Improving cardiovascular risk assessment in primary care

Boer, A.W. de

IMPROVING CARDIOVASCULAR RISK ASSESSMENT IN PRIMARY CARE

A.W. de Boer

Improving cardiovascular risk assessment in primary care
A.W. de Boer, 2018

ISBN: 978-94-6233-867-8

Cover design and layout: evelienjagtman.com
Printing: Gildeprint, Enschede

Financial support for printing of this thesis was kindly provided by the SBOH (employer of GP trainees in the Netherlands).

IMPROVING CARDIOVASCULAR RISK ASSESSMENT IN PRIMARY CARE

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus prof.mr. C.J.J.M. Stolker
volgens besluit van het College voor Promoties
te verdedigen op dinsdag 6 maart 2018
klokke 15.00 uur

door

Anna Wilhelmina de Boer

Geboren te Leiden in 1987

Promotor	Prof. dr. M.E. Numans
Copromotoren	Dr. J.W. Blom
	Dr. ir. R. de Mutsert
Leden promotiecommissie	Prof. dr. J.G. van der Bom
	Prof. dr. M. den Heijer
	Prof. dr. H.C.P.M. van Weert (Universiteit van Amsterdam)
	Dr. M. Hollander (UMC Utrecht)

Contents

CHAPTER 1

General Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide, with 30% of all global deaths.(1) In 2015, 39.300 persons in the Netherlands died from CVD.(2) Approximately 35% of all CVD deaths occur in those under the age of 75 years.(3) In addition, CVD causes a significant burden of morbidity, with a prevalence in the Netherlands of approximately one million persons with coronary heart disease, stroke or heart failure.(2) The main underlying cause of CVD is atherosclerosis.(4) Atherosclerosis is characterized by the development of fatty streaks, which may evolve into plaques and ultimately lead to an occlusive thrombus and subsequent CVD event.(5)

More than 75% of the cardiovascular mortality could be attributed to the combination of the risk factors hypertension, elevated cholesterol concentrations, diabetes, obesity and smoking.(6) All of these are modifiable risk factors. Reduction of these risk factors by life style changes or drug treatment has proven to be effective with respect to reducing the risk of CVD.(7-11) Many research projects have been performed to develop interventions aiming at the identification and treatment of patients at increased cardiovascular risk in primary care. However, more research is needed to further improve this cardiovascular risk management.

In this introduction, we describe the current state of conducting research on cardiovascular disease, specifically the challenges in data collection. Furthermore, we describe the current state of cardiovascular risk management in primary care, and propose approaches to improve the assessment of an individual's cardiovascular risk. Finally, the objective and outline of this thesis and used cohort studies are described.

Conducting research on cardiovascular disease

The study design which is most suitable to examine which patients have an increased cardiovascular risk is the prospective cohort study. In a cohort study, data is collected on a defined population, a cohort, to relate the determinants on baseline to the occurrence of disease during follow-up.(12)

The most influential prospective cohort study on cardiovascular disease is the Framingham Heart Study. This was the first long-term study in a large cohort from the general population. The original cohort was recruited between 1948 and 1952 and consisted of 5,209 residents from the town of Framingham, Massachusetts, United States.(13) In 1971, the Framingham Heart Study started with enrolment of the family members of the original cohort, the Offspring cohort, to examine the aggregation of cardiovascular traits within families.(14) In 2002, also the grandchildren of the original cohort were enrolled.(15) Finally, to reflect the changing racial and ethnical composition of the town Framingham, two Omni cohorts were enrolled in 1994 and 2003.(16) In each cohort, the participants return every 2-6 years for a detailed assessment of medical history, physical examination and laboratory tests.

Over the years, the investigators of the Framingham Heart Study published more than 1,200 peer-reviewed articles. The extensive phenotyping resulted in the identification of the major risk factors for cardiovascular disease: hypertension, hypercholesterolemia, smoking, obesity, diabetes and physical inactivity.(16) Furthermore, the Framingham Heart Study introduced the multifactorial prevention of cardiovascular disease. The Framingham risk score is the best-known risk estimation system for cardiovascular disease.(17, 18)

The collection of accurate information on exposures, confounding factors and participants' health outcomes is an important aspect in the design of a cohort study. Key issues are the selection of the methods for case definition and the disclosure of individual test results.

Data from general practice electronic health records

Methods to define cases status are often selected based on the combination of feasibility and validity. Careful definition of case status is important to minimize bias due to misclassification.(19) Self-report is a method that is often used in prospective cohort studies. Questionnaires are generally time- and cost-efficient, however disadvantages are the suboptimal response rate and the lack of details.(20) Data from general practice electronic health records may be a feasible and valid alternative to self-reported diagnosis. In general practice, clinical data is available from many patients over a long period of time. All symptoms and diseases are coded in an electronic health record using the International

Classification of Primary Care (ICPC).(21) These coded diagnoses may be an accurate method for case definition in cohort studies. However, the feasibility of obtaining ICPC-coded diagnoses from the electronic health records for large population-based cohort studies has not been investigated previously.

One of the cardiovascular risk factors which may be obtained from the general practice electronic health records is type 2 diabetes mellitus. Patients with diabetes mellitus are mainly diagnosed and treated in general practice, which suggests that general practice electronic health records are an accurate source for the definition of diabetes cases. However, it is unknown to what extent general practitioners code diagnoses of diabetes accurately.

Disclosure of test results in research

There is an ongoing debate in the literature about how individual test results should be disclosed to the participants of a research study.(22) Participants may benefit from the disclosure of test results with potential consequences for diagnosis, treatment or prevention. Examples of test results with potential health consequences are results from blood pressure measurements, blood tests, urine tests, pulmonary function tests and magnetic resonance imaging. Because many persons participate in research each year(23), research projects need guidance on how to disclose individual test results.

Test results with potential strong benefits for disclosure to research participants are incidental findings with serious health consequences that can be treated. Incidental findings are unexpected abnormalities that are found outside the purpose of the original research, but may be of potential health importance for the participant.(24) Research domains which often generate incidental findings are medical imaging and genetic testing. In the literature, the recommendations for communication of incidental findings are generally based on ethical, legal, scientific and clinical perspectives.(25) The perspective of research participants themselves who are confronted with incidental findings is lacking. Research is needed to investigate the communication of incidental findings from an insider's perspective.

Cardiovascular risk factors, particularly blood pressure and cholesterol concentrations, are often measured in cohort studies. Disclosure of these test results to the participants may benefit the primary prevention of cardiovascular diseases. Therefore, participants in research studies are often recommended to consult their general practitioner when one of the cardiovascular risk factors is abnormal. It is however yet unknown what the advantages and disadvantages are of such a protocol.

Cardiovascular risk management in the Netherlands

Various research projects have been performed within cohort studies to develop strategies to reduce cardiovascular risk factors, leading to national and international guidelines. In 1978, the first Dutch unifactorial guideline on hypertension was published by the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG), followed by a guideline on hypercholesterolemia in 1987. Around 2000, prevention of CVD has shifted from an unifactorial approach towards the assessment of an individual's total burden of cardiovascular risk.(26) The introduction of multifactorial risk factor management was based on the facts that 1) CVD has a multifactorial aetiology, 2) risk factors have a multiplicative effect, and 3) physicians deal with individuals, not with single risk factors.(27) For the assessment of an individual's total burden of risk, several risk estimation systems have been developed, e.g. Framingham risk score, Systematic COronary Risk Evaluation (SCORE), QRISK, PROCAM.(28)

Since 2006, this multifactorial approach is implemented in the Netherlands, using the risk estimation system SCORE-NL to estimate an individual's CVD risk.(29) The latest revision in 2011 is an adaptation of the original SCORE risk equation, using information on risk factors and CVD mortality in the Dutch population.(30) SCORE-NL 2011 is used to calculate the 10-year risk of fatal and nonfatal CVD, including the risk factors sex, age, systolic blood pressure, total cholesterol/high-density lipoprotein cholesterol ratio, smoking status, and medical history of diabetes mellitus and rheumatoid arthritis.

SCORE-NL 2011 is embedded in the Dutch Clinical Practice Guideline for Cardiovascular risk management. This guideline gives recommendations for risk assessment and follow-up of patients at increased cardiovascular risk. For the assessment of an individual's risk, information on the individual risk factors is acquired and the 10-year CVD risk is calculated. Every patient with an abnormal risk factor is advised about a healthy lifestyle to reduce the CVD risk. Treatment with antihypertensive and/or lipid-lowering drugs is indicated for patient with a high 10-year CVD risk of 20% or higher, or an intermediate 10-year CVD risk of 10 to 19% when other additional risk factors are present. These additional risk factors are having a first-degree family history of CVD, physical inactivity, overweight, low estimated glomerular filtration rate, poor metabolic control, and albuminuria. The method to calculate SCORE-NL 2011 is described in more detail in Chapter 5, Appendix 1.

Between 1980 and 2009, cardiovascular mortality has declined considerably in most European countries. In the Netherlands, cardiovascular mortality has declined by 71% in that period.(31) About half of the decline can be attributed to changes in the major risk

factors hypertension, elevated cholesterol concentrations, body mass index and smoking.(32) Despite decreasing mortality rates, the burden of CVD is still increasing. This is demonstrated, for example, by increasing hospitalization rates for CVD.(3) One of the approaches to further reduce the burden of CVD is to improve cardiovascular risk assessment in primary care. On the one hand this can be achieved by improving the identification of patients with a potential increased cardiovascular risk in daily clinical practice. On the other hand, the estimation of an individual's cardiovascular risk might be improved by adding novel risk factors to current risk estimation systems.

Identification of patients for cardiovascular risk assessment

Worldwide, there is serious undertreatment of cardiovascular risk factors in individuals at increased cardiovascular risk.(33) In 2013, the World Health Organization published a global action plan to reduce premature death from noncommunicable diseases by 2025.(34) One target aims for at least 50% of all individuals with an indication for preventive treatment to receive drug therapy. To be able to start timely preventive treatment, patients should be invited for cardiovascular risk assessment in primary care. However, cardiovascular risk assessment is time-consuming, with on average a first consultations of 20 minutes for history taking and examination of the patient and a second consultation of 20 minutes to discuss the results.(35, 36) Therefore, in primary care, a targeted high-risk approach is used to identify patients with a potential increased cardiovascular risk.

Previous studies mainly focused on the development of a programmatic approach to determine which patients should be invited for cardiovascular risk assessment.(37-39) In this context, the Dutch guideline Prevention Consultation has been developed for the prevention and early detection of CVD, diabetes and chronic kidney disease.(40) In this systematic screening programme, a risk questionnaire is sent to all patients aged 45-70 years from a general practice. Patients with a high-risk score are advised to consult their general practitioner for extensive measurements, including cardiovascular risk assessment. Of the patients who consult their general practitioner with a high-risk score, about 20% of the patients will have an indication for preventive cardiovascular treatment, diabetes or chronic kidney disease. However, only 30% of the general practices implemented this guideline due to the extra workload and costs this approach brings and the lack of scientific evidence for prevention programmes.(41) Nevertheless, primary care is considered to be the most important setting for the detection of cardio-metabolic diseases.(42) Therefore, different, more feasible, approaches are needed to guide the identification of eligible patients for risk assessment.

Ad hoc case-finding is an approach which can easily be implemented in daily clinical practice. In this approach, potential high risk patients are invited for cardiovascular risk

assessment during a regular consultation for other reasons. This approach is most commonly used in general practice, however it is unclear which patients should be invited to identify high-risk patients efficiently. As a consequence, ad hoc case-finding is often neglected and patients at increased risk may remain untreated. The identification of patients for cardiovascular risk assessment should be based on an easily obtained factor, because only a short consultation is planned for the actual reason of encounter. We hypothesised that overweight may be an important identifying factor because it is associated with the risk factors used in the risk estimation systems and is easy to obtain. It is yet unknown how many patients with a treatment indication can be identified when patients with overweight are invited for cardiovascular risk assessment by ad hoc case-finding.

Another approach, which may help to identify patients at increased cardiovascular risk, is to use readily available test results of cardiovascular risk factors. Risk factors are frequently measured outside primary care, without being part of a structured risk management programme. Blood pressure or cholesterol concentrations are measured for example in occupational health, for research purposes, in incidental health check-ups at pharmacies or by private companies.(43-45) Screening outside primary care offers an opportunity for general practitioners to identify more patients at high risk. On the other hand, patients may consult their general practitioner with an incomplete risk factor profile and may be unnecessarily worried. These advantages and disadvantages of screening outside primary care are yet unclear.

Cardiovascular risk assessment

Patients with a potential increased cardiovascular risk are invited for the calculation of an individual's estimated 10-year cardiovascular risk using a risk estimation system. Based on the estimated risk, the indication for preventive treatment is determined. Therefore, it is important that the calculated risk reflects the true cardiovascular risk. External validations of the most commonly used risk estimation systems have demonstrated an area under the receiver operating curve between 0.65 and 0.85.(28) This means that the prediction of an individual's 10-year cardiovascular risk is not optimal, which may lead to under- and overtreatment of patients.

Risk prediction may be improved by adding information about novel risk factors to the current risk estimation systems. A novel, emerging risk factor of CVD is the presence of hepatic steatosis. Hepatic steatosis is the early stage of non-alcoholic fatty liver disease (NAFLD), with a global prevalence of 25% in the general population.(46) NAFLD is a risk factor for the development of CVD(47), with a 64% increased risk of CVD(48). The reference measurements for the assessment of steatosis, proton magnetic resonance spectroscopy and liver biopsy, cannot be used in a cardiovascular risk estimation system

due to the invasiveness, availability and costs of the measurements. However, serological markers of liver function and combination scores developed for the prediction of hepatic steatosis may be a non-invasive alternative, which can be used in daily practice. Previous studies have reported conflicting results regarding the improvement of cardiovascular risk prediction when one of the serological markers are included in a risk estimation system.(49-51) It is suggested that the improvement may differ between men and women.(51) In addition, it is unknown whether combination scores developed for the prediction of hepatic steatosis have any added value in a risk estimation system. Therefore, it needs to be investigated whether cardiovascular risk prediction can be improved when markers of hepatic steatosis are added to an established risk estimation system.

Objective and outline of this thesis

The main objective of this thesis was to improve cardiovascular risk assessment in primary care. First, we examined two important aspects in the collection of data in a cohort study; case definition and the disclosure of research test results. Second, we investigated several approaches to improve cardiovascular risk assessment.

In Chapter 2, we examined the feasibility of obtaining ICPC-coded diagnoses from the general practice electronic health records. Furthermore, we aimed to examine the validity of ICPC-coded diagnoses of diabetes from electronic health records as an alternative to self-reported diabetes. In Chapter 3, we explored the experiences and preferences of research participants to whom an incidental finding detected on MRI was communicated in a qualitative study. Elements from both disclosure of research test results and cardiovascular risk assessment, are featured in Chapter 4. Here, we investigated the advantages and disadvantages of unstructured risk factor screening outside primary for both patients and general practitioners. In Chapter 5, we examined how many patients with a treatment indication can be identified when all patients with overweight or obesity are invited for cardiovascular risk assessment by ad hoc case-finding. In the last study, described in Chapter 6, we aimed to investigate whether cardiovascular risk prediction can be improved when non-invasive markers of hepatic steatosis are added to the Framingham risk score, and whether improvement differs between men and women. Finally, Chapter 7 summarizes the results of this thesis and discusses methodological considerations and implications.

Cohort studies used in this thesis

NEO study

The Netherlands Epidemiology of Obesity (NEO) study is a prospective population-based cohort study in persons aged 45-65 years, with an oversampling of participants with a body mass index ≥ 27 kg/m^2.(52) Participants with a self-reported body mass index ≥ 27 kg/m^2 were recruited between September 2008 and October 2012 from the greater area of Leiden (the Netherlands) via general practitioners, municipal registers and advertisements. Prior to the NEO study visit, participants were asked to complete a questionnaire including demographic, lifestyle and clinical information. During the baseline visit at the NEO study centre of the Leiden University Medical Centre an extensive physical examination was performed, including blood sampling and magnetic resonance imaging of the abdomen, heart and brain. Four years after the start of the NEO study, the general practitioners of the participants were contacted and visited to extract health information from the health records of the participants.

EPIC-NL

The two Dutch contributions to the European Prospective Investigation Into Cancer and Nutrition (EPIC) are included in the EPIC-NL cohort; the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort and Prospect cohort.(53) In both cohorts, the participants were recruited simultaneously between 1993 and 1997. The MORGEN cohort consists of a general population sample of 22,654 men and women aged 20-59 years. Prospect is a prospective cohort study in 17,357 women aged 49-70 years, who participated in the national breast cancer screening programme between 1993 and 1997. At baseline, the participants were asked to complete a questionnaire and physical examination was performed. During the follow-up, data on cardiovascular events was obtained through linkage with disease registries.

CHAPTER 2

Coded diagnoses from general practice electronic health records are a feasible and valid alternative to self-report to define diabetes cases in research

de Boer AW, Blom JW, de Waal MWM, Rippe RCA, de Koning EJP, Jazet IM, Rosendaal FR, den Heijer M, Numans ME, de Mutsert R

Submitted

Abstract

Introduction In the Netherlands, general practitioners code diagnoses of diabetes mellitus (DM) in electronic health records using the International Classification of Primary Care (ICPC). It is unknown to what extent DM is coded accurately. Our aim was to examine the feasibility and validity of obtaining ICPC-coded diagnoses of DM from electronic health records for case definition in epidemiological studies, as alternatives to self-reported DM.

Methods The Netherlands Epidemiology of Obesity study is a population-based cohort study in 6,671 persons aged 45-65 years at baseline, included between 2008-2012. Data from electronic health records were collected between 2012-2014. We defined a reference standard using diagnoses, prescriptions and consultation notes and investigated its agreement with ICPC-coded diagnoses of DM before and after baseline and with self-reported DM at baseline.

Results After a median follow-up of 1.8 years data from 6,442 (97%) participants were collected. With the reference standard, 506 participants (79/1000) were classified with prevalent DM at baseline and 131 participants (11/1000 person-years) were classified with incident DM during follow-up. The agreement of prevalent DM between self-report and the reference standard was 98% (kappa 0.86), the agreement between ICPC-coded diagnoses and the reference standard was 99% (kappa 0.95). The agreement of incident DM between ICPC-coded diagnoses and the reference standard was >99% (kappa 0.92).

Conclusion The excellent agreement with the reference standard, in combination with the high follow-up rate confirms that ICPC-coded diagnoses of DM from general practice electronic health records are a feasible and valid alternative to self-reported diagnoses of DM.

Introduction

Accurate information on the exposure, confounding factors and participants' health outcomes is crucial in epidemiological and clinical research. Methods such as questionnaires, medical registries and interviews can be used to define the case status. Self-report is a method that is often used for the definition of type 2 diabetes mellitus (DM) cases in research.(54-56) Although, previous studies have reported a high agreement between self-reported diagnoses of DM and medical records (kappa ranging between 0.71 and 0.92), there is still room for improvement.(57-61) In addition, the suboptimal response rate and the lack of the exact date of diagnosis are disadvantages of self-reporting.(20)

In the Netherlands, type 2 DM is mainly diagnosed and treated in general practice. Therefore, an alternative source to obtain information about diagnoses of DM is the general practitioner (GP) or his electronic health records. In previous cohort studies, questionnaires were sent to GPs to obtain information about the diagnoses of DM.(56, 62, 63) For example, in a Dutch cohort study, two out of three ascertained DM cases (via self-report, hospital discharge diagnoses or urinary glucose strip) were confirmed to have been diagnosed with DM, as reported by their GP or pharmacist on a questionnaire.(56) In the Netherlands, GPs code health problems in a patient's electronic health record using the International Classification of Primary Care (ICPC).(21) Case definition using ICPC-coded diagnoses from the general practice electronic health records may be even more accurate than a questionnaire among GPs. In addition, compared with self-reported diagnoses, using ICPC-coded diagnoses from electronic health record may provide the health information of more participants and more detailed information. However, the feasibility and validity of the definition of DM cases using ICPC-coded diagnoses from electronic health records has not been investigated previously. It is unknown to what extent GPs code health problems accurately.

In this study, we examined the feasibility of obtaining ICPC-coded diagnoses from the general practice electronic health records. Next, we aimed to examine the validity of ICPC-coded diagnoses of DM from electronic health records as an alternative to self-reported DM in the Netherlands Epidemiology of Obesity (NEO) study, a prospective cohort study in 6,671 persons aged 45-65 years at baseline. To that extent, we compared the ICPC-coded diagnoses of DM with the self-reported DM and with a reference standard based on all available information in the electronic health records.

Methods

Study design and study population

The NEO study is a population-based prospective cohort study in 6,671 persons aged 45-65 years with an oversampling of participants with a body mass index (BMI) ≥ 27 kg/m². Detailed information about the study design and data collection has been described elsewhere.(52) Participants with a self-reported BMI ≥ 27 kg/m² were recruited between 2008 and 2012 from the greater area of Leiden in the Netherlands through GPs, municipal registers and advertisements. In one municipality (Leiderdorp), all inhabitants aged 45-65 years were invited irrespective of their BMI, allowing for a reference distribution of BMI. Prior to the baseline visit, participants completed a questionnaire at home including questions about demography, lifestyle and clinical information. The participants were asked to bring all medication they were using in the month preceding the study visit to the NEO study site. Names and dosages of all medication were recorded by trained staff. During the baseline visit at the NEO study centre of the Leiden University Medical Center (LUMC), participants underwent an extensive physical examination, including fasting blood sampling. Plasma concentrations of glucose were determined in the central clinical chemistry laboratory of the LUMC. Within two weeks after the NEO study visit, the participants received a letter with several test results, including their fasting plasma glucose concentration and the upper limit of a normal fasting glucose concentration of 7 mmol/L. Body weight and height were measured during the study visit with a calibrated scale and a vertically fixed, calibrated tape measure during the study visit. The trained staff reported the height in cm, body weight was rounded to 100 g and one kilogram was subtracted to correct for the weight of clothing. BMI was calculated by dividing the weight (in kg) by the square of the height (in metres).

Between April 2012 and November 2014, the GPs of the participants were contacted and visited to extract health information from the electronic health records of the participants. In the Netherlands, 98% of all citizens are registered with a GP, the gatekeeper to secondary care.(64) GPs use an electronic primary care ICT system to store health information about their patients: e.g., demographic details, ICPC-coded medical history, consultation notes, hospital discharge records, laboratory and other test results, and prescriptions. The ICPC-coded lifetime medical history was extracted and the rest of the data was extracted from 2008 until the date of extraction. Almost twenty different primary care ICT systems are used in the Netherlands that store health information in a different way.(65) Data from the participants were extracted and merged into one database (the GP database). Detailed information of the methods of data extraction from electronic health records is provided in Appendix 1.

The study was approved by the medical ethics committee of the LUMC and all participants gave written informed consent for participation in the study and for obtaining medical information from their GP or medical specialists during follow-up of the study.

DM at baseline by self-report

Prevalent DM by self-report was defined as a self-reported medical history of DM, type 1 or type 2, on the questionnaire or the use of glucose lowering medication (oral or insulin) in the month preceding the baseline visit.

ICPC-coded DM diagnoses from general practice electronic health records

ICPC-coded diagnoses of DM and the corresponding dates were extracted from the medical history in the GP database. Diagnoses are coded by GPs in the primary care ICT system according to ICPC version 1.(21) The DM diagnosis is coded with code T90, T90.1 or T90.2. The index date was defined as the date of diagnosis. Coded diagnoses with an index date before the baseline visit were defined as prevalent ICPC-coded diagnoses of DM, while coded diagnoses with an index date at or after the baseline visit were defined as incident ICPC-coded DM diagnoses.

Reference standard of diagnosed DM

To evaluate the validity of self-reported DM and ICPC-coded diagnoses for the definition of DM cases, a reference standard was developed by the Diabetes adjudication committee of the NEO study, using all data from the GP database. The Diabetes adjudication committee was composed of GPs, endocrinologists, epidemiologists and data-managers, complemented with clinicians from the diabetes work package within the NEO study (Appendix 2). The Diabetes adjudication committee defined the reference standard of the diagnosis DM as having one of the following: 1) a correctly ICPC-coded diagnosis of DM or ICPC-coded consultation note for DM; or 2) a prescription of glucose-lowering medication; or 3) a strong indication for the diagnosis of DM by screening keywords in the GP database.

First, the GP database was searched for coded diagnoses and coded consultations with ICPC-code T90 and the corresponding date. To verify whether the diagnoses were correctly coded, the corresponding descriptions were screened for conflicting descriptions. The extracted data of all participants with a conflicting description were read and recoded when there was no diagnosis of DM. For example, a participant with the diagnosis 'Uterus extirpation 2002' coded with ICPC-code T90 (DM) rather than an ICPC-code in chapter X (Female genital system and breast), without a prescription of glucose-lowering medication or DM consultations was recoded as no DM diagnosis. In addition, temporary steroid-induced DM in the medical history was classified as no diagnosis of DM.

Second, the GP database was searched for prescriptions of glucose-lowering medication and the corresponding date, often registered according to the Anatomical Therapeutic Chemical (ATC) codes listed under A10 (Drugs used in diabetes).(66) Prescriptions without an ATC code were screened by the keywords insulin, metformin, tolbutamide, novomix, victoza, actrapid, novorapid, actos, mixtard, janumet, eucreas, avandamet, avandia, glucobay, diamicron, galvus, januvia, gliclazide, levemir, bydureon, pioglitazon, byetta, apidra, amaryl, humalog, sitagliptine, lantus, glimepiride, saxagliptine, glibenclamide and glucophage.

Third, of the remaining participants without an ICPC-coded diagnosis or consultation and without a prescription for glucose-lowering medication, the medical history and the consultation notes were screened by the keywords DM, diab, gluc, suiker. When a keyword was detected, the extracted data were read and coded using a decision rule developed by the Diabetes adjudication committee to code the data consistently. When there was a strong indication for the diagnosis of DM, the data was coded as DM with the corresponding date. A strong indication was defined as a written diagnosis of DM or DM consultations.

The index date was defined as the first date of an ICPC-coded diagnosis, ICPC-coded consultation notes, prescription or strong indication for the diagnosis DM. A diagnosis of DM according to the reference standard with an index date before the date of the baseline visit was defined as prevalent DM. A diagnosis of DM according to the reference standard with an index date at or after the date of the baseline visit was defined as incident DM.

Statistical analysis

Baseline characteristics of the total population were expressed as the mean (SD), or number (percentage). To examine the feasibility of data extraction from electronic health records, we calculated the proportion of participants who gave informed consent to extract data and the proportion of participants for whom data was obtained. We also determined the time and costs related to the extraction of data from electronic health records.

We estimated the prevalence and incidence of DM for each case definition, as described above, while excluding those with missing data on self-reported DM or without health information from the electronic health records. To evaluate the validity of the case definitions, we estimated sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios and kappa statistics. The strength of the agreement was classified as almost perfect for kappa values of more than 0.80.(67) For prevalent diagnosed DM, we compared two case definitions with the reference standard, namely, self-report and

ICPC-coded diagnoses. For incident diagnoses of DM, we compared ICPC-coded diagnoses with the reference standard.

Participants with a fasting plasma glucose concentration above the upper limit of 7.0 mmol/L at baseline, as reported in the test results letter, may have consulted their GP with this test result. These incident DM cases may have been detected earlier because of the test results. To examine this effect, we repeated the analyses after excluding participants with a fasting plasma glucose concentration >7.0 mmol/L and without an ICPC-coded DM diagnosis at baseline. For all analyses, STATA statistical software (Statacorp, College Station, TX), version 14 was used.

Results

In total, 6,671 persons have been included in the NEO study between September 2008 and October 2012. The baseline characteristics of the participants are shown in Table 1.

Table 1 Baseline characteristics of the participants of the Netherlands Epidemiology of Obesity study, aged 45 to 65 years with an oversampling of body mass index ≥27 kg/m² (n=6,671)

	N	Characteristics
Age (years)	6,671	56 (6)
Sex (men)	6,671	3156 (47)
Body mass index (kg/m²)	6,671	30.1 (4.9)
Fasting plasma glucose (mmol/L)	6,617	5.7 (1.1)
Self-reported diabetes	6,654	459 (7)
Glucose-lowering therapy	6,671	356 (5)

Data expressed as the mean (SD) or number (percentage)

Feasibility of data extraction from general practice electronic health records

Of all participants, 6,652 (99.7%) participants gave informed consent for the collection of medical information. Of these, 6,622 participants reported the contact details of their current GP when they made the appointment for the baseline visit. Between April 2012 and November 2014, 352 general practices received a letter with a request to extract data from electronic health records. In 264 general practices, data were extracted from twelve different primary care ICT systems. In addition, 52 general practices gave written information about diagnoses and prescriptions. Of 180 participants, no information was obtained due to non-response of the GP (11 participants of 11 general practices), a lack of permission from the GP (41 participants of 25 general practices), the participant was not registered in the reported general practice (120 participants), or death (8 participants).

In total, health information was obtained from 6,442 (97%) participants, after a median follow-up of 1.8 years (interquartile range 1.2 – 3.1) after baseline. The total costs of data extraction and processing was estimated at €148,800 and the total time was estimated at 4,850 hours (Table 2). When only coded diagnoses were extracted and processed, the time and costs were estimated to be 25% lower. A detailed overview of the costs and time is shown in Appendix 3. In total, 1,230 different ICPC-codes were registered in the obtained information from the electronic health records; 742 diseases/disorders, 404 complaints/symptoms and 84 process codes (e.g., preventive procedures, administration, referrals).

