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Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands

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Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands

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Abstract

Purpose: The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study is an ongoing prospective single-centre cohort study with the aim to assess important determinants and the prognosis of cardiovascular disease progression. This article provides an update of the rationale, design, included patients, measurements and findings from the start in 1996 to date.

Participants: The UCC-SMART study includes patients aged 18-90 years referred to the University Medical Centre (UMC) Utrecht, The Netherlands, for management of cardiovascular disease (CVD) or severe cardiovascular risk factors. Since September 1996, a total of 14,830 patients has been included, of whom 8,603 patients were enrolled because of CVD and 5,684 patients because of cardiovascular risk factors. Upon inclusion patients undergo a standardized screening program including questionnaires, vital signs, laboratory measurements, electrocardiogram, vascular ultrasound of carotid arteries and aorta, ankle-brachial index and ultrasound measurements of adipose tissue, kidney size and intima media thickness. Outcomes of interest are collected through annual questionnaires and adjudicated by an endpoint committee.

Findings to date: By May 2022, 14,830 included patients contributed to a total follow-up time of over 134,000 person years. During follow-up, 2,259 patients suffered from a vascular endpoint (including non-fatal myocardial infarction, non-fatal stroke and vascular death) and 2,794 all-cause deaths, 943 incident cases of diabetes and 2,139 incident cases of cancer were observed up until January 2020. The UCC-SMART cohort contributed to over 350 articles published in peer-reviewed journals, including prediction models recommended by the 2021 ESC CVD prevention guidelines.

Future plans: The UCC-SMART study is an ongoing cohort in both inclusion and follow-up and provides a large database of information on a population at high cardiovascular risk for future studies to improve understanding of aetiology, prediction and prognosis of cardiovascular disease. It will continue be expanded with additional measurements and linkage to external registries.

Strengths and limitations

- The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial disease (UCC-SMART) study is an ongoing cohort of over 14,000 patients with various manifestations of CVD and cardiovascular risk factors
- The UCC-SMART study covers a long follow-up duration and a comprehensive prospective capture of outcome data in a high cardiovascular risk population
- The use of a standardized screening program provides an extended resource of data for research on cardiovascular disease epidemiology
- Limitations of the cohort are measurement of the determinants only at baseline for the majority of patients, and the sparse information on socioeconomic status

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, causing around one-third of all deaths globally in 2019.[1] Atherosclerosis, the dominant cause of CVD, is fuelled by multiple mutually reinforcing and co-existing risk factors. Because of the progressive nature of atherosclerosis, patients with established CVD are at high risk of recurrent CVD and mortality.[2,3] Treatment of cardiovascular risk factors is known to markedly reduce the risk of new cardiovascular events.[4,5] Slowing down the process of atherosclerosis by timely identification and treatment of cardiovascular risk factors is therefore of the utmost importance.

In 1996, the Second Manifestations of Arterial Disease (SMART) cohort study was set up enrolling patients newly referred to the University Medical Centre (UMC) Utrecht with clinically manifest CVD or marked risk factors for atherosclerosis. The study was designed with the aim of determining the prevalence of concomitant atherosclerotic disease and risk factors, as well as studying the incidence of future cardiovascular events and its predictors. Furthermore, the SMART study contributes to the complete and protocolized multidisciplinary care of these high risk patients, by integrating a standardized set of measurements into usual patient care. The rationale and design of the study were previously published in 1999[6], with the study containing around 600 patients at that time. In 2018, the name of SMART changed to Utrecht Cardiovascular Cohort (UCC)-SMART. By now, 26 years after enrolment of the first patient, many baseline measurements have been added, substudies have been initiated, the study has been linked to national registries and the data have been used in several large (inter)national collaborations. At the same time, demographic and guideline changes have led to differences in the baseline characteristics and absolute risk of the patients included in the cohort. The aim of the current article is to provide an update on the rationale, design, included patients, baseline measurements and follow-up to date.

Cohort description

The UCC-SMART-study is a single-centre prospective cohort study, ongoing in both inclusion and follow-up, in which patient care and scientific research concerning cardiovascular risk factors and disease are integrated. This is depicted in Figure 1 and discussed in more detail in the sections below.

Study population

Starting from September 1996, patients aged 18 to 80 years referred to the UMC Utrecht, the Netherlands, for management of CVD or severe risk factors for CVD, have been recruited. Patients with cerebrovascular disease (CeVD), coronary artery disease (CAD), abdominal aortic aneurysm (AAA), peripheral artery disease (PAD), renal artery stenosis or one or more of the following cardiovascular risk factors, if rated as severe, are eligible to be included: hypertension, hyperlipidaemia, diabetes mellitus, renal insufficiency and a positive family medical history. Patients with a chronic human immunodeficiency virus infection as a cardiovascular risk-increasing condition or with hypertensive pregnancy disorders have been included since 2007 and 2012, respectively. Definitions of the inclusion criteria are listed in Supplementary Table 1. If patients have a history of multiple vascular events or risk factors, the referral reason (usually the most recent event) is listed as the qualifying inclusion diagnosis, and any comorbidities are also registered. Pregnant women, patients with a short life expectancy and those insufficiently fluent in Dutch are not eligible.

Qualifying patients with CVD and/or risk factors listed above are recruited upon their first visit to the outpatient clinics and hospital wards of the departments of vascular medicine, internal medicine, nephrology, neurology, cardiology, cardiac surgery, obstetrics and vascular surgery. From 2021 onwards, the outpatient clinic of the department of geriatric medicine has been added to this list and the maximum age to be eligible for inclusion has been raised from 80 to 90 years old. In case of a recent cardiovascular event or intervention as the reason for inclusion, patients are invited after discharge from the hospital. In such cases, baseline measurements were generally performed more than 30 days after the acute event. All qualifying patients receive written and oral information about study goals and methods and are included only after written informed consent to use of their data for study goals, the reporting of incidental findings to their treating physician, indefinite period storage of blood samples

for future research and follow-up through annual questionnaires. In addition, participants can opt in or out to the following items: retrieval of data from regional and national registries, use of their data in research collaborations with for-profit organizations, use of coded data and laboratory samples for research outside the European Union and possible future requests to participate in follow-up studies of UCC-SMART. When patients do not consent to any of these additional items, they can still partake in the UCC-SMART study. The study is in accordance with the Helsinki declaration and the Good Clinical Practice guidelines, and is approved by the ethics committee of the UMC Utrecht in 1996, 2014 and 2022 (reference number 22-088).

Baseline data collection

The screening program consists of questionnaires, physical examination, an electrocardiogram (ECG), blood, urine and radiology testing. Except for the questionnaires, to be filled out before the hospital visit, the diagnostic components of the program take place during a one-day visit. An overview of all the variables available in UCC-SMART is provided in Supplementary Table 2. Some measurements have only been collected for or starting from a certain time period (Figure 2 and Supplementary Table 3).

Health questionnaires

The questionnaires collect data on medical history including established CVD (CeVD, CAD, AAA and PAD as described in Supplementary Table 4), cardiovascular risk factors, symptoms of CVD (based on the Rose Angina Questionnaire)[7], medication use, family history and lifestyle. For women, a question on the age at menopause (if applicable) is included as well. From 2002 onward, information on obstetric history has been collected including the number of full-term pregnancies, miscarriages (<14 weeks of gestation), preterm deliveries (14 – 32 weeks of gestation), birth weight and pregnancy complications.

Physical examination

Anthropometric measurements are taken by trained (research) nurses and include body height in centimetres, weight in kilograms and waist and hip circumference in centimetres with patients wearing light clothing and no shoes. Weight and length are used to calculate body mass index in kg/m^2. Waist

circumference is measured horizontally at the midpoint between the iliac crest and lower costal margin and hip circumference is taken at the maximum horizontal circumference around the gluteal muscles. The mean of two measurements is calculated. If the two measurements differ by >2 cm, a third is taken and the mean of the closest two is calculated.

From 1996 up until 1999, office blood pressure was measured using a semiautomatic oscillometric device (Omega 1400; Invivo Research Laboratories Inc., Broken Arrow, OK, USA) every 4 minutes for a total of 25 minutes at the right brachial artery in supine position and the mean systolic (SBP) and diastolic blood pressure (DBP) were calculated. From April 1999 until 2015, using a non-random sphygmomanometer (Iso-Stabil 5; Speidel & Keller, Jungingen, Germany), 3 simultaneous measurements with an interval of 30 seconds were taken at both upper arms in upright position and the SBP and DBP of the last two measurements were calculated from the arm yielding the highest values. From 2015 onward, office blood pressure has been measured using an automatic oscillometric device (Microlife WatchBP Office AFIB; Microlife Corp, Widnau, Switzerland). The measurement is being performed unattended, in triplicate with an interval of 30 seconds, at both upper arms in supine position after the patient has rested for 30 seconds. The measurements on the arm with the highest blood pressure are recorded and the mean SBP and DBP is calculated.

