They are described under Neurological diseases.

Major findings

Recognized and unrecognized myocardial infarction

We found that a high proportion of incident myocardial infarctions remains clinically unrecognized. The incidence rate of recognized myocardial infarction in the Rotterdam Study was 5.0 per 1,000 person years. The incidence was higher in men (8.4) than in women (3.1). The incidence rate of unrecognized infarction was 3.8 per 1,000 person years. Men (4.2) and women (3.6) had approximately similar incidence. Hence, the proportion of unrecognized infarction is lower in men (33%) than in women (54%) [33].

Cardiovascular risk factors

Endocrine, inflammatory and hemostatic factors and risk of coronary heart disease were addressed in several studies. Subclinical hypothyroidism was an independent risk factor of atherosclerosis and myocardial infarction in older women [34]. Recently, we showed that amino-terminal pro-B-type natriuretic peptide (NT-ProBNP) improved cardiovascular and cerebrovascular risk prediction in an older population [35]. Plasma C-Reactive protein (CRP) and lipoprotein-associated phospholipase A2 (Lp-PLA2) activity were independent predictors of coronary heart disease [36, 37]. Early findings included the association of tissue plasminogen activator (TPA) with incident coronary heart disease [38].

Non-invasive measures of atherosclerosis

Multiple studies focused on the predictive value of non-invasive measures of atherosclerosis for risk of coronary heart disease. Strong associations with risk of coronary heart disease were found for carotid intima-media thickness [39], pulse wave velocity [40], and coronary calcification as assessed by electron-beam CT [41]. The relatively crude measures directly assessing plaques in the carotid artery and abdominal aorta predict coronary heart disease equally well as the more precisely measured carotid intima-media thickness [42]. In subjects at intermediate risk of cardiovascular disease, coronary calcium scoring proved to be a powerful method to reclassify persons into more appropriate risk categories [43].

Genetic studies

Genetic studies included candidate gene studies [44] and more recently genome-wide association studies of clinical disease and risk factor phenotypes. Genome-wide association studies are primarily conducted in the context of the

Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium [45] of which major findings are reported here. We identified 3 genetic loci associated with uric acid concentration and gout [46]. We also identified a significant association between chronic kidney disease and the UMOD gene which encodes Tamm-Horsfall protein [47]. In the same consortium, we found four genes for systolic blood pressure, six for diastolic blood pressure and one for hypertension [48]. We found multiple loci that influenced erythrocyte phenotypes in the CHARGE Consortium [49]. Recently, we identified 18 loci for CRP levels in a meta-analysis in more than 80,000 individuals from 25 studies. The study highlighted immune response and metabolic regulatory pathways involved in the regulation of chronic inflammation [50]. Novel associations of multiple genetic loci with plasma levels of factor VII, factor VIII, and von Willebrand factor were also detected [51].

Heart failure and atrial fibrillation

The Rotterdam Study enabled accurate assessment of the incidence and lifetime risk of heart failure and atrial fibrillation in an elderly population [52, 53]. It was shown that inflammation is associated with risk of heart failure [54]. Subclinical atherosclerosis, cigarette smoking and high-normal thyroid function were identified as new risk factors of atrial fibrillation [55–57]. In a large collaborative study as part of the CHARGE consortium, we investigated the genetic variation responsible for 6 traits related to cardiac structure and function. We found two replicated loci for left ventricular dimension and 5 replicated loci for aortic root size [58]. Another topic of interest was the search for genetic determinants of several rhythm and conduction disturbances on the ECG, notably RR-interval, QRS, and QT(c) interval, as well as PR-interval and atrial fibrillation, and sudden cardiac death. For example, we identified several new loci for PR interval [59] and a new gene (ZFHX3) associated with atrial fibrillation [60] in a meta-analysis of studies of the CHARGE consortium.

Methods update

Cardiovascular risk factors

Three groups of putative risk factors for cardiovascular conditions are examined. The first are endocrine factors, including diabetes, sex hormones, thyroid gland and adrenal gland hormones and natriuretic peptides (e.g. [34, 35, 61]). The second group comprises factors involved in hemostasis, inflammation and endothelial function (e.g. [36–38]). The third group, and currently a major focus, covers genetic factors in these areas. In addition to the

candidate gene approach, studies are more recently conducted through the genome-wide association approach (e.g. [46–51]). In genome-wide association studies, data from the Rotterdam Study are often combined with those from other studies in the context of the large collaborative CHARGE consortium [45].

Non-invasive measures of atherosclerosis

At baseline and follow-up examinations, ultrasonographic assessments of carotid intima-media thickness and carotid plaques were conducted in all subjects [39]. At these examinations, also measurements of the ankle-brachial index and aortic calcification (on X-rays of the lumbar spine) were performed [42]. Carotid-femoral pulse wave velocity, a measure of aortic stiffness, was measured in all subjects of RS-I-3 and RS-II-1 with an automatic device (CompliorArtech Medica) [40]. Measurements of coronary calcification by electron-beam CT and more recently by multi-detector CT (MDCT) were conducted from 1997 onwards in RS-I and RS-II [41, 43]. From 2003 to 2006, MDCT was also used to quantify calcification in the aortic arch and carotid arteries in RS-I and RS-II. Measurement of carotid plaque components with high-resolution MRI started in October 2007 and will be continued until performance is completed in all subjects with carotid wall thickening from RS-I, RS-II and RS-III.

Electrocardiographic, echocardiographic and other ultrasound measurements

At every exam, 12-lead resting ECGs are made and processed by the Modular ECG Analysis System (MEANS) to obtain a series of ECG measurements [62]. Abdominal aortic diameters were measured by ultrasound at baseline. From 2002 onwards (RS-I-4), repeated ultrasonographic measurements are conducted of structural and functional parameters of the left ventricle and atrium [63]. From 2009 (RS-I-5), measurements of structure and function of the right side of the heart are also performed to diagnose subclinical pulmonary hypertension.

Clinical follow-up

Data on clinical cardiovascular outcomes are collected through an automated follow-up system. The follow-up system involves linkage of the study base to files from general practitioners in the study area and subsequent collection of information from letters of medical specialists and discharge reports in case of hospitalisation. With respect to the vital status of participants, information is also obtained regularly from the municipal health authorities in Rotterdam. After notification, cause and circumstances

of death are established by questionnaire from the general practitioners. Clinical cardiovascular outcomes are coded by study physicians and medical experts in the field according to the International Classification of Diseases, 10th edition (ICD-10). Incident coronary heart disease is defined as the occurrence of a fatal or nonfatal myocardial infarction (I21), other forms of acute (I24) or chronic ischemic (I25) heart disease, sudden (cardiac) death (I46 and R96), death caused by ventricular fibrillation (I49), or death resulting from congestive heart failure (I50) during follow-up [37]. Other outcomes include heart failure [52] and atrial fibrillation [53]. For additional EJE references concerning cardiovascular disease see [64–111].

Dermatological diseases

Objectives

Dermatoepidemiologic research in the Rotterdam Study focuses on the frequency of the most common skin conditions as well as on genetic and environmental factors associated with these skin diseases. The emphasis of the skin component is on cutaneous malignancies such as basal and squamous cell carcinomas (BCC and SCC, respectively) and their precursor lesions, and inflammatory dermatoses such as eczema and psoriasis. In addition to skin diseases, we examine the contribution of genetics and environmental exposures to the skin phenotype (e.g., skin pigmentation, wrinkling and photodamage) of the cohort members.

Methods

In 2010, dermatology was introduced in the Rotterdam Study. To the home interview several items have been added questioning ultraviolet light exposure, history of (personal and familial) psoriasis, history of skin cancer, the diagnostic criteria of British association of dermatology for atopic eczema, adjusted diagnostic criteria for psoriatic arthritis.

A full body skin examination by physicians trained in dermatology with a focus on the most common skin diseases is the core contribution of dermatology. The clinical presence and extent of specific skin diseases (i.e., actinic keratosis, malignancies, psoriasis, xerosis, hand and flexural eczema, alopecia, and signs of chronic venous insufficiency based on the ‘C’ of the CEAP classification) at time of examination is assessed in a standardized fashion. Other dermatological diseases will just be noted.