Table 2 Feasibility of data extraction from general practice electronic health records in the Netherlands Epidemiology of Obesity study (n=6,671)

Informed consent to collect data, n (%)	6,652 (>99)
Participants of whom data was obtained, n (%)	6,442 (97)
Obtained unique ICPC-codes, n	1,230
Time to extract data[a], hours	2,850
Time to process data[b], hours	2,000
Costs to collect data, euro's	148,800

Abbreviations: ICPC, International Classification of Primary Care

[a] Contact with general practitioners, preparation of data extraction, travel to the general practices, data extraction

[b] Building a database, case definition

DM at baseline by self-report

Of the 6,654 (>99%) participants who answered the questions at baseline about a medical history of DM, 459 (7%) participants reported to be diagnosed with DM type 1 or type 2. All participants brought their medication to the study visit and 356 (5%) participants were using glucose-lowering medication. Of the participants with self-reported DM, 106 participants were not using glucose lowering medication. One participant was using glucose-lowering medication, but did not report being diagnosed with DM. Thus, according to the definition, in total 460 participants had DM by self-report at baseline.

Prevalence and incidence of DM according to the case definitions

Table 3 shows the case status definitions of prevalent diagnosed DM according to each case definition, including the overlap between the definitions. With self-report, 460 (69 per 1000) participants were defined as having prevalent diagnosed DM at baseline. With ICPC-coded diagnoses, 461 (72 per 1000) participants were defined as having prevalent DM at baseline. With the reference standard, 506 (79 per 1000) participants were defined as having prevalent DM at baseline.

After excluding participants with prevalent ICPC-coded DM at baseline, 5,981 participants were at risk of DM. During a total of 11,880 person-years of follow-up, 125 (21 per 1000) participants were defined as having incident DM, giving an overall incidence of 11 per 1000 person-years. With the reference standard, 5,936 participants were at risk of DM after excluding participants with prevalent DM at baseline. During a total of 11,777 person-years of follow-up, 131 (22 per 1000) participants were defined as having incident DM, giving an overall incidence of DM of 11 per 1000 person-years. Table 4 shows prevalent and incident DM cases according to each case definition.

Table 3 Prevalent diabetes diagnosed according to the case definitions in 6,671 participants of the Netherlands Epidemiology of Obesity study

		Self-report			ICPC-coded diagnoses		
		No diabetes	Diabetes	Missing	No diabetes	Diabetes	Missing
Reference standard	No diabetes	5,893	31	12	5,935	1	0
	Diabetes	89	413	4	46	460	0
	Missing	212	16	1	0	0	229
ICPC-coded diagnoses	No diabetes	5,919	50	12			
	Diabetes	63	394	4			
	Missing	212	16	1			

Abbreviations: ICPC, International Classification of Primary Care

Table 4 Prevalent and incident diagnosed diabetes cases according to the case definitions in participants of the Netherlands Epidemiology of Obesity study

Definition of diabetes cases	Study population (N)	Prevalent diabetes cases (N)	Prevalence (per 1,000 persons)	Incident diabetes cases (N)	Incidence rate (per 1,000 person-years)
Self-report	6,654	460	69		
ICPC-coded diagnoses	6,442	461	72	125	11
Reference standard	6,442	506	79	131	11

Abbreviations: ICPC, International Classification of Primary Care

Measures of agreement between the case definitions

All definitions of diagnosed DM showed an almost perfect agreement (kappa > 0.8) with the reference standard (Table 5). For prevalent diagnosed DM, the agreement between self-report and the reference standard was 98% (kappa 0.86) and the agreement between ICPC-coded diagnoses and the reference standard was 99% (kappa 0.95). The agreement between self-report and ICPC-coded diagnoses for prevalent diagnosed DM was 98% (kappa 0.87). Of the participants with self-reported DM who did not use glucose lowering medication, 68% had an ICPC-coded diagnosis for prevalent diagnosed DM. For incident diagnosed DM, the agreement between ICPC-coded diagnoses of incident DM and the reference standard of incident DM was 99% (kappa 0.92).

Exclusion of participants with a fasting plasma glucose > 7.0 mmol/L at baseline

Of all participants without an ICPC-coded diagnosis DM at baseline (n=5,981), 203 participants had a fasting plasma glucose concentration above the upper limit of 7.0 mmol/L at baseline, as was reported to them in the test results letter. After exclusion of these participants, 5,778 participants were at risk of DM. During a total of 11,531 person-years of follow-up, 63 (11 per 1000) participants were defined as having incident DM according to ICPC-coded diagnoses, giving an overall incidence of 5 per 1000 person-years.

Table 5 Measures of agreement and 95% confidence interval between the reference standard and the case definitions for the definition of diagnosed diabetes in participants of the Netherlands Epidemiology of Obesity study

	Prevalent diagnosed diabetes		Incident diagnosed diabetes
	Self-report (n=6,426)	ICPC-coded diagnoses (n=6,442)	ICPC-coded diagnoses (n=5,935)
Kappa	0.86 (0.84 – 0.89)	0.95 (0.93 – 0.96)	0.92 (0.88 – 0.96)
Sensitivity	82 (79 – 86)	91 (88 – 93)	86 (79 – 92)
Specificity	99.5 (99.3 – 99.6)	100 (99.9 – 100)	100 (99.9 – 100)
Positive predictive value	93 (90 – 95)	99.8 (98.8 – 100)	99.1 (95.2 – 100)
Negative predictive value	98.5 (98.2 – 98.8)	99.2 (99.0 – 99.4)	99.7 (99.5 – 99.8)
Likelihood ratio of positive test	157 (110 – 224)	5396 (760 – 3.8 * 10^4)	5001 (704 – 3.6 * 10^4)
Likelihood ratio of negative test	0.18 (0.15 – 0.22)	0.09 (0.07 – 0.12)	0.14 (0.09 – 0.21)

Abbreviations: ICPC, International Classification of Primary Care

Of all participants without DM at baseline according to the reference standard (n=5,936), 189 participants had a fasting plasma glucose concentration above the upper limit of 7.0 mmol/L at baseline. After exclusion of these participants, 5,747 participants were at risk of DM. During a total of 11,459 person-years of follow-up, 74 (13 per 1000) participants were defined as having incident DM according to the reference standard, giving an overall incidence of 6 per 1000 person-years.

The agreement between ICPC-coded diagnoses of incident DM and the reference standard was 99% (kappa 0.89).

Discussion

In this study, we aimed to examine ICPC-coded diagnoses of DM from electronic health records as an alternative to self-reported DM for the definition of case status in epidemiological studies. Both self-report and ICPC-coded diagnoses from electronic health records had an excellent agreement with the reference standard for the definition of DM diagnosis. Case definition with information from electronic health records provided a high follow-up rate of 97% and detailed health information was obtained.

In our study, we found a kappa value of 0.86 for self-reported DM compared with the reference standard. This is in line with previous studies that reported kappa values of 0.71 to 0.92 for self-reported DM compared with diagnoses in medical records.(57-61) We observed that the agreement between ICPC-coded diagnosis and the reference standard was higher, with a kappa value of 0.95 for prevalent DM and 0.92 for incident DM. This means that GPs code the diagnosis DM accurately in the electronic health records and this finding supports our hypothesis that extracting ICPC-coded diagnoses from electronic health records in the Netherlands is a valid and better alternative to self-reported DM.

A strength of this study is the availability of information from electronic health records of most the participants of the NEO study to make a reference standard of DM. In addition to comparing the feasibility and validity of ICPC-coded diagnosis from electronic health records with a reference standard, we could compare the results with DM by self-report, one of the most commonly used methods for DM diagnosis definitions in epidemiological studies.

A limitation of this study is that there is no gold standard for DM diagnosis. The DM definition for epidemiological studies according to the World Health Organization is a fasting plasma glucose ≥ 7.0 mmol/L, history of diabetes diagnosis, or use of insulin or oral glucose-lowering medication.(68, 69) However, the methods needed for this definition were not specified. We used a reference standard developed by the Diabetes adjudication committee of the NEO study using all information from the GP database, including diagnoses, consultation notes, and prescriptions. Because DM type 2 is mainly diagnosed and treated in general practice, this reference standard reflects the known diagnoses of DM in the general population. A new diagnosis of DM is not based on a single fasting plasma glucose, but requires confirmatory symptoms or laboratory tests on another day.(69) In our study, the fasting plasma glucose concentrations were not measured twice at baseline nor during the follow-up of this study, therefore unknown and undiagnosed DM could not be identified. Nevertheless, we showed that using ICPC-coded diagnoses is a valid method for the case definition of known DM in the population.

After the baseline study visit, all participants received a letter informing them about their fasting plasma glucose concentration and the upper limit of a normal fasting plasma glucose concentration of 7.0 mmol/L. We did not inform the GPs of the participants and do not know if participants with a fasting plasma glucose concentration >7.0 mmol/L consulted their GP with this test result. In a previous study, the onset of DM was estimated to occur 4 to 7 years prior to its clinical diagnosis.(70) Some of the incident DM cases in our study may therefore have been detected early because of the test results. When we considered participants without an ICPC-coded diagnosis of DM, but with a fasting plasma glucose concentration >7.0 mmol/L not at risk of developing DM during follow-up, the incidence of DM using the reference standard was 6 per 1,000 person-years, compared with 11 per 1,000 person-years when these participants were considered at risk of developing DM. The true incidence of DM in a median follow-up of 1.8 years most likely lies between these two estimates. In- or excluding these cases had no influence on the agreement between the ICPC-coded diagnoses and the reference standard. In the future, prospective analyses of the NEO study with DM as an outcome variable and a longer follow-up time, the effect of this potential early detection because of participation in the study will become negligible.

In this study, both participants with DM type 1 and participants with DM type 2 are included in the case definitions of DM diagnoses. We did not make separate subgroups in the case definitions of prevalent DM because both a medical history of DM type 1 and DM type 2 at baseline will be excluded in future prospective analyses on incident DM. Seven percent of all patients with DM aged between 50 and 59 years in the Netherlands have been diagnosed with DM type 1.(71) With regard to incident DM, we assume that almost all participants with incident DM are diagnosed with DM type 2, because DM type 1 is usually diagnosed before the age of 30 years.(72)

An advantage of using electronic health records for the follow-up of cohort studies is the high follow-up rate of 97%. The response rate of a follow-up questionnaire may be substantially lower. For example, the response rate of a follow-up questionnaire of the NEO study sent to the participants in 2013 was 78%. A higher follow-up rate increases the statistical power of the study and selection bias is less likely to occur.(73) Moreover, the reasons why we were unable to obtain health information from electronic health records are likely to be unrelated to the diagnosis DM. For future data extractions, we aim to trace the current GP of the participants with missing GP information. The high follow-up rate in combination with the excellent agreement with the reference standard supports that the ICPC-coded diagnoses of DM are a valid and better alternative than self-reported DM.

Another advantage of using general practice electronic health records is that these records are a great source of information. In the NEO study, 1,230 different ICPC-codes are registered in the obtained information from the electronic health records. In addition, detailed information about diseases is available in the consultation notes. In cohort studies, the number of obtained diseases via questionnaires is much lower (10-56 diseases) and often limited to the presence of a diagnosis and the year of diagnosis.(74) However, the validity of ICPC-coded diagnoses must be investigated for each disease.

Worldwide, electronic general practice data is increasingly used to conduct research.(75) ICPC-coded diagnoses of DM from general practice data are probably also a valid source for case-definitions in other countries with a primary care system that is comparable with that in the Netherlands, like in the United Kingdom. In addition, in many countries, an infrastructure for GP data-sharing is implemented in general practices to develop a research data warehouse.(76) In the NEO study, a Dutch research data warehouse will be used in future follow-up. A research data warehouse will reduce the time and costs related to the collection of diagnoses and other medical information and will make the use of GP data for researchers even more feasible.

In conclusion, the excellent agreement with the reference standard in combination with the high follow-up rate supports that ICPC-coded diagnoses of DM are a feasible, valid and a better alternative to self-reported diagnoses of DM for ascertainment of DM cases in large cohort studies.

Appendix 1 Method of data extraction from general practice electronic health records

The Dutch health care system

In the Netherlands, almost every citizen is registered with a general practitioner (GP), the gatekeeper to secondary care. GPs use a primary care ICT system to store health information about their patients: e.g., demographic details, International Classification of Primary Care (ICPC) coded medical history, consultation notes, hospital discharge records, laboratory and other test results, and prescriptions. Almost twenty different primary care ICT systems are used and store health information in a different way.(65)

Contact general practitioners

To allow access to the electronic health records, both written and oral informed consent were obtained from the participants. At the baseline visit, the participants reported their current GP when they made the appointment for the study visit. Data from the electronic health records of the participants were collected between April 2012 and November 2014. The general practices received a letter with a request to extract data from the electronic health records of the participants in their general practice. This letter included information about the Netherlands Epidemiology of Obesity (NEO) study, data extraction, compensation for the extraction, and the possibility to receive the protocol of extraction and a copy of the informed consent forms. After two weeks, a research nurse contacted the general practice to schedule an appointment for extraction. The documentation concerning these contacts was managed in a database at the NEO study centre in the Leiden University Medical Center (LUMC).

Data extraction

In the general practice, the research nurse accessed the primary care ICT system and marked the participants of the NEO study. Subsequently, the desired information was selected. The selected information was extracted in one or more files. The number of files and file type depended on the primary care ICT system. The extracted files were saved on an encrypted USB device and taken to the NEO study centre. At the NEO study centre, the extracted files were saved on a secured network server in the LUMC. Only authorized employees have access to the extracted files. In case the general practice gave no consent to extract the data or when the general practice was far from the study centre (and had only one or two participants), written information was obtained.

Data processing

To make the data accessible to researchers, all data was converted in a uniform way. Hereto we used STATA statistical software (Statacorp, College Station, TX) version 14. For every primary care ICT system, several do-files need to be made to convert the data. The

most challenging task was the conversion of single text-files into different tables. After creating uniform tables, these files were merged into one multi-table database. Directly identifying data was replaced with a unique NEO identification number. The psuedonymisation key was stored separate from the GP database, only accessible by the head of data management. Researchers only have access to the pseudonymised database.

Appendix 2 Diabetes adjudication committee, full names academic degrees, affiliations

F.R. Rosendaal, MD PhD, Professor of clinical epidemiology, Leiden University Medical Center, The Netherlands

M.E. Numans, MD PhD, Professor of public health and primary care, Leiden University Medical Center, The Netherlands

M.W.M. de Waal, PhD, Coordinator research data warehouse, Leiden University Medical Center, The Netherlands

I. de Jonge, MSc, Research data manager, Leiden University Medical Center, The Netherlands

E.J.P. de Koning, MD PhD, Professor of endocrinology, Leiden University Medical Center, The Netherlands

I.M. Jazet, MD PhD, Internist, Leiden University Medical Center, The Netherlands

M. den Heijer, MD PhD, Professor of endocrinology, VU Medical Center, The Netherlands

D.O. Mook-Kanamori, MD PhD, General practitioner, Leiden University Medical Center, The Netherlands

O.M. Dekkers, MD PhD, Professor of endocrinology, Leiden University Medical Center, The Netherlands

Appendix 3 Estimated time and costs of data extraction and data processing from general practice electronic health in the Netherlands Epidemiology of Obesity study (n=6,671)

	Time (hours)	Costs (euro's)
Data extraction		
Secretariat	400	9,600
Research assistants	2,250	60,000
Data management	200	5,700
Travel expenses		5,000
Compensation for the general practices		11,500
Data processing		
Data management	2,000	57,000
Total	4,850	148,800

CHAPTER 3

Incidental findings in research: a focus group study about the perspective of the research participant

de Boer AW, Drewes YM, de Mutsert R, Numans ME, den Heijer M, Dekkers OM, de Roos A, Lamb HJ, Blom JW, Reis R

JMRI. 2018;47(1):230-237

Abstract

Purpose To explore the experiences and preferences of healthy research participants to whom an incidental finding was communicated.

Materials and methods Of the 2,580 participants of the Netherlands Epidemiology of Obesity (NEO) study who underwent MRI scanning of the abdomen, heart and/or brain, an incidental finding with presumed health importance was disclosed to 56 (2%) participants. These participants were invited to discuss their experiences regarding the communication of the finding by the NEO research team in a focus group discussion. Transcripts of the discussions were analysed using thematic content analysis with an open coding system.

Results Twenty-three persons participated in four discussions; 57% male; mean age 58 years; 74% findings were suspect for a malignancy. Overall, the participants were grateful for the disclosure of the incidental finding. They had assumed that any finding would be disclosed, and this was an important reason to participate in research. None regretted their informed consent to be notified about incidental findings. Disclosure of the finding had great impact on the lives of most participants. Difficulties with the transition from research participant to patient were frequently mentioned.

Conclusion This study provides information to improve the communication of incidental findings by 1. giving clear information about which findings will be disclosed and 2. demarcating the transition from research participant to patient, by making clear arrangements with medical specialists to guarantee careful follow-up of the finding.

Introduction

In research projects involving healthy volunteers, medical data is collected without clinical indication. The procedures have the potential to yield information that is outside the scope of the original research, but may be of potential health importance for the participant. The prevalence of such incidental findings varies greatly with the kind of tests performed in research projects, or with population characteristics of participants. In research projects using brain magnetic resonance imaging (MRI), for example, the overall prevalence of incidental findings is 2.7%(77) and in projects using whole-body MRI a prevalence of 32% has been reported(78).

Consensus exists that incidental findings of potential health importance have to be disclosed to the research participants in any case.(25) Researchers should describe the process of communication of incidental findings as part of their research protocol.(25) However, the communication of incidental findings raise many questions for the researchers, e.g. how to define the health importance of the findings, how to explain the risks and benefits of discovering incidental findings in the informed consent process, how to disclose such findings, and how to organize the medical follow-up of incidental findings. Because many persons participate in research each year(23), attention for the communication of incidental findings is needed.

Currently, there is no legal precedent concerning the communication of incidental findings. In the literature, existing recommendations regarding the communication of incidental findings are generally based on ethical, legal, scientific and clinical perspectives. A recent study observed that little is known about the perspectives of the research participants themselves who are confronted with incidental findings.(79) Therefore, the aim of this qualitative study was to explore the experiences and preferences of healthy research participants to whom an incidental finding detected on MRI was communicated. MRI was chosen as it is frequently used for research applications and it often generates incidental findings. With this exploration we aim to improve the communication of incidental findings in research.

Methods

Methodological approach

The medical ethics committee approved this study and all participants gave informed consent. We have used the COREQ checklist to guide the design of the study and reporting of the data.(80) In August 2013, four focus group discussions were conducted with participants of the Netherlands Epidemiology of Obesity (NEO) study, who had been confronted with an incidental finding detected on MRI of the abdomen, heart or brain, made for research purposes. The NEO study is a non-clinical prospective cohort study in healthy individuals.(52)

A qualitative research method was chosen to allow participants to articulate and discuss their own experiences and preferences regarding the communication of incidental findings. In line with the exploratory aim of our study, focus group discussions were carried out instead of individual interviews as this method allows for interaction between the participants, and thus elicit a multiplicity of views within a group context.(81) A qualitative study design is characterised by collection of non-numerical data. Every statement is equally important for in-depth understanding of the research topic, irrespective of how frequent it is stated.(82) Moreover, frequencies cannot be measured due to the group context where topics are not explicitly addressed by each participant.

Study population

Of the 2,580 participants of the NEO study who underwent MRI scanning of the abdomen, heart or brain, an incidental finding was disclosed to 56 (2%) participants. The process of communication of incidental findings in the NEO study is described in more detail in Table 1. In July 2013, these 56 participants were invited by a letter to participate in a focus group discussion. After two weeks a reminder was sent by e-mail to the non-responders. The participants who were willing to participate in a focus group discussion were divided over four focus group discussions according to their preferred date and time.

Interview guide

A topic list was used as interview guide to explore the experiences and preferences of participants to whom an incidental finding was communicated. The topic list was based on the process of the communication of incidental findings in the NEO study. The first section addressed participants' experiences of the informed consent of disclosure of incidental findings, the way of disclosure, and the follow-up after disclosure. Thereafter, the topic list focused on participation in research in general. The interview guide was piloted in two semi-structured interviews with two randomly selected participants who were confronted with an incidental finding. After the two semi-structured interviews, minor adjustments were made to the interview guide.

Focus group discussions

The focus group discussions were led by the first author (AWB), assisted by a second researcher (JWB). Each focus group discussion (5-7 participants per group) lasted approximately 75 minutes. The researchers made notes after each discussion. With the consent of participants, the focus group discussions were recorded and transcribed verbatim. Data saturation was reached after four focus group discussions.

Coding and analysis

The transcripts were independently read and analyzed by two researchers (AWB and YMD) using thematic content analysis with an open coding system.(82) The coding system was grounded in the data to generate a comprehensive understanding of the experiences and preferences of the participants.(83) Emerging themes were organized in an analytical framework for axial coding; this was discussed by three researchers (AWB, YMD and RR) until consensus was reached. New codes were added when considered necessary. No qualitative software was used in the analysis of the qualitative data. After coding, the data were sorted according to the themes. Quotations were selected to illustrate each theme.

Table 1 Communication of incidental findings in the Netherlands Epidemiology of Obesity (NEO) study

A random subset of 35% participants without contraindications were invited to undergo magnetic resonance imaging (MRI) of abdominal subcutaneous and visceral fat, and pulse wave velocity of the aorta (n = 2,580), in combination with either cardiac function (n = 1,207), or the brain (n = 1,212) according to standardized protocols. Contraindications were metallic devices, claustrophobia, and a body circumference > 1.70 m. All scans were obtained with an MR system operating at a field strength of 1.5 Tesla (*Philips Medical Systems, Best, Netherlands*). The MRI scan were made for research purposes to study, for example, fat depots, cardiac function and brain morphology, and therefore not performed in accordance with the procedure of a clinically MRI scan. As a result, the quality of the images of the MRI scan may be not good enough to detect all abnormalities. The NEO study was approved by the medical ethics committee and all participants gave informed consent.
Informed consent process
Participants were recruited via general practitioners (GPs), municipal registers and advertisements. Extensive study information was sent to those who were interested to participate, along with a questionnaire and invitation for the baseline visit. In the extensive information the communication of incidental findings on the MRI scan was indicated.
"In principle, you do not receive the result of the MRI scan. The images of the MRI scan will be interpreted by a radiologist. When unexpected abnormalities are found that are likely to have serious health consequences when left undiagnosed, we will contact you and your GP within four weeks after the MRI scan. However, when no unexpected abnormalities are identified, this will not completely exclude medical abnormalities, as the quality of the images of the MRI scan performed for the NEO study may be not as good as an MRI scan for medical diagnostics."

Table 1 Continued

At the baseline visit, informed consent was obtained by trained staff. The participants were asked whether they wished to be notified of incidental findings on the MRI scan that are likely to have serious health consequences when left undiagnosed. During the informed consent process and the baseline visit there were many opportunities to raise questions to the research staff.
Disclosure of incidental findings All MRI scans were interpreted by radiologists. In case of an incidental finding with potential health importance, the imaging report was sent to an independent internist-researcher. Thereafter, the incidental finding was verified and its importance determined by protocol. An expert was consulted about the incidental finding when needed. Incidental findings with a suspicion of a malignancy, aortic aneurysms, brain aneurysms, and subdural hematomas were defined as incidental findings that were likely to have serious health consequences when left undiagnosed. Those incidental findings were disclosed by the internist-researcher to the participant and/or the GP, accompanied by either an advice for further work-up in general practice or an appointment with a medical specialist. Incidental findings with a high suspicion of a malignancy were disclosed immediately (median time from MRI scan to disclosure 10 days). The priority of the appointment with a medical specialist was based on the severity of the incidental finding. Within two weeks after the baseline visit, all participants received a letter with the results of tests on blood pressure, serum cholesterol concentrations, fasting or non-fasting plasma glucose, renal function, lung function, and bone mineral density. The disclosure of incidental findings was a separate pathway and therefore not related to the disclosure of other test results. In general, these test results were disclosed earlier than the disclosure of incidental findings on the MRI.
Follow-up procedures The GP or medical specialist was responsible for medical follow-up of the incidental finding. In this country, every citizen is legally obliged to take out health insurance, covering common medical care. The data of the MRI scans was stored anonymously at the research center, and therefore not available in the medical record of the participant. The NEO study did not provide aftercare for the participants with an incidental finding.

Results

Of the 56 persons who were invited to participate in this qualitative study, 31 did not participate in the focus group discussion. Of these, 18 persons responded they could not participate due to illness (n=1), vacation (n=5), other obligations (n=1) or no reason was reported (n=11), 13 persons did not respond. After two semi-structured interviews, 23 persons (41%) confronted with an incidental finding participated in four focus group discussions. The participants seemed to have more often a suspicion of a malignancy than non-participants. The baseline characteristics of the participants and non-participants are shown in Table 2.

Table 2 Baseline characteristics of the participants and non-participants of the focus group discussions

Characteristics	Participants focus group discussions (n=23)	Non-participants focus group discussions (n=33)[a]
Mean (SD) age, years	58 (5)	55 (7)
Sex, men	13 (57%)	19 (58%)
Type incidental finding		
Suspect for a malignancy	17 (74%)	16 (49%)
Aortic aneurysm	4 (17%)	6 (18%)
Brain aneurysm	1 (4%)	0
Subdural hematoma	0	1 (3%)
Other	1 (4%)	10 (30%)
Median (IQR) time from MRI scan to disclosure, days	34 (18-87)	55 (34-92)

Values are numbers (percentage) unless stated otherwise

Abbreviations: IQR,interquartile range; MRI, magnetic resonance imaging

[a] Including two participants who took part in the semi-structured interviews to pilot the interview guide for the focus group discussions

The experiences and preferences of the participants were clustered around six overarching themes: reasons for participation in the original study, informed consent process, disclosure of the incidental finding, transition from research to medical care, medical follow-up of the incidental finding and impact of the incidental finding. A summary of the findings is presented in Table 3.

Reasons for participation in the original study

The disclosure of test results, including results of the MRI scan, was an important reason to participate in the NEO study. Either to receive confirmation of good health, or to detect disease at an early stage:

"I wanted to prove that I was healthy" (Participant 04)

Informed consent process

In general, the participants were satisfied with the information they received about the communication of incidental findings in the informed consent process, although many participants had assumed that all incidental findings would be disclosed, not just incidental findings with serious health consequences:

"Why did they not disclose my back disorder, my general practitioner was already informed" (Participant 18)

All participants of the NEO study who underwent MRI wished to be notified of incidental findings on the MRI scan. The risk of discovering an incidental finding was perceived as a benefit to participate in this study:

*"But why would you participate (*if you don't want to know the MRI outcome*)? Someone else (*could participate*) instead of you" (Participant 05)*

In one focus group discussion the differences with incidental findings in genetic research were discussed. The participants felt that disclosure of incidental findings in genetic research could be burdensome: for example in relation to getting insurances or for what it means for their family members. Therefore they may not wish to be notified of incidental findings in genetic research.

Disclosure of the incidental finding

The participants expected that incidental findings would be disclosed quickly after the MRI scan. Mainly at the beginning of the NEO study several participants experienced more than one month between the MRI scan and disclosure of the incidental finding, which was considered too long. The participants were satisfied by whom the incidental finding was disclosed, either by the researcher or the general practitioner (GP). Irrespective of the GP's role in the disclosure, they preferred the researcher to inform their GP. The participants preferred not to inform their GP themselves, as was the case for a few participants. Disclosure was by telephone or by letter, but neither were preferred. The disclosure of an incidental finding after other (negative) test results had been disclosed (e.g. laboratory test results, within two weeks after the baseline visit) was experienced as confusing, because an abnormal result of the MRI was not expected anymore. The participants perceived not receiving any abnormal results as proof of being completely healthy.

Transition from research to medical care

The most intensely discussed theme in the focus group discussion was the transition from research to medical care. From the perspective of the NEO research team the disclosure of

an incidental finding to a research participant clearly marked his or her transition to being a patient. However, for participants this was ambiguous: they did not clearly distinguish between participating in research and entering medical care. An important issue was the felt need to have a timely appointment with a medical specialist. This was discussed in terms of reciprocity: in return of their research participation, they expected that researchers would make an effort to organize quick follow-up of the incidental finding:

"You cooperated here (in the hospital)*, so then you think, hey, shouldn't I have a little bit of priority?" (Participant 08)*

During the follow-up of the incidental finding, they were surprised that not all GPs and medical specialist were familiar with the NEO study:

"Nobody knew about what NEO was, even though it (the study) *is conducted in the same building" (Participant 01)*

Moreover, they expected that all information about the incidental finding, including the MRI scan would be available to the GP and medical specialist, whereas the data of the MRI scans was stored anonymously, and therefore not available in the medical record of the participant. In addition, they expected that all members of the research team would be informed about the disclosure of an incidental finding, especially the contact person of the study. In practice information about the disclosure of an incidental finding was available to the contact person after consulting a database.

Medical follow-up of the incidental finding

The period between disclosure of the incidental finding and the follow-up of the incidental finding by a GP or medical specialist was a worrying and uncertain time for many participants:

"Normally, a month flies by quickly, but then a month is 31 days, and that is 31 times 24 hours" (Participant 01)

"The rock-solid confidence in one's body is momentarily gone" (Participant 03)

During the follow-up of the incidental finding, the participants expected their GP to mainly give support.

Aftercare by the NEO study team for participants with an incidental finding was not expected, though it would be much appreciated. They were pleased to participate in

the focus group discussions to share their experiences with other participants This was experienced as a form of aftercare.

