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CHRONIC DISEASES

The Rotterdam Study: 2010 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 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 close to a 1,000 research articles and reports (see www.epib.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 · Endocrine diseases · Epidemiologic methods · Genetic epidemiology · Liver diseases · Neurological diseases · Ophthalmic diseases · Pharmacoepidemiology · Psychiatric diseases · Respiratory diseases

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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 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 basic design of the study is straight-forward: 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, 4]. 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 1999, 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. The overall response figure

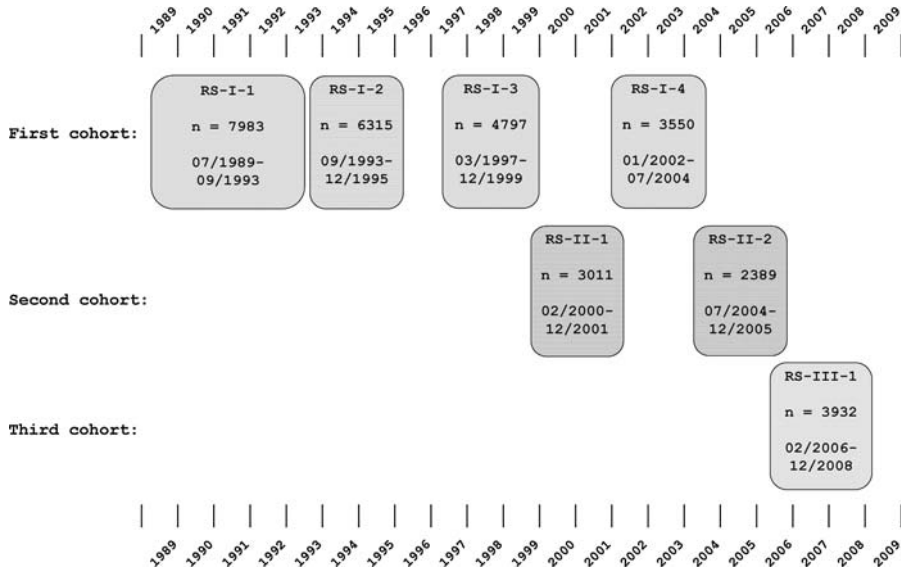

Fig. 1 Diagram of examination cycles of the Rotterdam Study (*RS*). RS-I-1 refers to the baseline examination of the original cohort (pilot phase 07/1989-12/1989; cohort recruitment 01/1990-09/1993). RS-I-2, RS-I-3 and RS-I-4 refer to re-examination of the original cohort members. RS-II-1 refers to the 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 to the study district. RS-II-2 refers to the 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 45–55 years)

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, 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 we had 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 and from 2006 to 2008 (Fig. 1). In 2009 a new examination cycle started (RS-I-5).

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 and osteoporosis.

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 methods for cardiovascular 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 [5–27].

Cardiovascular diseases

Objectives

Research on the epidemiology of cardiovascular diseases focuses on three primary areas of interest: studies on risk factors for atherosclerosis and coronary heart disease, studies on the detection of subjects at high risk of coronary heart disease, and studies on cardiovascular conditions at older age.

Three groups of putative risk factors for atherosclerosis and coronary heart disease are included. The first are endocrine factors, including diabetes, insulin and insulin-like growth factor I, estrogens and androgens, and thyroid gland and adrenal gland hormones. The second group contains factors involved in hemostasis, inflammation and endothelial function. The third group, and currently a major focus,

covers genetic factors in these areas in relation to risk of atherosclerosis and heart disease.

The ability of classical cardiovascular risk factors to identify subjects at high risk of coronary heart disease is limited. Risk stratification may be improved when based on the presence of atherosclerosis. To this end, repeated measurements of non-coronary atherosclerosis and measurements of coronary, carotid and aortic arch calcification have been included in the study.