The extent of facial photodamage and wrinkling are scored using a validated photonumeric scale and the Glogau

scale, respectively. The Norwood-Hamilton classification and the Ludwig classification is used for male and female pattern hair loss, respectively. Fully standardized 3-dimensional photographs (Premier 3dMDface3-plus UHD, Atlanta, USA) of the face are taken to further assess skin characteristics. The pigmentation of the facial skin and at the inner side of the upper arm are measured using a spectrophotometer (Konica Minolta Sensing, spectrophotometer CM-700d, Singapore). In a subgroup of the cohort, skin topography measures will be taken at the inner side of the upper arm as well.

As for other cancers, pathology data of the cutaneous malignancies is obtained from a network of pathology laboratories in Rotterdam and its surroundings and the Dutch pathology database (PALGA). In a further attempt to identify cohort members with psoriasis, medical files and dispenses at pharmacies will be studied.

Major findings

The prevalence of single and multiple BCC was studied in the Rotterdam Study and showed that a total of 524 patients (4.8% of included population) had developed this type of keratinocytic cancer and that 31.1% had developed more than one tumor during observation [112]. A multi-failure survival model suggested that people with red hair and higher levels of education, and those who had their first BCC at younger age were significantly more likely to develop multiple malignancies. In a candidate gene approach, Vitamin D-binding protein (VDBP) genotype was not associated with (multiple) BCC development, except possibly in the youngest age-group (A/T variant of rs7041 was associated with; adjusted HR = 1.88, 95% CI 1.10–3.20), whereas homozygote Gc1s carriers had a significantly lower BCC risk; adjusted HR = 0.53, 95% CI 0.31–0.91) [113].

In a pharmaco-epidemiologic study, the hypothesis that (prior) exposure to drugs such as high-ceiling diuretics increase skin cancer risk due to enhanced photosensitivity of the skin was tested. In line with the hypothesis, use of potassium sparing and thiazide agents were not and use of high-ceiling diuretics was associated with an increased hazard of BCC (highest quartile compared to non users; HR 1.6, 95% CI 1.1–2.4).

Endocrine diseases

Objectives

The main objective of the programme of endocrine epidemiology research is to study frequency and etiology of

major disorders of the endocrine glands (pituitary, reproductive, thyroid, parathyroid, adrenal, and neuro-endocrine pancreas) and the musculoskeletal system. These include endocrine and locomotor diseases, including diabetes mellitus, osteoporosis, osteoarthritis, growth-hormone deficiency, hypo- and hyper-thyroidism and parathyroidism. The evaluation of risk factors for the above mentioned conditions includes serum measurements (such as classical hormones and other endocrine molecules) and genetic determinants of endocrine factors and signalling pathways.

Major findings

We have provided epidemiological documentation on the hormone, growth factor and biomarker profiles in the general population and determined the association with several diseases. Within the topics of locomotor diseases and disability we have reported that heart failure, COPD, diabetes mellitus and chronic disorders leading to locomotor complaints, are risk factors which contribute considerably to locomotor disability [114, 115]. In relation to osteoporosis we have determined the incidence of vertebral [116] and non-vertebral fractures [117], and the relationship between bone mineral density (BMD), BMD change and the occurrence of fracture [117], as well as with heel ultrasound measurements [118] and bone resorption markers [119]. We have also studied the relation between endogenous sex hormones and their binding factors, with fractures [120], and showed that increased homocysteine levels are a strong and independent risk factor for osteoporotic fractures [121]. We studied the relations between osteoporosis and other chronic diseases like osteoarthritis [122], cancer [123], atherosclerosis [124] and diabetes [125, 126], and provided indications for the treatment and diagnosis of osteoporosis. Lastly, we were part of several large consortia studying epidemiological risk factors for osteoporosis [127–129]. For osteoarthritis (OA) we have shown how a new marker of disease (CTX-II), is associated with the prevalence and the progression of radiographic OA [130], independent of known clinical risk factors. In addition, we have studied different aspects of OA disease definition and classification [131], evaluation of disease progression [132] and determined the most prominent risk factors leading to OA [133, 134]. We have also studied inflammatory aspects of endocrine diseases like diabetes mellitus [135], and the relations of hypo/hyperthyroidism to cardiovascular and neurological disease [136]. We further examined the influence of genetic variation in endocrine genes influencing hormone levels [137, 138], interaction of genetic factors in relation to fracture risk [138, 139], to cardiovascular risk factors [140] and to neurological conditions [141]. Our team has played a

leading role in bringing together the global GENOMOS consortium which has performed prospective meta-analyses across many epidemiological cohorts for the most prominent candidate genes for osteoporosis (see also “[Genetic and biomarker studies](#)”).

Methods update

For all participants DXA-based BMD measurements of the lumbar spine, dual hip and total body BMD, as well as determination of body composition parameters are assessed with a Prodigy™ total body fan-beam densitometer (GE Lunar Corp, Madison, WI, USA). Hip structural analysis [142] of DXA scans is available in a subset of participants, while hip strength indexes (software by GE Lunar) are determined for all scans. In the current follow-up cycle we have introduced since 2009 iDXA measurements (GE Lunar) which performs lumbar spine, dual hip and total body scans. Measurements include L1–L4 BMD, bilateral total hip and femoral neck BMD and total body BMD. From the total body scan, we measure lean mass and fat mass body composition, including total body, trunk, arm, legs, and android and gynoid regions of interest. X-ray examinations of vertebral bodies, hips, knees and hand/wrist are obtained by a digitalized Fuji FCR system (FUJIFILM Medical Systems) and assessed for the presence of fractures and/or degenerative changes of the joints. Vertebral fractures are assessed using the qualitative algorithm-based technique termed the ABQ method, an update to the quantitative McCloskey–Kanis method [143]. Incident clinical fractures are obtained from computerized records of the general practitioners and hospital registries which are regularly checked by research physicians who review and code the fracture information. Muscle strength is assessed in all participants with a hand grip dynamometer. The incidence and progression of OA is done using Kellgren scores obtained from X-rays of hip, knee, hands, en spine. The complete set of X-rays is also available in digitized form. Novel diagnostic assessments for OA are currently underway using Magnetic Resonance Imaging (MRI) on a large subset of the population. Several specific biomarker assessments in blood/serum/plasma and urine are done for the diagnosis and evaluation of risk factors of endocrine and metabolic diseases. Candidate gene and genome-wide association studies (GWAs) are actively pursued within the scope of our research for many of the above mentioned endocrine and locomotor traits and diseases. Finally, validated questionnaires evaluating nutrient intake (e.g., calcium and vitamins) and activities of daily living, allow to evaluate the role of environmental factors in endocrine conditions and locomotor diseases of the elderly. For recent references in EJE see [144–172].

Liver diseases

Objectives

Fibrogenesis of the liver is most probably not only the result of well known liver diseases, such as viral hepatitis, alcoholic liver disease or non-alcoholic fatty liver disease (NAFLD), but rather a complex interaction between a genetic predisposition and these liver disorders. Liver research in the Rotterdam Study will concern the association between these known causes of liver disease and the occurrence, magnitude, and progression of fibrosis in combination with genetic and environmental factors. Additional research focus will be on NAFLD. NAFLD is considered the hepatic manifestation of the metabolic syndrome and has become the most common chronic liver disease in Western countries in parallel with epidemics of obesity and type II diabetes mellitus. We aim to study the occurrence and risk factors of NAFLD in a general population and generate insight into the association with cardiovascular morbidity and mortality.

Methods

Abdominal ultrasound

From February 2009 trained technicians perform abdominal ultrasonography in Rotterdam Study participants. Liver, biliary tract, gall bladder, spleen, pancreas, and kidneys in combination with Doppler examination of hepatic veins, hepatic artery and portal vein will be evaluated. All images are stored digitally and will be reevaluated by an ultrasound trained physician.

Assessment of steatosis The diagnosis and grading of liver steatosis will be based on ultrasonographic liver brightness, hepatorenal echo contrast, deep attenuation and vessel blurring [173].

Non alcoholic fatty liver is diagnosed by presence of steatosis on ultrasound and exclusion of excessive alcohol consumption, presence of viral hepatitis, use of fatty liver inducing pharmacological agents, recent bariatric surgery and a history of inflammatory bowel disease.

Assessment of fibrosis Ultrasonographic evaluation of the liver parenchyma and liver surface will be performed in order to assess severe fibrosis and/or cirrhosis. Additionally, sonographic signs of portal hypertension will be studied (splenomegaly, venous collaterals, portal vein diameter and flow, hepatic venous flow, and the presence of ascites).