Impact of the incidental finding

After disclosure of the incidental finding, the participants had reacted in different ways, such as by seeking information, denial, or anticipation of possible consequences. After medical follow-up, most participants had required (surgical) treatment. At the time of the focus group discussions, consequences of the incidental finding varied widely. Some participants did not experience any ongoing consequences. Others experienced physical consequences, such as functional status decline. Mental consequences were also mentioned as some participants were more alert for symptoms or had feelings of distress and anxiety:

> *"Of course there is a ticking time bomb somewhere."(Monitored but no primary tumour found at the moment) (Participant 09)*

All participants reported that they had been happy to participate in the NEO study, and grateful for the disclosure of an incidental finding. They emphasized the serendipity of participation, of being part of the subset who underwent an MRI scan, and of the discovery of an incidental finding:

> *"I don't win the lottery either" [diagnosis of cancer at an early stage] (Participant 04)*

Table 3 Overarching themes and findings expressed by participants confronted with an incidental finding

Theme	Findings
Reasons for participation in the original study	Disclosure of positive or negative test results and the risk of discovering an incidental finding were reasons for participation.
Informed consent process	Many participants assumed that all incidental findings were disclosed. All participants wished to be notified of incidental findings. This may be different for incidental findings in genetic research.
Disclosure of the incidental finding	More than one month between the MRI scan and disclosure of the incidental finding was considered too long. There was no clear preference for disclosure by telephone or by letter. Preference that the research team informs the participant's GP, instead of by the participants themselves. The two separate pathways of disclosure of the different test results were not clear. The disclosure of an incidental finding later than the disclosure of other test results (e.g. laboratory test results, within two weeks after the baseline visit) was experienced as confusing, because an abnormal result was not expected anymore. Participants perceived not receiving any abnormal results as being completely healthy.
Transition from research to medical care	Participants had difficulties with the transition from research participant to the patient role. In return of their participation, they expected rapid access to follow-up of the incidental finding. Participants expect that all research information about the incidental finding will be consigned to the GP or medical specialist. Participants expect that the whole research team was informed about the disclosure of incidental findings.
Medical follow-up of the incidental finding	Period between disclosure and the follow-up of the incidental finding by a GP or medical specialist was a worrying and uncertain time. The participants considered it the role of their GP to give support. Participants experienced the focus group discussions as aftercare.
Impact of the incidental finding	There was a wide variety in short-term and long-term consequences of the incidental finding. All participants were happy with participation and grateful for the disclosure of an incidental finding.

Abbreviations: GP, general practitioner; MRI, magnetic resonance imaging

Discussion

All participants in this study were grateful for the disclosure of an incidental finding. Disclosure of the incidental finding had great impact on the lives of most participants, which emphasizes the importance of guidance on how to manage incidental findings in research. The most intensely discussed theme in the focus group discussions with research participants was the transition of being a research participant to being a patient, including the need of quickly entering follow-up procedures, the expectation that all information about the incidental finding will be consigned to the GP or medical specialist, and the expectation that the whole research team will be informed about the disclosure of incidental findings. This is line with the finding that the disclosure of test results motivated participants to take part in the NEO study.

The participants in this study assumed that any clinical problem would be identified and disclosed. Although this was mentioned in the study information, they apparently did not realize that the MRI scan was not optimized for clinical diagnosis and that only incidental findings with serious health consequences would be disclosed. As a consequence the participants misinterpreted not receiving abnormal results as proof of being completely healthy. It is known that informed consent is frequently not understood by the participants.(84) Half of the participants in neuroimaging research expect all abnormalities to be detected despite being informed otherwise.(85) The most effective intervention to improve understanding is person-to-person interaction, as enhanced consent forms do not appear to result in better understanding.(84) When also other test results are communicated to the participants, participants need clear information about the different pathways of communicating the different results.

All participants in the NEO study wished to be notified of incidental findings. This is in accordance with other studies about incidental findings.(85) In our study, none of the participants confronted with an incidental finding regretted this choice. Some participants did state that genetic incidental findings are different because of the possible consequences for their family or insurance schemes.

According to our study, participants want to be informed about an incidental finding as soon as possible. At the beginning of the NEO study, the responsibilities of interpretation of the MRI scans and verification and disclosure of incidental findings were not assigned to a specific person, which has led to more time from MRI scan to disclosure. The NEO study team therefore revised the procedure on the communication of incidental findings, which decreased the median time from MRI scan to disclosure from 117 days to 41 days. In addition, the radiologists and the internist-researcher of the NEO study team experienced

that it was difficult to interpret the MRI scans without patient characteristics or context. As a consequence more incidental findings were verified and disclosed than originally anticipated in the research protocol, which resulted in a more time-consuming procedure. To be able to provide timely assessment of the test results, with identification of possible incidental findings, and prompt disclosure after identification researchers should make a detailed protocol on how to handle incidental findings before recruitment of participants.

The participants were satisfied by whom the incidental finding was disclosed, which was either by the responsible internist-researcher of the NEO study or their GP. Different opinions on who the best person would be to disclose incidental findings is also found in focus group discussions with participants from the general public.(86) The advantages of disclosure by the participants' GP are the pre-existing relationship between GPs and their patients. In a recent study primary care providers reported that patient's clinical context and personal traits affect how they communicated incidental findings.(87) Moreover, when the finding is not disclosed by a member of the research team, this will demarcate the transition from participating in research to entering medical care. Disadvantages are the violation of the participant's privacy, and the time the GP has to spend on communicating the incidental findings. When researchers decide to disclose the incidental findings to GPs, this way of disclosure has to be communicated in the informed consent process.(25)

A frequently mentioned topic was the need of rapid access to follow-up procedures, the expectation of which was discussed in terms of reciprocity. In the literature about the communication of incidental findings, there is an ethical and legal trend that researchers have duties toward research participants.(25) This includes timely disclosure of incidental findings to maximize benefits and minimize harms. Based on this trend, researchers should make arrangements with medical specialists before start of a research project to guarantee quick follow-up of the incidental finding. In reality this may be complicated, as in our healthcare system appointments with medical specialists are mainly based on triage, whereby the priority of care is based on the severity of the condition.

In our study, the participants did not clearly distinguish between participating in research and entering medical care. This is also been described in a previous study, where participants refer to researchers as doctors with medical knowledge.(88) To improve the transition from research participant to patient, several suggestions can be made on the basis of our findings. First, the medical specialists who may have to contribute in the follow-up of the incidental findings have to be informed before the start of the project, and during the research project for example by regular updates or when the follow-up of a specific participant is planned. Furthermore the test results, in this case the MRI scan, have to be promptly made available to the GP or the medical specialist in the follow-up

process. And last, the contact persons of the research team have to be updated on the disclosure of an incidental finding to a specific participant and, in general, instructed on how to handle questions about the incidental findings. Implementation of these suggestions takes time, though, they may be necessary to guarantee careful follow-up.

Researchers can consider organizing a meeting to provide peer-to-peer support for participants with an incidental finding. The participants in our study stated that this would be much appreciated. However, evidence about the effects of such intervention on wellbeing is lacking and should be investigated.

All participants were grateful for the disclosure of an incidental finding. This may be seen as a reason to support this policy. However, the disclosure of incidental findings is most likely an example of a system with lack of negative feedback. Previous research on cancer screening described that patients are positive about screening regardless of the outcome; persons with a negative screening result are grateful for reassurance and a positive result makes a person grateful for early detection.(89)

Previous studies mainly focused on the ethical, juridical and clinical perspectives.(25) With this study population we were able to explore the experiences and preferences from an insider's perspective.

Our study population consisted of twenty-three participants, a relatively small sample size compared with quantitative studies. In addition, the participants in our study seemed to have more often a suspicion of a malignancy than non-participants. As a consequence, our results may not be representative for other populations. However, representation of the total population is of less importance due to the exploratory aim of the research.(82)

The generalizability of our findings to other procedures may be limited due to a healthy research population and the specific characteristics of the communication of incidental findings in the NEO study. It is possible that experiences and preferences are different in genetic research, with the disclosure of a broader range of incidental findings, or in the course of clinical care or screening. More research is needed to explore these fields. However, we expect that the overarching themes are relevant to all types of procedures.

In conclusion, the findings of the focus group discussions support the need for guidance on how to communicate incidental findings in research. The perspective of the individual confronted with an incidental finding is a valuable addition to the current debate on incidental findings, where the perspective of research participants confronted with incidental findings was lacking. Before recruitment of the participants, researchers should design a

detailed protocol for the communication of incidental findings, including clear informed consent information, a protocol to guarantee timely disclosure and arrangements with medical specialists.

CHAPTER 4

Advantages and disadvantages of unstructured cardiovascular risk factor screening for follow-up in primary care

de Boer AW, de Mutsert R, den Heijer M, Rosendaal FR,
Jukema JW, Blom JW, Numans ME

Eur J Prev Cardiol. 2016;23(11):1195-201

Abstract

Background In contrast to structured, integrated risk assessment in primary care, unstructured risk factor screening outside primary care and corresponding recommendations to consult a general practitioner (GP) are often based on one abnormal value of a single risk factor. This study investigates the advantages and disadvantages of unstructured screening of blood pressure and cholesterol outside primary care.

Methods After the baseline visit of the Netherlands Epidemiology of Obesity study (population-based prospective cohort study in persons aged 45-65 years, recruited 2008-2012) all participants received a letter with results of blood pressure and cholesterol, and a recommendation to consult a GP if results were abnormal. Four years after the start of the study, participants received a questionnaire about the follow-up of their results.

Results The study population consisted of 6,343 participants, 48% men, mean age 56 years, mean BMI 30 kg/m^2. Of all participants 66% had an abnormal result and, of these, 49% had a treatment indication based on the risk estimation system SCORE-NL 2006. Of the 25% of the participants who did not consult a GP, 40% had a treatment indication. Of the participants with an abnormal result 19% were worried, of whom 60% had no treatment indication.

Conclusions In this population 51% of the participants with an abnormal result had unnecessarily received a recommendation to consult a GP, and 10% was unnecessarily worried. GPs should be informed about the complete risk assessment, and only participants at intermediate or high risk should receive a recommendation to consult a GP.

Introduction

The current strategy to reduce morbidity and mortality due to cardiovascular disease (CVD) is based on structured risk factor screening and management, carried out in primary care.(30, 90) In the past decade, cardiovascular risk management strategies have shifted from single risk factor screening and treatment towards structured multifactorial risk management using risk estimation systems as Framingham, SCORE, QRISK, and PROCAM.(28) In these risk estimation systems, risk assessment is based on analysis and weighing of risk factors to assess whether individual preventive treatment is indicated.(28)

However, single cardiovascular risk factors are still being measured without being part of a structured risk management program, e.g. in occupational health, for research purposes, or in incidentally offered health checkups at pharmacies or by private companies.(43-45) In the Netherlands, every year 1,875,000 individuals undergo health checks outside primary care.(91) In addition, another 317,000 individuals are involved in research each year(23) in which risk factors are often measured. Unstructured risk factor screening and corresponding recommendations to consult a general practitioner (GP) are often based on one abnormal risk factor only. As a result, patients may consult their GP with incomplete results of risk factors and this does not always lead to treatment. As a consequence, many persons may enter healthcare procedures unnecessarily and/or may be unnecessarily worried. On the other hand, unstructured risk factor screening offers an opportunity to identify all high-risk patients in primary care; however, not all individuals undergoing unstructured tests consult their GP after receiving an abnormal result.(43, 92-94)

The aim of the present study was to investigate the advantages and disadvantages of unstructured risk factor screening outside primary care for both patients and GPs, as estimated from a population-based study.

Methods

Study design and study population

The Netherlands Epidemiology of Obesity (NEO) study is a population-based prospective cohort study in persons aged 45-65 years, with an oversampling of participants with a body mass index (BMI) ≥ 27 kg/m². The study design has been described elsewhere.(52) Participants with a self-reported BMI ≥ 27 kg/m² were recruited between September 2008 and October 2012 from the greater area of Leiden (the Netherlands) via GPs, municipal registers and advertisements. In one municipality (Leiderdorp) all inhabitants aged 45-65 years were invited irrespective of their BMI, to provide a reference distribution of BMI. Prior to the NEO study visit, participants were asked to complete a questionnaire including details on demographics, lifestyle, and clinical information. During the baseline visit at the NEO study center of the Leiden University Medical Center (LUMC) several measurements were performed, including physical examination and blood sampling.

Within two weeks after the NEO study visit, the participants received a letter with the results of tests on blood pressure, serum cholesterol concentrations, fasting or non-fasting plasma glucose, renal function, lung function, and bone mineral density. When a result was abnormal on the basis of pre-defined cut-off points, a recommendation to consult a GP was indicated. The GP was not informed by the NEO study team about the test results. Four years after the start of the NEO study, we sent a questionnaire to all participants with questions about the follow-up of their test results (Appendix 1).

The medical ethics committee of the LUMC approved the NEO study and all participants gave informed consent.

The present study is a cross-sectional analysis of the baseline data and of the data derived from the questionnaire about the follow-up of their test results. In the NEO study, 183 participants participated twice, with a 3-month to 2.5-year interval in between, to obtain repeated measurements. However, because it was unclear for which of the two study visits these participants had answered the questions about the follow-up of their test results, they were excluded from the present analyses. In addition we excluded participants with missing data for the variables that are needed for cardiovascular risk assessment.

Data collection and definition of risk factors

We used SCORE-NL 2006 to estimate the 10-year risk of a fatal CVD event and corresponding indication for preventive treatment.(29) This method is described in more detail in Appendix 2.

A first-degree family history of myocardial infarction (MI) or stroke, and prevalent CVD, defined as a history of angina pectoris, MI, stroke, aortic aneurysm or peripheral arterial disease, was reported in the questionnaire. Smoking status was dichotomized in current smokers and non-smokers (including former smokers).

At the NEO study visit, body weight and height were measured with a calibrated scale and a vertically fixed, calibrated tape measure. The trained staff reported the height in cm; the weight was rounded to 100g, 1kg was subtracted to correct for the weight of clothing. BMI was calculated by dividing weight (in kg) by the square of height (in meters). Waist circumference (WC) was measured between the border of the lower costal margin and the iliac crest, with a precision of 0.1 cm.

Blood pressure was measured three times on the right arm by an automatic monitor after a 10-min rest in sitting position; the mean of the measurements was used in the analyses.

12-lead electrocardiograms were interpreted to detect left ventricular hypertrophy using the Minnesota Code 3.1 (RV_5/V_6 > 2.6 mV or RI/II/III/aVF > 2 mV or RaVL > 1.2 mV)(95).

Blood samples were taken after an overnight fast. Serum concentrations of cholesterol, albumin, and creatinine, and plasma concentrations of glucose were determined in the central clinical chemistry laboratory of the LUMC. Low-density lipoprotein (LDL) cholesterol concentrations were not determined but were calculated using the Friedewald formula(96). Glomerular filtration rate (eGFR) was estimated using the Modification of Diet in Renal Disease (MDRD).(97) A reduced eGFR was defined as an eGFR <60 ml/min/1.73m² in participants aged <65 years, and an eGFR <45 ml/min/1.73m² in participants aged ≥65 years. Albuminuria was defined as an albumin/creatinine ratio ≥2.5 mg/mmol for men and ≥3.5 mg/mmol for women. Prevalent diabetes mellitus (DM) was defined as a self-reported history of DM, the use of glucose-lowering drugs, or a fasting plasma glucose ≥ 7.0 mmol/L.(98)

Cut-off points of an abnormal result of blood pressure and cholesterol

The cut-off points of blood pressure and serum concentrations of cholesterol were defined as: total cholesterol (TC) > 6.5 mmol/L, high-density lipoprotein (HDL) cholesterol < 1.15 mmol/L, triglyceride > 2.3 mmol/L, TC/HDL ratio > 5, systolic blood pressure (SBP) > 140 mmHg, and diastolic blood pressure > 90 mmHg. Because LDL cholesterol concentrations were not measured, the participants did not receive this result.

Statistical analysis

Baseline characteristics were expressed as mean (SD), or number (percentage). We calcu-

lated the proportion of participants with a recommendation to consult a GP. Also, from the participants with and without a recommendation, we calculated the proportion of participants with a treatment indication using SCORE-NL 2006.

Descriptive statistics were used to summarize the answers to the follow-up questionnaire. The responses "a bit worried" and "very worried" were combined to "worried". Analysis of each question of the questionnaire was restricted to complete cases.

The first 863 participants included in the NEO study completed a questionnaire that did not contain questions about family history of CVD; these participants were considered as having a negative family history of CVD. However, we also performed a sensitivity analysis considering these participants as having a positive family history of CVD.

After December 31 2011 a revised guideline for cardiovascular risk assessment was implemented in the Netherlands.(30) The most important changes in this revised guideline are: estimation of the 10-year risk of a fatal and non-fatal CVD event, use of the SCORE function for patients with DM, and adaptation of the risk estimates for patients with DM or rheumatoid arthritis. In a sensitivity analysis we excluded participants with a study visit after December 31 2011.

In the NEO study there is an oversampling of participants with a BMI ≥27 kg/m^2. In order to translate our results to the general population, adjustments for the oversampling were made by weighting participants towards the BMI distribution of the participants from the Leiderdorp municipality(99, 100) whose BMI distribution was similar to that of the general Dutch population(101). Finally, we divided participants into BMI categories according to the World Health Organization categories(1) and evaluated whether the proportion of participants with a recommendation to consult a GP, and with a treatment indication, differed by BMI category. For all analyses, STATA statistical software (Statacorp, College Station, Texas, USA), version 12 was used.

Results

A total of 6,671 persons were included in the NEO study. Of these, the 183 participants with a second study visit were excluded. After consecutive exclusion of participants with missing data for blood pressure (n=14), cholesterol (n=45), smoking status (n=6), DM (n=19), history of CVD (n=18), WC (n=2), albuminuria (n=26), eGFR (n=14) or electrocardiogram (n=1), 6,343 participants were included in the present analysis. The baseline characteristics of the participants are shown in Table 1.

Table 1 Baseline characteristics of the participants of the Netherlands Epidemiology of Obesity study (n=6,343)

Age (years)	56 (6)
Sex (men)	3,018 (48)
Body mass index (kg/m²)	30 (4,8)
Smoking (current)	1,043 (16)
Systolic blood pressure (mmHg)	133 (17)
Total cholesterol/HDL ratio	4,2 (1,3)
Diabetes mellitus[a]	659 (10)
eGFR (ml/min/1.73m²)	86 (15)
Reduced eGFR[b]	161 (3)
Albuminuria	233 (4)
Left ventricular hypertrophy	109 (2)
First-degree family history of CVD	
≥1 member aged < 60 years	1,409 (22)

Data expressed as mean (SD) or number (percentage)

Abbreviations: CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate

[a] Known and newly diagnosed diabetes mellitus

[b] Reduced eGFR: eGFR <60 ml/min/1.73m² in patients aged <65 years, eGFR <45 ml/min/1.73m² in patients aged ≥65 year

Recommendation to consult a general practitioner

Of the study population, 4,497 (71%) participants had one or more abnormal results and were recommended to consult a GP. Of these, 4,159 (66% of all participants) participants had an abnormal result of blood pressure and/or cholesterol, of whom 1,229 participants had only an abnormal blood pressure result, 1,665 had only an abnormal cholesterol result, and 1,265 participants had both.

Of all participants, 41% of the participants had a treatment indication. Of the participants with an abnormal results of blood pressure and/or cholesterol, 49% had a treatment indication. Of the participants without an abnormal result, 26% had a treatment indica-

tion, which was based on an abnormal result of LDL cholesterol as calculated with the Friedewald formula (Table 2).

Questionnaire about the follow-up of test results

Of the study population, 4,982 (79%) participants responded to the questionnaire about the follow-up of their test results. Compared to the non-responders, the responders were older, had a lower BMI, were more frequently non-smokers, had a lower TC/HDL ratio, a lower eGFR, less frequently DM, and less frequently an abnormal result. The percentage of missing answers to questions was ≤ 1%.

Of the participants who answered the question about the presence of an abnormal result (n=4,933), 3,442 participants had received a recommendation to consult their GP. Of these: 1,541 participants stated in the questionnaire that they had an abnormal result, 511 participants did not know whether they had an abnormal result, and 1,390 participants stated that they had no abnormal result. Of these 1,390 participants, 49% had a treatment indication (Table 3).

Of the 1,642 participants who stated in the questionnaire that they had an abnormal result, 1,637 participants answered the question whether they consulted a GP, of whom 1,209 (74%) participants consulted a GP, 405 (25%) participants did not consult a GP, and

Table 2 SCORE risk categories and treatment indication for all participants (n=6,343)

SCORE-NL 2006(29)	Treatment indication
Prevalent CVD or DM or use of antihypertensive or lipid lowering drugs[a]	No treatment or meeting target levels
	Treatment or not meeting target levels
Definite indication[b]	Treatment
Low risk	No treatment
Intermediate risk[c]	No treatment
	Treatment
High risk	No treatment
	Treatment
Total	Treatment

Abbreviations: CVD, cardiovascular disease; DM, diabetes mellitus

[a] Treatment is indicated when systolic blood pressure ≥ 140 mmHg and/or LDL > 2.5 mmol/L

[b] Systolic blood pressure > 180 mmHg, total cholesterol(TC)/HDL ratio > 8, TC > 8 mmol/l or triglycerides >5 mmol/l

23 (1%) participants did not know. Of the 1,209 participants who consulted a GP, 558 (46%) participants had a treatment indication as calculated with SCORE-NL 2006. The most common actions in general practice were: 1) blood pressure measurement (48%), 2) blood sampling (29%), and 3) reassurance (24%).

Of the 405 participants who did not consult a GP, 162 (40%) participants had a treatment indication as calculated with SCORE-NL 2006. The most common reasons not to consult a GP were: 1) results already known (38%), 2) it does not seem a problem to me (37%), and 3) I do not expect that the GP will do anything (13%).

Of the participants who stated in the questionnaire that they had an abnormal result, 302 (19%) were worried due to the abnormal result. Of these, 60% had no treatment indication as calculated with SCORE-NL 2006.

Of the 863 participants who could not report their family history of CVD, in only seven participants a positive family history would change the treatment indication. In a sensitivity analysis, when we considered these participants as having a positive family history, this did not change the reported proportions (data not shown). Results were similar when participants with a study visit after December 31 2011 (n=1,364) were excluded from the study population (data not shown).

Only abnormal result blood pressure N=1,229	Only abnormal result cholesterol N=1,665	Both abnormal result blood pressure and cholesterol N=1,265	No abnormal result N=2,184	Total N=6,343
N (%)	N (%)	N (%)	N (%)	N (%)
20 (2%)	144 (9%)	18 (1%)	189 (9%)	371 (6%)
542 (44%)	462 (28%)	529 (42%)	541 (25%)[d]	2074 (33%)
24 (2%)	109 (7%)	124 (10%)	0	257 (4%)
542 (44%)	860 (52%)	441 (35%)	1404 (64%)	3247 (51%)
20 (2%)	31 (2%)	26 (2%)	16 (1%)	93 (1%)
66 (5%)	50 (3%)	100 (8%)	22 (1%)[d]	238 (4%)
0	0	0	1 (0%)	1 (0%)
15 (1%)	9 (1%)	27 (2%)	11 (1%)[d]	62 (1%)
647 (53%)	630 (38%)	780 (62%)	574 (26%)[d]	2631 (41%)

[c] Treatment in the intermediate group is dependent on additional risk factors(29)

[d] Treatment indication based on an abnormal result of LDL cholesterol as calculated with the Friedewald formula (LDL cholesterol concentrations were not measured at baseline and therefore not reported to the participants)

After weighting the analyses towards the BMI distribution of the general population, 56% of the participants had an abnormal result of blood pressure and/or cholesterol, and were recommended to consult a GP. Of these, 42% had a treatment indication (Table S2). After stratification by BMI category, the proportions of participants with a treatment indication of the participants with an abnormal result were 33% for BMI <25 kg/m^2, 43% for BMI 25-30 kg/m^2, and 56% for BMI≥30 kg/m^2. Results with regard to the follow-up and worry of the participants were similar (data not shown).

Table 3 Discrepancy between the test result of the baseline visit and follow-up questionnaire (n=4,933)

		Self-reported in follow-up questionnaire			
		No abnormal results	One or more abnormal results	I do not know	Total
		N=2,660	N=1,642	N=631	N=4,933
Test result[a]		N (%)	N (%)	N (%)	N (%)
No abnormal results	Total	1,270 (85%)	101 (7%)	120 (8%)	1,491 (100%)
One or more abnormal results	Total	1,390 (40%)	1,541 (45%)	511 (15%)	3,442 (100%)
	SCORE-NL 2006 treatment indication	677 (41%)	706 (43%)	258 (16%)	1,641 (100%)

[a] Test results of blood pressure, serum cholesterol concentrations, fasting or non-fasting plasma glucose, renal function, lung function, and bone mineral density

Discussion

Sixty-six percent of participants had an abnormal result of blood pressure and/or cholesterol and was recommended to consult their GP. In the general population with a normal BMI distribution, this percentage should be interpreted as 56%. Because half of these participants had no treatment indication, they can be considered as having received an unnecessary recommendation to consult their GP. This was especially the case for those with a low estimated CVD risk. Of all participants, 19% were worried due to the abnormal test result and, of that subgroup, more than half had no treatment indication. Thus, finally, 11% of the population that had unstructured screening can be considered as being unnecessarily worried and unnecessarily entering healthcare procedures, especially those with a low estimated CVD risk. Twenty-five percent of participants with an abnormal result did not consult a GP.

Our finding that 25% of the participants with an abnormal result did not consult a GP is comparable with a survey showing that 27.8% of the self-testers did not consult a physician after performing a self-test.(92) In our study, 40% of the participants with an abnormal result who did not consult a GP, did have an indication for preventive treatment. When only the participants, and not the GPs, are informed about the test results, these high-risk patients would not receive the treatment required to prevent cardiovascular events.

A qualitative study in 20 self-testers reported that little distress was experienced by self-testers who had an abnormal cardiovascular risk factor.(93) In our study, 19% of the participants were worried after receiving an abnormal result, and 10% were unnecessarily worried. Although this percentage is low, it could have been prevented if the recommendation to consult a GP was based on an integrated risk management approach, instead of on a single risk factor.

Strengths of this study are the large study population and the availability of many risk factors allowing to estimate the 10-year CVD risk and corresponding treatment indication using SCORE-NL 2006. Another strength is the availability of information about the follow-up of participants with an abnormal result.

A limitation is that the information on follow-up was based on self-report. There was a remarkable discrepancy between the number of participants who had an abnormal result and therefore received a recommendation to consult a GP, and the number based on self-report. Perhaps participants did not perceive the results as important, or were already aware of the problem, or had simply forgotten about them. Another limitation of our

study is that serum LDL concentration was not measured. Of the participants without an abnormal result, 26% still had a treatment indication based on a calculated LDL >2.5 mmol/L.

After stratification by BMI category the results showed that, with a higher BMI, more participants with an abnormal result had a treatment indication. This is in line with our previous study that showed that overweight is an important factor in risk assessment.(102)

With the introduction of an integrated approach for cardiovascular risk management, GPs have the responsibility to assess and follow-up cardiovascular risk factors. Unstructured testing outside primary care may be an opportunity for GPs to acquire information on risk factors in their patient population. However, the present study shows that not all participants with an abnormal result consult a GP. Therefore, it is important that the test provider informs the GPs about all the test results. In addition to the test results, it would be efficient to send a complete risk assessment to the GP, and only those participants at intermediate or high risk should receive a recommendation to consult a GP. Hopefully this may reduce the burden of unnecessarily entering healthcare procedures and prevent participants from being unnecessarily worried.

If either blood pressure *or* cholesterol is measured in the screening, a complete risk assessment cannot be made. Even in that case, the maximum risk can be estimated based on information about sex, age, smoking status, use of antihypertensive or lipid lowering drugs, and history of CVD or DM. The estimated maximum risk can guide the decision as to whether or not to recommend consultation of a GP.

Our findings suggest that it is important to inform the GP and the participant about all the test results, including the complete risk assessment. Only participants who are assessed to have an intermediate or high risk should receive a recommendation to consult their GP.

Appendix 1 Follow-up questionnaire with questions about the test results

Question	Possible answers
To what extent were you worried prior to receiving the test results?	Not worried A bit worried Very worried
Did you receive a recommendation to consult a general practitioner based on an abnormal result?	Yes No I do not know
Did you expect an abnormal result?	Yes No I had no expectations
What was your reaction to the recommendation to consult your general practitioner?	Not worried A bit worried Very worried
Did you consult your general practitioner after this recommendation?	Yes a new consultation Yes a regular consultation No I do not know
What were the follow-up actions of your general practitioner?	Blood sampling Blood pressure measurement Physical examination Information about healthy lifestyle Lung function test Referral to a dietician Referral to a specialist Prescription of medication Reassurance No action taken Do not remember Other, …

Why did you not consult your general practitioner?	Results already known It does not seem a problem to me I do not expect that the general practitioner will do something I do not trust the results I dread to think of the consequences Do not want to/no time I do not remember Other, …

Appendix 2 Cardiovascular risk assessment in primary care

We used SCORE-NL 2006 to estimate the 10-year risk of a fatal cardiovascular event and corresponding indication for preventive treatment.(29) The SCORE function is based on Dutch cohorts and is conceptually similar to risk estimation systems used elsewhere.(28) The SCORE function can be used for patients aged 40-65 years and includes sex, age, smoking status, systolic blood pressure (SBP), and total cholesterol/high-density lipoprotein (TC/HDL) ratio. The risk of participants with a SBP <120 mmHg or TC/HDL ratio <4 is calculated using SBP of 120 mmHg or TC/HDL ratio of 4.