In order to calculate the ankle-brachial index (ABI), blood pressure measurements are taken at rest at both upper arms every two minutes whilst the blood pressure is measured at both lower legs. For this, a Falcon Quad 8 MHz Doppler probe (Viasonix, Ra'anana, Israel) is used at a 60° angle at the dorsal pedal and posterior tibial arteries. The ABI is defined for each leg as the highest SBP at the ankle divided by the highest brachial SBP.

Laboratory testing

On the day of screening, a venous blood sample is drawn after at least eight hours of fasting to measure glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, creatinine, and haemoglobin. Laboratory measurements of fasting insulin, C-reactive protein (CRP) and thyroid stimulating hormone (TSH) were added in 2003 and glycated haemoglobin (HbA1c) and apolipoprotein B (apoB) were added in 2006. Lastly, measurement of lipoprotein(a) was added in June 2020.

Glucose is measured using an enzymatic colorimetric assay (Beckman Coulter, Brea, CA, USA). Total cholesterol and triglycerides are measured using a commercial enzymatic dry chemistry kit (Johnson & Johnson, New Brunswick, NJ, USA) and HDL-C with a commercial enzymatic kit (Boehringer, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) is calculated using the Friedewald formula up to a plasma triglyceride level of 9 mmol/L.[8] Estimated glomerular filtration rate (eGFR) is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[9] Spectrophotometry (Abbott Diagnostics, Santa Clara, CA, USA) is used to determine haemoglobin levels. CRP in plasma was initially determined using immunonephelometry (Nephelometer Analyzer BN II, Siemens, The Hague, The Netherlands) and from 2013 in heparin plasma on an AU5811 routine chemistry analyser (Beckman Coulter, Brea, CA, USA). Before November 2006, TSH was quantified using a third-generation assay on a Centaur analyser (Bayer, Germany). Since December 2006, TSH has been measured by a third-generation assay on a DXi analyser (Beckman Coulter, Woerden, The Netherlands). Correlation between the two analysers was r = 0.9991 (n = 69), with an intercept of –0.05 mU/L (95%CI 0.22-0.12) and a slope of 1.04 (95%CI 1.029–1.052) (range 0–95 mU/L). ApoB and lipoprotein(a) are measured using nephelometry (Atellica Neph 630, Siemens, The Hague, The Netherlands). A morning-void urine sample is collected to determine urine albumin, creatinine, sodium and potassium levels. Urine albumin is measured using immunoturbidimetric assays. Ion selective electrode (Beckman Coulter, Brea, CA, USA) is used to determine urine sodium and potassium levels. DNA can be isolated from 10 mL of EDTA-augmented blood stored at -80° for genotyping.

Radiology testing

Non-invasive vascular imaging testing is performed by specially trained ultrasound technicians. Duplex examination of the carotid arteries is conducted to assess possible stenosis using peak systolic velocity measurements at the brachiocephalic trunk, carotid arteries (mid- and distal common, external and proximal and distal internal) and vertebral arteries (proximal and distal). Measurements are performed using an EPIQ-7 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands). In case of abnormal signals and/or retrograde flow in the vertebral arteries, the proximal subclavian arteries are

evaluated in search of severe stenosis or occlusion. For research purposes, intima-media-thickness (IMT) of the carotid arteries is measured using a linear array transducer. With the patient lying down and the head turned 45° away from the side investigated, the ultrasound frame yielding an optimal longitudinal picture of the common carotid arterial wall is frozen at the time of the R-peak of ECG recording. Over a length of 1 cm starting from the carotid bulb towards proximal direction, the arterial wall thickness is measured from the lumen-intima interface to the media-adventitia interface. The mean of measurements in anterolateral, lateral and posterolateral directions is calculated.

Abdominal ultrasound examination is performed using the same ultrasound machine to obtain the maximal anterior-posterior diameter of the juxtarenal and infrarenal abdominal aorta and kidney length and volume. As of January 2000, visceral and subcutaneous adipose tissue measurements have been taken as well. The amount of subcutaneous fat is estimated by the distance from the linea alba to the skin. Visceral adipose tissue thickness is measured as the distance between the lumbar spine and the peritoneum. Measurements are taken at the end of quiet expiration on a frozen ultrasound frame at three points on the imaginary transversal line halfway between the iliac crest and lower costal margin: at the midsternal line and 10 cm to the left and right on the transversal line. Each measurement is taken three times and then the mean of the measurements is recorded as the actual thickness. Moreover, from September 1998 on, a protocolized 12-lead resting ECG has been recorded.

In the near future, echocardiography will be added to the UCC-SMART program to facilitate research on the presence of heart failure at baseline. Echocardiography will be performed using a Philips Affiniti 70 ultrasound machine (Philips Medical Systems, Andover, MA, USA) by using a specific protocol involving 2-dimensional (2D), M-mode, Doppler, tissue Doppler and 2D speckle tracking (STE) imaging in accordance with the European Association of Cardiovascular Imaging 2016 recommendations for chamber quantification.[10] In particular, left ventricular dimensions will be measured in order to calculate the left ventricular mass index.[11] Left ventricular ejection fraction will be assessed quantitatively, preferably with automated three-dimensional imaging or alternatively with the Simpsons biplane method. Left atrial maximal volume and right ventricular dimensions and function will be measured as recommended.[10] Multiple parameters of left ventricular diastolic function will be assessed, including pulsed-wave Doppler of the mitral inflow and tissue Doppler imaging of the mitral

annulus motion. Left ventricular diastolic function will be evaluated according to current diagnostic algorithms.[12] A minimal of 3 sequential complexes will be recorded. Standard image analysis will be then performed off-line in accordance with clinical guidelines using Philips IntelliSpace Cardiovascular software and will include 2D STE analysis of the left ventricle and left atrium.

Treatment recommendation

After completion of the screening, the findings are assessed by a multidisciplinary team of two medical specialists (internist, cardiologist, neurologist or vascular surgeon). A treatment recommendation is formulated based on current applicable guidelines, according to which patients are already treated by their general practitioner or medical specialist. The screening results and treatment recommendation are reported in a medical letter which is sent to the treating specialist and general practitioner. Patients receive a summary of relevant findings and recommendations.

Incidental medical findings during the screening are reported to one of the study physicians and if needed, discussed with specialists from the multidisciplinary team. The findings are added to the medical record and sent to the treating specialist or general practitioner for further action.

Follow-up

Patients receive annual questionnaires with questions on hospital admissions and outpatient clinic visits, regardless of whether they are still under the care of the UMC Utrecht. In case patients no longer wish to complete the questionnaires, they are asked if they consent to collection of information from their general practitioner. When the replies indicate possible outcome events, additional information is collected through hospital discharge letters and relevant laboratory and radiology examinations. Clinical events of interest include stroke, myocardial infarction, heart failure, AAA rupture, renal insufficiency, vascular interventions, bleeding, diabetes and vascular and non-vascular mortality as defined in Supplementary Table 5. Incident type 2 diabetes has been assessed since July 2006. To assess incident diabetes between 1996 and 2006, a questionnaire was sent to all patients without diabetes at baseline who were included before July 2006. Incident heart failure has been assessed since October 2011. Subsequently, three members from the endpoint committee independently judge reported events. The

endpoint committee consists of medical specialists from the recruiting departments. If all three physicians judge differently, the event is discussed with two other physicians from the committee to reach consensus. Secondary outcomes are adjudicated by trained research nurses. As of 2021, diagnoses of dementia and mild cognitive impairment have been added to the annual questionnaire as a self-reported diagnoses

Linkage to external registries

Data in the UCC-SMART study can be enriched by collecting data from various registries and organizations, for example to obtain additional information on outcomes and medication use. Some examples of this linkage so far are described below.

Netherlands Cancer Registry

CVD and cancer share many risk factors and pathophysiological mechanisms, including body fat distribution, diet, physical inactivity, smoking, chronic inflammation burden, and oxidative stress.[13] To evaluate the relation between several cardiovascular risk factors and the risk of cancer, the UCC-SMART cohort has been linked to the Netherlands Comprehensive Cancer Organisation (IKNL), a nationwide registry receiving notifications of all new cancer diagnoses. By linking the cohort to the national cancer registry several times, with the most recent linkage taking place in 2022, information on cancer incidence and details of cancer types and histopathology was obtained.

Central Agency for Statistics (CBS) Netherlands

The UCC-SMART cohort can be linked to *Statistic Netherlands* (also known as CBS), which contains data on ICD-10 coded diagnoses and hospital admissions since 1996. This allows for, amongst others, collection of endpoints that are not regularly collected in UCC-SMART or have been collected from a later time point, such as heart failure diagnoses.

Utrecht Patient Oriented Database (UPOD)

The UCC-SMART cohort can be linked to UPOD[14], a database containing electronic patient data of patients treated at the UMC Utrecht. This database has been collecting patient characteristics, medication orders, laboratory test results, hospital discharge diagnoses and medical procedures since 2000.