To assess and quantify the grade of fibrosis trained technicians will perform elastography in all participants. This test measures non-invasively and quantitatively the liver stiffness using a probe which includes an ultrasonic transducer transmitting a vibration wave through the liver. The velocity of the ultrasonic wave correlates directly with tissue stiffness [174, 175].

Determinants of interest

The association between factors known to influence liver function and the occurrence of steatosis and fibrosis will be studied. Additionally the association of these conditions with age, gender, nutritional intake, concurrent alcohol intake, risk factors for viral hepatitis, BMI, waist-to-hip ratio, serum glucose, insulin, and diabetes mellitus, serum cholesterol and triglycerides will be studied. All clinical information will be obtained by interview (updated with liver specific questions) and clinical examination. For recent EJE references see [176–183].

Neurological diseases

Objectives

Neuroepidemiologic research in the Rotterdam Study focuses on the frequency, etiology and early recognition of the most frequent neurologic diseases in the elderly, including dementia, in particular Alzheimer disease, Parkinson disease and stroke. In neurodegenerative and cerebrovascular disorders clinical symptoms typically become manifest late in the disease course, the occurrence of clinical disease does not reflect the underlying spectrum of disease-related pathology, and most of the clinical syndromes are etiologically heterogeneous. Therefore, an additional research focus is on the causes and consequences of pre-symptomatic brain pathology that can be assessed with non-invasive modalities, which include MR-imaging, neuropsychological testing and more recently gait assessment.

Major findings

Neurodegenerative and cerebrovascular diseases are highly frequent in the elderly. The prevalence increases from age 55 to 65 years to age 90 years and above from less than 1% to over 40% for dementia [184], from less than 0.5% to more than 4% for Parkinson disease [185], and from approximately 1% to nearly 10% for stroke [186]. The incidence figures follow this pattern of a strong increase with age over the entire age range, with the age-specific

incidence of dementia being identical for men and women at least until the age of 85 [187] but with men having a higher age-specific incidence of both stroke and Parkinson disease than women throughout the age range [186, 188].

Vascular pathology and vascular risk factors are associated with worse cognitive performance [189], which also translates in people with vascular pathology or risk factors for vascular disease having an increased risk of dementia, including Alzheimer disease [190]. Moreover, several life style factors are associated with the risk of dementia and Alzheimer disease [191–193], suggesting that onset of dementia may at least partly be delayed or prevented. Commonly used drugs may have a role in this [194]. Similar risk factor profiles also underlie cognitive decline prior to the clinical diagnosis of dementia [195, 196].

The classical risk factors for stroke also predict risk of stroke in the Rotterdam Study [197]. Novel risk factors, including inflammatory markers, may be etiologically relevant but thus far add little to the identification of people at risk <http://www.ncbi.nlm.nih.gov/pubmed/17015791> [198]. Possibly underlying this is that a large amount of stroke goes clinically undetected [199]. Nearly 20% of elderly people have at least one silent brain infarct, and thereby a nearly fourfold increased risk of clinical stroke, a more than doubled risk of dementia including Alzheimer disease, and an increased risk of depression [199].

With the advent of genome-wide association studies, the Rotterdam Study has contributed to large-scale collaborations and contributed to the identification of novel genes underlying the risk of Alzheimer disease and stroke [200, 201].

Neuroimaging reveals that brain pathology is widespread [202] and can go clinically undetected for a long time. In addition to the silent infarcts, many apparently healthy elderly have ischemic changes in their cerebral white matter, i.e. white matter lesions, that are associated with an increased risk of dementia, stroke and depression. Also brain atrophy, especially of the hippocampus, is already present years before onset of even the earliest sign of cognitive impairment or subjective complaints. This emphasizes the need to shift the attention in etiologic research of neurodegenerative and cerebrovascular disease to the causes of pre-symptomatic and underlying brain changes. Technological advances in image acquisition, optimized imaging sequences and automated post-processing of multispectral MR data are major drivers of the rapid developments in this field. With our current imaging protocol we can now not only investigate established markers of brain pathology, such as infarcts, white matter lesions, and atrophy, but also extend towards novel markers, such as cerebral microbleeds and diffusion tensor imaging (see further section on “Population imaging”).

Methods update

Assessment of dementia and Alzheimer disease

In the baseline and follow-up examinations participants undergo an initial screen for dementia with the Mini Mental State Examination (MMSE) and the Geriatric Mental Schedule (GMS), followed by an examination and informant interview with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) in screenpositives (MMSE < 26 or GMS > 0), and subsequent neurological, neuropsychological and neuroimaging examinations [184, 187]. Of subjects who cannot be reexamined in person, information is obtained from the GPs and the regional institute for outpatient mental health care. A consensus panel makes the final diagnoses in accordance with standard criteria (DSM-III-R criteria; NINCDS-ADRDA; NINDS-AIREN).

Assessment of Parkinsonism and Parkinson disease

Participants are screened in the baseline and follow-up examinations for cardinal signs of Parkinsonism (resting tremor, rigidity, bradykinesia, or impaired postural reflexes). Persons with at least one sign present are examined with the Unified Parkinson’s Disease Rating Scale and a further neurologic exam. PD is diagnosed if two or more cardinal signs are present in a subject not taking antiparkinsonian drugs, or if at least one sign has improved through medication, and when all causes of secondary Parkinsonism (dementia, use of neuroleptics, cerebrovascular disease, multiple system atrophy, or progressive supranuclear palsy) can be excluded [185, 188].

Assessment of stroke and stroke subtypes

History of stroke at baseline was assessed through interview and verified in medical records. Putative incident strokes get identified through the linkage of the study database with files from general practitioners, the municipality, and nursing home physicians’ files, after which additional information (including brain imaging) is collected from hospital records. A panel discusses all potential strokes and subclassifies strokes into ischemic, hemorrhagic or unspecified [186, 198].

Assessment of cognitive function and motor function

Global cognitive function is measured through the Mini Mental State Examination (MMSE) in all surveys. From the third survey (RS-I-3) onwards we added a 30 min test battery that was designed to assess executive function and memory function, and which includes a Stroop test, a

Letter Digit Substitution Task, a Word Fluency Test, and a 15 words Word List Learning test. This test battery was expanded from the fourth survey onwards (RS-I-4) to include motor function assessment using the Purdue Peg-board Test. Moreover, from 2009 onwards we expanded further by including the Design Orientation Test (DOT) and a modified version of the International Cooperative Ataxia Rating Scale (ICARS), which assess visuo-spatial orientation and ataxia respectively [203, 204]. Halfway through RS-III-1, we successfully implemented the assessment of gait in all participants using the GAITRite walkway (<http://www.gaitrite.com/>).

Rotterdam Scan Study: brain imaging within the Rotterdam Study

In 1991, a random sample of 111 participants underwent axial T2-weighted magnetic resonance (MR) imaging to assess presence and severity of white matter lesions [205]. In 1995, a random sample of 563 non-demented participants underwent brain MR imaging in the context of the Rotterdam Scan Study. From August 2005 onwards (RS-II-2 and further), a dedicated 1.5 Tesla scanner is operational in the research center of the Rotterdam Study, and brain imaging is performed in all study participants without contra-indications (see section on “Population imaging”). Currently, the follow-up of this latter sample extends to up to 5 years. Therefore, in the coming years we will be able to investigate how cerebral microbleeds and DTI-markers relate to incident neurological diseases. However, already cross-sectionally we have evidence that these novel MRI markers relate to cognitive function and motor speed [206]. For relevant recent EJE references see [207–214].

Ophthalmic diseases

The ophthalmic part of the Rotterdam Study focuses on frequency and risk factors of chronic ophthalmic diseases and on ophthalmological characteristics of systemic diseases. Our main research topics are age-related macular degeneration, open angle glaucoma, myopia, and retinal vessel diameters.

Major findings

Age-related macular degeneration (AMD)

During the last 5 years, international research strategies were directed towards revealing the genetic background of AMD. This has been very fruitful, and led to the

identification of several genes which were consistently replicated. Many more genes had been launched by small studies and awaited validation. Our focus for AMD in 2010 was aimed at sorting out these relationships, as well as identification of gene-environment interactions. Working together with large consortia, we investigated the proposed genes *C5*, *SERPING1*, and *TLR3*. None of these genes appeared to show a consistent relation when studied in large populations [215–218]. The genetic associations with the already known major genes, *CFH* and *ARMS2*, remained without a doubt considerable; risks were increased up to 10–15 times for individuals homozygous for both risk variants. These genes point to complement overactivation and oxidative stress as major pathways in AMD pathogenesis.