For the indication for preventive treatment, the risk estimates were categorized into low, intermediate and high risk, corresponding to the 10-year risk of a fatal cardiovascular event of < 5%, 5-9%, and ≥10%, respectively. According to SCORE-NL 2006, in the category 'low risk' no treatment is indicated. In the category 'intermediate risk' treatment is indicated when SBP ≥ 140 mmHg and/or low-density lipoprotein (LDL) > 2.5 mmol/L and at least one additional risk factor is present. Additional risk factors are: a first-degree relative with a cardiovascular event before age 60 years; body mass index > 30 kg/m², waist circumference > 88 cm for women or > 102 cm for men; end organ damage (albuminuria, a reduced estimated glomerular filtration rate, or left ventricular hypertrophy). In the category 'high risk' treatment is indicated when SBP ≥ 140 mmHg and/or LDL > 2.5 mmol/L. Individuals with a SBP > 180 mmHg, TC/HDL ratio > 8, TC > 8 mmol/L or triglycerides >5 mmol/L have a definite treatment indication regardless of the estimated risk. Patients with diabetes mellitus or cardiovascular disease have a treatment indication when SBP ≥ 140 mmHg and/or LDL > 2.5 mmol/L. The recommended target SBP and serum LDL concentration for patients using antihypertensive or lipid-lowering drugs is SBP < 140 mmHg or LDL < 2.5 mmol/L.

CHAPTER 5

Overweight can be used as a tool to guide case-finding for cardiovascular risk assessment

de Boer AW, de Mustert R, den Heijer M, Jukema JW, Rosendaal FR,
Blom JW, Assendelft WJJ

Fam Pract. 2015;32(6):646-51

Abstract

Background In general practice it is too time-consuming to invite all patients for cardiovascular risk assessment.

Objective To examine how many patients with an indication for treatment with cardiovascular medication can be identified by ad hoc case-finding when all patients with overweight/obesity are invited for risk assessment.

Methods A cross-sectional analysis of the baseline measurements of the Netherlands Epidemiology of Obesity study, a population-based prospective cohort study in 6,673 persons aged 45-65 years. We calculated the proportion of participants with a treatment indication using the risk prediction Systematic COronary Risk Evaluation (SCORE-NL 2011), for lean, overweight and obese participants. Participants with a history of cardiovascular disease, diabetes mellitus or rheumatoid arthritis or using cardiovascular medication were not eligible for ad hoc case-finding, because they were already identified as being at risk and/or had been treated.

Results Of the study population, 30% had already been identified and/or treated with cardiovascular medication and were therefore not eligible for ad hoc case-finding. Of the eligible participants, 47% were lean, 41% overweight, and 12% obese. Of the participants with overweight 12% had a treatment indication, of the participants with obesity 19% had a treatment indication. Of all participants with a treatment indication 24% were not yet treated. Of all participants with a new treatment indication, 70% had overweight or obesity.

Conclusions Of the participants with a treatment indication 24% were not yet treated. Inviting patients with overweight/obesity for cardiovascular risk assessment may help to detect 70% of these residual patients with a treatment indication.

Introduction

To calculate the risk of cardiovascular disease (CVD) and corresponding treatment indication several risk estimation systems have been developed for primary prevention based on cardiovascular risk factors (e.g., Framingham, SCORE, QRISK, PROCAM).(28) Cardiovascular risk assessment in general practice is time-consuming, with on average a first consultation of 20 minutes for history taking and examination of the patient and a second consultation of 20 minutes to discuss the results.(35, 36) Therefore, at present in the Netherlands not all patients are invited for risk assessment, however high-risk patients are usually identified first, either based on a more programmatic approach or by ad hoc case-finding. In a programmatic approach, for example, all patients of 45 years or older are invited to complete a risk questionnaire.(40) Patients at increased risk are advised to consult their general practitioner (GP) for cardiovascular risk assessment. However, this method is time-consuming and it is reported that only 36% of patients at risk responds to the invitation.(40) Ad hoc case-finding among general practice attendants is the most commonly used approach, which is less expensive and has better coverage since potential high-risk patients are invited for cardiovascular risk assessment during a regular consultation for other reasons. However, a disadvantage of ad hoc case-finding is that it is unclear what strategy can best be followed to identify high-risk patients efficiently, in addition only a short consultation is planned for the actual reason for the encounter. As a consequence, ad hoc case-finding is often neglected and high-risk patients with a treatment indication may remain untreated.

Further optimization of the yield of case-finding may reduce time and costs related to cardiovascular risk management; however the identifying factor needs to be obtained within a few seconds during a regular consultation. Overweight may be a promising candidate because this is a visible and (combined with simple measurements) easily obtained risk factor. Therefore, we aimed to examine how many patients with a treatment indication can be identified when all patients with overweight or obesity are invited for cardiovascular risk assessment by ad hoc case-finding. Hereto we used the data of the Netherlands Epidemiology of Obesity (NEO) study, a population-based prospective-cohort study including lean, overweight and obese participants.(52) This study population allowed us to calculate the gain in identification of patients with a treatment indication when using weight as guidance for ad hoc case-finding.

Methods

Study design and study population

The NEO study is a population-based prospective cohort study in persons aged 45-65 years with an oversampling of participants with a body mass index (BMI) ≥ 27 kg/m². The study design has been described elsewhere.(52) Participants with a self-reported BMI ≥ 27 kg/m² were recruited from the greater area of Leiden, the Netherlands, via GPs, municipal registers and advertisements. In one municipality (Leiderdorp) all inhabitants aged 45-65 years were invited, irrespective of their BMI, to allow for a reference distribution of BMI. Prior to the NEO study visit, participants were asked to complete a questionnaire including questions about demographics, lifestyle, and clinical information. During the baseline visit at the NEO study center of the Leiden University Medical Center (LUMC) several measurements were performed, including a physical examination and blood sampling. This study is a cross-sectional analysis of the baseline measurements of the NEO study. The study was approved by the medical ethics committee of the LUMC and all participants gave informed consent.

Data collection in the NEO study

We used SCORE-NL 2011 to calculate the 10-year CVD risk for participants eligible for ad hoc case-finding; this includes sex, age, systolic blood pressure (SBP), total cholesterol (TC)/HDL ratio, smoking status, diabetes mellitus (DM), first-degree family history of CVD, physical activity, BMI, estimated glomerular filtration rate (eGFR), poor metabolic control, and albuminuria.(30) The method of SCORE-NL 2011 is described in more detail in Appendix 1.

Participants without a history of CVD, DM or rheumatoid arthritis (RA) and without using antihypertensive or lipid-lowering drugs were eligible for ad hoc case-finding. The rationale for this selection is that all other participants are regularly assessed due to being at increased risk, or have already been identified with a treatment indication.

We defined prevalent CVD as a history of angina pectoris, myocardial infarction (MI), stroke, aortic aneurysm and peripheral arterial disease as reported in the questionnaire. First-degree family history of MI or stroke was reported in the questionnaire in five age groups: before age 50 years, 50-60 years, 60-70 years, after age 70 years, and age unknown. In SCORE-NL 2011 an event before age 60 years (one member) and before age 65 years (two members) is used as additional risk factor. For the latter, we used a CVD event before age 70 years.

We defined newly discovered DM as a fasting plasma glucose ≥7.0 mmol/l or a non-fasting glucose ≥11.1 mmol/l(98) and a history of DM as having a self-reported history of DM or using glucose-lowering therapy. Poor metabolic control was defined as hemoglobin A1c (HbA1c) ≥7%.(103, 104)

We defined participants with RA who regularly visit a physician, as participants using disease-modifying antirheumatic drugs, such as methotrexate, sulfasalazine, immunosuppressive drugs, and biopharmaceuticals.

Physical activity was assessed with the Short QUestionnaire to ASsess Health-enhancing physical activity(105), with a sedentary lifestyle as being zero days per week physically active for at least 30 minutes with at least a moderate intensity. Smoking status was dichotomized into current smokers and non-smokers (including former smokers).

Body weight and height were measured during the study visit with a calibrated scale and a vertically fixed, calibrated tape measure during the study visit. The trained staff reported the height in cm; body weight was rounded to 100g, one kilogram was subtracted to correct for the weight of clothing. BMI was calculated by dividing weight (in kg) by the square of height (in meters). Overweight was defined according to the World Health Organization as a BMI 25-30 kg/m², obesity as a BMI ≥30 kg/m².(106)

Waist circumference (WC) was measured between the border of the lower costal margin and the iliac crest rounded to 0.1 cm. An increased WC was defined as a WC ≥102cm for men and ≥88cm for women.(107)

SBP was measured three times on the right arm by an automatic monitor after 10 minutes rest in sitting position. The mean of these measurements was used in the analyses.

Blood samples were taken after an overnight fast. Serum cholesterol concentrations, glucose, HbA1c, and creatinine were determined in the central clinical chemical laboratory of the LUMC. Albuminuria was defined as an albumin/creatinine ratio (ACR) ≥2.5 mg/mmol for men and ≥ 3.5 mg/mmol for women. eGFR was calculated using the Modification of Diet in Renal Disease.(97) A reduced eGFR was defined as eGFR <60 ml/min/1.73m² in participants aged <65 years, and eGFR <45 ml/min/1.73m² in participants aged ≥65 years.

Statistical analysis

In the NEO study there is an oversampling of participants with a BMI ≥27 kg/m². To correctly represent the general population participants were weighted towards the BMI distribution of the participants from the Leiderdorp municipality(99, 100) whose BMI dis-

tribution was similar to the BMI distribution of the Dutch general population(101). Hereto, participants with a BMI <27 kg/m², who were underrepresented in the study population, received a greater weight in the analyses. All results were based on weighted analyses. Consequently, the results apply to a population-based study without oversampling of participants with a BMI ≥ 27 kg/m².

For participants eligible for ad hoc case-finding, we calculated the predicted 10-year CVD risk and treatment indication according to SCORE-NL 2011. Differences in proportions were tested using the Pearson's chi-squared test. We also calculated the proportion of participants with a new treatment indication of all patients with a treatment indication for primary prevention, and. the proportion of participants with a treatment indication of all participants with an increased WC.

The first 863 participants included in the study completed a questionnaire that did not contain questions about family history of CVD; these participants were considered as having no first-degree relative with a CVD event. However, we also performed a sensitivity analysis considering these participants as having two first-degree relatives with a CVD event before age 65 years.

All analyses are stratified by BMI category into BMI <25 kg/m², BMI 25-30 kg/m² and BMI ≥30 kg/m². Only proportions, not counts, could be reported due to the weighted analysis. For all analyses, STATA statistical software (Statacorp, College Station, Texas, USA), version 12 was used.

Results

Of the 6,673 persons included in the NEO study 5,215 had a BMI ≥27 kg/m². The individual participants were weighted towards the BMI distribution of the general Dutch population. After weighting, 42% of the participants had a BMI <25 kg/m², 42% a BMI 25-30 kg/m², and 16% a BMI ≥30 kg/m². Six percent of the participants were excluded due to missing data for SCORE risk prediction.

The weighted baseline characteristics of the participants included in the present analysis stratified by BMI category, are shown in Table 1. Participants with overweight or obesity had a higher SBP, a higher TC/HDL ratio and more newly diagnosed DM compared with lean participants.

The eligibility for ad hoc case-finding and the 10-year CVD risk and treatment indication were calculated. Of the total study population, 30% of the participants were already identified and/or treated. With increasing levels of BMI, more participants were already identified and/or treated and not eligible for ad hoc case-finding; i.e. 20% of the participants with a BMI <25 kg/m² were already identified and/or treated, 32% with a BMI 25-30 kg/m², and 49% with a BMI ≥30 kg/m². This was mainly due to a higher proportion of participants with a history of DM, RA or CVD and a higher proportion of participants using antihypertensive or lipid-lowering drugs in the groups with a higher BMI. (Table 2, Figure 1)

Table 1 Baseline characteristics of the participants of the Netherlands Epidemiology of Obesity study, aged 45-65 years, recruited in 2008-2012, and stratified by body mass index group[a]

	BMI (kg/m²)		
	< 25 (42%)	25-30 (42%)	≥30 (16%)
Age (years)	56 (3)	56 (6)	56 (10)
Sex (% men)	35	54	44
BMI (kg/m²)	22.6 (0.8)	27.1 (1.4)	33.9 (6.6)
Smoking (% current)	15	17	16
SBP (mmHg)	127 (9)	132 (17)	134 (29)
TC/HDL ratio	3.4 (0.6)	4.2 (1.3)	4.4 (2.2)
Newly discovered DM (%)	1	3	5
HbA1c (%)	6.1 (0.8)	6.1 (0.8)	6.3 (1.2)
ACR	0.6 (0,1)	1.1 (2.5)	3.6 (28.6)
eGFR (ml/min/1.73m²)	85 (7)	85 (14)	86 (26)
Reduced eGFR (%)[b]	2	2	3
First-degree family history of CVD			
≥1 member aged < 60 years (%)	21	22	23
≥1 member aged < 65 years (%)	36	34	36
≥2 members aged <65 years (%)	8	8	10
Sedentary lifestyle (%)[c]	3	5	8

Data are expressed as mean (SD) or %

Abbreviations: ACR, albumin/creatinine ratio; BMI, body mass index; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; TC/HDL ratio, total cholesterol/HDL ratio

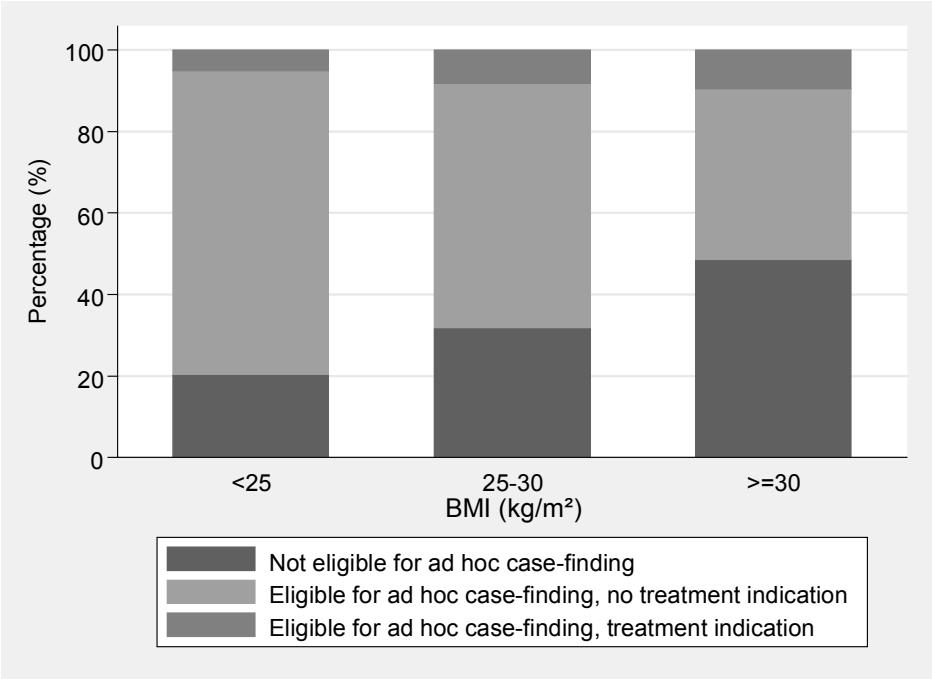
[a] Results are based on weighted analyses and therefore represent the general population

[b] Reduced eGFR: eGFR <60 ml/min/1.73m² in patients aged <65 years, eGFR <45 ml/min/1.73m² in patients aged ≥65 years

[c] Sedentary lifestyle: being zero days per week physically active for at least 30 minutes with at least a moderate intensity.

Overall, 80% of the participants eligible for ad hoc case-finding had a low CVD risk, 13% an intermediate risk, and 4% a high risk based on the SCORE function, and 3% had a definite treatment indication based on a single high risk factor. Of all eligible participants treatment was indicated in 10% (19% of the men, 4% of the women).

Figure 1 Eligibility for ad hoc case-finding for cardiovascular risk assessment and cardiovascular treatment indication calculated by SCORE-NL 2011 in participants aged 45-65 years of the Netherlands Epidemiology of Obesity study[a]



For all participants within a BMI group the percentage is shown of participants not eligible and the percentage eligible for ad hoc case-finding. Not eligible for ad hoc case-finding were participants with a history of cardiovascular disease, diabetes mellitus or rheumatoid arthritis, or who are using antihypertensive or lipid-lowering drugs. The percentage of the participants eligible for ad hoc case-finding is divided into participants with and without a treatment indication.

Abbreviations: BMI, body mass index

[a] Results are based on weighted analyses

Of the eligible participants with a BMI 25-30 kg/m² 12% (18% of the men, 6% of the women) had a treatment indication, of the eligible participants with a BMI ≥30 kg/m² 19% (35% of the men, 6% of the women) had a treatment indication. (Table 3) When combining all eligible participants with overweight or obesity (BMI ≥25 kg/m²), 14% (men 21%, women 6%) had a treatment indication.

Table 2 Eligibility for ad hoc case-finding for cardiovascular risk assessment in participants aged 45-65 years of the Netherlands Epidemiology of Obesity study, stratified by body mass index group[a]

	BMI (kg/m²)		
	< 25 (42%)	25-30 (42%)	≥30 (16%)
	% (95% CI)	% (95% CI)	% (95% CI)
Eligible for ad hoc case-finding	80 (77 – 83)	68 (66 – 70)	51 (50 – 53)
Not eligible for ad hoc case-finding[b]	20 (17 – 23)	32 (30 – 34)	49 (47 – 50)
History of DM or RA	2 (1 – 3)	4 (3 – 5)	12 (11 – 13)
History of CVD	5 (3 – 6)	7 (5 – 8)	9 (8 – 10)
Use of antihypertensive or lipid-lowering drugs	18 (15 – 21)	29 (27 – 31)	45 (44 – 47)

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; RA, rheumatoid arthritis

[a] Results are based on weighted analyses

[b] More than one reason can be present in the participants not eligible for ad hoc case-finding

When considering all participants with a treatment indication (including those already using primary preventive medication and those with a new treatment indication), 24% were not yet treated; i.e. 26% of the participants with a BMI <25 kg/m², 26% with a BMI 25-30 kg/m², and 20% with a BMI ≥30 kg/m² (p=0.19). Of all participants with a new treatment indication 70% had overweight or obesity.

Of all participants eligible for ad hoc case-finding 32% had an increased WC; of those with an increased WC, 14% had a treatment indication.

Of the 863 participants who did not report their family history, only 60 participants were both eligible for ad hoc case-finding and fell in the category "intermediate risk", in which family history may influence the treatment indication. In a sensitivity analysis, when we considered these participants as having two first-degree relatives with a CVD event before age 65 years, this had no marked effect on our results: i.e. 14% of the eligible participants with a BMI 25-30 kg/m² had a treatment indication, and 19% of the eligible participants with a BMI ≥30 kg/m² had a treatment indication.

Table 3 SCORE risk categories and corresponding treatment indication for participants aged 45-65 years of the Netherlands Epidemiology of Obesity study, who were eligible for ad hoc case-finding for cardiovascular risk assessment, stratified by body mass index group[a]

		BMI (kg/m²)		
		< 25 (47%)	25-30 (41%)	≥30 (12%)
SCORE-NL 2011(30)	Treatment indication	% (95% CI)	% (95% CI)	% (95% CI)
Low risk	No treatment	85 (82 – 88)	75 (73 – 78)	76 (74 – 78)
Intermediate risk[b]	No treatment	8 (6 – 11)	12 (10 – 14)	6 (5 – 7)
	Treatment	**2 (1 – 3)**	**3 (2 – 4)**	**9 (7 – 10)**
High risk	No treatment		0 (0 – 1)	0 (0 – 0)
	Treatment	**2 (1 – 4)**	**5 (4 – 6)**	**6 (5 – 7)**
Definite indication[c]	**Treatment**	**2 (1 – 3)**	**4 (3 – 5)**	**4 (3 – 5)**
Total *	**Treatment**	**6 (4 – 8)**	**12 (10 – 14)**	**19 (17 – 21)**

* Chi squared test p=<0.001

Due to rounding, percentages may not add up to 100%

Abbreviations: BMI, body mass index; CI, confidence interval

[a] Results are based on weighted analyses

[b] Treatment in the intermediate group is dependent on additional risk factors(30)

[c] Systolic blood pressure > 180 mmHg , or total cholesterol (TC) > 8 mmol/l, or TC/HDL ratio > 8, or triglycerides >10

Discussion

This study used data from a large population-based prospective cohort study with all the information present to calculate the 10-year CVD risk and corresponding treatment indication. We aimed to identify high-risk patients for cardiovascular risk assessment by ad hoc case-finding among patients visiting their GP for other reasons. We observed that with higher levels of BMI more participants were already identified with a high risk or disease by the GP, leading to treatment. However, 24% of the participants with a treatment indication were not yet identified and treated. In the participants eligible for ad hoc case-finding, 12% of the participants with overweight and 19% of the participants with obesity had a treatment indication. Importantly, most of them were men. Hence, the risk of eight patients with overweight or five patients with obesity needs to be assessed to detect one patient with a treatment indication.

When the results are applied to a standard general practice in the Netherlands (2400 patients registered, 590 patients aged 45-64 years old), 413 patients are eligible for ad hoc case-finding. Of the 50 patients that would have obesity (BMI ≥30 kg/m²) 9 patients would have a treatment indication. When patients with overweight (BMI 25-30 kg/m²) could also be identified, then 219 patients (BMI ≥25 kg/m²) would be selected for further risk assessment, of which 31 with a treatment indication.

To our knowledge, few studies have examined the yield of identification of high-risk patients by ad hoc case-finding in general practice. Previous studies mainly focused on improving the risk estimation systems, or on the development of a programmatic approach for identification of high-risk patients.

For example, in the *Prevention Consultation*, a programmatic approach in the Netherlands for the prevention and early detection of CVD, DM and chronic kidney disease (CKD), a risk questionnaire is sent to all patients aged 45-70 years, and patients with a high-risk score are referred to their GP for extensive measurements including cardiovascular risk assessment. As a result, 20% of the patients who visited their GP with a high risk score had a cardiovascular treatment indication, DM or CKD.(40) An advantage of our approach, identifying high-risk patients by ad hoc case-finding, is that it costs less in terms of time and money to invite patients for risk assessment.

A prospective modeling study compared different screening strategies to identify high-risk patients with the invitation of all patients aged 40-79 years. When patients aged 40-79 years with overweight (BMI ≥27,5 kg/m² or a WC >94 cm in men or >80 cm in women) are identified for cardiovascular risk assessment, 70% of the CVD events can

be prevented that would have been prevented had all patients had been invited for risk assessment (with a number needed to intervene to prevent one new CVD event of 100). (108) This may imply that, compared with inviting all patients, a major proportion of the preventable CVD events are prevented when only patients with overweight are identified.

Strengths of this study are the large sample size, and the extensive and uniform measurements of all information needed for calculating the 10-year CVD risk. A limitation is that the identification of patients for further risk assessment by ad hoc case-finding depends on whether patients regularly consult their GP. On average, 74% of the registered patients visit a GP at least once a year(109), with a higher attendance rate with higher BMI(110). Though, for GPs it will be a challenging task to fit identification for cardiovascular risk assessment into a consultation that has another reason for the encounter. Another limitation is oversampling of participants with a BMI ≥27 kg/m², which is corrected by weighted analyses to represent the general population. Without these adjustments, the proportion participants with a BMI ≥27 kg/m² would be higher and therefore the proportion participants with a treatment indication would be higher. In contrast, the weighted results can be translated to the general population.

Remarkably, 30% of all participants had already been identified and/or received treatment. This may even be an underestimation, because there may have been eligible participants without a treatment indication whose risk had already been assessed in general practice, resulting in no treatment indication. Overall, 24% of all participants with a treatment indication had not yet been treated, with no differences between BMI-groups.

Case-finding by inviting patients with overweight or obesity does not imply measuring weight and height and calculating BMI at each consultation. In practice, GPs can visually identify patients based on their perception of the patient's weight status. It is reported that GPs correctly classify 75% of overweight patients (BMI ≥25 kg/m²) as having overweight, with higher rates with increasing BMI levels.(111) In our study WC, a measure reflecting abdominal obesity, also showed a similar proportion of participants with a treatment indication compared with BMI.

Due to the lower costs and because it is initially less time-consuming, the most frequently used approach to identify high-risk patient for cardiovascular risk assessment is ad hoc case-finding. We hypothesized that patients with overweight/obesity are an important subgroup to identify for further risk assessment, because overweight is associated with the cardiovascular risk factors used in risk estimation systems and is easy to obtain. We observed that with higher levels of BMI more participants had a treatment indication, some already identified and treated. When all eligible patients with overweight/obesity

are invited for further risk assessment, 70% of the residual patients with a treatment indication could be identified, who would otherwise remain untreated.

In conclusion, our findings show that although a large part of the participants had already been identified and treated, inviting patients with overweight or obesity (especially men) for cardiovascular risk assessment may help to detect a substantial additional group of patients with a treatment indication.

Appendix 1 Cardiovascular risk assessment

In the Netherlands, SCORE-NL 2011 is used to calculate the 10-year CVD risk.(30) The SCORE function is based on Dutch cohorts and conceptually similar to risk estimation systems used elsewhere.(28) The SCORE risk chart can be used for persons aged 40-70 years. We conservatively imputed the risk for participants with an age > 70 years, SBP <120 mmHg or TC/HDL ratio <4 by using an age of 70 years, a SBP of 120 mmHg or a TC/HDL ratio of 4, respectively.

To determine the indication for treatment with antihypertensive and/or lipid-lowering drugs, we categorized the risk estimates into low, intermediate, and high risk, corresponding to a 10-year risk of a non-fatal or fatal CVD event of <10%, 10-19%, and ≥20%, respectively. According to SCORE-NL 2011treatment is indicated in the category "intermediate risk" when SBP >140 mmHg and/or LDL >2.5 mmol/l and at least one strong additional risk factor or two mild additional risk factors are present. Strong additional risk factors are: at least two first-degree relatives with a CVD event before age 65 years or one with an event before age 60 years; a sedentary lifestyle; BMI >35 kg/m²; eGFR <30ml/min/1.73m²; poor metabolic control of DM; DM and (micro-)albuminuria. Mild additional risk factors are: one first-degree relative with a CVD event before age 65 years; physical activity <30min/day ≤5days a week (not a sedentary lifestyle); BMI 30-35 kg/m²; eGFR 30-60 ml/min/1.73m² for persons aged <65 years, age ≥65 years 30-45 ml/min/1.73m². In the category "high risk" treatment is indicated when SBP >140 mmHg and/or LDL >2.5 mmol/l. Persons with a SBP >180 mmHg, TC/HDL ratio > 8, TC >8 mmol/l or triglycerides >10 mmol/l have a definite treatment indication, irrespective of the predicted CVD risk.

CHAPTER 6

Markers of hepatic steatosis do not improve current cardiovascular risk prediction systems

de Boer AW, le Cessie S, van der Schouw YT, den Heijer M, Verschuren WMM, de Mutsert R, Blom JW, Numans ME

Awaiting submission

Abstract

Background Hepatic steatosis is increasingly prevalent worldwide and is associated with a 64% increased cardiovascular disease (CVD) risk.

Objective To examine whether cardiovascular risk prediction can be improved by adding non-invasive markers of hepatic steatosis to the Framingham risk score.

Methods Data was used from the European Prospective Investigation into Cancer and Nutrition-Netherlands study, which comprises 40,011 men and women aged 20-70 years at recruitment in 1993-1997. We analysed participants aged 30-70 years without prevalent CVD and not using preventive treatment. Serological markers of liver function (alanine aminotransferase (ALT), aspartate transaminase (AST), gamma glutamyltransferase (GGT)) and scores developed for the prediction of hepatic steatosis (fatty liver index, hepatic steatosis index, ALT/AST ratio) were added to the calibrated sex-specific Framingham risk score. The outcome was defined as a CVD event in 10 years of follow-up. Model performance was evaluated by measures of discrimination, calibration and reclassification.

Results During 10 years of follow-up, a CVD event occurred in 7% of the men and 5% of the women. None of the markers of hepatic steatosis was a predictor for CVD in men when added to the Framingham risk score. In women, GGT, ALT, the fatty liver index, and the AST/ALT ratio were predictors. Adding these markers did not lead to a relevant improvement in discrimination, calibration or reclassification.

Discussion Easily accessible markers of hepatic steatosis did not improve cardiovascular risk prediction in addition to the established risk factors. Future research is needed to examine the added predictive value of other markers of hepatic steatosis.

Introduction

In clinical practice, patients at increased cardiovascular risk are currently identified by estimating an individual's 10-year risk of cardiovascular disease (CVD) using a risk estimation system. Examples of those risk estimation systems are the Framingham risk score, Pooled Cohort Equations, SCORE, and QRISK.(28) Based on the estimated risk, physicians decide whether preventive treatment is indicated. This requires an optimal estimation of an individual's cardiovascular risk. External validations of the most commonly used risk estimation systems have demonstrated an area under the receiver operating curve (AUC) between 0.75 and 0.80.(28) This means that the prediction of an individual's 10-year cardiovascular risk is not optimal, which may lead to under- and overtreatment of patients.

Possibilities to improve cardiovascular risk prediction are explored in various studies and adding information about the presence of hepatic steatosis, the early stage of non-alcoholic fatty liver disease (NAFLD) is one of the approaches. NAFLD covers a broad clinical spectrum ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, with varying degrees of inflammation and fibrosis, in the absence of excessive alcohol consumption.(112) Currently, the global prevalence of NAFLD in the general population is 25%, with a prevalence of up to 90% in persons with obesity.(46) NAFLD is strongly related to several cardiometabolic diseases(47) and associated with a 64% increased risk of CVD(48), and is therefore a likely candidate to improve cardiovascular risk prediction.

Proton magnetic resonance spectroscopy and liver biopsy are reference measurements for the assessment of hepatic steatosis and fibrosis.(113) However, these measurements cannot be used in a cardiovascular risk estimation system in clinical practice, due to the invasiveness, availability and costs of the measurements. Serological markers of liver function and combination scores developed for the prediction of hepatic steatosis may be non-invasive alternatives that probably can be used in daily practice. In a previous study in men, cardiovascular risk prediction improved when gamma glutamyltransferase (GGT) was included in the Framingham risk score.(49) However, other studies in men and women showed no improvement when GGT or the ratio of aspartate transaminase (AST) and alanine aminotransferase (ALT) was included in current risk estimation systems.(50, 51) It is suggested that the improvement may differ between men and women.(51) In addition, it is unknown whether combination scores developed for the prediction of hepatic steatosis have any added value in a risk estimation system. Therefore, the aim of this study was to examine whether cardiovascular risk prediction can be improved when non-invasive markers of hepatic steatosis are added to the Framingham risk score and if improvement differed between men and women.