Another line of research focuses on cardiovascular diseases in the elderly that are in large part the consequence of ischemic heart disease, like heart failure and atrial fibrillation. An important topic in this area is the early diagnosis of heart failure using echocardiographic assessment of asymptomatic systolic and diastolic dysfunction of the left ventricle. Atrial fibrillation is another major chronic condition frequent at older age. Examination of the determinants and prognosis of atrial fibrillation is part of this research line.

Major findings

Recent findings include the association between structural and diastolic echocardiographic parameters and all-cause mortality in individuals initially free of myocardial infarction, heart failure, atrial fibrillation, or atrial flutter [28]. The study found that gender differences in atherosclerosis are larger in coronary vessels than in carotid, aortic, or lower extremity vessels [29]. The insertion/deletion polymorphism of the angiotensin converting enzyme gene was found to be associated with increased mean changes of systolic blood pressure and pulse pressure [30].

We studied the validity of the Framingham Points Scores in our population and found that they perform reasonably well in elderly women, but need recalibration in elderly men [31]. The study showed that C-reactive protein (CRP) levels are associated with the extent and progression of ankle-brachial-index and carotid plaques and, albeit less pronounced, with aortic calcification and intima-media thickness [32].

The study enabled accurate assessment of the incidence and lifetime risk of heart failure and atrial fibrillation in an elderly population [33, 34]. It was shown that inflammation is associated with heart failure [35]. Subclinical atherosclerosis, cigarette smoking and high-normal thyroid function were identified as new risk factors of atrial fibrillation [36–38].

The study showed that serum CRP is associated with the risk of type 2 diabetes independent of obesity. Moreover, genetic variants in the CRP gene were associated with the risk of diabetes [39]. The study showed that subjects with higher levels of serum uric acid have an increased risk of developing type 2 diabetes [40]. In collaborative work with the Framingham Heart Study, we identified 3 genetic loci associated with uric acid concentration and gout [41]. In a large collaborative consortium, the CHARGE consortium, we identified a significant association between chronic kidney disease and the UMOD gene which encodes Tamm-Horsfall protein [42]. In the same consortium, we found four genes for systolic blood pressure, six for diastolic blood pressure and one for hypertension, as well as 1 genetic locus associated with variation in left ventricular diastolic dimensions and five loci associated with aortic root size [43, 44].

Methods update

Repeated measures of non-coronary atherosclerosis include carotid intima-media thickness and plaques by ultrasound and the ankle-arm index [45]. In previous examinations, electron-beam CT and, more recently, multi-detector CT were used to accurately quantify calcification in the coronary, aortic arch and carotid arteries [46]. Measurement of plaque vulnerability with high-resolution MRI of the carotid arteries started in October 2007 and will be continued. Other outcome measures include electrocardiography, echocardiography and abdominal aortic diameter measured by ultrasound [28]. In addition to repeated measures of structural and functional parameters of the left ventricle and atrium, measurements of structure and function of the right side of the heart will be performed.

Determinants are assessed by physical examinations, collection of blood samples, and by questionnaires and interview. The role of genetic factors and gene-environment interactions is studied using the candidate gene approach and more recently genome wide association studies, in which our data are often combined with those from other studies in the context of the large collaborative CHARGE consortium [47].

Clinical cardiovascular outcomes are collected during our continuous follow-up and include non-fatal myocardial infarction and cardiac death, revascularisations, heart failure, atrial fibrillation, gout, kidney failure, complications of diabetes and pulmonary hypertension [33, 34, 41, 42, 48]. For additional EJE references concerning cardiovascular disease see [49–67].

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 [68, 69].

In relation to osteoporosis we have determined the incidence of vertebral [70] and non-vertebral fractures [71], and the relationship between bone mineral density (BMD), BMD change and the occurrence of fracture [71], as well as with heel ultrasound measurements [72] and bone resorption markers [73]. We have also studied the relation between endogenous sex hormones and their binding factors, with fractures [74], and showed that increased homocysteine levels are a strong and independent risk factor for osteoporotic fractures [75]. We studied the relations between osteoporosis and other chronic diseases like osteoarthritis [76], cancer [77], atherosclerosis [78] and diabetes [79, 80], and provided indications for the treatment and diagnosis of osteoporosis. Lastly, we were part of several large consortia studying epidemiological risk factors for osteoporosis [81–83]. 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 [84], independent of known clinical risk factors. In addition, we have studied different aspects of OA disease definition and classification [85], evaluation of disease progression [86] and determined the most prominent risk factors leading to OA [87, 88].