Earlier in RS, we found that a diet rich in antioxidants could lower the risk of early AMD. We now aimed to assess whether this diet could also lower risks in persons with a high genetic predisposition. This was indeed so, persons with high risk variants and a high dietary intake of beta-carotene, lutein and zeaxanthin, and omega-3 fatty acids, had significantly lower risks of early AMD than those who were genetically predisposed but had low intakes of these nutrients [219]. This biological interaction was statistically significant.

Research aims for 2012 and beyond are improving risk estimates for (combinations of) risk alleles using incident data from several population-based prospective studies; evaluation of gene effects on subclinical manifestations of disease, such as drusen on optical coherence tomography (OCT); and more in depth investigation of gene-environment interactions.

Open angle glaucoma (POAG)

In contrast to AMD, the genetic background of POAG was still largely unknown up to 2009. We aimed to elucidate associated genes for optic disc parameters using the GWAS platform in the RS I-III studies as well as the family-based ERF population. These cohorts revealed two genome-wide significant loci for optic disc area, one near the *CDC7* gene and one near the *ATOH7* gene; and two significant loci for vertical cup-disc ratio (VCDR), one in the *CDKN2B* gene and one near the *SIX1* gene. Meta-analysis with Twins UK study confirmed associations and launched several other significant loci. Interestingly, *ATOH7* was also associated with VCDR independent of optic disc area, suggesting a common pathway [220]. In collaboration with a large cohort from Singapore, these genes were validated and a novel locus near *CARD10* was found for optic disc area [221].

Using the identified genes, we performed genetic risk modeling, and found that a polygenic model best explained

VCDR and POAG, while an oligogenic model best fitted intra-ocular pressure (IOP) [222].

Non-genetic analyses were performed as well. We studied incidence of glaucomatous visual field loss during 10 years of follow up, and found that the overall incidence rate of field loss was 2.9 per 1,000 person-years, and that the 10-year risk of GVFL was 2.8% (95% CI 2.3–3.4). We determined whether lifestyle-related risk factors, such as socioeconomic status, smoking, alcohol consumption, and obesity, were associated with POAG, and found that obesity was associated with a higher intraocular pressure and a lower risk of developing POAG [223]. Future investigations will focus on further elucidation of the genetic background of POAG, risk modeling incorporating all known risk factors, and study of gene-environment interactions.

Myopia

Recently, we incorporated refractive error and myopia as a disease outcome in the Rotterdam Study. Using the Illumina platform, we performed a GWAS using the mean spherical equivalent of both eyes as an outcome, and found a significant locus on chrom. 15q14, near the genes *GJD2* and *ACTC1* [224]. More comprehensive analyses showed that variants in these genes could not explain the relationship, but that the associated region included regulatory elements which may influence these genes. A collaborative group in the UK found a locus on chromosome 15q25, which we were able to replicate [225]. The plans for the near future are a joint meta-analysis of virtually all studies with refractive error and GWAS data, and an in depth search for the causal variants at 15q14 by next generation sequencing.

Retinal vessel diameters

One of the current goals was to find genes which determine retinal vessel diameters. Within the CHARGE consortium, we found four novel loci associated with retinal venular caliber one within the *RASIP1* locus, one adjacent to *VTA1* and *NMBR*, one in the region of *ATXN2*, *SH2B3* and *PTPN11*, and one adjacent to *MEF2C* [226].

Relationships with other disorders were investigated as well. Retinal venular widening appeared to be associated with an increased risk of vascular dementia [227]. We evaluated the relationship with stroke and found that larger retinal venular caliber was associated with an increased risk for stroke, in particular with an increased risk for intracerebral hemorrhage [228]. Lastly, we assessed whether smaller retinal arteriolar or larger venular calibers were associated with incident late-life depression, and found no evidence of an association. [229].

Methods update

At baseline and follow-up examinations participants undergo ophthalmic measurements including best-corrected ETDRS visual acuity, refractive error, Goldmann applanation tonometry, keratometry, slit lamp examination of the anterior segment and visual field testing. In pharmacological mydriasis we made 35° color photographs of the macular area, and 20° simultaneous stereoscopic imaging of the optic disc and macular area. Since the fifth follow-up, 35° stereoscopic color photographs of the optical disc and the macular area were made (RS-I-5). Analog fundus photography was replaced by stereoscopic digital imaging of the macular area and optic disc since the third follow-up examination. Optic nerve head analysis with a Heidelberg Retina Tomograph, macular pigment density, and melanin optical density measurements were added during the third follow-up (RS-I-3). At fifth follow-up examination, fourier domain optical coherence tomography of the macular area and optical disc, axial length and width measurements of cornea, anterior chamber, lens, posterior chamber and retina measured with Lensstar; and fundus autofluorescence, infra-red and red-free measurements were added (RS-I-5).

Classification of AMD, POAG, and retinal vessel diameters remained unchanged; refractive error was evaluated as spherical value + half cylindrical value, following clinical standards.

Psychiatric diseases

Objectives

The aim of the psychiatric research in the Rotterdam Study is to investigate the determinants, correlates and consequences of common psychiatric problems in the elderly. The focus has been on depressive disorders but anxiety disorders, sleep disturbances, addiction to smoking, and complicated grief are also being studied.

In the first years of the Rotterdam Study (RS-I-1) psychiatric data collection was very limited. However, in the second visit most participants were screened for depressive symptoms and from the third examination onwards, which began in 1997, depressive symptoms and disorders have been ascertained in all participants. An assessment of anxiety disorders, sleeping disturbances and complicated grief were added in the fourth examination and have been included in all follow-up visits of the Rotterdam Study I and II, and in the baseline of the Rotterdam Study III. Recent additions to the protocol include a screening for psychotic symptoms and, starting with the third examination of the Rotterdam Study II, ambulatory polysomnography.

Major determinants

Psychiatric research in the Rotterdam Study focuses on biological risk factors. The vascular depression hypothesis was tested with different measures of atherosclerosis, arterial stiffness and cerebral blood flow [230]. We also examined whether blood levels of vitamins and fatty acids, immune parameters, and markers of folate metabolism increased the likelihood of depression [231]. In one ongoing project, diurnal patterns of cortisol secretion are related to psychiatric and other disorders such as subclinical atherosclerosis [232]. Studies of genetic polymorphisms and brain morphology are underway [233]. Current data collection includes a dexamethasone suppression test to measure hypothalamic–pituitary–adrenal axis activity in all participants, which is unique in a population-based study. Also, psychiatric problems and psychological traits such as happiness, sleep duration and depression are increasingly studied as determinants of health and mortality [234, 235].

Major outcomes

Information on *depression* is obtained from (a) psychiatric examinations, (b) self-reported histories of depression, (c) medical records, and (d) registration of antidepressant use [236]. The psychiatric examination during follow-up visits consists of a screening with the Center for Epidemiologic Studies Depression Scale (CES-D), and in the screen-positive participants a semi-structured interview performed by a trained clinician (Schedules for Clinical Assessment in Neuropsychiatry, [237]). To continuously monitor incidence of depression throughout follow-up, trained research-assistants scrutinize the medical records of the general practitioners and copy the information about possible depressive episodes.

The following *anxiety disorders* are assessed with a slightly adapted Munich version of the Composite International Diagnostic Interview: generalized anxiety disorder, specific and social phobia, agoraphobia without panic disorder, and panic disorder [238, 239].

Sleep quality and disturbance is measured with the Pittsburgh Sleep Quality Index. In addition, sleep duration and fragmentation are assessed with actigraphy, a method that infers wakefulness and sleep from the presence or absence of limb movement [240]. In total, nearly 2,000 persons participated in this actigraphy study: they wore an actigraph and kept a sleep diary for, on average, six consecutive nights. In 2011 we have begun to follow these participants up with another 6 day assessment using actigraphy. In addition, 1,000 persons will receive one night of polysomnography in their home setting.

The Inventory of Complicated Grief is used to identify *traumatic grief* [241]. This is a condition distinct from normal grief and bereavement-related depression, characterized by symptoms like disbelief about the death and searching for the deceased.