Consortia

The data collected in UCC-SMART is added to several consortia such as a genetics consortium (GENIUS-CHD[15] on genetics of subsequent coronary heart disease), the Netherlands consortium of dementia cohorts and the Chronic Kidney Disease Prognosis Consortium[16].

Substudies

SMART-2

Patients with a history of CVD or diabetes are invited to participate in the SMART-2 substudy. In this study, the baseline measurements of UCC-SMART are repeated in order to investigate the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment. Until May 2022, 2,313 patients have participated in UCC-SMART-2 after a median of 9.9 years (IQR 9.2 – 10.8) since their inclusion in UCC-SMART. As with UCC-SMART, the findings of UCC-SMART-2 with an accompanying treatment recommendation are communicated to the patient, his or her treating medical specialist and general practitioner.

SMART-ORACLE

SMART-ORACLE aims to determine the additional value of contrast-enhanced computed tomography (CT) of the coronary and carotid arteries on top of traditional cardiovascular risk factors in patients with a history of CVD, diabetes or hypertension.[17] The study is still ongoing and has currently been conducted in 1,252 patients.

SMART-MR and SMART Medea

SMART-MR and SMART Medea target the investigation of brain changes in patients with CVD using 1.5T magnetic resonance imaging (MRI) (and 7T MRI in a subset of patients).[18,19] This study was conducted in 1,309 patients. Amongst others, measurements of the total cerebral blood flow have been performed and characteristics of white matter lesions and microbleeds have been mapped.

Athero-Express

In May 2022, the Athero-Express biobank and study cohort have been incorporated into the UCC-SMART study.[20] The objective of Athero-Express is to investigate the value of plaque characteristics in relation to long term cardiovascular events. This ongoing prospective study, initiated in April 2002, includes patients undergoing femoral or carotid endarterectomy. During surgery, the atherosclerotic plaque is harvested and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells.

Other substudies

Several other substudies have been carried out within the UCC-SMART cohort. As part of **SMART-Junior**, additional questionnaires have been sent to 4,270 patients in order to investigate the presence of cardiovascular risk factors and CVD in their offspring.[21] In **DISH**, diffuse idiopathic skeletal hyperostosis was scored on chest X-rays of 4,791 patients, performed in the context of health care, using the Resnick criteria.[22,23] **SMART-HEART** aimed to detect patient characteristics related to the development of left ventricle hypertrophy using 1.5T cardiac MRI in 536 patients with hypertension, but free of known coronary or valvular disease.[24] In order to determine whether intima and media calcification differ in their associated CVD risks and to elucidate which risk factors lead to the development of those types of calcification, CT-scans of the femoral head to the feet have been performed in 520 patients as part of **ARTEMIS**.[25] The aim of the **Small aneurysms trial** was to estimate the overall rupture rates of small AAAs and to investigate demographic characteristics and cardiovascular risk factors for association with AAA growth using ultrasound scanning of the aorta in 230 patients with an initial AAA diameter of 30-55 mm.[26] In **Brown adipose tissue**, supraclavicular and subcutaneous adipose tissue fat-signal-fractions were assessed in 50 patients with CVD using 1.5T

water-fat MRI.[27] **SPAIN** evaluated the feasibility of a web-based coaching program for vascular risk factor treatment, described the patterns of use of this program and measured changes in risk factors in 50 patients with CVD.[28] **RULE** investigated the impact of the UCC-SMART study compared to usual care on cardiovascular risk factors in 604 patients with CVD or type 2 diabetes.[29]

A few clinical trials have been conducted within the UCC-SMART study. **TEMPUS** was a randomized crossover trial in 78 patients that investigated the effects of a cardiovascular polypill on LDL-C, ambulatory blood pressure and adherence as compared to the administration of the individual, identically dosed components of the polypill.[30] **SMART-Inform** was a three-armed randomized controlled trial (RCT) in 303 patients using a statin with CVD.[31] The aim was to determine whether communicating personalized statin therapy-effects leads to lower decisional conflicts associated with statin use compared with standardized (non-personalized) therapy-effects. **BEST** was an RCT investigating whether a clearly written agreement on risk factor management between general practitioners and hospitals improved the vascular risk profile of 197 patients compared with usual care.[32] Another RCT was **VENUS**, which included 236 patients with ≥2 modifiable risk factors, investigating whether risk factor management in the hospital improved with nurse practitioner care on top of usual care compared with usual care alone.[33] Lastly, **IRIS** was an RCT that evaluated whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in 330 patients with CVD.[34] Supplementary Table 6 provides a detailed overview of the substudies. A timeline showing the different substudies is presented in Supplementary Figure 1.

Data quality and management

Data collected in the UCC-SMART program is stored in the electronic medical record of the UMC Utrecht. Blood samples (serum, citrate plasma, EDTA plasma and erythrocytes concentrate aliquots) are stored at -80°C according to the Biobanks Regulations to be found at the UMC Utrecht website (https://www.umcutrecht.nl/nl/centrale-biobank). The central biobank of the UMC Utrecht is ISO9001 certified (certificate number 2175592). Release of material for future research is reviewed by the UMC Utrecht Biobanks Review Committee.

Recorded data is downloaded from the electronic medical record and pseudonymized by the data manager who holds the encryption key, only to be accessed after permission of the principal investigator. The UCC-SMART study group periodically performs quality checks for missing values and inconsistencies compared to source documents, or values outside of the range deemed likely.

Patient and public involvement

Patients were not involved in the study design. Their experiences of burden and required time are considered in the implementation of new components in the program. Relevant findings of the UCC-SMART screening program and corresponding recommendations are sent to the patients. In addition, patients regularly receive a newsletter containing up-to-date facts and figures of the UCC-SMART study and substudies and findings of publications using UCC-SMART data. The UMC Utrecht policies are in line with open science, for opening up the research agenda to societal stakeholders, open research data and open access publications.

Characteristics of study population

By May 2022, a total of 14,830 patients has been included (Figure 3). Of those, 3,294 patients died and 1,546 patients are lost to follow-up. Reasons for loss to follow-up include withdrawal of informed consent or being unreachable for further questionnaires. Figure 4 shows the numbers and distribution of the reasons for inclusion. The most common inclusion diagnosis was CAD (n = 4,729), followed by hypertension (n = 2,344) and CeVD (n = 2,276). PAD was the enrolment diagnosis in 1,173 patients and AAA in 369 patients. Hyperlipidaemia was the inclusion diagnosis in 1,433 patients and diabetes mellitus in 730 patients.

Patient characteristics, medication use and measurements at baseline are listed in Table 1. This table is stratified for medical history at baseline, with the items of medical history either being the inclusion diagnosis or a comorbidity. This means that patients may fall into more than one category as listed in Table 1. The majority of patients included in the cohort is male (65%), especially among the subgroup of patients with established CVD (73% men, 27% women). The mean age of the total population is 56.8

±12.5 years. In total, 2,608 individuals (18%) had diabetes and 9,633 individuals (65%) had established CVD at inclusion. Of these CVD patients, 1,399 (15%) have polyvascular disease, i.e. multiple vascular beds (cerebral, coronary, abdominal aorta or lower extremity) being affected. The proportion of missing variables is less than 3% for all variables, except for adipose tissue measurements on ultrasound (3.6%), albuminuria (4.7%) and CRP level (9.0%). Vascular screening indicated significant carotid artery stenosis (>50% occlusion) in 526 (4%) patients, AAA in 188 (1%) patients and low ABI (≤0.9) in 829 (6%) patients who were not previously diagnosed with CeVD, AAA or PAD, respectively. Of the 3095 patients with established CVD included between 2012 and 2022 (to account for applicable guidelines), 2075 (67%) had a SBP <140 mmHg, 753 (25%) had a LDL-C ≤1.8 and 2737 (88%) were using antithrombotic agents at baseline.