We have also studied inflammatory aspects of endocrine diseases like diabetes mellitus [89], and the relations of hypo/hyperthyroidism to cardiovascular and neurological disease [90]. We further examined the influence of genetic variation in endocrine genes influencing hormone levels [91], interaction of genetic factors in relation to fracture risk [92, 93], to cardiovascular risk factors [94] and to neurological conditions [95]. 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^{TM} total body fan-beam densitometer (GE Lunar Corp, Madison, WI, USA). Hip structural analysis [96] 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 [97]. 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 locomoter 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 [98–104].

Liver diseases

Objectives

The objectives are to study the prevalence and incidence of liver disease, as well as to investigate the role of genetic and environmental determinants. The focus will be on liver fibrosis and steatosis. Fibrinogenesis 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. Hepatologic focus in the Rotterdam Study will be on the association between these known causes of liver disease and the occurrence, magnitude, and progression of fibrosis in combination with genetic and environmental effect modifiers. The incidence of steatosis in this population will also be studied. Steatosis of the liver is the hepatic manifestation of the metabolic syndrome (type 2 diabetes, abdominal obesity, dyslipidemia and arterial hypertension) with interesting relations to other scientific research topics in the Rotterdam Study.

Abdominal ultrasound

As of February 2009, trained technicians perform abdominal ultrasonography in all RS-I-5 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 a physician with expertise in hepatic ultrasonography.

Assessment of steatosis

Hepatic ultrasonography

The diagnosis of liver steatosis will be based on evident ultrasonographic contrast between the hepatic and right renal parenchyma (high-level echoes arising from the hepatic parenchyma). Steatosis will be graded on a three-grade scale (none, mild and severe) [105].

Assessment of fibrosis

Hepatic ultrasonography and elastography

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 [106, 107].

Determinants of interest

The association between genetic and environmental factors known to influence liver function and the occurrence of steatosis and fibrosis will be studied. Additionally, the association of these conditions with numerous determinants will be studied such as, for example, age, gender, food intake, concurrent alcohol intake, risk factors for viral hepatitis, BMI, waist-to-hip ratio, serum glucose and diabetes mellitus, serum cholesterol and triglycerides, insulin like growth factor (IGF), C-reactive protein and interleukins. All clinical information will be obtained by interview (updated with liver specific questions) and clinical examination.

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 imaging modalities.

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 [108], from less than 0.5% to more than 4% for Parkinson disease [109], and from approximately 1% to nearly 10% for stroke. 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 [110] but with men having a higher age-specific incidence of both stroke and Parkinson disease than women throughout the age range [111, 112].

Vascular pathology and vascular risk factors are associated with worse cognitive performance [113], which also translates in people with vascular pathology or risk factors for vascular disease having an increased risk of dementia, including Alzheimer disease [114]. Moreover, several life style factors are associated with the risk of dementia and Alzheimer disease [115–117], suggesting that onset of dementia may at least partly be delayed or prevented. Commonly used drugs may have a role in this [118].

The classical risk factors for stroke also predict risk of stroke in the Rotterdam Study [119]. More recently identified risk factors, including inflammatory markers, may be etiologically relevant but thus far add little to the identification of people at risk [120]. Possibly underlying this is that a large amount of stroke goes clinically undetected [121]. 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 [121].