Methods

Study design and study population

The EPIC-NL cohort includes two Dutch contributions to the European Prospective Investigation Into Cancer and Nutrition (EPIC), the Monitoring Project on Risk Factors for Chronic Diseases (MORGEN) cohort and Prospect cohort. The study design has been described elsewhere.(53) In both cohorts, the participants were recruited simultaneously between 1993 and 1997. The MORGEN cohort consists of a general population sample of 22,654 men and women aged 20-59 years. Prospect is a prospective cohort study in 17,357 women aged 49-70 years, who participated in the national breast cancer screening programme between 1993 and 1997.

At baseline, the participants completed a questionnaire, a brief physical examination was performed, and a non-fasting blood sample was drawn, fractionated into aliquots, and stored in liquid nitrogen for future analyses. Biochemical measurements were performed in a random sample of 6.5% of the baseline cohort (sub-cohort of 2,604 participants) and in all incident cases of cardiovascular disease that occurred before 2006 for the purpose of a previous case-cohort study.(114, 115)

In the present study, we included all participants from the sub-cohort and all incident cases of CVD during 10 years of follow-up. A total of 2,332 CVD events occurred, of which 2,177 events occurred in participants outside the sub-cohort. The Framingham risk score is developed for persons aged 30-70 years without a history of CVD. So, we consecutively excluded participants outside this age range (n=3,805) and participants with a history of CVD (defined as a medical history of coronary heart disease, cerebrovascular disease, pulmonary embolism, peripheral artery disease, abdominal aortic aneurysm or heart failure, n=1,255). Furthermore, we excluded participants who did not consent to linkage with disease registries as well as participants who were lost to follow-up (n=1,467). The local medical ethics committees approved the cohort studies and all participants gave informed consent.

Cardiovascular risk estimation system

We used the sex-specific Framingham risk score to estimate 10-year CVD risk.(18) This model includes the risk factors age, treated and nontreated systolic blood pressure (SBP), total cholesterol and high-density lipoprotein (HDL) cholesterol concentrations, diabetes mellitus and smoking status. According to the guideline, the risk estimates were categorized into a low, intermediate and high risk, corresponding to a 10-year CVD risk of <10%, 10-20%, and ≥20%, respectively.

The blood pressure was measured twice in supine position, in Prospect on the right arm using a Boso Oscillomat (Bosch & Son, Jungingen, Germany) and in MORGEN on the left arm using a random zero sphygmomanometer. The average of the measurements was used in the analyses. Total cholesterol concentrations were measured using an enzymatic method and HDL cholesterol concentrations were measured using a homogeneous assay with an enzymatic endpoint, both on an autoanalyser (LX20, Beckman Coulter, Mijdrecht, the Netherlands).

Information on the medical history of diabetes mellitus, use of antihypertensive medication and smoking status were reported in the baseline questionnaire. The information on the medical history of diabetes mellitus was clinically validated.(56)

Markers of hepatic steatosis

We examined three serological markers of liver function and three combination scores developed for the prediction of hepatic steatosis. The serological markers ALT, AST and GGT were measured using enzymatic methods on an autoanalyser (LX20, Beckman Coulter, Mijdrecht, the Netherlands). We examined the added value of the markers both as continuous variables and dichotomized. The markers were dichotomized using the upper limit of the normal range: 45 U/L for ALT, 35 U/L for AST and 50 U/L for GGT.

In addition, we examined the combination scores: the fatty liver index, the hepatic steatosis index, and the AST/ALT ratio. The fatty liver index predicts steatosis by using body mass index, waist circumference, triglycerides and GGT.(116) This combination score is the most promising score for the detection of steatosis, with an AUC of 0.84 in the general population.(117) We examined the added value of the continuous score, a threshold of <30 to rule out steatosis and a threshold of ≥60 to rule in steatosis. The hepatic steatosis index is an algorithm based on ALT, AST and body mass index. We examined the added value of the continuous score, a threshold of <30 to rule out steatosis and a threshold of ≥36 to rule in steatosis. The AST/ALT ratio is the ratio between AST and ALT. In the absence of excessive alcohol use, a ratio >1 suggests a more advanced stage of NAFLD.(118) We examined the added value of the continuous ratio and the threshold of 1.

Conform the predictors in the Framingham risk score, all markers were mean standardized and all continuous markers were naturally logarithmically transformed.

Outcome assessment

Data on cardiovascular mortality was obtained through linkage with the municipal population registries. Causes of death were collected from 'Statistics Netherlands'. Morbidity data was obtained from the National Medical Registry (NMR), which keeps a standardized

computerized register of discharge diagnoses coded according to the Ninth Revision of the International Classification of Diseases (ICD-9). The NMR collected and checked these data in the Hospital Discharge Diagnosis Database. This database was linked to the EPIC-NL cohort based on information on the date of birth, sex, postal code, and general practitioner with a validated probabilistic method.(119) CVD was defined according to the definition used to develop the Framingham risk score and included coronary heart disease, heart failure, cerebrovascular disease and peripheral artery disease (ICD-9 402, 410, 411.89, 414.8, 413, 428, 430, 431, 432, 433, 434, 435, 436, 440-449). Follow-up was complete until January 1, 2011. The first fatal or non-fatal CVD event in the first 10 years of follow-up after baseline was used as the endpoint in the analysis.

Statistical analysis

Baseline characteristics were expressed as mean (SD), or percentages. Mean imputation stratified by case status was used for missing data in the original predictors. Participants with missing smoking status were considered as non-smokers. The Framingham risk scores for men and women were calibrated by adjustment for the mean levels of the risk factors and the event rates.(120)

To account for the overrepresentation of cases in our study population, we used inverse probability weighting to weight the participants according to their case-cohort sampling probability.(121) For cases, the weights were set to 1, since all cases were sampled. The non-cases in the sub-cohort were weighted to represent the non-cases in het full cohort. Hereto, weights were calculated by the sampling fraction of the non-cases in the sub-cohort.

Blood samples were missing in cases outside the sub-cohort with an event after 31 December 2005 or an event other than coronary heart disease, stroke or death. In addition, in some participants blood samples were missing due to an unsuccessful blood draw or failed laboratory analysis. The participants with complete blood samples were considered comparable with participants with missing blood samples. Therefore, participants with complete blood samples were weighted to represent the full cohort. Due to the weighted analysis, only proportions could be reported, not counts.

First, cox proportional hazards regression was used to build a prediction model for each marker of hepatic steatosis by adding the marker to the Framingham risk score. Second, we fitted a model by adding all markers of hepatic steatosis as continuous variables to the Framingham risk score, and applied stepwise backward selection of statistically significant variables ($p< 0.05$) on the markers forcing the predictors of the Framingham risk score to be retained in the model.

Third, the models were compared with the Framingham risk score in terms of discrimination and calibration. Discrimination of the models was expressed by Harrell's c-statistics. Calibration was expressed by the calibration slope and visualised by calibration curves. The predicted cardiovascular risk was compared with the observed cardiovascular risk, in deciles of the predicted risk. The observed risks were determined using Kaplan Meier survival estimates.

Furthermore, the benefit for clinical practice was evaluated by measures of reclassification. Participants without a CVD event who were censored before reaching the endpoint of 10 year were considered as having no event. The category-based net reclassification index (NRI) indicates the percentage of correct shifting across risk categories for those with and without an event.(122) We calculated a three-category NRI where the risk categories represented a 10-year CVD risk of <10%, 10-19% and ≥ 20%. Correct shifting is an upward shift after adding new markers in those with an event and a downward shift in those without an event. We have visualised the reclassification in a reclassification graph. The improvement in net benefit (ΔNB) represents the net improvement of true positives calculated *by (Δtrue positives – weight * Δ false positves) / number of subjects*, where the weight is the odds of the decision threshold. The ΔNB was calculated for the treatment thresholds of a 10-year CVD risk of 20%. In this analysis we excluded the cases outside the sub-cohort to be able to calculate with absolute numbers instead of percentages.
Persons with an excessive alcohol consumption are usually excluded in the definition of NAFLD. Therefore, we repeated the analyses after exclusion of participants with an alcohol intake of more than 20 grams per day. We also repeated all analyses after exclusion of participants without a CVD event who were censored before reaching 10 years of follow-up in the analysis on reclassification.

We investigated the robustness of our results by examining the added value of the markers of hepatic steatosis in a second cardiovascular risk prediction system, the Pooled Cohort Equations.(123) The Pooled Cohort Equations is used to estimate the 10-year CVD risk for men and women separately. This model includes the same risk factors as the Framingham risk score. In this model, CVD was defined as a nonfatal myocardial infarction, coronary heart disease death or a fatal or nonfatal stroke (ICD 410, 430-434). According to the guideline, the risk estimates were categorized into a low, intermediate and high risk, corresponding to a 10-year risk of <5%, 5-7.5%, and ≥7,5%, respectively.(123)

For all analyses, STATA statistical software (Statacorp, College Station, Texas, USA), version 12 was used.

Results

The weighted baseline characteristics of the participants included in the analysis, stratified by sex, are shown in Table 1.

Table 1 Baseline characteristics of the participants of the EPIC-NL cohort, stratified by sex[a]

	Men	Women
Risk factors included in the Framingham risk score		
Age (years)	46 (9)	53 (9)
Treated SBP (mmHg)	140 (14)	140 (16)
Untreated SBP (mmHg)	126 (16)	127 (19)
Blood pressure lowering therapy (%)	6	2
Total cholesterol (mmol/L)	4.8 (0.9)	4.9 (0.9)
HDL cholesterol (mmol/L)	1.1 (0.7)	1.3 (0.5)
Smoking (% current)	38	27
Diabetes mellitus (%)	2	1
Markers of hepatic steatosis		
ALT (U/L)	17 (8)	15 (8)
>45 U/L (%)	1	1
AST (U/L)	21 (7)	19 (5)
>35 U/L (%)	3	1
GGT (U/L)	29 (22)	22 (19)
>50 U/L (%)	8	4
Fatty liver index	47 (28)	29 (24)
<30 - rule out hepatic steatosis (%)	33	64
30-60 (%)	32	21
≥60 - rule in hepatic steatosis (%)	35	15
Hepatic steatosis index	33 (7)	34 (5)
<30 - rule out hepatic steatosis (%)	28	20
30-36 (%)	51	52
>36 - rule in hepatic steatosis (%)	21	29
AST/ALT ratio	1.4 (0.4)	1.4 (0.4)
>1 - rule in advanced disease	86	89

Data are expressed as mean (SD) or %

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; SBP, systolic blood pressure

[a] Results are based on weighted analyses and therefore represent the total cohort

Cardiovascular risk prediction in men

Our study population comprised of 23% men, with a mean age of 46 (9) years at baseline. After calibration of the original Framingham risk score, 74% of the men had a low estimated CVD risk, 21% an intermediate risk and 6% a high risk of CVD. The C-statistic of the calibrated Framingham risk score for men was 0.72 (95% CI 0.69-0.75) and the calibration slope was 0.86 (95% CI 0.71-1.01). During 10 years of follow-up, a CVD event occurred in 7% of the male participants.

None of the markers of hepatic steatosis was a predictor for cardiovascular disease when they were added univariably to the calibrated Framingham risk score for men. Also after adding all markers of hepatic steatosis simultaneously to the Framingham risk score and applying backwards selection, none of the markers were retained in the model. (Table 2)

Cardiovascular risk prediction in women

Our study population comprised of 77% women, with a mean age of 53 (9) years at baseline. After calibration of the original Framingham risk score, 87% of the women had a low estimated CVD risk, 11% an intermediate risk and 2% a high risk of CVD. The C-statistic of the calibrated Framingham risk score for women was 0.71 (95% CI 0.69-0.73) and the calibration slope was 0.95 (95% CI 0.84-1.05). During 10 years of follow-up, a CVD event occurred in 5% of the female participants.

The following markers were a predictor when they were added to the calibrated Framingham risk score for women: GGT, ALT, fatty liver index, fatty liver index to rule out hepatic steatosis, AST/ALT ratio or AST/ALT ratio >1. (Table 2) Measures of discrimination, calibration and clinical benefit are shown in Table 3. The C-statistic of these models ranged between 0.71 and 0.72 and the calibration slope ranged between 0.91 and 1.05. Reclassification graphs are visualised in Figure 1. The addition of GGT to the Framingham risk score had the largest improvement in net benefit of 0.08 at the threshold of 20%. After adding all markers of hepatic steatosis simultaneously to the Framingham risk score and applying backwards selection, GGT and ALT were retained in the model. The C-statistic of this model was 0.72 and the calibration slope was 0.98. The improvement in net benefit of the addition of GGT and ALT to the Framingham risk score at the threshold of 20% was 0.12.(Table 3, Figure 1) Calibration curves of all models are shown in Supplemental figure 1 and density plots are shown in Supplemental figure 2.

Table 2 The cox proportional hazards model coefficients of the markers of hepatic steatosis when added to the Framingham risk score in men participating in the EPIC-NL cohort

Markers added to the Framingham risk score[a]	Coefficient (95% CI)
Single marker	
ALT	-0.14 (-0.55;0.28)
ALT >45 U/L	0.54 (-0.77;1.85)
AST	-0.20 (-0.64;0.25)
AST >35 U/L	-0.03 (-0.88;0.82)
GGT	0.00 (-0.31;0.32)
GGT >50 U/L	0.19 (-0.30;0.68)
Fatty liver index	0.02 (-0.20;0.23)
Fatty liver index to rule in hepatic steatosis	-0.01 (-0.31;0.29)
Fatty liver index to rule out hepatic steatosis	0.03 (-0.31;0.37)
Hepatic steatosis index	0.03 (-0.97;1.03)
Hepatic steatosis index to rule in hepatic steatosis	0.18 (-0.16;0.51)
Hepatic steatosis index to rule out hepatic steatosis	0.17 (-0.19;0.52)
AST/ALT ratio	0.00 (-0.50;0.51)
AST/ALT ratio >1	0.11 (-0.30;0.53)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase

[a] All markers were standardized and all the continuous markers were naturally logarithmically transformed

Sensitivity analyses

Of the study population, 34% of the men and 18% of the women reported alcohol intake of more than 20 grams per day. Exclusion of these participants from the analysis did not markedly change our results (data not shown).

Of the study population, 6% of the men and 4% of the women did not have a CVD event and were censored before completing 10 years of follow-up. When these participants were excluded from the analyses, there was no marked effect on our results (data not shown).

Pooled Cohort Equations

In men, similar to adding the markers to the Framingham risk score, none of the markers of hepatic steatosis improved the risk prediction when they were added to the calibrated Pooled Cohort Equations, both one by one and all at once using backwards selection.

The C-statistic of the calibrated Pooled Cohort Equations for women was 0.73 and the calibration slope was 0.96. The following markers were a predictor when added to the calibrated Pooled Cohort Equations for women: ALT, AST, GGT, AST/ALT ratio or AST/ALT ratio >1. Risk prediction did not improve when the fatty liver index was added to the model. The C-statistic of the models ranged between 0.73 and 0.74 and the calibration slope ranged between 0.96 and 1.02. After adding all markers of hepatic steatosis to the Pooled Cohort Equations and applying backwards selection, ALT and GGT were retained in the model. The C-statistic of this model was 0.72 and the calibration slope was 0.98. Detailed information about the performance of the models is shown in Supplemental table 1.

Table 3 Cox proportional hazard model coefficients, discrimination, calibration and reclassification of the addition of markers of hepatic steatosis to the Framingham risk score in women participating in the EPIC-NL cohort

Markers added to the Framingham risk score[a]	Coefficient (95% CI)	Area under the curve (95% CI)	Calibration slope (95% CI)
Single marker			
ALT	-0.51 (-0.77; -0.25)	0.71 (0.69;0.73)	1.05 (0.88;1.21)
ALT >45 U/L	-0.18 (-1.07;0.71)		
AST	-0.23 (-0.65;0.20)		
AST >35 U/L	0.58 (-0.26;1.41)		
GGT	0.25 (0.06;0.44)	0.71 (0.69;0.73)	0.94 (0.82;1.05)
GGT >50 U/L	0.18 (-0.25;0.60)		
Fatty liver index	0.10 (0.00;0.20)	0.71 (0.69;0.73)	0.92 (0.83;1.01)
Fatty liver index to rule in hepatic steatosis	0.06 (-0.15;0.28)		
Fatty liver index to rule out hepatic steatosis	-0.19 (-0.37; -0.02)	0.71 (0.69;0.73)	0.93 (0.87;0.98)
Hepatic steatosis index	-0.26 (-0.92;0.40)		
Hepatic steatosis index to rule in hepatic steatosis	0.08 (-0.10;0.26)		
Hepatic steatosis index to rule out hepatic steatosis	0.30 (0.05;0.55) [b]		
AST/ALT ratio	0.82 (0.46;1.18)	0.72 (0.70;0.74)	1.04 (0.97;1.10)
AST/ALT ratio >1	0.64 (0.40;0.88)	0.72 (0.70;0.74)	1.04 (0.96;1.11)
Backward selection			
ALT	-0.86 (-1.17;-0.56)	0.72 (0.70;0.74)	0.98 (0.91;1.06)
GGT	0.57 (0.35;0.80)		

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase; NRI, net reclassification index

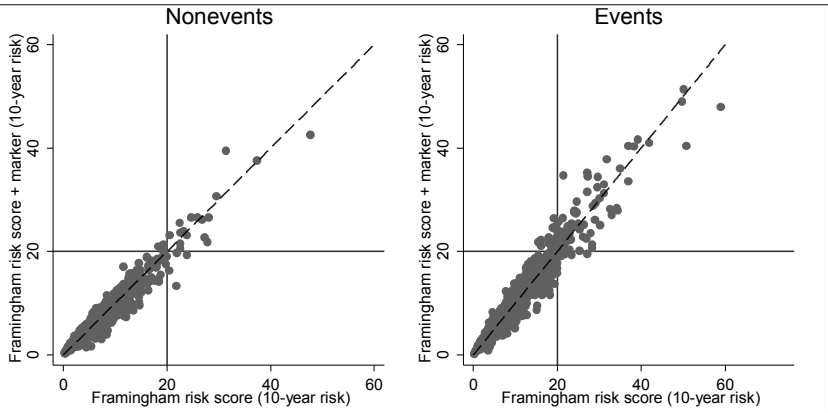
	Threshold 20%			Threshold 10% and 20%	
	NRI non-event (%)	NRI event (%)	Δ Net benefit (%)	NRI non-event (%)	NRI event (%)
	0	0	0.02	1	0
	0	1	-0.03	-1	2
	0	1	-0.05	-1	2
	0	1	-0.05	-1	2
	0	0	0	0	1
	0	1	0.08	0	1
	0	3	0.12	-1	7

[a] All markers were standardized and all the continuous markers were naturally logarithmically transformed

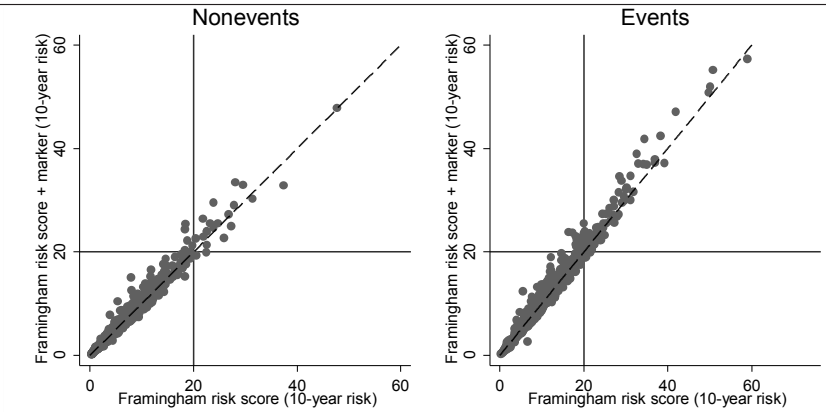
[b] Hepatic steatosis index to rule out hepatic steatosis predicted cardiovascular disease in the opposite direction than expected. Therefore, we did not evaluate the quality of this model

Figure 1 Reclassification graphs for the addition of markers of hepatic steatosis to the Framingham risk score, for participants with and without a cardiovascular event. The threshold of a 10-year risk of 20% is indicated with solid lines, the dashed line indicates no improvement. Correct reclassification of participants without an event is indicated by smaller predicted probabilities, the dots will lie below the diagonal line. Correct reclassification of participants with an event is indicated by larger predicted probabilities, the dots will lie above the diagonal line. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; GGT, gamma-glutamyl transferase

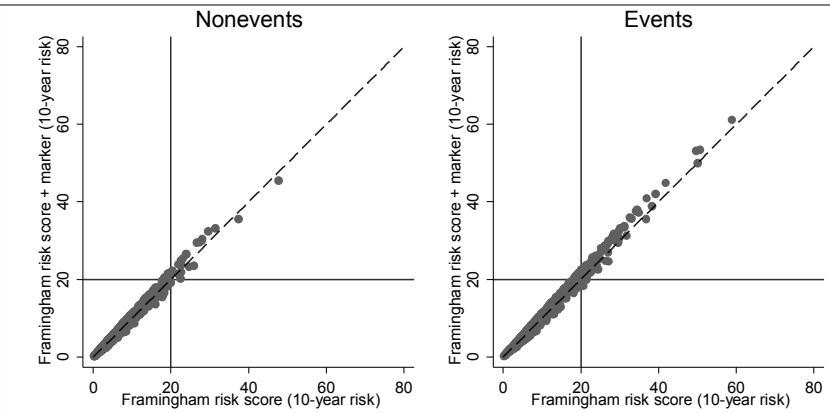
A: ALT



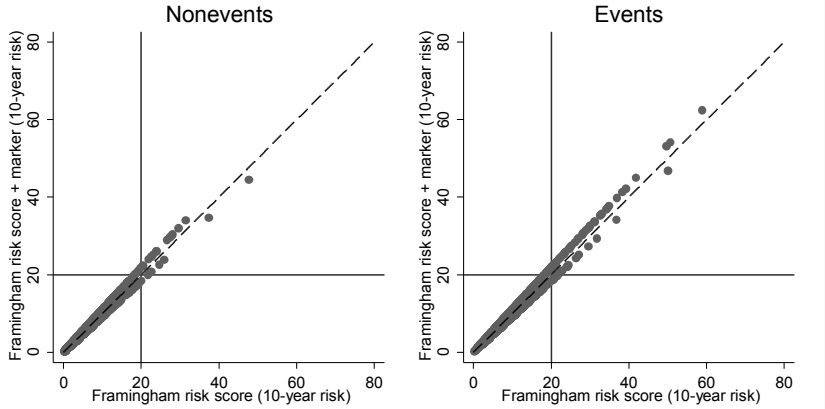
B: GGT



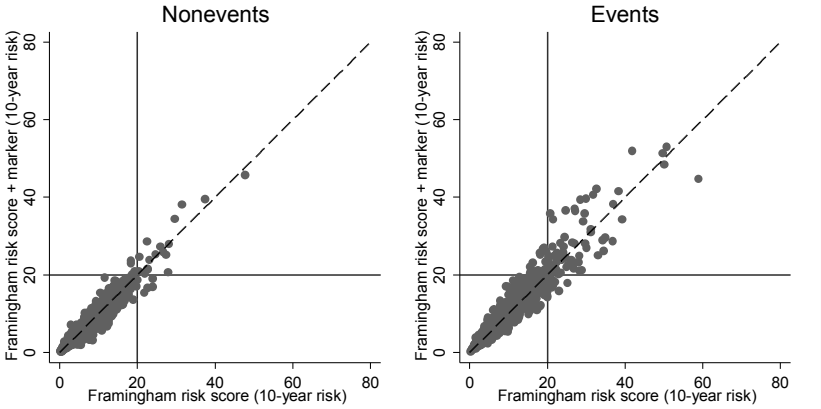
C: Fatty liver index



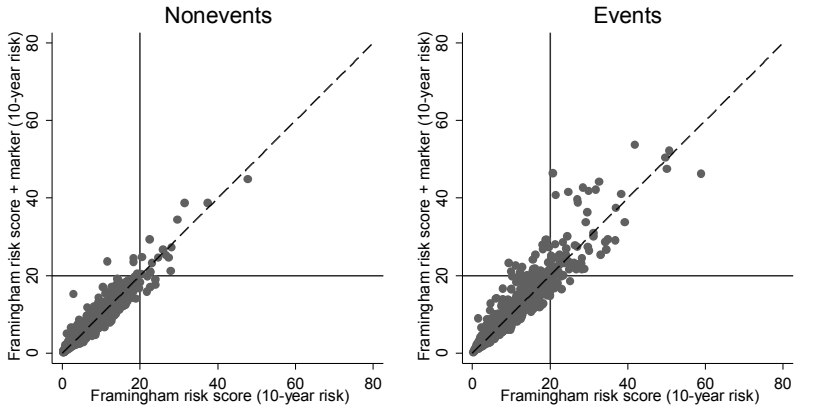
D: Fatty liver index to rule out hepatic steatosis



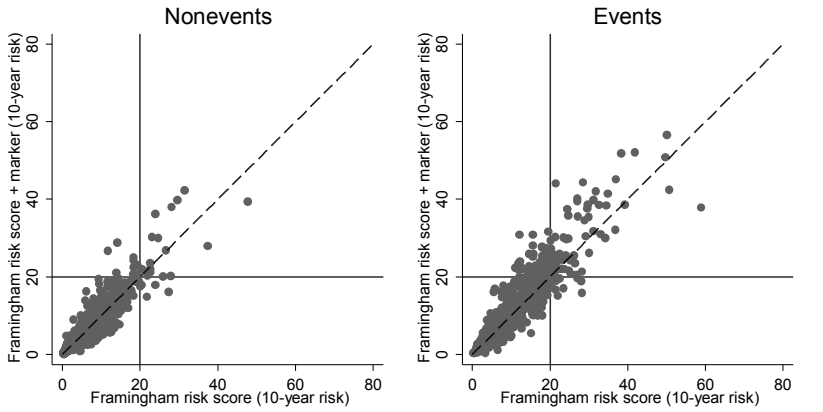
E: AST/ALT ratio



F: AST/ALT ratio >1



G: GGT, ALT



Discussion

In this large prospective cohort study, the addition of markers of hepatic steatosis to the established risk estimation systems Framingham risk score and Pooled Cohort Equations slightly improved the prediction of 10-year CVD risk in women, but not in men. However, this resulted in only a small improvement in discrimination, calibration and reclassification.

In a previous study, the AST/ALT ratio was a predictor of cardiovascular risk in men when the ratio was added to the risk prediction systems Framingham risk score or QRISK, but not in women.(51) However, the addition of the AST/ALT ratio did not improve discrimination. In contrast, in our study, the AST/ALT ratio was a predictor of cardiovascular risk in women only, also without improvement in discrimination. These discrepant results might be due to chance.

In contrast to our findings, a previous prospective study in 6,997 men stated that the addition of GGT to the Framingham risk score may be useful to improve cardiovascular risk prediction.(49) The C-statistic was significantly increased when GGT was added to the model, though the improvement was very small (C-statistic increased from 0.725 to 0.729). No information about calibration or benefit for clinical practice was provided. Another study in 6,969 men and women showed no improvement in discrimination and reclassification when GGT was added to the risk factors in the Framingham risk score.(50) In our study, the addition of GGT did not improve cardiovascular risk prediction in men and we judged the improvement in women not clinically relevant.

A strength of this study is the large study population with a large number of CVD events and the availability of information on all established risk factors and the markers of hepatic steatosis. Another strength is that we investigated the added value of the markers in two different established risk estimation systems, which allowed us to examine the robustness of our findings.

A limitation of this study is the missing data, specifically missing blood samples. These blood samples were missing in cases outside the sub-cohort with an event after 31 December 2005 or an event other than coronary heart disease or stroke or due to an unsuccessful blood draw or failed laboratory analysis. The participants with complete blood samples were representative of all participants, which allowed us to weight these participants in the analysis to represent the full cohort.

Another limitation of this study is the absence of information about the reference standards of hepatic steatosis and fibrosis, proton magnetic resonance spectroscopy and liver

biopsy. The markers of hepatic steatosis used in this study may be not accurate enough to improve risk prediction. The serological markers of hepatic steatosis used in this study are often not very sensitive and specific.(124) Moreover, the combination scores have an AUC between 0.81 and 0.84.(117, 125) Other, more accurate, (bio)markers of hepatic steatosis may have an added value in addition to the established risk factors. However, these markers are currently not measured on a large scale.

Compared with the 1990s, when the participants of the EPIC-NL cohort were recruited, the prevalence of NAFLD has doubled in the last years, in parallel with the increasing prevalence of obesity.(46) The predictive value of markers of hepatic steatosis may be different in a population with a higher prevalence of NAFLD. Furthermore, our study population was predominantly white. Therefore, our results need to be confirmed in other ethnicities.

Different pathophysiological pathways link NAFLD with CVD, including atherogenic dyslipidaemia and insulin resistance.(47) In most established risk estimation systems, cholesterol concentrations are included as marker of dyslipidaemia and diabetes as marker for insulin resistance.(28) As a result, markers of NAFLD may not have added value in addition to the cholesterol concentrations and diabetes.

Interestingly, in our study, some of the markers were predictors of cardiovascular disease in women, but not in men. It is often reported that the strength of cardiovascular risk factors is different between men and women.(126) This emphasizes the importance of making different models for men and women. However, due to source population of the Prospect cohort, more women were included in this study. As a result, predictors with a small effect size may be significant in women and not in men. Nevertheless, this will not change our conclusion that none of the markers of hepatic steatosis showed a clinically meaningful improvement in the prediction of CVD, since predictors with a small effect will probably not affect clinical care.