Major findings

Depression

Recently we completed our study of the incidence and recurrence of depression [236]. During the follow-up period of 8 years on average, 566 depressive syndromes and 1,073 episodes of clinically relevant depressive symptoms occurred. For depressive syndromes, the incidence rate was 7.0 (95% CI: 6.0–8.3) per 1,000 person-years and the recurrence rate was 27.5 (95% CI: 23.7–32.1) per 1,000 person-years. The recurrence rate of depressive syndromes was equal for women and men.

In a series of initial studies we found some evidence for the vascular depression hypothesis. More severe coronary and extra-coronary atherosclerosis were associated with a higher prevalence of depression, as were cerebral haemodynamic changes [230, 231]. However, our data did not support a specific symptom profile of vascular depression as previously defined [242]. Most importantly, we found no longitudinal relation between peripheral atherosclerosis and incident depression [243]. This study refutes the vascular depression hypothesis that was largely based on cross-sectional data. Prospective studies to test the vascular hypothesis using cerebral imaging data are ongoing.

Sleep

We investigated the relationships of sleep duration with both cardiovascular risk factors and psychiatric disorders. We found a marked U-shaped association of actigraphically measured total sleep time with BMI and obesity [235]. Sleep fragmentation also increased the likelihood of a higher BMI and obesity, although, in the very old sleep fragmentation is a risk factor for low cholesterol levels [244]. We also investigated and aimed to explain sex differences in subjective and actigraphic sleep parameters [245]. If assessed by diary or interview, elderly women consistently reported shorter and poorer sleep than elderly men. In contrast, actigraphic sleep measures showed shorter and poorer sleep in men. These discrepancies were partly explained by sleep medication use and alcohol consumption.

Anxiety

We found that prevalent anxiety disorders fulfilling DSM-IV criteria may be much less co-morbid with depressive

disorders than previously thought if the disorders are assessed with different diagnostic instruments. On the other hand, a history of depression is very common in persons with prevalent anxiety disorder (more than 50%; [246]).

Smoking

Typically, determinants of smoking cessation are studied by comparing former with current smokers [247]. We also used a prospective approach of studying smoking cessation in 1,200 smokers (mean years of smoking: 40 years, minimum: 10 years). Smoking status was repeatedly assessed during follow-up every 3- to 4-years. Thus, an individual could contribute any number of person-years to the analyses. In other words, people were classified as smokers or quitters on a day-by-day basis. This approach enabled us to detect genetic effect on the incidence of smoking cessation [248].

Complicated grief

In our population-based study of 5,741 elderly persons, current grief was reported by 1,089 participants, and of these 277 (25 or 4.8% of total) were diagnosed with complicated grief, the vast majority of which had no clinical symptoms of anxiety or depression. Persons with complicated grief were older, had a lower level of education, and more often had lost a child [249].

Genetics of common psychiatric disorders

In the past year, we have performed a series of genome-wide association studies of the above psychiatric and psychological phenotypes, mostly as part of the CHARGE consortium. Whereas several analyses have yielded no convincing genome wide significant results—possibly because initial studies were underpowered, psychiatric phenotypes do not present very homogenous entities, or are highly very multi-genetic—the genome wide analyses of intermediate phenotype such as cortisol or behavioural traits are more promising [250]. To study the genetics of cortisol, we have established a dedicated consortium of population-based studies: CORNET.

Finally, ongoing psychiatric research projects examine whether and how psychological well-being or psychiatric problems contribute to survival. Most importantly, we are interested in whether the effects are specific to certain behaviour or emotions, are independent of confounding by physical disease, or can be explained by lifestyle, immunological or hormonal regulation. For recent EJE references see [251–259].

Respiratory diseases

Objectives

The objectives are to study the incidence of chronic obstructive pulmonary disease (COPD), to investigate genetic and environmental risk factors for COPD, and to study the effect of COPD on mortality. COPD is defined as a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases such as tobacco smoke [260]. COPD is a worldwide leading and still increasing cause of chronic morbidity and mortality that will change from the sixth to the third most common cause of death worldwide by 2020, whilst rising from fourth to third in terms of morbidity [261].

Major findings

In the first cohort of the Rotterdam Study (RS-I) of 7,983 participants, 648 cases were identified with incident COPD after a median follow-up time of 11 years. This resulted in an overall incidence rate of 9.2/1,000 person-years (PY) (95% CI, 8.5–10.0). The incidence rate of COPD was higher among men (14.4/1,000 PY; 95% CI, 13.0–16.0) than among women (6.2/1,000 PY; 95% CI, 5.5–7.0) and higher in smokers than in never-smokers (12.8/1,000 PY; 95% CI, 11.7–13.9 and 3.9/1,000 PY; 95% CI, 3.2–4.7, respectively). Remarkable was the high incidence in the youngest females in the age category of 55–59 years (7.4/1,000 PY; 95% CI, 4.1–12.6). For a 55 year-old man and woman, still free of COPD at cohort entry, the risk to develop COPD over the coming 40 years was 24 and 16%, respectively [260]. Since COPD is not only affecting the lungs, but is also characterised by extrathoracic manifestations, another line of research focuses on the role of systemic inflammation in the pathogenesis of COPD and its comorbidities. High levels of hsCRP (3 mg/l), a marker of systemic inflammation, were associated with a significantly increased risk of incident COPD (hazard ratio (HR), 1.7; 95% confidence interval (95% CI), 1.16–2.49) compared with persons with low CRP levels (<1 mg/l). The risk remained increased after adjustment for potential confounders and introduction of a potential latency period of 3 years. The risk was most pronounced for former smokers (HR, 2.2; 95% CI, 1.12–3.74). No CRP single nucleotide polymorphism or haplotype was associated with a significantly increased or decreased COPD risk [262].

Spirometric measures of lung function are heritable traits that reflect respiratory health and predict morbidity and mortality. We meta-analyzed genome-wide association studies for two clinically important lung-function measures: forced expiratory volume in the first second (FEV₁) and its

ratio to forced vital capacity (FEV_1/FVC), an indicator of airflow obstruction. This meta-analysis included 20,890 participants of European ancestry from four CHARGE Consortium studies: Atherosclerosis Risk in Communities, Cardiovascular Health Study, Framingham Heart Study and Rotterdam Study. We identified eight loci associated with FEV_1/FVC (HHIP, GPR126, ADAM19, AGER-PPT2, FAM13A, PTCH1, PID1 and HTR4) and one locus associated with FEV_1 (INTS12-GSTCD-NPNT) at or near genome-wide significance [$P < 5 \times 10(-8)$] in the CHARGE Consortium dataset [263]. The Hedgehog signalling pathway plays an important role in lung morphogenesis and cellular responses to lung injury. A genome-wide association study has demonstrated that two single nucleotide polymorphisms (SNPs) near the Hedgehog-interacting protein (Hip) gene, SNP identifiers rs1828591 and rs13118928, are associated with risk of chronic obstructive pulmonary disease (COPD). We investigated the association between genetic variation near the Hip gene and COPD, and whether risk estimates were modified by smoking behaviour in the Rotterdam Study. Both SNPs were significantly associated with risk of COPD (OR 0.80; 95% CI 0.72–0.91). Homozygosity for the minor G allele resulted in a decreased risk of COPD of approximately 40% (95% CI 0.47–0.78). There was a significant interaction with the number of pack-years of smoking ($P = 0.004$). The meta-analysis yielded an odds ratio for COPD of 0.80 per additional G allele [$P = 3.4 \times 10(-9)$]. Genetic variation near the Hedgehog-interacting protein gene was significantly associated with risk of COPD, depending on the number of pack-years of smoking [264].

Methods update

Clinical assessment of COPD

For the validation of the COPD cases, we had access to hospital discharge letters, files from the general practitioners, spirometry reports and pharmacy dispensing data for patients participating in the Rotterdam Study. Spirometry was performed in the context of the first Rotterdam cohort study (RS-I) in 3,550 participants. In addition, throughout the entire study period, spirometries were also performed on clinical indication by respiratory specialists and internists with a subspeciality in respiratory medicine. In the absence of spirometry, all medical information of subjects who used respiratory medication for at least 6 months and all hospital discharge letters or mortality reports with a coded diagnosis of COPD were reviewed. Definite COPD was defined by a moderate-to-severe obstructive spirometry ($FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted), and/or as COPD diagnosed by a specialist in internal medicine (mainly respiratory physicians or internists with a subspeciality in respiratory medicine) based upon the combination of clinical history,

physical examination and spirometry. Probable COPD was defined by a mild obstructive spirometry ($FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ predicted) and/or as COPD diagnosed by a physician in another medical speciality (e.g., a general practitioner). Clinical outcomes are collected during our continuous follow-up and include respiratory and non-respiratory death, hospitalisations due to exacerbations of COPD as well as moderate to severe COPD exacerbations treated with systemic corticosteroids and/or antibiotics. For pulmonary function testing in the 5th round of the first cohort of the Rotterdam Study (RS-I-5), the 3rd round of the second cohort (RS-II-3), and the 2nd round of the third cohort (RS-III-2), more detailed and sophisticated techniques are used to assess pulmonary function. Since COPD encompasses small airway disease (obstructive bronchiolitis) and parenchymal destruction of the lungs (emphysema), both components will be investigated by spirometry and measurement of pulmonary diffusion capacity, respectively.