Neuroimaging reveals that brain pathology is widespread [122] 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 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. The 3D T2* GRE sequence that we use was specifically developed to increase the conspicuity of cerebral microbleeds [123]. With this optimized sequence, we found that microbleeds were present in nearly 20% of persons over the age of 60 years, mounting to a prevalence of over 1 in 3 in persons aged 80 years and older; a much higher prevalence than was reported hitherto [124]. Moreover, we found supportive evidence that deep or infratentorial microbleeds reflect arteriolosclerotic angiopathy, whereas strictly lobar microbleeds are caused by cerebral amyloid angiopathy. 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 [125]. Diffusion tensor imaging (DTI) allows the assessment of the microstructural integrity of white matter. White matter microstructure looses its integrity with increasing age, but this can largely be explained by presence of white matter atrophy and white matter lesions [126]. 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 [127].

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 [108, 110]. 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 [109, 112].

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 [111, 120].

Assessment of cognitive 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.

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 [128]. In 1995, a random sample of 563 non-demented participants underwent brain MR imaging in the context of the Rotterdam Scan Study. The scanning protocol included series of axial proton-density, T2-weighted and T1-weighted images, as well as a high-resolution 3D-HASTE sequence [129]. From August 2005 onwards, 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. The 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).

Ophthalmic diseases

Objectives

The ophthalmic part of the Rotterdam Study focuses on frequency and risk factors of chronic ophthalmic diseases and on ophthalmological characteristics of systemic diseases in the elderly. Emphasis is laid on age-related macular degeneration, open angle glaucoma, retinal vessel diameters and, recently, myopia and other refractive abnormalities.

Major findings

Age-related macular degeneration (AMD)

AMD prevalence increased exponential with age [130] and AMD was the main cause of blindness in the high age-group [131]. Risk factors that were found for AMD are smoking, atherosclerosis, hyperopia [132–134]. The APO-E ε-4 allele showed an inverse association with AMD [135]. First-degree relatives of patients with late ARM developed ARM at an increased rate at a relatively young age [136]. The heterogeneity of genetic risk among AMD families is considerable, and the proportion of high-risk families is relatively small [137, 138]. The anticipated protective effect of statins on AMD could not be substantiated in participants of the Rotterdam Study [139, 140]. A high dietary intake of beta carotene, vitamins C and E, and zinc was associated with a substantially reduced risk of AMD [141]. Alcohol consumption was not a risk factor for AMD [142]. The CFH Y402H polymorphism accounted for a substantial proportion of AMD cases in the Rotterdam Study and particularly in the presence of environmental and genetic stimulators of the complement cascade [143, 144]. Three common SNPs in the VEGF gene were not associated with AMD [145]. Cataract surgery increased the risk of dry AMD, particularly in homozygous CFH Y402H carriers [146]. Lipoprotein-associated phospholipase A2 levels were not an important risk factor for AMD despite the partly inflammatory pathogenesis of AMD [147].

Open angle glaucoma (OAG)

The prevalence of OAG was highly dependent on the applied criteria. That was a major reason for proposing a classification system without final, subjective adjudication [148]. Systemic blood pressure and hypertension were associated with elevated intraocular pressure but not with prevalent OAG. Relatives of patients with OAG had a strongly increased risk of glaucoma. Enlarged cup-disc ratio was the earliest and most prominent feature of familial aggregation. The incidence of OAG rose with increasing age, most of these patients were unaware of having OAG. The incidence of visual field loss rises five-fold between 55 and 80 years in the general population. Glaucoma is the main cause for visual field loss, followed by stroke. Atherosclerosis, serum CRP level and diabetes mellitus were not a risk factor for OAG. Calcium channel antagonists were associated with open-angle glaucoma in Rotterdam Study participants. These results do not support the use of calcium channel antagonists for the treatment of normal-tension glaucoma. Polymorphisms in the estrogen receptor beta genes were associated with an increased risk of OAG in men. Use of topical beta-blockers seems not to be associated with excess mortality. We estimated that in a white population with a low prevalence of pseudoexfoliation, about one in 1,000 persons screened with a periodic OAG screening program could be saved from bilateral end-stage OAG.