404 **Table 1. Baseline characteristics stratified for medical history**

	History of CVD				Cardiovascular risk factors			
	Cerebrovascular disease	Coronary artery disease	Abdominal aortic aneurysm	Peripheral artery disease	Hypertension	Hyperlipidaemia	Diabetes mellitus (type 1 + 2)	Renal insufficiency
Number of patients	2801	5999	767	1646	8228	12972	2608	1118
Medical history[a]								
Cerebrovascular disease	2801 (100)	553 (9)	117 (15)	209 (13)	1655 (20)	2492 (19)	442 (17)	248 (22)
Coronary artery disease	553 (20)	5999 (100)	322 (42)	433 (26)	3192 (39)	5762 (44)	1131 (43)	497 (44)
Abdominal aortic aneurysm	117 (4)	322 (5)	767 (100)	134 (8)	466 (6)	693 (5)	114 (4)	151 (14)
Peripheral artery disease	209 (7)	433 (7)	134 (17)	1646 (100)	906 (11)	1492 (12)	328 (13)	205 (18)
Hypertension	1655 (60)	3192 (54)	466 (62)	906 (57)	8228 (100)	7285 (57)	1736 (68)	902 (82)
Hyperlipidaemia	2492 (90)	5762 (96)	693 (91)	1492 (92)	7285 (90)	12972 (100)	2275 (88)	1016 (92)
Diabetes mellitus	442 (16)	1131 (19)	114 (15)	328 (20)	1736 (21)	2275 (18)	2608 (100)	365 (33)
Health questionnaire								
Age (years)	60.0 ± 11.2	61.5 ± 9.5	65.2 ± 9.3	59.9 ± 10.6	58.7 ± 11.7	58.0 ± 11.7	59.3 ± 12.1	63.4 ± 11.3
Male sex	1744 (62)	4849 (81)	636 (83)	1100 (67)	5174 (63)	8699 (67)	1815 (70)	911 (82)
Previous or current smoking	2106 (76)	4511 (75)	661 (86)	1473 (90)	5697 (69)	9265 (72)	1865 (72)	847 (76)
Packyears in (former) smokers	20.2 (9.4 – 35.1)	20.7 (9.4 – 33.6)	28.0 (13.8 – 42.3)	27.9 (14.6 – 40.6)	18.9 (8.3 – 33.3)	18.9 (8.8 – 32.5)	21.0 (9.5 – 36.2)	22.8 (10.5 – 37.8)
Current alcohol use	1484 (53)	3641 (61)	368 (48)	770 (47)	4787 (58)	7584 (59)	1229 (47)	511 (46)
Highest level of education								
- Primary/secondary school	554 (31)	1248 (29)	128 (34)	315 (40)	1764 (31)	2569 (29)	553 (35)	210 (32)
- Vocational school	631 (35)	1466 (35)	117 (31)	236 (30)	1824 (32)	2891 (33)	519 (33)	223 (34)
- University (of applied science)	560 (31)	1415 (33)	125 (33)	196 (25)	1914 (34)	3031 (35)	422 (27)	194 (30)
Exercise (METh/week)	0.0 (0.0 – 10.5)	0.0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)	0 (0.0 – 11.0)	0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)
Medication use								
Lipid-lowering therapy	1682 (60)	4995 (83)	417 (54)	849 (52)	4720 (57)	8253 (64)	1664 (64)	678 (61)
Antihypertensive therapy	1724 (62)	5409 (90)	545 (71)	912 (55)	7130 (87)	9080 (70)	1980 (76)	965 (86)

Platelet inhibitors	2062 (74)	5263 (88)	450 (59)	987 (60)	4532 (55)	7694 (59)	1453 (56)	640 (57)
Oral anticoagulant therapy	311 (11)	821 (14)	123 (16)	234 (14)	743 (9)	1188 (9)	271 (10)	182 (16)
Glucose lowering therapy	287 (10)	757 (13)	67 (9)	189 (11)	1176 (14)	1475 (11)	1621 (62)	216 (19)
Anthropometric measurements								
Systolic blood pressure (mmHg)	141 ± 22	137 ± 20	142 ± 20	144 ± 21	150 ± 23	140 ± 22	144 ± 21	150 ± 24
Diastolic blood pressure (mmHg)	82 ± 12	80 ± 11	83 ± 12	81 ± 11	87 ± 14	83 ± 13	82 ± 12	85 ± 14
Ankle-brachial index ≤ 0.9	398 (14)	680 (11)	165 (22)	1063 (66)	1195 (15)	1751 (14)	434 (17)	283 (26)
Body mass index (kg/m^2)	26.6 ± 4.2	27.3 ± 4.0	26.4 ± 3.8	26.3 ± 4.3	27.6 ± 4.6	27.0 ± 4.3	28.7 ± 5.0	27 ± 4
Waist circumference (cm)	93.7 ± 12.9	97.4 ± 11.6	97.6 ± 12.1	95.0 ± 12.5	96.4 ± 13.3	95.1 ± 12.7	100.7 ± 13.7	98.9 ± 12.5
Hip circumference (cm)	103.6 ± 8.7	104.2 ± 7.6	103.8 ± 7.8	103.0 ± 8.7	105.1 ± 9.2	104.1 ± 8.5	106.3 ± 9.8	104.4 ± 8.4
Visceral fat (cm)	8.6 ± 2.6	9.3 ± 2.6	9.5 ± 2.6	9.2 ± 2.7	9.0 ± 2.8	8.8 ± 2.7	10.1 ± 2.9	9.9 ± 2.8
Subcutaneous fat (cm)	2.5 ± 1.2	2.4 ± 1.2	2.2 ± 1.1	2.4 ± 1.5	2.6 ± 1.4	2.5 ± 1.3	2.4 ± 1.4	2.2 ± 1.4
Carotid artery stenosis	652 (24)	443 (8)	84 (11)	255 (16)	77 (10)	1104 (9)	283 (11)	181 (16)
cIMT (mm)	0.9 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)
Aortic aneurysm	81 (3)	244 (4)	307 (41)	72 (4)	289 (4)	458 (4)	61 (2)	108 (10)
Kidney size (cm)	11.1 ± 1.0	11.3 ± 1.0	11.3 ± 1.0	11.2 ± 1.1	11.2 ± 1.0	11.2 ± 1.0	11.5 ± 1.0	10.9 ± 1.3
Laboratory measurements								
Haemoglobin (mmol/L)	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.9 ± 0.9	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.5 ± 1.0
Total cholesterol (mmol/L)	4.9 ± 1.2	4.5 ± 1.1	5.1 ± 1.3	5.3 ± 1.3	5.0 ± 1.3	5.1 ± 1.4	4.7 ± 1.3	5.0 ± 1.4
LDL-C (mmol/L)	2.9 ± 1.1	2.6 ± 0.9	3.1 ± 1.1	3.2 ± 1.1	2.9 ± 1.1	3.1 ± 1.2	2.7 ± 1.0	2.9 ± 1.1
HDL-C (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Apolipoprotein B (g/L)	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
Triglycerides (mmol/L)	1.3 (0.9 – 1.9)	1.4 (1.0 – 2.0)	1.5 (1.1 – 2.1)	1.5 (1.1 – 2.3)	1.4 (1.0 – 2.1)	1.4 (1.0 – 2.1)	1.6 (1.1 – 2.4)	1.7 (1.2 – 2.5)
HbA1c (%)	5.6 (5.4 – 6.0)	5.7 (5.4 – 6.1)	5.7 (5.4 – 6.1)	5.8 (5.5 – 6.5)	5.7 (5.4 – 6.2)	5.6 (5.4 – 6.1)	6.9 (6.3 – 7.8)	5.9 (5.5 – 6.9)
Fasting glucose (mmol/L)	5.7 (5.3 – 6.3)	5.9 (5.4 – 6.6)	5.8 (5.4 – 6.5)	5.8 (5.3 – 6.7)	5.8 (5.4 – 6.6)	5.8 (5.3 – 6.4)	8.1 (6.9 – 10.0)	6.0 (5.5 – 7.2)
eGFR (mL/min/1.73 m^2)	47.7 ± 39.9	63.12± 34.3	58.2 ± 32.3	51.2 ± 39.9	48.7 ± 40.4	53.6 ± 40.4	55.4 ± 40.5	39.8 ± 25.6
Albuminuria (mg/L)	10.0 (6.0 – 24.1)	9.0 (6.0 – 20.0)	12.9 (8.0 – 39.9)	11.0 (7.0 – 32.0)	11.0 (7.0 – 29.0)	9.0 (6.0 – 22.0)	14.0 (8.0 – 41.0)	82.0 (16.0 – 257.6)
CRP (mg/L)	2.1 (1.0 – 4.5)	1.9 (1.0 – 4.0)	3.3 (1.6 – 6.9)	3.1 (1.4 – 6.3)	2.2 (1.0 – 4.7)	2.0 (1.0 – 4.2)	2.4 (1.1 – 5.1)	3.2 (1.5 – 7.2)
TSH (mU/L)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.8 (1.2 – 2.6)	1.8 (1.2 – 2.5)	1.9 (1.3 – 2.7)	1.8 (1.3 – 2.7)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

[a] Based on inclusion diagnosis, items of the health questionnaire and/or measurements at baseline:

Cerebrovascular disease: history of stroke, carotid surgery or percutaneous transluminal angioplasty;

Coronary artery disease: history of myocardial infarction, cardiac arrest, coronary bypass surgery or percutaneous transluminal coronary angioplasty;

Abdominal aortic aneurysm: history of abdominal aortic aneurysm, transluminal or surgical treatment of abdominal aortic aneurysm;

Peripheral artery disease: history of amputation of (part of) lower limb, lower limb peripheral artery surgery or percutaneous transluminal angioplasty;

Hypertension: treatment with antihypertensive drugs or blood pressure ≥160/95 mmHg at baseline measurement;

Hyperlipidaemia: treatment with lipid-lowering agents, total cholesterol ≥5 mmol/L or LDL-cholesterol ≥3.2 mmol/L at baseline measurement;

Diabetes mellitus: treatment with antidiabetic agents, fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥11.1 mmol/L at baseline measurement;

Renal insufficiency: creatinine >120 mmol/L and/or microprotein/creatinine ratio in urine >20.