Spirometry

Spirometry is performed by trained paramedical personnel using an electronic spirometer with pneumotachograph (Jaeger Masterscreen PFT, Cardinal Health, Hoechberg, Germany), according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines. Forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and FEV_1/FVC ratio are measured; the spirogram (volume-time curve) and maximal expiratory flow-volume curve are also recorded. The interpretation of spirometries is performed independently by two research physicians; in case of discordance between both physicians, a senior respiratory physician decides. Measurement of pulmonary diffusion capacity Measurement of diffusion capacity by single-breath determination of carbon monoxide (CO) uptake in the lung (DL, CO) assesses the uptake of carbon monoxide (CO) from the lung over a breath-holding period [265]. The DL, CO is measured using the Jaeger Masterscreen PFT Pro Diffusion apparatus (Cardinal Health, Hoechberg, Germany) according to the guidelines of the ATS/ERS task force on standardisation of lung function testing [265]. The test gases used to calculate DL, CO include a tracer gas (methane), to measure alveolar volume (VA), as well as carbon monoxide (CO 0.3%). The remainder of the test gas mixture includes O_2 and N_2 . For recent EJE references in this area see [266–279].

Genetic and biomarker studies

Objectives

The first objective of the laboratory team is to collect, store and manage the biological tissues mainly blood and urine

sampled in the Rotterdam Study. The second objective of the group concerns genotyping and assessment of biomarkers.

Major findings

Among the biomarker analyses our study documenting the relationship between homocysteine and osteoporosis was novel [121] and has since been widely replicated. Across all research lines in the Rotterdam Study, several candidate gene studies have also yielded new insights coming from both exploratory studies as well as from collaborative replication efforts. A unique feature of the Rotterdam Study is exploited by studying the relationship between pleiotropic gene variants and multiple diseases and disease related endpoints. For example, the studies on the promoter region of the IGF-1 gene revealed a series of consistent associations ranging from birth weight to diabetes [280], while other consistent associations involve the estrogen receptor alpha (ESR1) gene in relation to osteoporosis [281], osteoarthritis, height, myocardial infarction [282], age-at-menopause, and depression. Rotterdam Study investigators are playing leading roles in the emerging large global consortia focussed on assessing the contribution of complex disease gene variants by prospective meta-analysis across many epidemiological cohorts [283], such as CHARGE, ENGAGE and the GENOMOS/GEFOS [284, 285]. Since 2005 the genome wide association study (GWAs) has changed the field of complex genetics, and identified an ever growing list of common variants contributing to disease risk and explaining genetic variance of traits. Initial findings in the Rotterdam Study from individual collaborations replicating early GWAs hits included CFH in age-related macula degeneration [286], NOS1AP in QT interval [287], and several SNPs involved in height, type 2 diabetes, and breast cancer (collaboration with WTCCC investigators). The Rotterdam Study has generated GWAs data for almost the complete dataset summing to over 11,000 DNA samples, and is involved as a major collaborative centre for meta-analysis studies of GWAs data, including national programs (RIDE, NGI-NCHA), EU-funded projects (GEFOS, TREATOA, ENGAGE), and voluntary collaborations (GIANT, MAGIC, CHARGE). Especially, from the CHARGE consortium (the Rotterdam Study together with the Framingham Study, AGES, CHS, and ARIC) many important publications have emerged on a wide variety of phenotypes and diseases from all major research lines in the Rotterdam Study [288–292].

Data collection, storage and management

At each examination, blood, serum, plasma (citrate, heparine, and EDTA based), sputum, and urine are collected. Fasting blood samples are collected along with challenged

samples as part of a glucose tolerance test. Sputum is collected before and after a dexamethasone-suppression test. Sputum is frozen at -196°C before and after the challenge and stored at -80°C . To obtain serum and plasma, tubes are centrifuged according to a protocol standardising time and conditions from the drawing of blood to centrifugation. All samples are snap frozen at -196°C using liquid nitrogen and stored at -80°C . RNA is isolated from blood within 5 h after sampling and stored at -20°C . DNA is isolated from blood and extraction has been recently automated using a Hamilton STAR pipetting platform and AGOWA magnetic bead technology. DNA sample storage is in Matrix 2D-barcode tubes in 96 well format. Overnight urine samples are collected, frozen at -196°C and stored at -80°C . For data management, an in-house customized laboratory management system has been developed. Sample retrieval will be automated with an in-house customized laboratory track and trace system.

Blood assessments

For all participants, serum cholesterol, HDL, LDL, triglycerides, glucose and glucose levels are assessed. In urine, micro albumin and creatinine are determined in all participants. There have been a large number of specific blood/serum/plasma-based biomarker assessments, including steroids (e.g., estrogens, androgens, vitamin D, cortisol), interleukins, CRP, IGF1, insulin, iron-parameters (iron, ferritin and transferrin saturation), fibrinogen, homocysteine, folic acid, riboflavine, pyridoxine, SAM/SAH ratio, cobalamine, Lp-PLA2, Fas/Fas-L, vitamins, abeta42/40 and thyroid hormones (TSH).

Genotyping facilities

Affiliated laboratory facilities include a medium/high-throughput platform for candidate genes studies and GWAs analyses. The facilities use high-end automated machinery including a Caliper/Zymark ALH 3000 pipetting robot (including a TwisterII, and integrated plate sealer, plate reader (OD 260/280), a Tecan EVO 150 Freedom pipetting robot, a Deerac Equator NS808 nanoliter liquid dispenser, 15 electronic PCR machines (ABI 9700, 2 9 384), an ABI7900HT Taqman machine (running 1 ng gDNA in 2l reactions), a WAVE 3500HT dHPLC, Sequenom iPLEX, and two ABI3100 sequencing machines. DNA sample handling is centred on 384-well plates. Candidate gene studies are done mostly using Taqman and Sequenom genotyping with throughputs at 30,000 genotypes per day. Continuous efforts are focussed on reducing the required amount of genomic DNA which is now down to 1 ng per genotype. GWAs genotyping studies are based on 500 K Affymetrix arrays (a pilot project of 450 women) and 550

and 610 K Illumina arrays for the complete Rotterdam Study cohort encompassing over 11,000 DNA samples. The in-house GWAs genotyping facility has been partly sponsored by NWO investment grants (911-03-012; 175.010.2005.011), is part of the Erasmus Medical Center Biomics core facility, and serves as knowledge center for polymorphism analysis attracting national and international interested parties, both academic and industrial.

Candidate gene studies

We have genotyped over 300 individual polymorphisms as part of candidate gene studies across the complete cohort and conducted a large number of candidate gene studies in the Rotterdam Study. These mostly concern individual potentially functional single nucleotide polymorphisms (SNPs) per gene, but sometimes also haplotype tagging (delete space) SNPs (e.g., ESR1, ESR2, HSD11B1, fibrinogen), and also high density SNP screening (e.g., the vitamin D receptor gene). The candidate genes studied include the apolipoprotein E gene (APOE), the angiotensin-converting enzyme (ACE), the gene encoding angiotensinogen (AGT), angiotensin II type 1 receptor (AT1R) gene, G protein beta3 (GNB3), adducine gene, Cholesteryl Ester Transfer Protein (CETP), Hepatic Lipase, Phosphodiesterase 4D (PDE4D), ALOX5AP encoding 5-lipoxygenase activating protein, a polymorphism in the regulatory region of the Insulin-like Growth Factor 1 (IGF-1) gene, the hemochromatosis (HFE) gene, Complement factor H gene (CFH), and several polymorphisms in genes from the estrogen-, thyroid-, cortisol-, vitamin D-, IGF-, and Wnt signalling pathways, the homocysteine pathway, and several matrix molecules.