In conclusion, our findings suggest that indirect and easily accessible markers of hepatic steatosis do not improve cardiovascular risk prediction in addition to the established cardiovascular risk factors. Future research is needed to examine the added predictive value of other markers of hepatic steatosis and also of markers of NASH and advanced fibrosis or cirrhosis.

Supplemental table 1 The cox proportional hazards model coefficients of the markers of hepatic steatosis when added to the Pooled Cohort Equations in men participating in the EPIC-NL cohort

Markers added to the Pooled Cohort Equations[a]	Coefficient (95% CI)
Single marker	
ALT	-0.19 (-0.70;0.32)
ALT >45 U/L	-1.09 (-3.48;1.29)
AST	-0.19 (-0.77;0.40)
AST >35 U/L	0.02 (-1.10;1.13)
GGT	-0.27 (-0.70;0.16)
GGT >50 U/L	-0.19 (-0.83;0.45)
Fatty liver index	-0.16 (-0.44;0.11)
Fatty liver index to rule in hepatic steatosis	-0.26 (-0.64;0.13)
Fatty liver index to rule out hepatic steatosis	0.07 (-0.40;0.53)
Hepatic steatosis index	-0.89 (-2.31;0.54)
Hepatic steatosis index to rule in hepatic steatosis	-0.01 (-0.44;0.43)
Hepatic steatosis index to rule out hepatic steatosis	0.24 (-0.21;0.70)
AST/ALT ratio	0.11 (-0.56;0.78)
AST/ALT ratio >1	0.17 (-0.34;0.68)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase

[a] All markers were standardized and all the continuous markers were naturally logarithmically transformed

Supplemental table 2 Cox proportional hazard coefficients, discrimination, calibration and reclassification of the addition of markers of hepatic steatosis to the Pooled Cohort Equations in women participating in the EPIC-NL cohort

Markers added to the Pooled Cohort Equations[a]	Coefficient (95% CI)	Area under the curve (95% CI)	Calibration slope (95% CI)
Single marker			
ALT	-0.59 (-0.93;-0.25)	0.73 (0.70;0.75)	1.02 (0.83;1.21)
ALT >45 U/L	-0.87 (-2.38;0.64)		
AST	-0.61 (-1.15;-0.06)	0.73 (0.70;0.75)	0.98 (0.81;1.15)
AST >35 U/L	-0.31 (-1.48;0.86)		
GGT	0.30 (0.05;0.54)	0.73 (0.70;0.75)	0.96 (0.76;1.16)
GGT >50 U/L	0.29 (-0.22;0.79)		
Fatty liver index	0.08 (-0.05;0.21)		
Fatty liver index to rule in hepatic steatosis	0.15 (-0.12;0.43)		
Fatty liver index to rule out hepatic steatosis	-0.20 (-0.42;0.03)		
Hepatic steatosis index	-0.40 (-1.27;0.47)		
Hepatic steatosis index to rule in hepatic steatosis	0.10 (-0.13;0.34)		
Hepatic steatosis index to rule out hepatic steatosis	0.38 (0.07;0.69)[b]		
AST/ALT ratio	0.69 (0.21;1.16)	0.73 (0.70;0.75)	0.98 (0.82;1.14)
AST/ALT ratio >1	0.54 (0.23;0.86)	0.73 (0.70;0.75)	0.98 (0.83;1.14)
Backward selection			
ALT	-1.00 (-1.38;-0.61)	0.74 (0.71;0.76)	1.00 (0.84;1.15)
GGT	0.68 (0.38;0.97)		

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CI, confidence interval; GGT, gamma-glutamyl transferase; NRI, net reclassification index

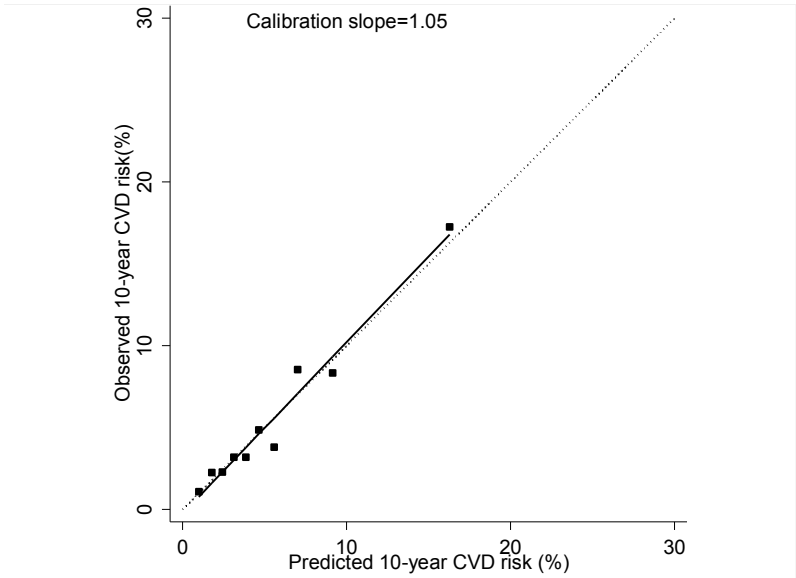
	Threshold 7.5%			Threshold 5% and 7.5%	
	NRI non-event (%)	NRI event (%)	Δ Net benefit (%)	NRI non-event (%)	NRI event (%)
	0	0	0	0	-4
	0	-4	0	0	-7
	0	7	0.11	-1	14
	-1	0	0	0	-7
	-1	0	0	0	-7
	-1	4	0.02	-1	0

[a] All markers were standardized and all the continuous markers were naturally logarithmically transformed

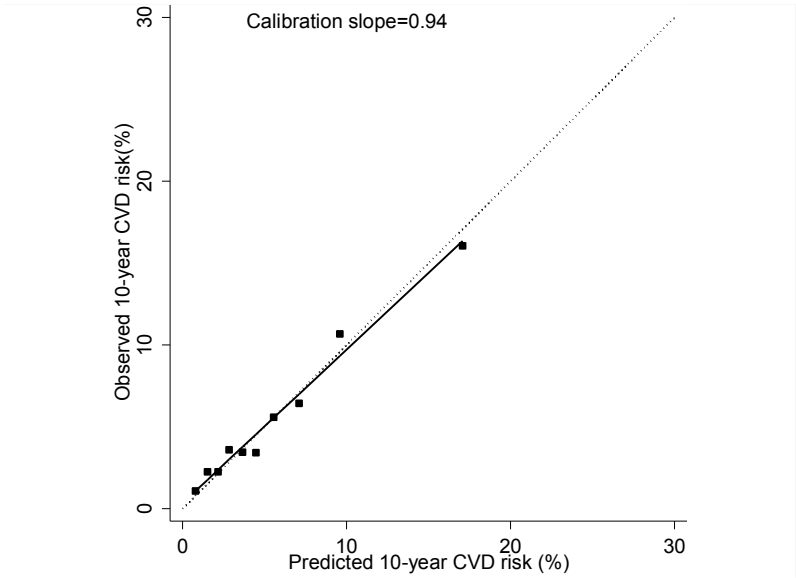
[b] Hepatic steatosis index to rule out hepatic steatosis predicted cardiovascular disease in the opposite direction than expected. Therefore, we did not evaluate the quality of this model

Supplemental figure 1 Calibration curves of the Framingham risk score + markers of hepatic steatosis based on the predicted and observed cardiovascular risk, in deciles of the predicted risk. The solid line represents the calibration slope. The dashed line represents the ideal prediction.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; GGT, gamma-glutamyl transferase

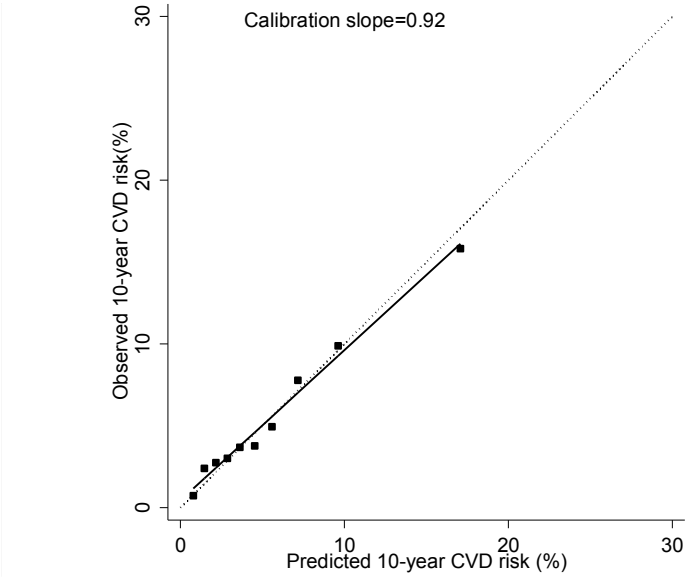
A: ALT



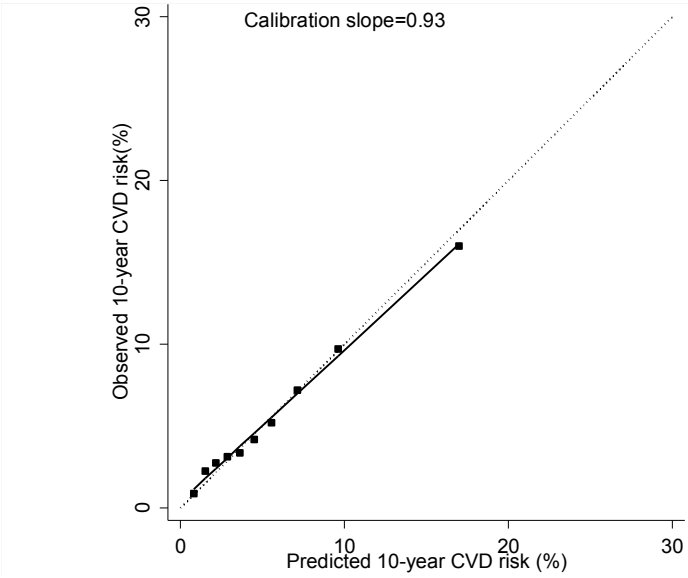
B: GGT



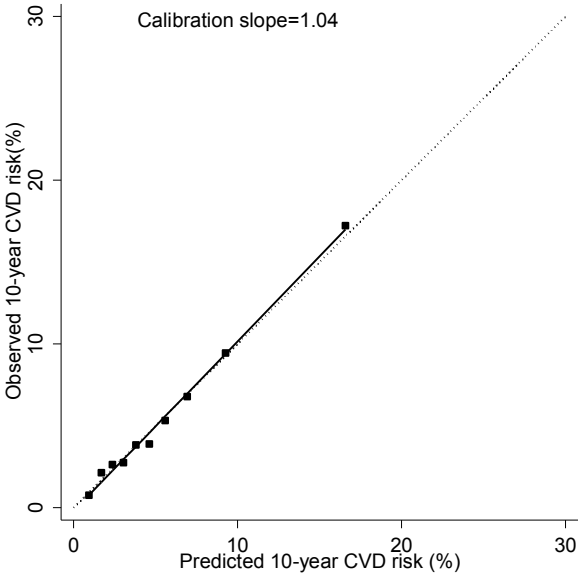
C: Fatty liver index



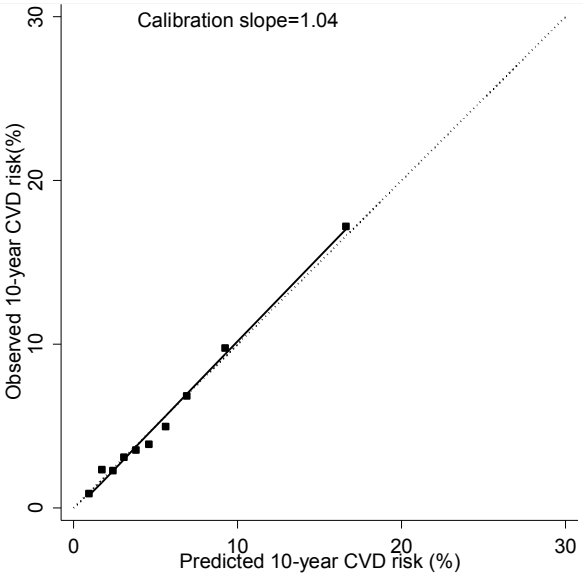
D: Fatty liver index to rule out hepatic steatosis



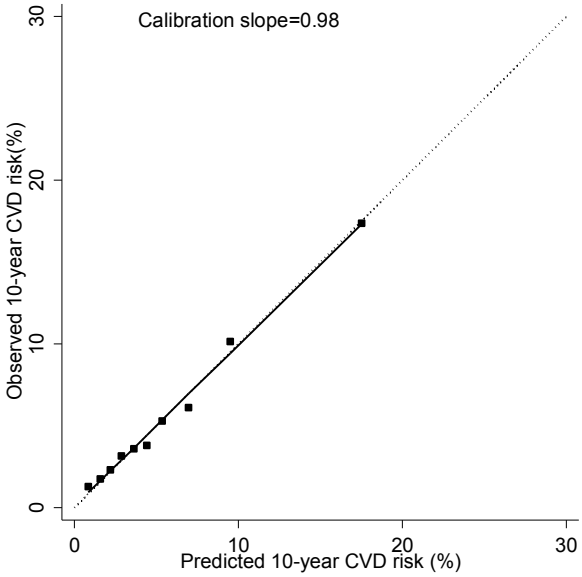
E: AST/ALT ratio



F: AST/ALT ratio >1

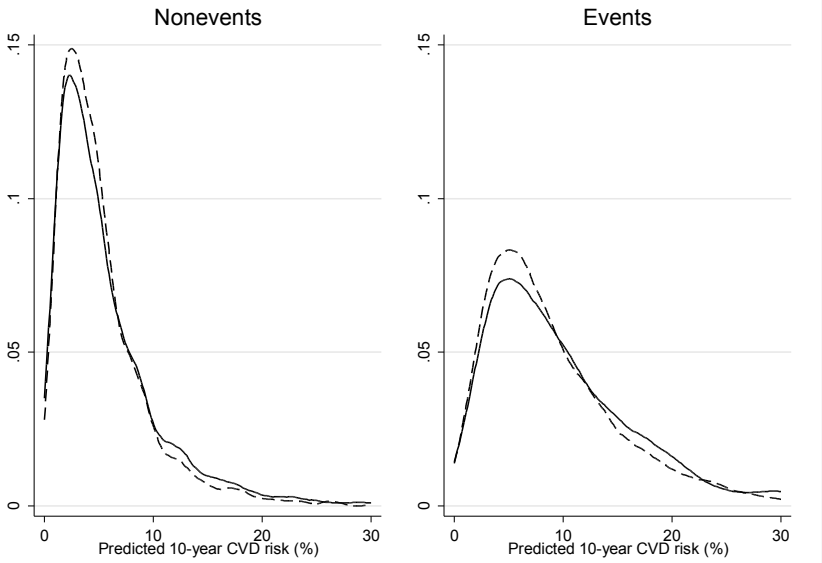


G: GGT, ALT

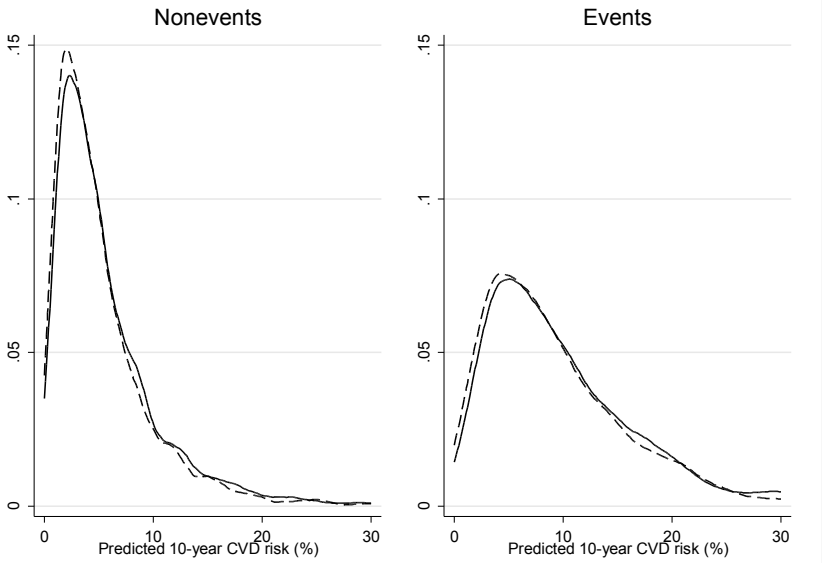

Calibration slope=0.98
Observed 10-year CVD risk(%)
Predicted 10-year CVD risk (%)
0
10
20
30

Supplemental figure 2 Density plots of the predicted 10-year cardiovascular risk, for participants with and without a cardiovascular event. The solid line represents the calibrated Framingham risk score. The dashed line represents the Framingham risk score + markers of hepatic steatosis.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CVD, cardiovascular disease; GGT, gamma-glutamyl transferase

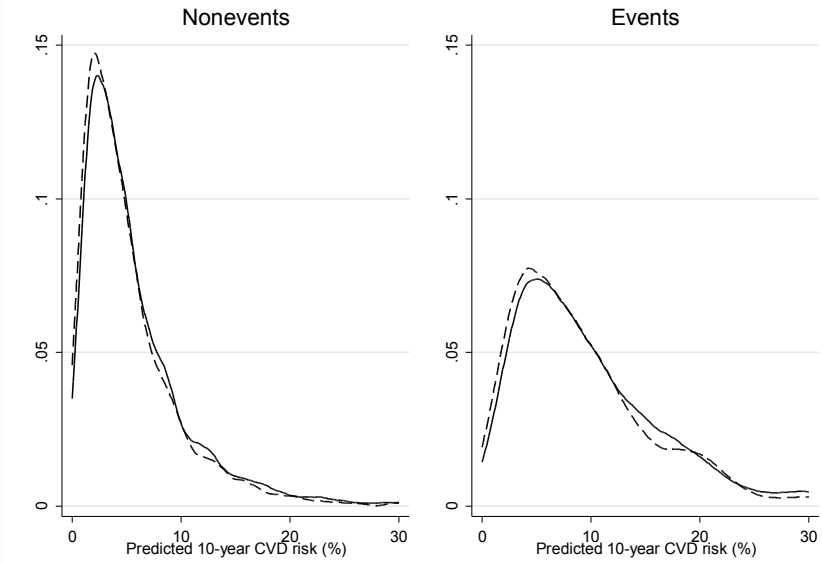
A: ALT



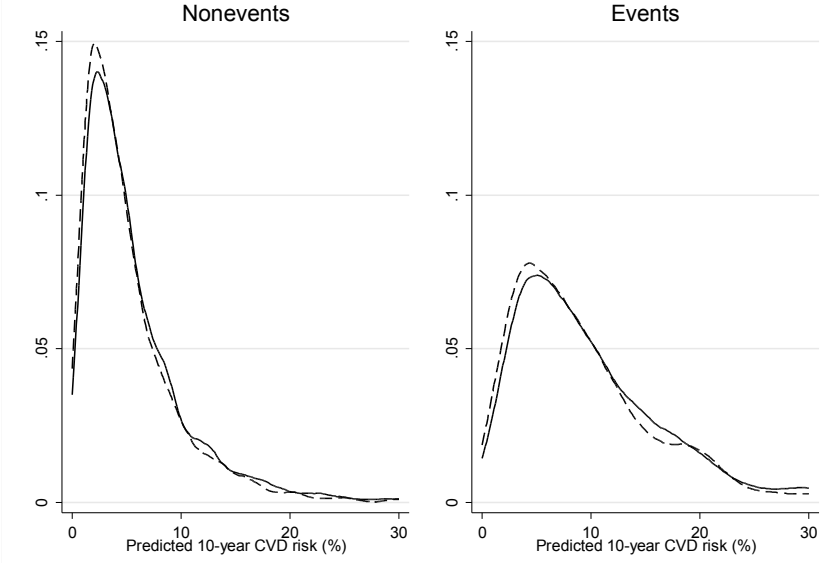
B: GGT



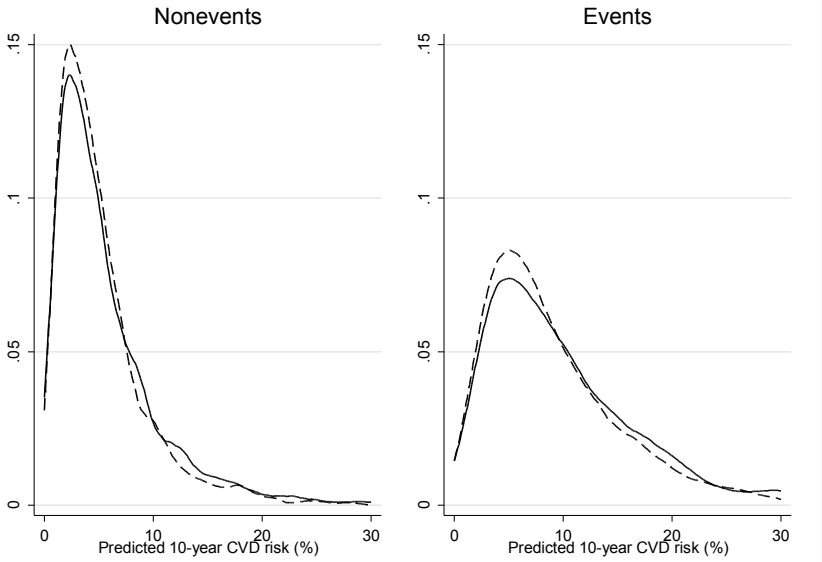
C: Fatty liver index



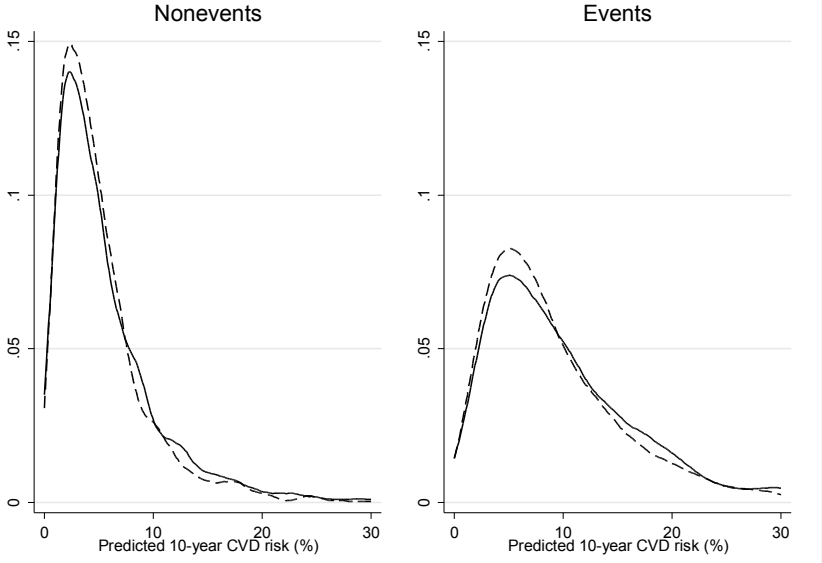
D: Fatty liver index to rule out hepatic steatosis



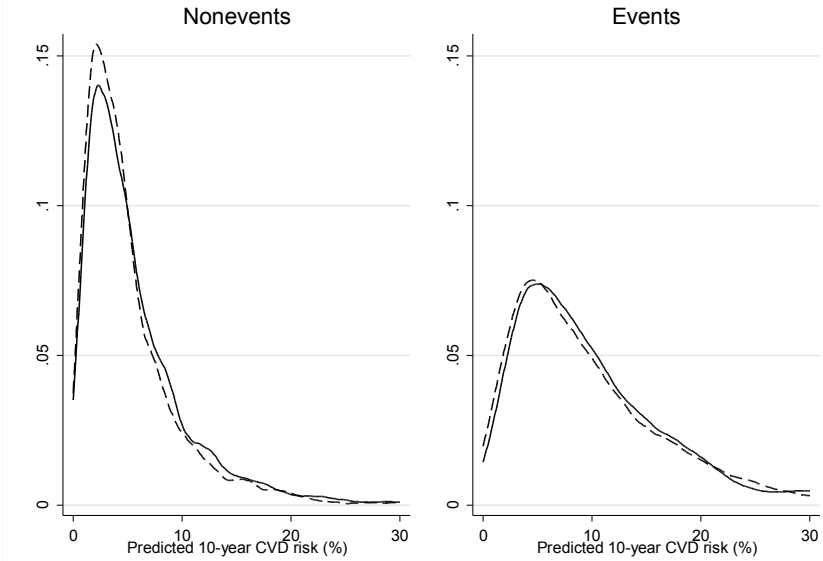
E: AST/ALT ratio



F: AST/ALT ratio >1



G: GGT, ALT


Nonevents
Events
.15
.1
.05
0
0
10
20
30
Predicted 10-year CVD risk (%)

CHAPTER 7

General Discussion

The main objective of this thesis was to improve cardiovascular risk assessment in primary care. Hereto, we studied two important aspects in the design of cohort studies on cardiovascular disease; case definition and the disclosure of research test results. In addition, we investigated the identification of patients for cardiovascular risk assessment and the assessment of an individual's risk. In this chapter, we first discuss the main findings and the methodological considerations of this thesis. Second, we discuss per topic the findings, the implications and the directions for further research. Finally, we present our conclusions based on this thesis.

Summary of main findings

Chapter 2 provides evidence that coded diagnosis from general practice electronic health records are a feasible and valid alternative to self-report to define diabetes cases in epidemiological studies. Based on the results of focus group discussions with research participants confronted with an incidental finding, as described in Chapter 3, we concluded that a detailed study protocol is needed on the disclosure of incidental findings before recruitment of participants. We gave several recommendations to improve the disclosure of incidental findings. Our findings in Chapter 4 suggest that it is important to inform the general practitioner and the research participants about the individual cardiovascular test results. Only participants with an estimated intermediate of high cardiovascular risk should receive a recommendation to consult their general practitioner. In Chapter 5, we concluded that inviting patients with overweight or obesity for cardiovascular risk assessment can help to identify a substantial additional group of patients at increased cardiovascular risk. In Chapter 6, we did not find evidence that cardiovascular risk assessment can be improved when non-invasive markers of hepatic steatosis are added to an established risk estimation system.

Methodological considerations

Before we are able to address the implications of the findings presented in the various chapters of this thesis, it is important to discuss factors which may affect the validity of the results.

The cohort studies used in this these are both conducted in the Netherlands, which may have consequences for the generalizability of the results to other countries. In the Netherlands, primary care is strong and general practitioners have broad service profiles.(127) General practitioners have a gatekeeping function to hospital and specialist care. However, the Dutch general practitioners are less actively involved in systematic screening of blood pressure and cholesterol when compared to other European countries.(128). So, the Dutch patients in our study population may benefit more from improvement of cardiovascular risk assessment than patients in other European countries.

The Netherlands Epidemiology of Obesity (NEO) study, on which we based the majority of our studies, is a population-based cohort study with an oversampling of persons with a body mass index ≥ 27 kg/m². However, in the municipality Leiderdorp, persons were invited irrespective of their body mass index. The body mass index distribution of these Leiderdorp participants was comparable to the Dutch general population.(52) This allowed us, in Chapter 4 and 5, to weight the participants towards the body mass index distribution of the participants of the municipality Leiderdorp. With these adjustments, the results can be translated to the general population with a normal distribution of body mass index. Another factor which may influence the external validity is that the participants in the used cohort studies are predominantly white. This may limit the generalisability of the conclusion in most chapters. Previous research on the ethnic differences in cardiovascular disease reported variation in cardiovascular disease rates and strength of the cardiovascular risk factors.(129) Risk estimation systems, however, perform well in other ethnic groups after recalibration.(130)

In this thesis, we used data from two population-based cohort studies, the NEO study and the European Prospective Investigation into Cancer and Nutrition-Netherlands study (EPIC-NL). In these cohort studies, participants were recruited from the general population. Participants of population-based cohort studies tend to be higher educated, more health-conscious and in better general health than the overall population.(131) EPIC-NL showed that, after a median follow-up of 15 years, the mortality due to cardiovascular disease was 30% lower than the general population.(132) Underrepresentation of persons at increased cardiovascular risk is also reported in other cohorts.(133, 134) This healthy volunteer effect may lead to difficulties in the translation of the findings from cohort

studies to daily clinical care. One of the consequences is that absolute cardiovascular risks are underestimated and contributions of the predictors in the risk estimation systems may be underestimated.

In cohort studies, loss to follow-up occurs when researchers lose contact with some participants. Loss to follow-up can threaten the validity of the results when participants lost to follow-up are different to those not lost to follow-up.(135) In Chapter 2 and Chapter 6, data on disease outcomes were missing in less than 5% of all participants. In most cohort studies some loss to follow-up is considered to be inevitable, and 5% is considered to be of little concern.(136) In Chapter 5, we experienced a high rate of non-response, almost 20% of the participants did not respond to a questionnaire in the follow-up. The responders had a slightly better cardiovascular risk profile than the non-responders. We do not expect that this has changed the conclusions from our study based on the questionnaire: that some participants are worried due to abnormal test results and not all participants with an abnormal test result consult a general practitioner.

In EPIC-NL, on which we based our study presented in Chapter 6, follow-up data on cardiovascular disease was obtained through linkage with disease registries. In a sub sample of the EPIC-NL cohort, the validity of the incidence rates estimated using those disease registries was investigated.(137) A considerable part of the coronary heart disease events in medical records coded by trained registrars were not found in the disease registries. As a consequence, the incidence of cardiovascular disease in the disease registries may be underestimated, which may have led to biased effect estimates in Chapter 6.