Cut-off values applied at the start of UCC-SMART study, please note target values have changed over time and continuous variable are available.

cIMT, carotid intima media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; TSH: thyroid stimulation hormone.

Findings to date

The findings of this section are reported for patients included up to January 2020, because the collection and processing of outcome events has been completed up until this date. These patients contributed to a total follow-up time of 134,439 person-years. Median follow-up time was 9.2 years (interquartile range 4.8 – 14.1 years). During follow-up, 2,259 (16%) patients suffered from a first combined major cardiovascular endpoint (including non-fatal myocardial infarction, non-fatal stroke or cardiovascular death). Furthermore, there were 943 cases of incident diabetes, 105 cases of end-stage kidney disease, 161 cases of heart failure and 434 cases of major bleeding. A total of 3,264 patients underwent a vascular intervention during follow-up. Of patients with previously established CVD, 1906 patients (21%) suffered from the combined vascular endpoint mentioned above as subsequent event, whereas 353 patients (7%) with severe risk factors without prior CVD experienced this combined outcome as their first ever event. Of the 2,450 individuals with diabetes at baseline, 568 (23%) individuals suffered from the combined vascular endpoint. Corresponding incidence rates are 21.2 per 1000 person years for patients with established CVD and 8.2 per 1000 person years for patients without a history of CVD. Numbers and observed incidence rates of all specific outcome events of interest are listed in Table 2. Through linkage with the Dutch National Cancer Registry, a total of 2,139 patients were diagnosed with cancer during follow-up. This includes 414 diagnoses of lung cancer, 354 of prostate cancer, 294 of intestinal cancer and 163 of breast cancer as most common diagnoses.

437 **Table 2. Number and incidence rates of outcome events from 1996 to 2020**

Outcome event	Number of first events	Person-years of follow-up	Incidence rate per 1000 person-years
Non-fatal stroke	613	131,684	4.66
Ischemic stroke	502	132,042	3.80
Haemorrhagic infarction	20	134,362	0.15
Intracerebral haemorrhage	66	134,285	0.49
Subarachnoid haemorrhage	17	134,322	0.13
Type not determined	8	134,430	0.06
Retinal syndromes	16	134,338	0.12
Infarction	13	134,353	0.10
Haemorrhage	3	134,424	0.02
Non-fatal myocardial infarction	793	130,065	6.10
Heart failure	161	134,075	1.20
Systolic heart failure, due to	115	134,203	0.86
coronary disease	85	134,266	0.63
valve disorders	11	134,425	0.08
other causes	19	134,390	0.14
HFpEF, due to	46	134,311	0.34
coronary disease	15	134,390	0.11
valve disorders	8	134,418	0.06
other causes	23	134,381	0.17
Non-fatal rupture AAA	5	139,895	0.04
End-stage kidney disease	105	134,118	0.78
Vascular intervention	3,264	110,154	29.6
Heart	1606	121,936	13.2
Carotid or intracranial arteries	240	132,611	1.81
Aorta	439	131,553	3.34
Peripheral arteries	953	127,914	7.45
Renal artery	62	133,970	0.46
Major bleeding			
ISTH major bleeding	434	129,804	3.34
BARC 3 or 5 bleeding	457	132,497	3.45
Incident diabetes	943	124,310	7.59
Type 1 diabetes	1	131,417	0.01
Type 2 diabetes	942	124,330	7.58

Vascular mortality	1,267	134,439	9.42
Fatal cerebral infarction	85		0.63
Fatal cerebral haemorrhage	65		0.48
Fatal stroke – type not determined	21		0.16
Fatal myocardial infarction			
Fatal heart failure	63		0.47
Fatal rupture AAA	198		1.47
Sudden death	29		0.22
Other	401		2.98
	405		3.01
Non-vascular mortality	1317	134,439	9.80
Fatal malignancy	800		5.95
Fatal infection	169		1.26
Unnatural death	58		0.43
Other	290		2.16
All-cause mortality	2,794	134,439	20.78
Malignancy[a]	2,139	127,514	16.77
Lung	414		3.25
Prostate	354		2.78
Breast	163		1.28
Intestinal	294		2.31
Other	914		7.17

[a] Other subtypes of cancer in the dataset include cancer of the lip, oral cavity or pharynx; oesophagus; stomach; liver, intrahepatic bile ducts, or gallbladder; pancreas; respiratory tract; thymus; bone or articular cartilage of limb; melanoma; mesothelial or soft tissue; vulva or vagina; cervix uteri or corpus uteri; ovary; penis or testes; kidney, renal pelvis or ureter; bladder; eye, brain, and other parts of the central nervous system; thyroid gland; lymphatic/hematopoietic.

AAA, abdominal aortic aneurysm; BARC, Bleeding Academic Research Consortium; HFpEF, heart failure with preserved ejection fraction; ISTH, International Society on Thrombosis and Haemostasis.

The large database of observational data is used for over 350 etiological and prognostic studies so far, and the coverage of a wide age range and long follow-up provides opportunity to develop and validate prediction models. This has been done with the SMART risk score[35,36], the SMART-REACH lifetime model for patients with previous CVD[3] and the DIAL lifetime model[37] for patients with type 2 diabetes (to be found at https://u-prevent.com and the ESC 'CVD risk calculation'-app). These estimates serve clinical practice by providing insight into risk and thus supporting patient education and shared decision making. Moreover, routinely collection of patient data allows for embedding clinical trials within the cohort, as has been done with, amongst others, TEMPUS[30] and SMART-Inform[31].

The vascular screening in the UCC-SMART study is a structured uniform program to detect risk factors and asymptomatic atherosclerosis and provides a basis for optimizing treatment of high-risk patients. In a previous study comparing the UCC-SMART screening program to usual care in another university hospital in the Netherlands, a beneficial effect of the screening program on SBP and LDL-C was seen.[29] Previous research on screening programs in the general population shows improvement of cardiovascular risk factors and detection of patients at risk, but conflicting results are found on mortality and cardiovascular events.[2,38] In a population at risk (e.g. with hypertension or diabetes) the beneficial effect of cardiovascular screening is more clearly pronounced.[2,39] In addition, a higher baseline achievement of secondary prevention targets is associated with improved cardiovascular health outcomes in an patients with established CVD and type 2 diabetes.[40]

Strengths and limitations

The UCC-SMART study is a unique ongoing prospective cohort study in more than 14,000 patients with a history of various manifestations of CVD or severe cardiovascular risk factors, providing a large database of information on a population at high cardiovascular risk. Collecting diverse outcome events in this population allows for research on risk factors for different manifestations of CVD and incident diabetes. Linkage to multiple registries facilitates the investigation of relationships between cardiovascular risk factors and diseases and other conditions such as cancer and dementia.

By the integration of health care and scientific research, patient care becomes more complete and data already to be collected for patient care is used to increase knowledge of CVD, whilst the additive burden for participating patients is limited.

The main strengths of the UCC-SMART cohort include the large size, its capture of a high-risk population with various CVD manifestations and risk factors with few exclusion criteria, the use of a standardized diagnostic protocol, the long follow-up duration and the comprehensive prospective capture of a wide range of data. Because inclusion of patients is still ongoing, the UCC-SMART cohort provides a good representation of the past and current population of patients at high cardiovascular risk. Due to the high risk study population, the prevalence and incidence of the main outcome variables are higher than in the general population, thereby increasing the power to study these outcomes. Furthermore, all outcome events are adjudicated independently by three physicians of the endpoint committee, reducing the risk of misclassification. The proportion of missing data is small, possibly explained by the protocolized screening program taking place in one day. The substudies provide additional information on specific cardiovascular risk factors (e.g. parental history of CVD[41], characteristics related to left ventricle hypertrophia[24], and the presence of diffuse idiopathic skeletal hyperostosis[42]), manifestations of atherosclerosis (e.g. brain changes on MRI[18] and cognitive decline[19]), and other important aspects in cardiovascular risk management (e.g. the effect of a cardiovascular polypill[43]).

Limitations also need to be considered. Due to the prospective observational design, for the majority of the patients, risk factors are only measured at baseline and may have changed during follow-up. This could be reflected by the finding of this article that not all patients with CVD meet treatment goals for modifiable risk factors at baseline. Since patients are included several weeks to months after an index CVD event, risk factors are likely to be further optimized during this period after baseline examination. For a subset of patients with CVD or diabetes, a repeat of the baseline measurements after a median of 9.9 years is indeed available, allowing for investigating the course of atherosclerosis over time. Furthermore, ten percent of the included patients is lost to follow-up. Yet, the median time to loss to follow-up is 7.4 years, so those patients still contribute to a fair amount of patient-years. In addition, because UCC-SMART is a single-centre study in a university hospital, it can be disputed whether it

represents the general high risk population and patients with established CVD. The UMC Utrecht provides care to nationwide patients referred for complex and specialized care, but also to patients referred by general practitioners from the region. Moreover, the UCC-SMART study does not include patients requiring highly specialized care (including heart transplantation and rare causes of vascular disease). Lastly, except for information on education level, the database does not contain extensive information on socioeconomic status.