Genome wide association studies (GWAs)

Genome Wide Association studies (GWAs) are based on genotyping epidemiological cohorts with ultra-high density SNP arrays with up to 1 million SNPs. The method has been shown to successfully identify common genetic factors for hundreds of traits and diseases (see www.genome.gov/GWAsstudies). Through a large grant from the Dutch research organisation NWO one of the world's largest GWAs datasets has been facilitated involving over 11,000 DNA samples from the Rotterdam Study cohorts. This GWAs dataset is based on the Illumina 550 and 610 K arrays and will be useful for all research lines within the Rotterdam Study. In addition, it will also serve as a control GWAs dataset for other research centers in and outside The Netherlands for both SNP frequencies as well as copy number variations (CNVs). In addition our group has also been active in developing new software for GWAs analyses [292].

New developments

The new development in the basic sciences will be to move to transcriptomic studies and proteomic studies. With this view, the data collection protocol has been adjusted, standardizing blood collection. For recent EJE references see [290–310].

Pharmaco-epidemiologic studies

Objectives

A major objective of the pharmaco-epidemiologic studies is to investigate the role of drugs as determinants of disease in the Rotterdam Study. This includes studying efficacy and effectiveness of drugs, as well as adverse reactions to drugs.

Major findings

Important findings have been published on pharmaco-epidemiological topics concerning the main outcomes in the Rotterdam Study. Studies about the association between dementia, and antihypertensive drugs [293] and NSAIDs [194] have strongly suggested a protective effect of both groups of drugs. However, beta-blockers were associated with an increased risk of depression [294]. Several studies have been performed on cardiovascular topics [62, 295, 296]. In one of these studies, NSAIDs were associated with an increased risk of heart failure. A recent study demonstrated that short-term use of NSAIDs is associated with transient impairment of echocardiographic parameters [297]. In line with the suspicion that QTc-prolonging drugs may cause sudden cardiac death, it was demonstrated in the Rotterdam Study that a prolonged QTc is indeed an important risk factor [62]. Non-cardiovascular drugs which inhibit hERG-encoded potassium channels were associated with an increased risk of sudden cardiac death [298]. Furthermore, in one study it was demonstrated that high-dose corticosteroids increase the risk of atrial fibrillation [296]. In how far this effect is modified by susceptibility markers on chromosome 4q25 [299] or on KCNN3, a gene of which variants were associated with lone atrial fibrillation in a meta-analysis in the Rotterdam Study and several cohorts from the USA [300], is currently being investigated. Other important susceptibility genes for PR-interval [59], resting heart rate [301] and QRS duration [302] may prove to be important effect modifiers for drug effects. In the important area of locomotor diseases, studies have demonstrated that thiazide diuretics protect against hip fracture [303] and that statins reduce the risk of vertebral fracture [304]. On the other hand, the risk that long-term

use of certain NSAIDs may aggravate signs of osteoarthritis has been emphasized [305]. In the area of ophthalmic diseases, a protective effect of cholesterol-lowering agents on macular degeneration has been studied [306, 307]. In other areas, such as pharmacogenetics and other causes of interactions between drugs, several important findings have been published [287, 308–328]. In this regard, there proved to be important genetic variations in OCT1 and MATE1 transporters with consequences for metformin response in diabetics [329]. Genetic variation in the OCT1 transporter was also associated with response and survival time in users of drugs against Parkinsonism [330]. Interesting were the results of a GWA in users of the anticoagulant phenprocoumon which confirmed the important genetic variant for VKORC1, CYP2C9 and 4F2 [331]. An increasingly important topic is the association between long-term drug use and cancer. In the Rotterdam Study, high-ceiling diuretics were associated with an increased risk of basal cell carcinoma [332]. The importance of cytochrome P450 enzymes as effect modifiers was underlined by 2 studies, one of which showed increased survival in breast cancer patients on tamoxifen with a CYP2C19*2 polymorphism [333, 334].

Methods update

For several reasons, a drug is a highly attractive determinant in clinical epidemiologic research. First, drugs are probably the most important therapeutic intervention in health care. Despite rigorous clinical research before registration, many important effects of drugs are discovered after marketing. Second, all marketed drugs have proven biological activity, meaning that it concerns a determinant which really matters. Third, and as a consequence of the availability of complete medication histories in Dutch health care, the role of drug exposure can be assessed in a detailed way. In the Rotterdam Study, there is an almost complete coverage of the population as of January 1, 1991, thanks to the fact that all pharmacies which serve the Ommoord district are on one computer network. To date, more than three million prescriptions have been delivered to the population of the Rotterdam Study and of each prescription, details are available about the product name and contents, ATC-code, dosage and duration of drug therapy. This facilitates the use of detailed analyses with the drug as a time-varying determinant [335]. Drugs are a group of determinants which can be studied in association with a large variety of diseases. In the Rotterdam Study there is a strong interest in the association between drugs and the cardiovascular, neurological, endocrine, and ophthalmic diseases which have been the main topics since its start. However, there is also important information about the association with psychiatric diseases, cancer, and

chronic obstructive pulmonary disease. Moreover, important information about secondary outcomes, such as drug blood levels, other laboratory information, and information about hospital discharge diagnoses, is gathered on a continuous basis to facilitate pharmaco-epidemiological studies. Further EJE references can be found in [336–342].

Imaging studies

Objectives

Biomedical imaging allows for non- or minimally-invasive assessment of structural and functional changes that may reflect specific pathology. Recent developments in image data acquisition and analysis enable to use these techniques on a large scale. The Population Imaging Unit within the Rotterdam Study aims to assess imaging biomarkers of disease in a pre-symptomatic phase at the population level. Advantages of imaging measures include that they mark early disease, can be assessed reliably and reproducibly, and are quantitative rather than qualitative which makes them more powerful than most conventional outcome measures such as clinical phenotypes. The main imaging modalities that are currently being applied in the Population Imaging Unit are multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI).

Imaging infrastructure and storage

MDCT

CT imaging is currently performed with hospital-based 16-slice or 64-slice MDCT scanners (SOMATOM Sensation 16 or 64, Siemens, Forchheim, Germany), located at Erasmus University Medical Center. Scanners are operated by clinical technicians. CT images are acquired without contrast-enhancement and according to standardized protocols. Imaging data are transferred from the CT scanner to a securely backed-up research picture archiving system.

MRI

From August 2005 onwards, a dedicated 1.5 Tesla MRI scanner (GE Healthcare, Milwaukee, Wisconsin, USA) is operational in the Rotterdam Study research center. This scanner is operated by trained research technicians and all imaging data are collected according to standardized imaging protocols. Changes or updates in hardware or software configuration are avoided and regular quality checks are performed to secure validity of cross-subject and cross-scan comparisons. Imaging is performed without administration of contrast agents. All imaging data are

directly transferred from the scanner facility to the Erasmus University Medical Center. Data are stored on a securely backed-up research picture archiving system, using programmed scripts to check for completeness of the data received.

Data management and processing

Assessment of incidental findings

All imaging data are visually evaluated within days after acquisition by trained physicians for the presence of clinically relevant incidental findings [202, 343]. Expert radiologists are consulted for all abnormal findings and the management of clinically relevant findings is based on protocols defined by expert panels. These protocols are updated on a regular basis incorporating the current best available knowledge regarding treatment and prognosis of the various abnormalities discovered.

Automated processing of MRI data

Though some measurements are still performed manually or scored visually, the majority of imaging data is now processed using semi- and fully-automated computer algorithms. The Population Imaging Unit collaborates with the Biomedical Imaging Group Rotterdam (BIGR) of Erasmus University Medical Center in the application and development of automated processing pipelines for high-throughput of large data quantities. These pipelines comprise on the one end image quality checks and procedures for non-uniformity correction, normalization and image registration and on the other end advanced algorithms to extract image features to use for analyses. Grid architectures and networked processing pipelines are used to process the large quantities of imaging data that are acquired in the Rotterdam Study.

Major findings

The Rotterdam Study research lines currently applying imaging within the Population Imaging Unit are those on neurological diseases and cardiovascular diseases.

Brain imaging (MRI)

Neurodegenerative and cerebrovascular disease are common disorders in the elderly that exert a large influence on brain functioning. Identifying underlying pathology in a preclinical state may help to recognize persons at risk, assess determinants of disease and develop preventive measures. Main objective for the Population Imaging Unit with respect to brain imaging is therefore to identify and

quantify brain imaging biomarkers that mark the development of neurodegenerative and cerebrovascular disease.