Retinal vessel diameters

Larger retinal venular diameters were associated with generalized atherosclerosis, inflammation and cholesterol levels and may play their own independent role in predicting cardiovascular disorders [149]. Larger retinal

venular diameters were related to incident stroke and cerebral infarction [150], progression of cerebral small vessel disease [151] and incident impaired glucose tolerance and diabetes mellitus [152]. Smaller retinal artery diameters were related to incident hypertension [153].

Methods update

At baseline and follow-up examinations participants undergo ophthalmic measurements including best corrected ETDRS visual acuity, refractive error, Goldmann applanation tonometry, keratometry, slitlamp 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. 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). Fourier domain optical coherence tomography of the macular area and optic disc, axial-length and fundus autofluorescence measurements were added at the fifth follow-up examination (RS-I-5).

Assessment of AMD

To diagnose AMD, 35° color photographs were taken of the macular area of each eye at each follow-up examination after pharmacologic mydriasis. The images were graded with 12.5× magnification according to the International Classification and Grading System for age-related maculopathy [154].

Assessment of OAG

At baseline and follow-up, identical ophthalmic examinations on each eye were performed that consisted of Goldmann applanation tonometry, visual field screening and ophthalmoscopy, and stereoscopic fundus photography with pharmacologic mydriasis. OAG was diagnosed using an algorithm for the diagnosis of OAG based on presence or absence of glaucomatous optic neuropathy (GON), glaucomatous visual field loss, or both, yielding a classification as no, possible, probable, or definite OAG [148].

Assessment of retinal vessel diameters

Vessel measurements were performed on digitized fundus color transparencies of the optic disc. For each subject, the image with the best quality was analyzed with a semiautomated system. Vessel measures were computed using the improved Parr-Hubbard formula, adjusted for magnification errors [149].

Psychiatric diseases

Objectives

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

Major findings

Depression

Recently we completed our study of the incidence and recurrence of depression [155]. 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 incidence and recurrence rates more than doubled when episodes of depressive symptoms were included. The recurrence rate of depressive syndromes was equal for women and men, but all other rates were almost twice as high for women compared with men. The rates did not seem to change with age.

In a series of 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 [156, 157]. However, we could not rule out that earlier depressive episodes may have contributed to the development of atherosclerosis. Moreover, our data did not support a specific symptom profile of vascular depression as previously defined [158].

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 [159]. 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 [160]. Self-reported total sleep time was also examined in relation to depressive disorders and anxiety disorders in more than 5,000 persons

[161]. Again, both short and long sleepers were more likely to be depressed or to have an anxiety disorder than persons with a total sleep time of 7–8 h.

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%, unpublished data).

Smoking

Typically, determinants of smoking cessation are studied by comparing former with current smokers. We recently introduced 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. In all examination rounds participants were asked whether they still smoked and if not, when they had stopped. Thus, an individual could contribute any number of person-years (maximum 14 person-year) 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 [162].

Genetics of common psychiatric disorders

Several SNPs have been investigated as potential determinants of depression, mostly with negative results. However, we found that an ER-alpha polymorphism had a substantial effect on anxiety but not on depression in women [163]. 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 [47]. 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 poly-genetic—the genome wide analyses of the intermediate phenotype cortisol is more promising. Replication in other general population studies and genetic isolate studies is attempted and may yield new candidate genes for psychiatric disorders.

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 independent of confounding by physical disease or can be explained by lifestyle, immunological or hormonal regulation.

Methods update

In the first years of the Rotterdam Study I (RS-I-1, see Fig. 1) psychiatric data collection was very limited. In the second visit (RS-I-2) most participants were screened for depressive symptoms and from the third examination (RS-I-3) onwards, which began in 1997, depressive symptoms and disorders are have been ascertained in all participants. An assessment of anxiety disorders, sleeping disturbances and complicated grief were added in the fourth examination (RS-I-4) and have been included in all follow-up visits of the Rotterdam Study I and II cohorts, and in the baseline of the Rotterdam Study III cohort.