In conclusion, we have provided an updated extensive overview of the design of the UCC-SMART study as well as an overview of the findings to date. A future goal is to make the UCC-SMART data Findable, Accessible, Interoperable and Reusable (FAIR).[44]

Collaboration

The UCC-SMART study group directs the academic focus of research using the UCC-SMART data and consists of members from both epidemiological and clinical cardiovascular research. Datasets are provided to interested researchers after approval of request by the UCC-SMART study group. Access to the data request module can be applied for via ucc-smart@umcutrecht.nl.

Conflict of interest

The authors declare no conflict of interest.

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Author contributions

F.L.J.V., S.H.J.H., J.W., M.C.C. and M.A.G.H. contributed to the conception and design of the work. All authors contributed to the analysis or interpretation of data for the work. M.A.G.H. and M.C.C. drafted the manuscript. All authors critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Figure legends

Figure 1. Course of the UCC-SMART study

ECG, electrocardiogram; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease; UMC Utrecht, University Medical Centre Utrecht

Figure 2. Timeline of measurements collected for or starting from a certain period

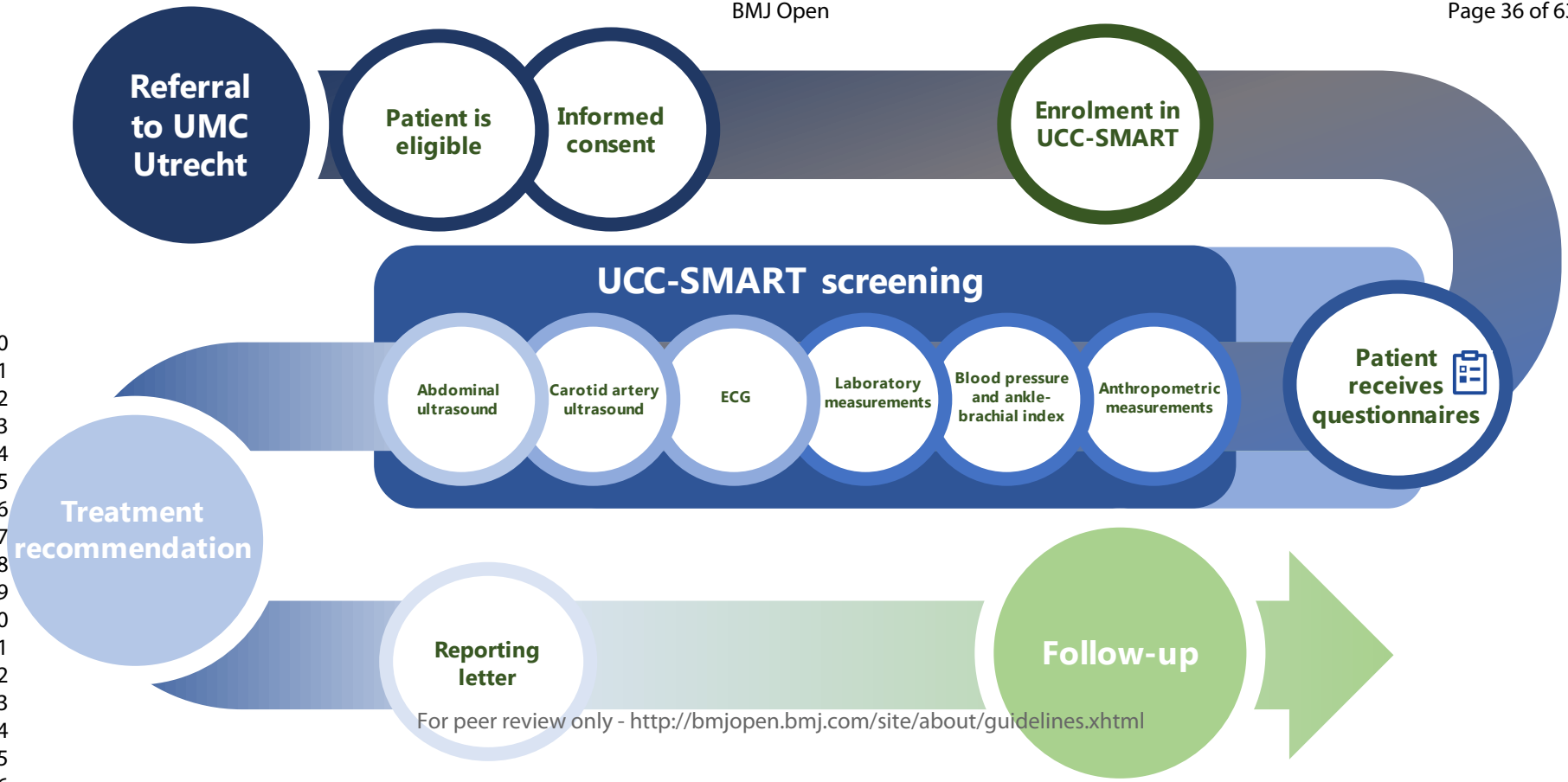
ACE, angiotensin converting enzyme; apoB, apolipoprotein B; CAC, coronary artery calcium; CRP, C-reactive protein; CT, computerized tomography; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; Lp(a), lipoprotein a; MRI, magnetic resonance imaging; T, Tesla; TSH, thyroid stimulating hormone

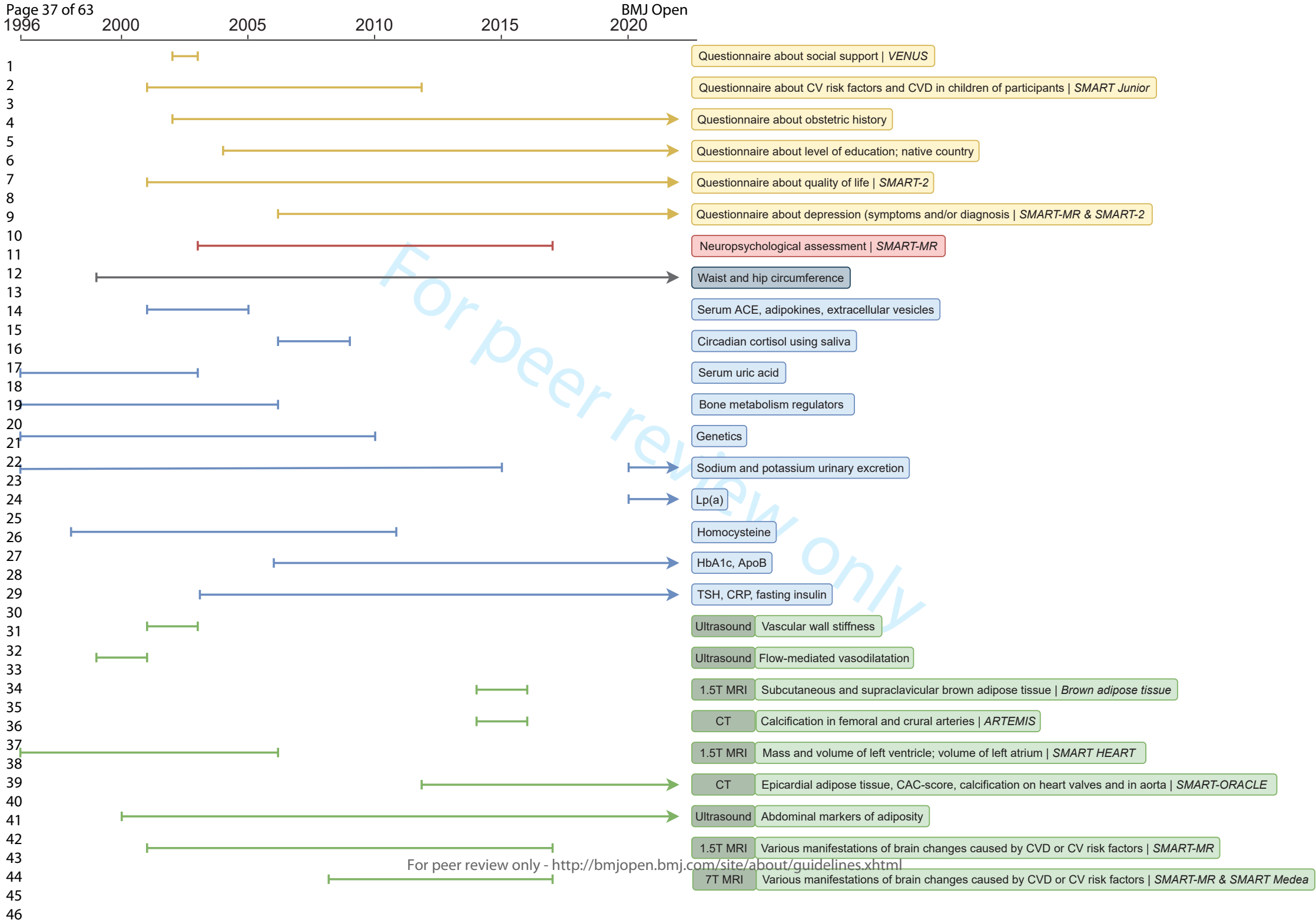
Figure 3. Cumulative number of patients over time