From August 2005 onwards (RS-II-2 and onwards), brain imaging in the Population Imaging Unit is performed in all study participants without contra-indications in the context of the Rotterdam Scan Study. The current scanning protocol includes 4 high-resolution axial sequences (3D T1-weighted; 2D PD-weighted; 2D FLAIR; and 3D T2* GRE), 2D phase-contrast imaging, and diffusion tensor imaging (DTI). Total scanning time amounts to approximately 30 min. Currently, over 5,000 unique brain MRI scans and over 800 follow up scans after a time interval of three to 4 years have been acquired.

Fully automated methods are applied to quantify atrophy of brain tissues and structures and the severity of white matter lesions [343–345]. Automated hippocampal segmentation has been successfully applied on multi-scanner acquired MR images (on scans acquired in the Rotterdam Scan Study in 1995 [346] and follow up examinations in 2006), showing that a decline in hippocampal volume over a 10-year follow up period predicted onset of clinical dementia [347].

Phase-contrast imaging allows for assessment of blood flow in the carotids and basilar artery. This yields measures of total brain perfusion [348], which when lower was found to be related to worse cognition, an association that is mediated by brain atrophy [349].

The 3D T2* GRE sequence that we use was specifically developed to increase the conspicuity of cerebral microbleeds [350]. With this optimized sequence, we found that microbleed prevalence gradually increases with age, from 6.5% in persons aged 45–50 years to 35.7% in participants of 80 years and older; and that overall, 15.3% of all subjects over the age of 45 years has at least 1 microbleed; a much higher prevalence than was reported before [351, 352]. We found supportive evidence that deep or infratentorial microbleeds reflect arteriosclerotic angiopathy, whereas strictly lobar microbleeds are caused by cerebral amyloid angiopathy [351, 352]. We furthermore recently demonstrated that incidence of microbleeds over a 3-year time interval is high and that risk factors for new microbleeds again differ according to microbleed location, in line with our findings regarding prevalent microbleeds [353]. These findings impact research into the causes of cerebral amyloid angiopathy, as well as fuel the ongoing discussion about the safety of antithrombotic therapy in persons with microbleeds [354, 355].

Diffusion tensor imaging (DTI) allows the assessment of the microstructural integrity of white matter. White matter microstructure loses its integrity with increasing age, but this can largely be explained by presence of white matter atrophy and white matter lesions [356]. Nevertheless, the microstructural integrity in the normal appearing white

matter and in white matter lesions relates to cognitive function regardless of concurrent macrostructural changes, emphasizing the importance of the microstructural integrity of white matter [206]. Recent advances in image processing now allow us to quantify the degree of connectivity between brain regions [357], enabling the further exploration of structural integrity in relation to functional processes in aging.

Imaging of atherosclerotic calcifications (MDCT)

Main objectives with respect to imaging of vascular calcifications are to investigate distribution of and risk factors for atherosclerotic calcifications in the general elderly population and to study prognosis associated with calcifications in different vessel beds.

From September 2003 until February 2006, all participants from RS-I-4 and RS-II-2 who completed a center visit were invited to a MDCT scan of the coronary arteries and a second scan of the aortic arch and carotid arteries. A total of 2,521 participants (response rate 79%) were scanned. The cardiac scan reached from the apex of the heart to the tracheal bifurcation. The second scan reached from the aortic arch to the intracranial circulation. Images were analyzed by trained reviewers and calcification in the different vessel beds (coronaries, aortic arch, extracranial and intracranial carotids) were quantified using the Agatston score [358].

As expected, we found that calcification load was higher overall in men compared to women, though aortic arch calcification was more prevalent among women [359]. Age and current smoking were found to be the strongest independent risk factors for arterial calcification [360]. Furthermore, strong and graded associations of prevalent stroke were found with carotid artery, aortic arch and coronary artery calcification, independent of cardiovascular risk factors [361]. We are currently investigating the relation between arterial calcification in various vessel beds and ischemic brain disease on MRI.

Carotid plaque imaging (MRI)

Carotid wall thickening and atherosclerosis are highly prevalent at older age and are considered a major cause of cerebrovascular events [197]. Carotid atherosclerotic plaque constituents such as lipid core and hemorrhage, so-called “vulnerable” components, are considered important factors in development of clinical neurological events [362]. With MRI, it is possible to separately identify these plaque components [363]. Main objectives with respect to carotid imaging in the Rotterdam Study are to investigate distribution of and risk factors for carotid plaque components in the

general elderly population and to study prognosis associated with specific carotid plaque composition.

From October 2007 onwards, all participants with carotid wall thickening of 2.5 mm or larger on ultrasound (approximately 25% of the Rotterdam Study population) are invited for carotid MRI. Imaging is performed with a bilateral phased-array surface coil (Machnet, Eelde, The Netherlands), stabilizing subjects in a custom-designed head holder to reduce motion. The imaging protocol consists of a series of high-resolution MRI sequences to image the carotid bifurcations on both sides: a PDw Fast Spin Echo (FSE) Black-blood (BB) sequence; a PDw-FSE-BB with an increased in-plane resolution; a PDw-Echo Planar Imaging (EPI) sequence and a T2w-EPI sequence; and 2 three-dimensional (3D) sequences: a 3D-T1w-Gradient Echo (GRE) sequence; and a 3D phased-contrast MR-Angiography. Total scanning time amounts to approximately 30 min. Plaques are reviewed by trained raters for the presence of three different plaque components (calcification, hemorrhage and lipid core). Furthermore, carotid plaque size is quantified by obtaining maximum carotid wall thickness and degree of luminal stenosis using the NASCET criteria [364] on the PDw-FSE images. Postprocessing techniques aimed at automated quantification of plaque volume and identification of different plaque components are currently being developed. So far, over 1,300 participants underwent a complete carotid MRI scan and data are currently being analyzed. There is a complete overlap between carotid and brain MRI participants, allowing for the investigation of carotid plaque constituents in relation to brain imaging markers.

New developments

New developments to be expected within the Population Imaging Unit are on the one hand implementation of new imaging methods and on the other hand to integrate imaging data with other available data such as genetic data. Also, focus will shift from purely structural imaging to also including functional imaging data, e.g. by incorporating functional MRI into the brain imaging protocol. Furthermore, besides ever-increasing advances in imaging hardware, software and sequence design, major advances are to be expected from (fully) automated image analysis. Computer processing of images will enable to make use of all information contained within the image, introducing new imaging biomarkers. Besides, the vast amount of imaging data that are acquired in population-based studies like the Rotterdam Study renders visual assessment or manual measurements virtually impossible, strengthening the need for (fully) automated methods of data extraction and analysis. For recent EJE references see [182, 365–369].

Management

The Rotterdam Study is directed by a Management Team comprising the scientific principal investigators Cornelia van Duijn (PI Genetic epidemiologic studies), Oscar Franco (PI Cardiovascular diseases), Albert Hofman (chairman, PI Rotterdam Study), Arfan Ikram (PI Neurological diseases), Harry Janssen (PI Hepatic diseases), Caroline Klaver (PI Ophthalmic diseases), Ernst Kuipers (PI Internal Medicine), Tamar Nijsten (Dermatological diseases), Bruno Stricker (PI Pharmaco-epidemiology), Henning Tiemeier (PI Psychiatric diseases), André Uitterlinden (PI Genomic studies), and Meike Vernooij (PI Population Imaging); and Jan Heeringa, MD, PhD, study coordinator, Eric Neeleman, head IT, and Frank van Rooij, DSc, head data-management. The study of respiratory diseases is conducted in close collaboration with Prof Guy Brusselle, Department of Respiratory Medicine, University of Gent, Belgium.

The following persons are Principal Investigator Emeritus of the Rotterdam Study: Frank van den Ouweland (PI Internal Medicine 1990–1992), Diederick Grobbee (PI Cardiovascular diseases 1990–1996), Albert Hofman (PI Neurological diseases 1990–1996), Paulus de Jong (PI Ophthalmic diseases 1990–2005), Huibert Pols (PI Internal Medicine 1993–2006), Monique Breteler (PI Neurological diseases 1997–2010), Gabriel Krestin (PI Population Imaging 1998–2010), Johannes Vingerling (PI Ophthalmic diseases 2005–2010), Jacqueline Witteman (PI Cardiovascular diseases 1997–2011).

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