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 [156]. We also examined whether blood levels of vitamins and fatty acids, immune parameters, and markers of folate metabolism increased the likelihood of depression [157, 164, 165]. In one ongoing project, diurnal patterns of cortisol secretion are related to psychiatric and other disorders such as subclinical atherosclerosis [166]. Studies of genetic polymorphisms and brain morphology are underway [167]. 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 [168].

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 [155]. 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 [169]. The self-reported history of depression includes standardized questions to ascertain whether participants had experienced a depressive episode, and if they had been treated. In order to continuously monitor incidence of depression throughout follow-up, trained research-assistants scrutinize the medical records of the general practitioners (GPs) and copy the information about a potential depression.

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 [161, 170].

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 [171]. 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.

The Inventory of Complicated Grief is used to identify *traumatic grief* [172]. 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.

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 [173]. 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 [174].

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 [173].

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 [175].

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.

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 will be 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 [176]. 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 [176]. The test gases used to calculate DL, CO include a tracer gas (methane), to measure alveolar volume (V_A), 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 [177–184].

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 [185] 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 [186], while other consistent associations involve the estrogen receptor alpha (ESR1) gene in relation to osteoporosis [187], osteoarthritis, height, myocardial infarction [188], 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 [189], such as CHARGE, ENGAGE and the GENOMOS/GEFOS [190, 191]. 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 [143], NOS1AP in QT interval [192], 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 [193–196].

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, a-beta42/40 and thyroid hormones (TSH).

Genotyping facilities

Affiliated laboratory facilities include a medium/high-throughput platform for candidate gene 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 × 384), an ABI7900HT Taqman machine (running 1 ng gDNA in 2 µl 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 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 patways, 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/GWAstudies). 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 [197].

New developments

The new development in the basic sciences will be to move to transciptomic studies and proteomic studies. With this view, the data collection protocol has been adjusted, standardizing blood collection. Further new developments

target lipidomics and glycomic research. Other references may be found elsewhere [198–205].

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 [206] and NSAIDs [118] have strongly suggested a protective effect of both groups of drugs. Several studies have been performed on cardiovascular topics [207–209]. In one of these studies, NSAIDs were associated with an increased risk of heart failure. 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 [208]. Furthermore, in one study it was demonstrated that high-dose corticosteroids increase the risk of atrial fibrillation [209]. In the important area of locomotor diseases, studies have demonstrated that thiazide diuretics protect against hip fracture [210] and that statins reduce the risk of vertebral fracture [211]. On the other hand, the risk that long-term use of certain NSAIDs may aggravate signs of osteoarthritis has been emphasized [212]. In the area of ophthalmic diseases, a protective effect of cholesterol-lowering agents on macular degeneration has been studied [139, 140]. In other areas, such as pharmacogenetics and other causes of interactions between drugs, several important findings have been published [192, 213–234].

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, almost 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.

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 [235–238].

Management

The Rotterdam Study is directed by a Management Team comprising Jan Heeringa, MD, PhD, study coordinator, Eric Neeleman, head IT, Frank van Rooij, MSc, head data-management, and the scientific principal investigators Albert Hofman (PI Rotterdam Study, chairman), Monique Breteler (PI Neurological diseases), Cornelia van Duijn (PI Genetic studies), Harry Janssen (PI Hepatic diseases), Gabriël Krestin (PI Radiology), Ernst Kuipers (PI Internal Medicine), Bruno Stricker (PI Pharmaco-epidemiology), Henning Tiemeier (PI Psychiatric diseases), André Uitterlinden (PI Genome wide analysis), Johannes Vingerling (PI Ophthalmic diseases) and Jacqueline Witteman (PI Cardiovascular diseases). The study of respiratory diseases is conducted in close collaboration with Prof Guy Brusselle, Department of Respiratory Medicine, University of Gent, Belgium.

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Grobbee (Cardiovascular diseases), Paulus de Jong (Ophthalmic diseases) and Huibert Pols (Endocrine diseases). The contribution of Guy Brusselle to the study of respiratory diseases is also gratefully acknowledged.

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