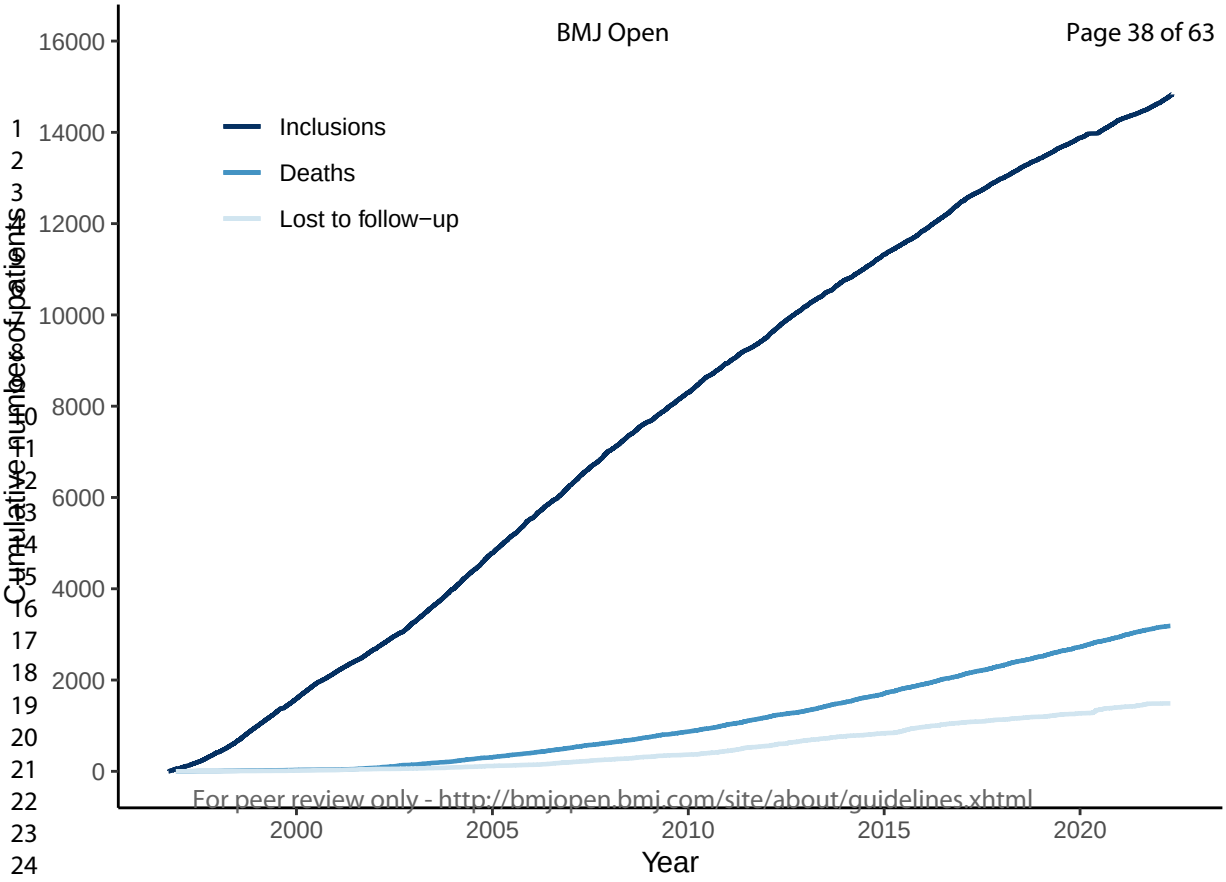
Inclusion in the UCC-SMART study started in September 1996.

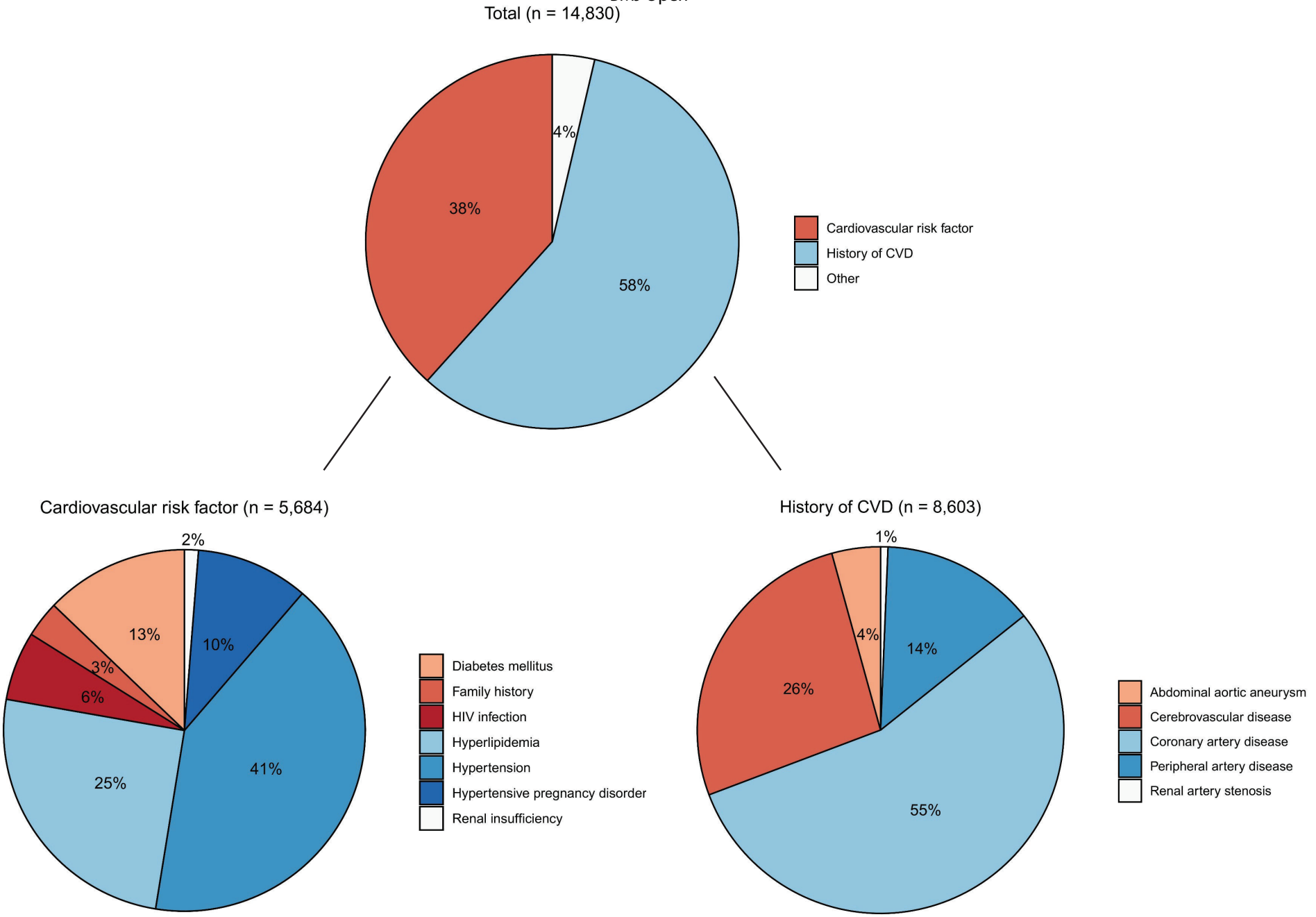
Figure 4. Distribution of inclusion diagnoses

CVD, cardiovascular disease; HIV, human immunodeficiency virus








Total (n = 14,830)
4%
38%
58%
Cardiovascular risk factor
History of CVD
Other
Cardiovascular risk factor (n = 5,684)
2%
13%
10%
3%
6%
25%
41%
Diabetes mellitus
Family history
HIV infection
Hyperlipidemia
Hypertension
Hypertensive pregnancy disorder
Renal insufficiency
History of CVD (n = 8,603)
1%
4%
14%
26%
55%
Abdominal aortic aneurysm
Cerebrovascular disease
Coronary artery disease
Peripheral artery disease
Renal artery stenosis