Qualitative research usually aims to reflect diversity, rather than generalisability. However, the impact of the research to clinical practice depends on the degree to which the results of the research can be transferred to other contexts.(138) In Chapter 3, we provided a detailed description of the context of the NEO study which readers can use to determine the transferability to their specific context. For example, the participants were confronted with an incidental finding on MRI. The experiences and preferences of participants confronted with genetic information may be different.

Data from general practice electronic health records

Health information from general practice electronic health records is increasingly re-used for conducting research.(75) In Chapter 2, we showed that data extraction from general practice electronic health records is feasible. Almost all participants gave informed consent for the collection of medical information and the follow-up rate was high, health information was obtained from 97% of the participants. However, the extraction of the data was time consuming and expensive. Therefore, in many countries, an infrastructure for data-sharing is implemented in general practices to develop a research data warehouse.(76) A research data warehouse will make the use of data from general practice electronic health records even more feasible.

An advantage of the data from electronic health records for researchers is that all information that is considered relevant for patient care in clinical practice is included in these electronic health records. In addition, complaints and disease are coded in the electronic health records using the International Classification of Primary Care (ICPC) and prescriptions are often registered according to the Anatomical Therapeutic Chemical (ATC) codes.(21, 66) The information in these records is, however, not collected in a standardized way, it is restricted by the individual nature of the consultations. This means that first, the patient has to decide to visit the general practitioner and mention a complaint and second, the general practitioner has to decide to register and code the symptom and/or disease the patient presents. The re-user of coded information cannot be sure that symptoms or diseases not mentioned in the database, indeed are not present.

For researchers, completeness and accuracy of the data is of great importance. Therefore, it is crucial to check the quality of the data from general practice electronic health records for case definition in epidemiological studies. In Chapter 2, we showed that ICPC-coded diagnoses of DM had an excellent agreement of 99% with the reference standard using diagnoses, prescriptions and consultation notes. In future research studies, ICPC-coded diagnoses of DM are a feasible and valid alternative to self-reported DM. Other studies suggest that the ICPC-coded diagnoses from general practice electronic health record are also valid for the diagnosis inflammatory arthritis, acute myocardial infarction, and oncologic diagnoses.(139-141) Though, the validity is higher when a combination is used of coded diagnoses, prescriptions, keywords and results of diagnostic tests. In addition, a systematic review investigated the validity of diagnoses in the General Practice Research Database containing general practice electronic health record from the United Kingdom. The investigators reported that overall 89% of all diagnoses were confirmed.(142) However, as mentioned above, it is not always clear how many diagnosis are being missed in re-use of routine health care data.

Electronic health record datasets contain a substantial amount of potentially missing information. There are three main reasons why data on a disease is missing: a person doesn't have the disease, the general practitioner did not document the diagnosis of the disease or the presence of a disease was not investigated.(143) Moreover, diseases with difficult or vague diagnostic criteria and diseases with nonspecific or no alarming symptoms are probably the least reliable coded diagnoses. Common practice in research is to assume that a disease is not present when data is missing. Misclassification of persons with a disease as not having the disease can lead to loss of power and bias.(19) In our study described in Chapter 2, the negative predictive value of ICPC-coded diagnoses DM was very high, more than 99%. Therefore in future studies, all persons without an ICPC-coded diagnosis DM could be considered as not being diagnosed with DM. More research is needed to investigate the validity of other diseases and symptoms from general practice electronic health records. Hereby, it is not only important to investigate to what extent the coded diagnosis can be confirmed by a reference standard, but also to investigate how many cases are being missed.

Disclosure of test results in research

In large cohort studies, extensive medical examinations are performed to collect detailed information on exposure, confounding factors and health outcomes. These procedures are associated with several potential risks, including the risk of finding unexpected abnormalities that are outside the purpose of the data collection. Consensus exists that incidental findings of potential health importance have to be disclosed to the research participants.(25) The experiences and preferences of participants confronted with an incidental finding regarding the communication of such incidental finding by the research team are described in Chapter 3. Overall, the participants were grateful for the disclosure of the incidental finding. They had assumed that any finding would be disclosed, and this was an important reason to participate in research. None regretted their informed consent to be notified about incidental findings. Disclosure of the finding had great impact on the lives of most participants. In addition, the research participants stated that they want to be informed about an incidental finding as soon as possible. Difficulties with the transition from research participant to patient were frequently mentioned.

Based on these results, three key recommendations can be made. First, researchers should give clear information during the informed consent procedure about which findings will be disclosed. The most effective method to improve informed consent procedures is person-to-person interaction.(84) Second, before start of the research study, researchers should make a detailed protocol to guarantee timely disclosure of the finding. Hereto, the responsibilities for the detection and disclosure should be assigned to specific specialists. And third, arrangements should be made with the medical specialists involved in the follow-up of an incidental finding to improve the transition from research participant to patient. Hereto, the medical specialists involved in the follow-up of an incidental finding need to be informed about the research study by regular updates, and when the follow-up of a specific participant is planned.

The term incidental finding suggests that the finding is unforeseen. However, incidental findings can no longer be considered fully unexpected. Incidental findings are frequently detected during research procedures, due to improvements in imaging techniques and developments in genetic research. In research projects using brain magnetic resonance imaging, for example, the overall prevalence of incidental findings is 2.7%,(77) in genetic research using exome sequence data 8.8% incidental findings have been found,(144) and in projects using whole-body MRI a prevalence of 32% has been reported(78). In addition, the issue of incidental findings in research has received increasing attention in literature recent years. Therefore, researchers should anticipate on incidental findings by making a detailed protocol for the communication of incidental findings to the participants of their research study.

Besides the disclosure of incidental findings with potential health importance, research studies often disclose test results with relevance for clinical care. For example, participants of the NEO study received a letter after their baseline visit with the results of tests on blood pressure, serum cholesterol concentrations, fasting or non-fasting plasma glucose, renal function, lung function, and bone mineral density. Results of blood pressure measurements and cholesterol concentrations have potential implications for cardiovascular risk management in general practice. Therefore, we examined in Chapter 4 the advantages and disadvantages of the disclosure of these individual test results. The participants were recommended to consult their general practitioner based on one abnormal result of blood pressure or cholesterol. Half of the participants who received a recommendation to consult their general practitioner did not have a treatment indication according to their estimated 10-year cardiovascular risk and received this recommendation unnecessarily. In addition, 10% of the participants were unnecessarily worried due to this recommendation. Our findings suggest that only participants at intermediate or high risk should receive a recommendation to consult their general practitioner. This may reduce the burden of unnecessarily entering into healthcare procedures and prevent participants from being unnecessarily worried. Furthermore, we suggest that general practitioners should be informed about all the results of cardiovascular risk factors of all participants, since it is an opportunity for general practitioners to collect information about the cardiovascular risk of their patients.

Currently, there are no regulations concerning the communication of individual research results. As a result, research protocols on the communication of test results differ between research projects. Research participants are often informed about aggregate research results, but not about their individual test results. However, most participants are interested in receiving individual research results(145-148), which was also noted in the NEO study, as described in Chapter 3. The main argument in favour of disclosure of individual test results is that it promotes participants' autonomy. Participants can use the information of the test results to make medical, reproductive or lifestyle choices. The most frequent concern about the disclosure of individual test results is the possibility that disclosure may harm participants, such as distress and unnecessary entering health care. However, previous studies suggest that these consequences are low.(149)

Consensus exist that test results with potential consequences for clinical care should be disclosed.(22) The disclosure of incidental findings with potential serious consequences and the disclosure of cardiovascular risk factors belong to this group of test results with clinical significance. However, there is still debate whether researchers should disclose also clinically insignificant results, such as genetic variants. To be able to make recommendations on this topic, more research is needed to investigate the balance between the

benefits and harms of disclosure. Furthermore, more research is needed on how research results should be communicated. We suggest disclosure protocols in research projects should be evaluated from the perspectives of the researchers, participants and health care providers. A qualitative research design may help to explore this topic.

Identification of patients for cardiovascular risk assessment

In primary care, patients with a potential increased cardiovascular risk are invited for the assessment of an individual's cardiovascular risk. Based on this estimated risk, the indication for preventive treatment is determined. Previous studies mainly focused on the development of a programmatic approach to determine which patients should be invited for cardiovascular risk assessment.(37-39) A recent Cochrane review concluded that programmatic cardiovascular risk assessment has no effect on cardiovascular events compared with ad hoc case-finding.(150) However, five ongoing trials were identified which will further explore the potential effect of programmatic risk assessment. Until the results from these trials are reported, general practitioners may use other approaches to identify patients at increased cardiovascular risk. In this thesis, we examined two possible approaches.

In Chapter 4, we suggest that general practitioners should be informed about all results of cardiovascular risk factor screening outside primary care. We observed that a quarter of the participants in the NEO study with an abnormal result of blood pressure or cholesterol did not consult their general practitioner, half of whom had a treatment indication. These patients with a potential increased cardiovascular risk are not identified despite the abnormal test results. In addition, normal test results are also of great value to the general practitioner. Patients with a presumed low cardiovascular risk based on the test results do not have to be invited for cardiovascular risk assessment for the time being. At the same time, general practitioners can focus cardiovascular risk assessment on patients with a presumed intermediate or high risk based on the test results, and on patients without information on cardiovascular risk factors.

Cardiovascular risk factors are not only measured for research purposes, but also in occupational health, in pharmacies or during health check-ups at private companies.(43-45) Efficient use of all available test results can help general practitioners to identify patients at increased cardiovascular risk. Therefore, we suggest that general practitioners should be informed about all results of screening outside primary care. More collaboration is needed between general practitioners and organisations outside primary care to improve the use of all available information which may be relevant for disease-management.

In Chapter 5, we observed that a quarter of the persons with an indication for preventive cardiovascular treatment were not yet identified and treated. To identify those patients, we hypothesised that general practitioners could invite patients with overweight or obesity for cardiovascular risk assessment during a regular consultation for other rea-

sons, so-called ad hoc case-finding. This is an important subgroup to identify because overweight is associated with the risk factors used in the risk estimation system and is easy to obtain. In our study, 12% of the persons with overweight had a new treatment indication and 19% of the persons with obesity had a new treatment indication. Our results indicated that inviting all patients with overweight or obesity for cardiovascular risk assessment will help to detect 70% of the patients with a new treatment indication. These patients with overweight can be visually identified by general practitioners based on their perception of the patient's weight status.

These two approaches to identify patients at increased cardiovascular risk in primary care are based on results of observational research in cohort studies. In daily clinical practice, it may be difficult to invite patients for cardiovascular risk assessment during regular consultation or to make arrangements with organisations outside primary care about cardiovascular risk factor screening. However, these approaches have the potential to identify patients at increased cardiovascular risk, especially in general practices without programmatic cardiometabolic screening. It is important to note that, although we have focused on the identification of patients with a treatment indication, life style advices are at least as important in the prevention of cardiovascular disease.(151)

Cardiovascular risk assessment

In clinical practice, risk estimation systems are used to calculate an individual's 10-year risk of cardiovascular disease. However, the established cardiovascular risk prediction systems do not optimally predict an individual's risk.(28) Risk prediction may be improved by adding information about novel risk factors to these risk estimation systems. We hypothesised that hepatic steatosis is a potential risk factor, because it is increasingly prevalent worldwide and is associated with a 64% increased cardiovascular risk.(46, 48) In Chapter 6 we concluded that some non-invasive markers of hepatic steatosis were predictors of cardiovascular disease when added to the Framingham risk score or the Pooled Cohort Equations in women, but not in men. However, the addition of these markers did not result in a clinically meaningful improvement in discrimination, calibration and reclassification.

Cardiovascular risk assessment by estimating an individual's 10-year risk is implemented in many guidelines on the prevention of cardiovascular disease. However, only three studies investigated the effect of cardiovascular risk assessment on the prevention of cardiovascular events.(152) These studies provided low quality evidence that cardiovascular risk assessment has no or little effect on cardiovascular events compared with usual care. Currently, the INTEGRATE study investigates the effectiveness and cost-effectiveness of the Dutch guideline Prevention Consultation, a cardiometabolic online risk assessment and treatment program.(153) This may provide evidence for systematic identification of patients at increased risk, risk assessment and treatment according to the estimated risk. In current literature, the ideal design of a risk estimation system is debated. Age is undoubtedly the most powerful risk factor in the established risk estimation systems. The area under the receiver operating curve for age and sex alone is 0.75.(154) When the other traditional risk factors are added to the risk prediction model, the area under the curve only slightly increases to 0.80. This raises the question whether cardiovascular risk estimation systems mainly predict the increasing risk of cardiovascular disease with increasing age, which is unavoidable. It is suggested that, besides the ageing-associated risk of cardiovascular disease which affects everyone, age also reflects the length of exposure to other cardiovascular risk factors.(155) Patients with an optimal cardiovascular risk profile at 50 years of age have a substantially lower lifetime risk of cardiovascular disease than participants with two or more traditional risk factors.(156) This suggests that the prevention of the development of risk factors should be promoted in younger individuals. In addition, patients may benefit more from early reduction of the modifiable cardiovascular risk factors.(155)

Current cardiovascular risk management, however, estimates 10-year cardiovascular disease risk for individuals of 40 years and older. This relatively short-term risk approach

neglects the negative effects of the presence of risk factors in younger patients. Estimating long-term risk or lifetime risk in addition to current cardiovascular risk management may identify patients with a low or intermediate short-term risk but high long-term risk. More research is needed to investigate the advantages and disadvantages of long-term risk assessment. Notably, the risk of overdiagnosis, overtreatment and medicalisation are topics which needed to be addressed.

Conclusions

This thesis provides additional evidence that general practice electronic health records are a feasible method for case definition in epidemiological studies. Coded diagnosis of diabetes from these records are a valid alternative to self-reported diabetes. This thesis gives recommendations to improve the disclosure of research test results. A detailed protocol is needed on the disclosure of individual test results in research studies before recruitment of participants. Furthermore, this thesis gives suggestions to improve the identification of patients at increased cardiovascular risk in primary care. Inviting patients with overweight or obesity for cardiovascular risk assessment can help to identify a substantial additional group of patients at increased cardiovascular risk and collaboration with organisations outside primary care may help general practitioners to obtain information about cardiovascular risk factors. In this thesis, we did not find evidence that cardiovascular risk assessment can be improved when non-invasive markers of hepatic steatosis are added to an established risk estimation system. In conclusion, this thesis leads to improvement of data collection in research and proposed approaches to improve cardiovascular risk assessment in primary care.

CHAPTER 8

References

References

1. World Health Organization. NCD mortality and morbidity. 2008.
2. Hart- en vaatziekten, cijfers en context. www.volksgezondheidenzorg.info/onderwerp/hart-en-vaatziekten. 2016.
3. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37(42):3232-45.
4. Mendis S, Puska P, Norrving B, editors. Global Atlas on Cardiovascular Disease Prevention and Control. Geneva: 2011.
5. Singh RB, Mengi SA, Xu YJ, Arneja AS, Dhalla NS. Pathogenesis of atherosclerosis: A multifactorial process. Experimental & Clinical Cardiology. 2002;7(1):40-53.
6. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. Archives of internal medicine. 2001;161(22):2657-60.
7. Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? Bmj. 1994;308(6925):367-72.
8. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387(10022):957-67.
9. Szuszkiewicz-Garcia MM, Davidson JA. Cardiovascular disease in diabetes mellitus: risk factors and medical therapy. Endocrinology and metabolism clinics of North America. 2014;43(1):25-40.
10. Poirier P, Giles TD, Bray GA, Hong Y, Stern JS, Pi-Sunyer FX, et al. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. Circulation. 2006;113(6):898-918.
11. Jha P, Ramasundarahettige C, Landsman V, Rostron B, Thun M, Anderson RN, et al. 21st-century hazards of smoking and benefits of cessation in the United States. The New England journal of medicine. 2013;368(4):341-50.
12. Grobbee DE, Hoes AW. Cohort and cross-sectional studies. Clinical Epidemiology: Principles, methods and applications for clinical research. Second ed. Burlington: Jones & Bartlett Learning; 2015.
13. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. American journal of public health and the nation's health. 1951;41(3):279-81.
14. Kannel WB, Feinleib M, McNamara PM, Garrison RJ, Castelli WP. An investigation of coronary heart disease in families. The Framingham offspring study. American journal of epidemiology. 1979;110(3):281-90.
15. Splansky GL, Corey D, Yang Q, Atwood LD, Cupples LA, Benjamin EJ, et al. The Third Generation Cohort of the National Heart, Lung, and Blood Institute's Framingham Heart Study: design, recruitment, and initial examination. American journal of epidemiology. 2007;165(11):1328-35.
16. Tsao CW, Vasan RS. Cohort Profile: The Framingham Heart Study (FHS): overview of milestones in cardiovascular epidemiology. International journal of epidemiology. 2015;44(6):1800-13.
17. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.
18. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-53.
19. Chen Q, Galfalvy H, Duan N. Effects of disease misclassification on exposure-disease association. American journal of public health. 2013;103(5):e67-73.

20. Kelley K, Clark B, Brown V, Sitzia J. Good practice in the conduct and reporting of survey research. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2003;15(3):261-6.
21. Wonca International Classification Committee. The international classification of primary care 2013.
22. Resnik DB. Disclosure of individualized research results: a precautionary approach. Accountability in research. 2011;18(6):382-97.
23. Centrale Commissie Mensgebonden Onderzoek. Jaarverslag 2013. Gendt: Rikken Print; 2014.
24. Germino JC, Elmore JG, Carlos RC, Lee CI. Imaging-based screening: maximizing benefits and minimizing harms. ClinImaging. 2015.
25. Wolf SM, Lawrenz FP, Nelson CA, Kahn JP, Cho MK, Clayton EW, et al. Managing incidental findings in human subjects research: analysis and recommendations. JLaw MedEthics. 2008;36(2):219-48, 1.
26. van Dis I, Geleijnse JM, Verschuren WM, Kromhout D. Cardiovascular risk management of hypertension and hypercholesterolaemia in the Netherlands: from unifactorial to multifactorial approach. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2012;20(7-8):320-5.
27. Pyorala K, De Backer G, Graham I, Poole-Wilson P, Wood D. Prevention of coronary heart disease in clinical practice. Recommendations of the Task Force of the European Society of Cardiology, European Atherosclerosis Society and European Society of Hypertension. Eur Heart J. 1994;15(10):1300-31.
28. Cooney MT, Dudina A, D'Agostino R, Graham IM. Cardiovascular risk-estimation systems in primary prevention: do they differ? Do they make a difference? Can we see the future? Circulation. 2010;122(3):300-10.
29. Kwaliteitsinstituut voor de Gezondheidszorg CBO en Nederlands Huisartsen Genootschap. Multidisciplinaire richtlijn Cardiovasculair risicomanagment 2006. 2006.
30. Nederlands Huisartsen Genootschap. Multidisciplinaire richtlijn Cardiovasculair risicomanagment herziening 2011. Houten: Bohn Stafleu van Loghum; 2011.
31. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980-2009. Eur Heart J. 2013;34(39):3017-27.
32. Di Cesare M, Bennett JE, Best N, Stevens GA, Danaei G, Ezzati M. The contributions of risk factor trends to cardiometabolic mortality decline in 26 industrialized countries. International journal of epidemiology. 2013;42(3):838-48.
33. Hobbs FDR. Cardiovascular disease: different strategies for primary and secondary prevention? Heart. 2004;90(10):1217-23.
34. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020. Geneva: 2013.
35. Schuster RJ, Steichen O, Ogunmoroti O, Ellison S, Terwoord N, Duhot D, et al. Physician cardiovascular disease risk factor management: practices in France vs the United States. JClinHypertens(Greenwich). 2011;13(1):10-8.
36. Tiessen AH, Smit AJ, Broer J, Groenier KH, van der Meer K. Randomized controlled trial on cardiovascular risk management by practice nurses supported by self-monitoring in primary care. BMCFamPract. 2012;13:90.
37. Effectiveness of health checks conducted by nurses in primary care: results of the OXCHECK study after one year. Imperial Cancer Research Fund OXCHECK Study Group. Bmj. 1994;308(6924):308-12.
38. Frieden TR, Berwick DM. The "Million Hearts" initiative--preventing heart attacks and strokes. The New England journal of medicine. 2011;365(13):e27.
39. Chang KC, Soljak M, Lee JT, Woringer M, Johnston D, Khunti K, et al. Coverage of a national cardiovascular risk assessment and management programme (NHS Health Check): Retrospective database

study. Preventive medicine. 2015;78:1-8.
40. Assendelft WJ, Nielen MM, Hettinga DM, van der Meer V, van Vliet M, Drenthen AJ, et al. Bridging the gap between public health and primary care in prevention of cardiometabolic diseases; background of and experiences with the Prevention Consultation in The Netherlands. FamPract. 2012;29 Suppl 1:i126-i31.
41. Vos HM, Van Delft DH, De Kleijn MJ, Nielen MM, Schellevis FG, Lagro-Janssen AL. Selective prevention of cardiometabolic diseases in general practice: attitudes and working methods of male and female general practitioners before and after the introduction of the Prevention Consultation guideline in the Netherlands. JEvalClinPract. 2014;20(4):478-85.
42. Nielen MM, Assendelft WJ, Drenthen AJ, van den Hombergh P, van Dis I, Schellevis FG. Primary prevention of cardio-metabolic diseases in general practice: a Dutch survey of attitudes and working methods of general practitioners. The European journal of general practice. 2010;16(3):139-42.
43. Ayorinde AA, Porteous T, Sharma P. Screening for major diseases in community pharmacies: a systematic review. IntJPharmPract. 2013;21(6):349-61.
44. Tan N, Taylor DM. Feasibility and outcomes of screening for cardiovascular risk factors in the emergency department. EmergMedAustralas. 2013;25(2):175-81.
45. Milani RV, Lavie CJ. Impact of worksite wellness intervention on cardiac risk factors and one-year health care costs. AmJCardiol. 2009;104(10):1389-92.
46. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology (Baltimore, Md). 2016;64(1):73-84.
47. Mikolasevic I, Milic S, Turk Wensveen T, Grgic I, Jakopcic I, Stimac D, et al. Nonalcoholic fatty liver disease - A multisystem disease? World journal of gastroenterology. 2016;22(43):9488-505.
48. Targher G, Byrne CD, Lonardo A, Zoppini G, Barbui C. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: A meta-analysis. Journal of hepatology. 2016;65(3):589-600.
49. Wannamethee SG, Lennon L, Shaper AG. The value of gamma-glutamyltransferase in cardiovascular risk prediction in men without diagnosed cardiovascular disease or diabetes. Atherosclerosis. 2008;201(1):168-75.
50. Kunutsor SK, Bakker SJ, Kootstra-Ros JE, Gansevoort RT, Dullaart RP. Circulating gamma glutamyltransferase and prediction of cardiovascular disease. Atherosclerosis. 2015;238(2):356-64.
51. Weng SF, Kai J, Guha IN, Qureshi N. The value of aspartate aminotransferase and alanine aminotransferase in cardiovascular disease risk assessment. Open heart. 2015;2(1):e000272.
52. de Mutsert R, den Heijer M, Rabelink TJ, Smit JW, Romijn JA, Jukema JW, et al. The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection. European journal of epidemiology. 2013;28(6):513-23.
53. Beulens JW, Monninkhof EM, Verschuren WM, van der Schouw YT, Smit J, Ocke MC, et al. Cohort profile: the EPIC-NL study. International journal of epidemiology. 2010;39(5):1170-8.
54. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Krolewski AS, Rosner B, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Archives of internal medicine. 1991;151(6):1141-7.
55. Margolis KL, Lihong Q, Brzyski R, Bonds DE, Howard BV, Kempainen S, et al. Validity of diabetes self-reports in the Women's Health Initiative: comparison with medication inventories and fasting glucose measurements. Clinical trials (London, England). 2008;5(3):240-7.
56. Sluijs I, van der AD, Beulens JW, Spijkerman AM, Ros MM, Grobbee DE, et al. Ascertainment and verification of diabetes in the EPIC-NL study. NethJMed. 2010;68(1):333-9.
57. Ngo DL, Marshall LM, Howard RN, Woodward JA, Southwick K, Hedberg K. Agreement between

self-reported information and medical claims data on diagnosed diabetes in Oregon's Medicaid population. JPublic Health ManagPract. 2003;9(6):542-4.
58. Okura Y, Urban LH, Mahoney DW, Jacobsen SJ, Rodeheffer RJ. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. JClinEpidemiol. 2004;57(10):1096-103.
59. Robinson JR, Young TK, Roos LL, Gelskey DE. Estimating the burden of disease. Comparing administrative data and self-reports. MedCare. 1997;35(9):932-47.
60. Simpson CF, Boyd CM, Carlson MC, Griswold ME, Guralnik JM, Fried LP. Agreement between self-report of disease diagnoses and medical record validation in disabled older women: factors that modify agreement. JAmGeriatrSoc. 2004;52(1):123-7.
61. Skinner KM, Miller DR, Lincoln E, Lee A, Kazis LE. Concordance between respondent self-reports and medical records for chronic conditions: experience from the Veterans Health Study. JAmbulCare Manage. 2005;28(2):102-10.
62. Kriegsman DM, Penninx BW, van Eijk JT, Boeke AJ, Deeg DJ. Self-reports and general practitioner information on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients' self-reports and on determinants of inaccuracy. Journal of clinical epidemiology. 1996;49(12):1407-17.
63. Galenkamp H, Huisman M, Braam AW, Schellevis FG, Deeg DJ. Disease prevalence based on older people's self-reports increased, but patient-general practitioner agreement remained stable, 1992-2009. Journal of clinical epidemiology. 2014;67(7):773-80.
64. Poortvliet MC, Lamkaddem M, Devillé W. Niet op naam ingeschreven (NONI) bij de huisarts, Inventarisatie en gevolgen voor de ziekenfondsverzekerden. Utrecht: 2005.
65. Dijkstra R. Mijn HIS is het best! https://wwwnhgorg/actueel/columns/mijn-his-het-best 2015.
66. WHO Collaborating Centre for Drug Statistics Methodology. Anatomical Therapeutic Chemical (ATC) classification system. http://wwwwhoccno/atc/structure_and_principles/ 2013.
67. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
68. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30.
69. World Health Organization. Global report on diabetes. Geneva: 2016.
70. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. Diabetes Care. 1992;15(7):815-9.
71. Rijksinstituut voor Volksgezondheid en Milieu. Diabetes mellitus, cijfers en context 2017 Available from: https://www.volksgezondheidenzorg.info/onderwerp/diabetes-mellitus.
72. Maahs DM, West NA, Lawrence JM, Mayer-Davis EJ. Epidemiology of type 1 diabetes. Endocrinology and metabolism clinics of North America. 2010;39(3):481-97.
73. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? European journal of epidemiology. 2004;19(8):751-60.
74. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity. a critical review of available methods. Journal of clinical epidemiology. 2003;56(3):221-9.
75. de Lusignan S, van Weel C. The use of routinely collected computer data for research in primary care: opportunities and challenges. Fam Pract. 2006;23(2):253-63.
76. Cole AM, Stephens KA, Keppel GA, Lin CP, Baldwin LM. Implementation of a health data-sharing infrastructure across diverse primary care organizations. The Journal of ambulatory care management. 2014;37(2):164-70.
77. Morris Z, Whiteley WN, Longstreth WT, Jr., Weber F, Lee YC, Tsushima Y, et al. Incidental findings on

brain magnetic resonance imaging: systematic review and meta-analysis. Bmj. 2009;339:b3016.
78. Hegenscheid K, Seipel R, Schmidt CO, Volzke H, Kuhn JP, Biffar R, et al. Potentially relevant incidental findings on research whole-body MRI in the general adult population: frequencies and management. EurRadiol. 2013;23(3):816-26.
79. Wardlaw JM, Davies H, Booth TC, Laurie G, Compston A, Freeman C, et al. Acting on incidental findings in research imaging. BMJ. 2015;351:h5190.
80. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International journal for quality in health care : journal of the International Society for Quality in Health Care. 2007;19(6):349-57.
81. Kitzinger J. Qualitative research. Introducing focus groups. BMJ. 1995;311(7000):299-302.
82. Pope C, Ziebland S, Mays N. Qualitative research in health care. Analysing qualitative data. Bmj. 2000;320(7227):114-6.
83. Charmaz K. Constructing grounded theory: A practical guide through qualitative analysis. Thousand Oaks, CA: SAGE Publications; 2006 2006.
84. Flory J, Emanuel E. Interventions to improve research participants' understanding in informed consent for research: a systematic review. JAMA. 2004;292(13):1593-601.
85. Kirschen MP, Jaworska A, Illes J. Subjects' expectations in neuroimaging research. JMagn ResonImaging. 2006;23(2):205-9.
86. Daack-Hirsch S, Driessnack M, Hanish A, Johnson VA, Shah LL, Simon CM, et al. 'Information is information': a public perspective on incidental findings in clinical and research genome-based testing. ClinGenet. 2013;84(1):11-8.
87. Zafar HM, Bugos EK, Langlotz CP, Frasso R. "Chasing a Ghost": Factors that Influence Primary Care Physicians to Follow Up on Incidental Imaging Findings. Radiology. 2016;281(2):567-73.
88. Cole C, Petree LE, Phillips JP, Shoemaker JM, Holdsworth M, Helitzer DL. 'Ethical responsibility' or 'a whole can of worms': differences in opinion on incidental finding review and disclosure in neuroimaging research from focus group discussions with participants, parents, IRB members, investigators, physicians and community members. JMedEthics. 2015;41(10):841-7.
89. Ransohoff DF, McNaughton Collins M, Fowler FJ. Why is prostate cancer screening so common when the evidence is so uncertain? A system without negative feedback. The American journal of medicine. 2002;113(8):663-7.
90. Zannad F, Dallongeville J, Macfadyen RJ, Ruilope LM, Wilhelmsen L, De BG, et al. Prevention of cardiovascular disease guided by total risk estimations--challenges and opportunities for practical implementation: highlights of a CardioVascular Clinical Trialists (CVCT) Workshop of the ESC Working Group on CardioVascular Pharmacology and Drug Therapy. EurJPrevCardiol. 2012;19(6):1454-64.
91. Panteia. Effecten van preventief zelfonderzoek op zorgkosten. Zoetermeer2014.
92. Ickenroth MH, Ronda G, Grispen JE, Dinant GJ, de Vries NK, van der Weijden T. How do people respond to self-test results? A cross-sectional survey. BMCFamPract. 2010;11:77.
93. Ickenroth MH, Grispen JE, Ronda G, Tacken M, Dinant GJ, de Vries NK, et al. Motivation and experiences of self-testers regarding tests for cardiovascular risk factors. Health Expect. 2011.
94. Nielen MM, Schellevis FG, Verheij RA. The usefulness of a free self-test for screening albuminuria in the general population: a cross-sectional survey. BMCPublic Health. 2009;9:381.
95. Blackburn H. Classification of the electrocardiogram for population studies: Minnesota Code. JElectrocardiol. 1969;2(3):305-10.
96. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. ClinChem. 1972;18(6):499-502.
97. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate

glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. AnnInternMed. 1999;130(6):461-70.
98. World Health Organization. Defenition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006.
99. Rothman KJ. Standardization. Epidemiology: An Introduction: Oxford University Press; 2002. p. 158-62.
100. S.Lumley T. Simple and Stratified sampling. Complex Surveys: A Guide to Analysis Using R. 1 ed2013. p. 17-35.
101. Ministerie van volksgezonheid welzijn en sport. Nederland de maat genomen, hoeveel mensen hebben overgewicht? 2013.
102. de Boer AW, de Mutsert R, den Heijer M, Jukema JW, Rosendaal FR, Blom JW, et al. Overweight can be used as a tool to guide case-finding for cardiovascular risk assessment. Fam Pract. 2015;32(6):646-51.
103. American Diabetes Association. Standards of medical care in diabetes-2012. Diabetes care. 2012;35 Suppl 1:S11-S63.
104. Rutten GEHM, De Grauw WJC, Nijpels G, Goudswaard AN, Uitewaal PJM, Van der Does FEE, et al. NHG-standaard diabetes mellitus type 2 (tweede herziening). Huisarts Wet. 2006;49(3):137-52.
105. Wendel-Vos GC, Schuit AJ, Saris WH, Kromhout D. Reproducibility and relative validity of the short questionnaire to assess health-enhancing physical activity. JClinEpidemiol. 2003;56(12):1163-9.
106. World Health Organization. Global database on Body Mass Index. 2005.
107. World Health Organization. Waist Circumference and Waist-hip Ratio: Report of a WHO Expert Consultation, Geneva, 8-11 December 2008: World Health Organization; 2011 2011.
108. Chamnan P, Simmons RK, Khaw KT, Wareham NJ, Griffin SJ. Estimating the population impact of screening strategies for identifying and treating people at high risk of cardiovascular disease: modelling study. BMJ. 2010;340:c1693.
109. Centraal Bureau voor de Statistiek. Trendcijfers Gezondheidsenquete 1981-2009, gebruik geneeskundige voorzieningen, gezondheidsindicatoren en leefstijl. 2013.
110. van Steenkiste B, Knevel MF, van den Akker M, Metsemakers JF. Increased attendance rate: BMI matters, lifestyles don't. Results from the Dutch SMILE study. FamPract. 2010;27(6):632-7.
111. Caccamese SM, Kolodner K, Wright SM. Comparing patient and physician perception of weight status with body mass index. AmJMed. 2002;112(8):662-6.
112. Liu H, Lu HY. Nonalcoholic fatty liver disease and cardiovascular disease. World journal of gastroenterology. 2014;20(26):8407-15.
113. Lee SS, Park SH. Radiologic evaluation of nonalcoholic fatty liver disease. World journal of gastroenterology. 2014;20(23):7392-402.
114. van der A DL, Grobbee DE, Roest M, Marx JJ, Voorbij HA, van der Schouw YT. Serum ferritin is a risk factor for stroke in postmenopausal women. Stroke. 2005;36(8):1637-41.
115. van der A DL, Marx JJ, Grobbee DE, Kamphuis MH, Georgiou NA, van Kats-Renaud JH, et al. Non-transferrin-bound iron and risk of coronary heart disease in postmenopausal women. Circulation. 2006;113(16):1942-9.
116. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC gastroenterology. 2006;6:33.
117. Papagianni M, Sofogianni A, Tziomalos K. Non-invasive methods for the diagnosis of nonalcoholic fatty liver disease. World journal of hepatology. 2015;7(4):638-48.
118. Hall P, Cash J. What is the Real Function of the Liver 'Function' Tests? The Ulster Medical Journal. 2012;81(1):30-6.
119. Herings RM, Bakker A, Stricker BH, Nap G. Pharmaco-morbidity linkage: a feasibility study comparing

morbidity in two pharmacy based exposure cohorts. Journal of epidemiology and community health. 1992;46(2):136-40.
120. D'Agostino RB, Sr., Pencina MJ, Massaro JM, Coady S. Cardiovascular Disease Risk Assessment: Insights from Framingham. Global heart. 2013;8(1):11-23.
121. Klein J, van Houwelingen H, Ibrahim J, Scheike T. Handbook of survival analysis. Boca Raton: CRC Press; 2013.
122. Pencina MJ, D'Agostino RB, Sr., D'Agostino RB, Jr., Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Statistics in medicine. 2008;27(2):157-72; discussion 207-12.
123. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular. J Am Coll Cardiol. 2014;63(25 0 0):2935-59.
124. Hu KC, Wang HY, Liu SC, Liu CC, Hung CL, Bair MJ, et al. Nonalcoholic fatty liver disease: updates in noninvasive diagnosis and correlation with cardiovascular disease. World journal of gastroenterology. 2014;20(24):7718-29.
125. Chin JL, Pavlides M, Moolla A, Ryan JD. Non-invasive Markers of Liver Fibrosis: Adjuncts or Alternatives to Liver Biopsy? Frontiers in pharmacology. 2016;7:159.
126. Goh LG, Dhaliwal SS, Lee AH, Bertolatti D, Della PR. Utility of established cardiovascular disease risk score models for the 10-year prediction of disease outcomes in women. Expert review of cardiovascular therapy. 2013;11(4):425-35.
127. Kroneman M, Boerma W, van den Berg M, Groenewegen P, de Jong J, van Ginneken E. The Netherlands: health system review. Health Systems in Transition. 2016;18(2):1–239.
128. Schäfer WLA, Van den Berg MJ, Boerma WGW, Schellevis FG, Groenewegen PP. Taakprofielen van huisartsen in Nederland en Europa. Huisarts Wet. 2016;59(7):286-91.
129. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation. 2001;104(23):2855-64.
130. D'Agostino RB, Sr., Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. Jama. 2001;286(2):180-7.
131. Ederer F, Church TR, Mandel JS. Sample sizes for prevention trials have been too small. American journal of epidemiology. 1993;137(7):787-96.
132. Struijk EA, May AM, Beulens JW, van Gils CH, Monninkhof EM, van der Schouw YT, et al. Mortality and cancer incidence in the EPIC-NL cohort: impact of the healthy volunteer effect. European journal of public health. 2015;25(1):144-9.
133. Leening MJ, Heeringa J, Deckers JW, Franco OH, Hofman A, Witteman JC, et al. Healthy volunteer effect and cardiovascular risk. Epidemiology (Cambridge, Mass). 2014;25(3):470-1.
134. Gordon T, Moore FE, Shurtleff D, Dawber TR. Some methodologic problems in the long-term study of cardiovascular disease: Observations on the Framingham study. Journal of clinical epidemiology.10(3):186-206.
135. Howe CJ, Cole SR, Lau B, Napravnik S, Eron JJ, Jr. Selection Bias Due to Loss to Follow Up in Cohort Studies. Epidemiology (Cambridge, Mass). 2016;27(1):91-7.
136. Dettori JR. Loss to follow-up. Evidence-Based Spine-Care Journal. 2011;2(1):7-10.
137. Merry AH, Boer JM, Schouten LJ, Feskens EJ, Verschuren WM, Gorgels AP, et al. Validity of coronary heart diseases and heart failure based on hospital discharge and mortality data in the Netherlands using the cardiovascular registry Maastricht cohort study. European journal of epidemiology. 2009;24(5):237-47.
138. Houghton C, Casey D, Shaw D, Murphy K. Rigour in qualitative case-study research. Nurse researcher.

2013;20(4):12-7.
139. Nielen MMJ, Ursum J, Schellevis FG, Korevaar JC. The validity of the diagnosis of inflammatory arthritis in a large population-based primary care database. BMC Fam Pract. 2013;14:79.
140. Coloma PM, Valkhoff VE, Mazzaglia G, Nielsson MS, Pedersen L, Molokhia M, et al. Identification of acute myocardial infarction from electronic healthcare records using different disease coding systems: a validation study in three European countries. BMJ open. 2013;3(6).
141. Sollie A, Sijmons RH, Helsper C, Numans ME. Reusability of coded data in the primary care electronic medical record: A dynamic cohort study concerning cancer diagnoses. International journal of medical informatics. 2017;99:45-52.
142. Khan NF, Harrison SE, Rose PW. Validity of diagnostic coding within the General Practice Research Database: a systematic review. Br J Gen Pract. 2010;60(572):e128-36.
143. Wells BJ, Chagin KM, Nowacki AS, Kattan MW. Strategies for Handling Missing Data in Electronic Health Record Derived Data. EGEMS (Washington, DC). 2013;1(3).
144. Lawrence L, Sincan M, Markello T, Adams DR, Gill F, Godfrey R, et al. The implications of familial incidental findings from exome sequencing: the NIH Undiagnosed Diseases Program experience. GenetMed. 2014;16(10):741-50.
145. Beskow LM, Smolek SJ. Prospective biorepository participants' perspectives on access to research results. Journal of empirical research on human research ethics : JERHRE. 2009;4(3):99-111.
146. Fernandez CV, Gao J, Strahlendorf C, Moghrabi A, Pentz RD, Barfield RC, et al. Providing research results to participants: attitudes and needs of adolescents and parents of children with cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(6):878-83.
147. Partridge AH, Burstein HJ, Gelman RS, Marcom PK, Winer EP. Do patients participating in clinical trials want to know study results? Journal of the National Cancer Institute. 2003;95(6):491-2.
148. Shalowitz DI, Miller FG. Communicating the results of clinical research to participants: attitudes, practices, and future directions. PLoS medicine. 2008;5(5):e91.
149. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. European journal of human genetics : EJHG. 2000;8(10):731-8.
150. Dyakova M, Shantikumar S, Colquitt JL, Drew CM, Sime M, MacIver J, et al. Systematic versus opportunistic risk assessment for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2016(1):Cd010411.
151. Rippe JM, Angelopoulos TJ. Lifestyle strategies for cardiovascular risk reduction. Current atherosclerosis reports. 2014;16(10):444.
152. Karmali KN, Persell SD, Perel P, Lloyd-Jones DM, Berendsen MA, Huffman MD. Risk scoring for the primary prevention of cardiovascular disease. The Cochrane database of systematic reviews. 2017;3:Cd006887.
153. Badenbroek IF, Stol DM, Nielen MM, Hollander M, Kraaijenhagen RA, de Wit GA, et al. Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. BMC Fam Pract. 2014;15:90.
154. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. The New England journal of medicine. 2006;355(25):2631-9.
155. Sniderman AD, Furberg CD. Age as a modifiable risk factor for cardiovascular disease. Lancet. 2008;371(9623):1547-9.
156. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.

CHAPTER 9

Samenvatting (Summary in Dutch)
Dankwoord
Curriculum Vitae

NEDERLANDSE SAMENVATTING

Hart- en vaatziekten zijn wereldwijd de belangrijkste doodsoorzaak. In 2015 overleden er in Nederland bijna 40 duizend mensen ten gevolge van hart- en vaatziekten. Hiernaast leven er in Nederland ongeveer 1 miljoen mensen met een hartziekte, hartfalen of met de gevolgen van een beroerte. Meer dan 75% van de sterfte aan hart- en vaatziekten wordt veroorzaakt door een combinatie van de risicofactoren verhoogde bloeddruk, verhoogd cholesterol, suikerziekte, obesitas en roken. Het risico op hart- en vaatziekten wordt verminderd wanneer deze risicofactoren worden teruggedrongen door middel van een verandering in leefstijl of behandeling met medicatie. Hoewel de sterfte aan hart- en vaatziekten de afgelopen 30 jaar is gedaald met wel ruim 70%, is het belangrijk om het risico op hart- en vaatziekten verder terug te dringen.

Het terugdringen van het risico op hart- en vaatziekten vindt voor een groot deel plaats in de huisartsenpraktijk. Patiënten met een mogelijk verhoogd risico op hart- en vaatziekten worden door de huisarts uitgenodigd voor het opstellen van een persoonlijk risicoprofiel. Hiervoor worden alle belangrijke risicofactoren voor hart- en vaatziekten in kaart gebracht en wordt het risico ingeschat om de komende tien jaar hart- en vaatziekten te krijgen. Op basis van het geschatte risico wordt bepaald of er een indicatie is voor behandeling met bloeddruk- of cholesterolverlagende middelen. Het uitnodigen van de juiste patiënten voor het opstellen van een risicoprofiel blijft echter een uitdaging en het inschatten van het risico op hart- en vaatziekten is nog niet optimaal.

Het doel van het in dit proefschrift beschreven onderzoek was om huisartsen handvatten te bieden om het risico op hart- en vaatziekten van hun patiënten beter in kaart te brengen en hiermee ziekte en sterfte als gevolg van hart- en vaatziekten verder terug te dringen. Hiervoor onderzochten we verschillende strategieën om het opstellen van het risicoprofiel te verbeteren. Aan de ene kant door patiënten met een mogelijk verhoogd risico op hart- en vaatziekten waarbij een risicoprofiel opgesteld zou moeten worden beter te ontdekken. En aan de andere kant door het verbeteren van het risicoprofiel zelf.

Om uit te zoeken welke patiëntgroepen een verhoogd risico hebben op hart- en vaatziekten is goed wetenschappelijk onderzoek nodig. Daarom hebben we in dit proefschrift eerst twee aspecten onderzocht die van belang zijn bij het doen van wetenschappelijk onderzoek, namelijk het verzamelen van medische gegevens van de deelnemers en het delen van individuele onderzoeksresultaten met de deelnemers.

Gebruik van gegevens uit de huisartsinformatiesystemen

Van elke patiënt worden bij de huisarts alle medische gegevens bewaard in een persoonlijk

patiëntendossier, opgeslagen in een huisartsinformatiesystemen (HIS). De medische gegevens uit deze HISsen worden toenemend (her-)gebruikt voor wetenschappelijk onderzoek en kwaliteitsbeleid. In Hoofdstuk 2 laten we zien dat het mogelijk is om voor dit hergebruik geschikte gegevens uit de HISsen te halen. Bijna alle deelnemers aan de Nederlandse Epidemiologie van Obesitas (NEO) studie, een grote wetenschappelijke studie, gaven toestemming om hun medische gegevens bij hun huisarts op te vragen. Uiteindelijk zijn er van 97% van alle deelnemers medische gegevens uit de HISsen verzameld. Het verzamelen en verwerken van de gegevens kostte echter veel tijd en geld. Op dit moment wordt er in Nederland een infrastructuur ontwikkeld die zorgt voor betere toegang tot de gegevens uit de HISsen.

Ook laten we in Hoofdstuk 2 zien dat we patiënten met suikerziekte goed kunnen identificeren in de HISsen. Onderzoekers kunnen daarom de gegevens uit de HISsen gebruiken voor onderzoek naar suikerziekte. Ook voor andere diagnosen en symptomen moet in de toekomst onderzocht worden hoe de gegevens uit de HISsen het beste bruikbaar zijn om patiëntgroepen te identificeren.

Terugrapportage van onderzoeksresultaten in wetenschappelijk onderzoek

In grote wetenschappelijke studies worden veel medische gegevens verzameld van de deelnemers. Een 'bijwerking' hiervan is dat er onverwachte afwijkingen gevonden kunnen worden bij deze onderzoeken. Er is overeenstemming in de literatuur dat afwijkingen met mogelijk ernstige gevolgen moeten worden teruggerapporteerd aan de deelnemer. In Hoofdstuk 3 staan de resultaten beschreven van groepsdiscussies met deelnemers die zo'n onverwachte afwijking teruggerapporteerd hebben gekregen. In deze discussies zijn de ervaringen en voorkeuren besproken rondom de communicatie vanuit het onderzoeksteam over de onverwachte afwijkingen. De deelnemers waren over het algemeen dankbaar voor de terugrapportage van de afwijking. Wel hadden ze verwacht dat alle (niet alleen de ernstige afwijkende) bevindingen teruggerapporteerd zouden worden, ondanks dat dit anders naar de deelnemers was gecommuniceerd door het onderzoeksteam. Het feit dat afwijkingen teruggerapporteerd zouden worden was een belangrijke reden om deel te nemen aan het wetenschappelijk onderzoek. Niemand had spijt toestemming gegeven te hebben voor terugrapportage van afwijkingen. Bij de meeste deelnemers had de terugrapportage van een afwijking grote impact op hun leven. De deelnemers gaven aan dat ze zo snel mogelijk geïnformeerd zouden willen worden over een op deze manier gevonden afwijking. Tijdens de groepsdiscussies werden vaak moeilijkheden genoemd met de overgang van de rol van onderzoeksdeelnemer naar de rol van patiënt.

Op basis van deze resultaten hebben wij drie aanbevelingen gedaan. Ten eerste moet het informatiemateriaal over de studie heel duidelijk zijn in wat er wel en niet wordt

teruggerapporteerd. Ten tweede moeten onderzoekers een gedetailleerd protocol maken voordat het wetenschappelijk onderzoek begint, om zo tijdige terugrapportage van onverwachte afwijkingen te waarborgen. En ten derde moeten er afspraken gemaakt worden met medische specialisten die betrokken zijn bij de behandeling en/of controles van een bevinding, om zo de overgang van de rol van onderzoeksdeelnemer naar die van patiënt te verbeteren.

Naast de terugrapportage van bevindingen met mogelijk ernstige gevolgen, worden vaak ook andere onderzoeksuitslagen teruggerapporteerd. Deze onderzoeksuitslagen kunnen van belang zijn voor patiëntenzorg. Uitslagen van bloeddrukmetingen of cholesterolbepalingen kunnen mogelijk gebruikt worden in de huisartsenpraktijk om het risico op hart- en vaatziekten in te schatten. In Hoofdstuk 4 onderzochten we de voor- en nadelen van het delen van deze uitslagen met de deelnemers van de NEO studie. Alle deelnemers kregen twee weken na deelname de uitslagen van onder andere de bloeddruk en de cholesterolwaardes. Deelnemers met één afwijkende uitslag kregen hierbij het advies om hun huisarts te consulteren. Van deze deelnemers had de helft geen indicatie voor behandeling met bloeddruk- of cholesterolverlagende middelen. Hiernaast was 10% van de deelnemers onnodig ongerust door dit advies. Deze resultaten suggereren dat al in de terugrapportage alleen deelnemers met een mogelijke behandelindicatie het advies zouden moeten krijgen om de huisarts te consulteren. Dit vermindert het aantal mensen dat 'onnodig' zorg gebruikt en voorkomt dat patiënten onnodig ongerust worden over de uitslagen. We stellen daarnaast voor dat de huisartsen wel geïnformeerd zouden moeten worden over alle uitslagen, omdat dat een aanleiding kan zijn om patiënten uit te nodigen voor het opstellen van een risicoprofiel.

Identificatie van patiënten voor het opstellen van een risicoprofiel

In de huisartsenpraktijk worden patiënten met een mogelijk verhoogd risico op hart- en vaatziekten uitgenodigd voor het opstellen van een persoonlijk risicoprofiel. Op basis van het risicoprofiel wordt bepaald of er een indicatie is voor behandeling met bloeddruk of cholesterolverlagende middelen. Eerdere wetenschappelijke studies hebben screeningsprogramma's ontwikkeld om te bepalen bij welke patiënten een risicoprofiel moet worden opgesteld. Het is echter nog onduidelijk of deze screeningsprogramma's ook een gunstig effect hebben op de sterfte aan hart- en vaatziekten. Tot hierover meer duidelijkheid is, kan de huisarts ook andere strategieen gebruiken om patiënten met een mogelijk verhoogd risico op hart- en vaatziekten op te sporen. In dit proefschrift hebben we twee strategieen onderzocht.

In Hoofdstuk 4 gaven we aan dat huisartsen geinformeerd zouden moeten worden over alle uitslagen van bloeddrukmetingen en cholesterolbepalingen die buiten de huisartsen-

praktijk worden gedaan. In ons onderzoek zagen we dat een kwart van de deelnemers van de NEO studie met een afwijkende uitslag van bloeddruk of cholesterol de huisarts niet consulteerde, ondanks het advies vanuit het onderzoeksteam. Van deze deelnemers had de helft wel een indicatie om de bloeddruk of cholesterol te behandelen. Deze deelnemers zijn dus helaas niet in beeld gekomen bij hun huisarts. Maar ook niet-afwijkende uitslagen zijn van belang voor de huisarts. Bij deze patiënten hoeft de huisarts voorlopig geen risicoprofiel op te stellen. De huisarts kan zich in dat geval dus richten op patiënten met mogelijk een indicatie voor behandeling en op patiënten waarvan er geen recent risicoprofiel is.

Bloeddruk en cholesterol worden niet alleen gemeten in onderzoeksverband, maar ook binnen de bedrijfsgeneeskunde, in apotheken en bij gezondheidschecks. Meer samenwerking is nodig tussen huisartsen en organisaties buiten de huisartsenpraktijk om zo meer efficiënt gebruik te maken van alle beschikbare gezondheidsgegevens.

In Hoofdstuk 5 zagen we dat een kwart van de mensen met een indicatie voor behandeling met bloeddrukverlagers of cholesterolverlagers nog niet werd behandeld. We onderzochten in dit hoofdstuk in hoeverre huisartsen deze patiënten konden identificeren als ze een risicoprofiel zouden opstellen bij alle patiënten met overgewicht of obesitas. In dit onderzoek had 12% van de mensen met overgewicht een behandelindicatie en 19% van de mensen met obesitas had een behandelindicatie. Wanneer alle patiënten met overgewicht of obesitas worden uitgenodigd voor het opstellen van een risicoprofiel, wordt 70% van alle patiënten met een behandelindicatie ontdekt. Patiënten bij wie de huisarts overgewicht of obesitas vermoedt kunnen worden uitgenodigd voor het opstellen van een risicoprofiel als een patiënt het spreekuur bezoekt voor een andere reden.

Het opstellen van een risicoprofiel

Bij het opstellen van een risicoprofiel in de huisartsenpraktijk wordt het risico geschat dat iemand de komende tien jaar hart- en vaatziekten krijgt. De huidige schattingsmethoden gebruiken informatie over de leeftijd, het geslacht, wel of niet roken, hoogte van de bloeddruk, cholesterolwaardes en de aanwezigheid van suikerziekte om het risico in te schatten. Deze schattingsmethoden zijn echter niet optimaal. Mogelijk kan de schatting verbeterd worden wanneer er informatie wordt toegevoegd over andere risicofactoren. In Hoofdstuk 6 hebben wij onderzocht of de schatting verbeterde wanneer we informatie over leververvetting toevoegen aan de huidige schatting. Leververvetting komt wereldwijd steeds meer voor en de aanwezigheid van een vette lever verhoogt het risico op hart- en vaatziekten met 64%. We concludeerden in dit hoofdstuk dat sommige markers van leververvetting de schatting van het risico op hart- en vaatziekten verbeterden bij vrouwen, maar niet bij mannen. Echter de door ons gevonden mate van verbetering

van de schatting was niet relevant voor de dagelijkse praktijk. Ander wetenschappelijk onderzoek moet uitwijzen of er mogelijk andere markers van leververvetting zijn die de schatting wel verbeteren.

Conclusie

In dit proefschrift hebben we onderzocht hoe huisartsen het risico op hart- en vaatziekten beter in kaart kunnen brengen. We lieten zien dat wetenschappelijk onderzoek naar hart- en vaatziekten verbeterd kan worden door gebruik te maken van gegevens uit de huisarts informatiesystemen en door het maken van protocollen waarin beschreven wordt hoe individuele onderzoeksresultaten worden gedeeld met de deelnemers. Hiernaast hebben we verschillende strategieën onderzocht om het opstellen van een risicoprofiel voor hart- en vaatziekten te verbeteren. Huisartsen kunnen patiënten met overgewicht of obesitas uitnodigen voor het opstellen van een risicoprofiel en kunnen gebruik maken van gezondheidsgegevens die gemeten zijn buiten de huisartsenpraktijk. Het toevoegen van markers van leververvetting aan het risicoprofiel leidde niet tot een verbetering van de schatting van het risico op hart- en vaatziekten.

DANKWOORD

Graag wil ik van de gelegenheid gebruik maken om even stil te staan bij iedereen die het traject tot dit proefschrift heeft meebeleefd.

Allereerst mijn begeleiders Mattijs, Jeanet en Renée, maar ook Martin, Pim en Frits. In wisselende formaties heb ik met jullie kunnen sparren over mijn onderzoek, bedankt voor jullie inzichten uit de verschillende invalshoeken. Aangevuld met de adviezen van de coauteurs is hierdoor een mooi, divers proefschrift ontstaan.

Debbie, samen hebben we het onderzoek naar de Patiënt Partner practica in het geneeskundeonderwijs geleid, onze eerste kennismaking met de wetenschap. We kunnen het LAK-theater niet vinden, maar hierin waren we een goed team. Zuzanna, jouw enthousiasme over de wetenschap werkte aanstekelijk.

Mijn wetenschapsstage op de Public Health en Eerstelijnsgeneeskunde (PHEG) bij Monique liet zien hoe leuk het was om onderzoek te doen: van het includeren van patiënten voor de CRANBERRY studie met de onderzoeksmedewerkers tot het bijwonen van mijn eerste promotie. Dit heeft me geïnspireerd om voor een AIOTHO-plek te gaan.

Na het afronden van mijn geneeskundestudie ben ik begonnen als AIOTHO bij de NEO studie, met als kernteam Martin, Renée, Ingeborg, Petra en Pat. In dit team werden alle plannen tot in de puntjes uitgedacht. Als snel gingen de data-extracties in de huisartsenpraktijken van start in samenwerking met het onderzoeksteam van de PHEG, het was een goed geoliede machine. Maar uiteraard geen cohortstudie zonder deelnemers, wat fijn dat er zoveel mensen mee hebben gedaan aan de NEO studie en EPIC-NL.

Inspirerende meetings, gezellige uitjes, broodnodige theepauzes en reuzeveel gezelligheid, collega's van de Epi en PHEG, het waren topjaren. Met als kers op de taart natuurlijk alle kamergenootjes en een stel vissen. Suz, wij waren een half jaar een gouden combinatie. Super dat jij als paranimf naast me staat.

Mede-AIOTHO's, wat doorlopen we toch een fantastisch traject. Collega HAIO's, we hebben een mooi vak met veel uitdagingen en kansen. Opleiders binnen en buiten de huisartsenpraktijk en het hele team eromheen, jullie passie werkt aanstekelijk. Familie en vrienden, hier is het dan, dit heb ik de afgelopen jaren gedaan. Wat is het heerlijk om bij te kletsen onder het genot van een hapje en drankje.

Pap en mam, van jullie krijg ik altijd support en vertrouwen, heel fijn. Stephanie en Klaas,

wat hebben we het gezellig, uiteraard ook met Jet en Kees. Klaas, echt tof dat jij als paranimf naast me staat. Benjamin, met jou als klankbord kan ik de wereld aan. Ik hoop nog vele avonturen met je te beleven.

Anne

CURRICULUM VITAE

Anna Wilhelmina de Boer werd geboren op 20 maart 1987 te Leiden. In 2005 behaalde zij haar VWO-diploma aan het Coornhert Lyceum te Haarlem, waarna zij begon met de opleiding Geneeskunde aan de Universiteit Leiden. In 2008 deed zij naast de opleiding onderzoek naar de Patiënt Partner practica. In het vierde studiejaar volgde een wetenschapsstage op de afdeling Public Health en Eerstelijnsgeneeskunde van het Leids Universitair Medisch Centrum. De opleiding eindigde met een semi-artsstage binnen de huisartsgeneeskunde. Na het artsexamen is zij in 2012 begonnen aan een AIOTHO-traject, waarbij de huisartsopleiding gecombineerd werd met promotieonderzoek. Het theoretisch deel van de huisartsopleiding werd gevolgd aan het Leids Universitair Medisch Centrum. Voor het praktische deel is zij werkzaam geweest in Leiderdorp, Delft, Katwijk en Leiden. Het promotieonderzoek deed zij op de afdeling Klinische Epidemiologie en de afdeling Public Health en Eerstelijnsgeneeskunde van het Leids Universitair Medisch Centrum onder begeleiding van prof. dr. M.E. Numans, dr. J.W. Blom en dr. ir. R. de Mutsert. Tijdens het promotietraject volgde zij verschillende epidemiologische cursussen voor de opleiding tot Epidemioloog B. De resultaten van het promotieonderzoek zijn beschreven in dit proefschrift. Tevens heeft zij de resultaten gepresenteerd op verschillende nationale en internationale congressen. Sinds september 2017 is zij werkzaam in huisartsenpraktijk De Linde in Leimuiden voor het laatste jaar van de huisartsopleiding.