Supplementary material

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in The Netherlands

Content list

Supplementary Table 1. Inclusion criteria and exclusion criteria

Inclusion criteria	Definition
One or more of the following cardiovascular diseases or risk factors:	
Cardiovascular disease	
Transient ischemic attack	Sudden onset, ≤24 hours of: *carotid:* temporary motor weakness in one half of the body, language disorder, blindness in one eye *vertebrobasilar*: ≥2 simultaneously: bilateral motor weakness or paraesthesia, dizziness, diplopia, dysphagia, ataxia, dysarthria *unknown vascular region:* hemianopia, dysarthria
Cerebral infarction	Criteria as for TIA, but duration of >24 hours
Subarachnoid haemorrhage	Sudden headache and (temporary) loss of consciousness, often accompanied by neck stiffness, nausea and vomiting, with blood in basal cisterns confirmed by CT or xantochromia in cerebrospinal fluid
Carotid artery stenosis	Duplex ultrasound confirmed stenosis or occlusion of ≥1 carotid artery with diameter reduction ≥50%
Ischemic retinal syndrome	Visual field defect diagnosed as retinal syndrome by ophthalmologist
Angina pectoris	Chest pain with proven stenosis on coronary angiogram
Myocardial infarction	≥2 of following: - Chest pain >20 minutes, not relieved by nitrates; - ST elevation >1 mm in 2 contiguous ECG leads, or left bundle branch block; - Troponin levels >60 ng/L with rise and fall pattern*
Coronary syndrome requiring PCI or CABG	
Abdominal aortic aneurysm	Ultrasound confirmed local dilatation of abdominal aorta with anterior-posterior diameter ≥3 cm and/or distal-proximal ratio of >1,5
Renal artery stenosis	Stenosis of ≥1 renal artery with lumen narrowing ≥50%, caused by atherosclerosis
Peripheral artery disease of the lower limbs	Fontaine classification: - Fontaine II: intermittent claudication: pain (or other symptoms) in one or both legs after certain walking distance, disappearing at rest; - Fontaine III: rest/nocturnal pain; - Fontaine IV: ischemic ulceration, necrosis or gangrene; confirmed by ABI ≤0.90 at rest and/or ≥20% post-exercise decrease
Cardiovascular risk factors	
Hypertension	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hypertension, target organ damage, medical or family history
Hyperlipidaemia	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hyperlipidaemia, suspected lipid metabolism disorder, medical or family history

Diabetes mellitus	Fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or use of oral antidiabetic agents or insulin
Renal insufficiency	Serum creatinine >120 µmol/L
HIV infection	Chronic infection with human immunodeficiency virus
Family medical history	Positive family history for premature cardiovascular disease in 1st degree relatives
Pre-eclampsia†	Gestational hypertension accompanied by proteinuria, other maternal organ dysfunction or uteroplacental dysfunction
HELLP syndrome†	Haemolysis, elevated liver enzymes, low platelets as a manifestation of pre-eclampsia
Placental abruption†	Gestational hypertension accompanied by placental abruption as an effect of uteroplacental insufficiency
Intrauterine growth restriction†	Gestational hypertension accompanied by fetal growth restriction as an effect of uteroplacental insufficiency
Remaining inclusion criteria	
18 – 90 years of age	
Independent in most daily activities	Rankin scale ≤3[1]
Exclusion criteria	
Pregnancy	
Short life expectancy	
Insufficient understanding and expression of the Dutch language	
No informed consent	
Follow-up impossible	

* In earlier years of the UCC-SMART study, this laboratory item was defined as CK elevation of ≥2x upper limit and MB-fraction >5% of total CK level.
† Hypertensive pregnancy complications are based on the ISSHP criteria[2]

ABI, ankle-brachial index; CABG, coronary artery bypass grafting; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; HELLP, haemolysis, elevated liver enzymes and low platelets; HIV, human immunodeficiency virus; ISSHP, International Society for the Study of Hypertension in Pregnancy; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 2. Variables available in UCC-SMART

Health questionnaire	Medication use	Physical examination	Radiology measurements	Laboratory measurements
Medical history	Statins	Weight (kg)	Visceral fat (cm)	Haemoglobin (mmol/L)
Age (years)	Ezetimibe	Height (m)	Subcutaneous fat (cm)	Haematocrit (%)
Sex	Fibrates	Blood pressure (mmHg)	Carotid artery stenosis (%)	Total cholesterol (mmol/L)
Smoking and pack years	Thiazide diuretics	Ankle-brachial index	Carotid intima thickness (mm)	LDL-C (mmol/L)
Alcohol use and number of units	Loop diuretics	Body mass index (kg/m^2)	Aortic artery diameter (cm)	HDL-C (mmol/L)
Level of education	Potassium saving diuretics	Waist circumference (cm)	Kidney size and volume (cm; mL)	Apolipoprotein B (g/L)
Country of birth	ACE-inhibitors	Hip circumference (cm)	Electrocardiography	Triglycerides (mmol/L)
Quality of life*	Angiotensin II-receptor blockers		Echocardiography†	HbA1c (%)
Exercise (MET-hours per week)	Aldosterone antagonists			Fasting glucose (mmol/L)
	Beta-blockers			Fasting insulin (mU/L)
	Calcium antagonists			Creatinine (µmol/L)
	Alpha blockers			eGFR (ml/min/1.73 m^2)
	Central acting antihypertensives			Albuminuria (mg/L)
	Direct vasodilators			Albumin-to-creatinine ratio
	Aspirin			CRP (mg/L)
	Clopidogrel			TSH (mU/L)
	Dipyridamole			Lp(a)
	DOAC			Urine sodium
	Vitamin K antagonists			Urine potassium
	LMWH			
	Oral glucose-lowering therapy			
	Insulin			
	Antidepressants			
	Benzodiazepines			

* Based on EQ-5D questionnaire

† Echocardiography will be added to the UCC-SMART program in the near future

ACE, angiotensin converting enzyme; CRP, C-reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low molecular weight heparin; Lp(a), lipoprotein(a); MET, metabolic equivalent of task; TSH, thyroid stimulating hormone; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Diseas

Supplementary Table 3. Measurements that have been performed in the past

Vascular wall stiffness was determined from 2001 until 2003 using the Wall Track System that captures vascular diameter changes using radio-frequent signals. At the first signal, the position of the anterior and posterior vascular wall of the common carotid artery are marked at 2 cm proximal to the carotid bulb. Then, for five times on both the left and right side, changes in arterial diameter (ΔD) and end-diastolic diameter (D_d) are registered during four seconds, and the mean is calculated. Carotid distension is defined as the change in artery diameter in systole relative to diastolic diameter. Other stiffness indices include β stiffness index ($\ln(SBP/DBP)/(\Delta D/D_d)$), compliance coefficient ($(\pi \times D_d \times \Delta D)/2 \times$pulse pressure), distensibility coefficient ($(2 \times \Delta D/D_d)$/pulse pressure), Peterson's modulus (pressure change required for theoretical 100% increase in diameter) and Young's elastic modulus (pressure per mm^2 required for theoretical 100% extension).
Flow-mediated vasodilatation (FMD) was assessed temporarily starting from March 1999. Here, the Wall Track System described above was used to capture the diameter of the brachial artery in the elbow crease. Following 3 baseline readings, new measurements were taken every 30 seconds for 5 minutes: first after a blood pressure cuff at the forearm was inflated to 100 mmHg above SBP for 4 minutes, and then after sublingual administration of 400 µg of nitroglycerin. Endothelial function was defined as the proportional increase of diameter after nitrate and the baseline-adjusted maximal diameter following ischemia. This examination was stopped in June 2001, since analysis in the first 400 patients showed this measurement was not related to other known measures of atherosclerosis.
Quality of life information was collected through questionnaires based on the 36-Item Short Form Health Survey (SF-36)[3], sent to participants from 2001 until 2019. This quality of life assessment contains scales for 1) limitations in physical activities; 2) limitations in social activities; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality and 8) general health perceptions.
Homocysteine was measured from 1998 until 2011 in fasting blood samples by high performance liquid chromatography with fluorescence detection. Up until 2000, a methionine loading test was performed in patients younger than 50 years. Plasma homocysteine was measured six hours after oral administration of 100mg methionine per kilogram bodyweight.

DBP, diastolic blood pressure; SBP; systolic blood pressure

Supplementary Table 4. Definitions of established cardiovascular disease

Cardiovascular disease	Definition of cardiovascular disease*
Cerebrovascular disease	TIA, cerebral infarction, ischemic retinal syndrome, carotid surgery or angioplasty in medical history
Coronary artery disease	Myocardial infarction, angina pectoris, ≥ 1 vessel disease on coronary angiography, PCI or CABG in medical history
Abdominal aortic aneurysm	Abdominal aortic aneurysm, surgical or endovascular treatment of abdominal aortic aneurysm in medical history
Peripheral artery disease	Fontaine classification ≥ II, amputation, vascular surgery or angioplasty in medical history

* Definitions of these items are listed in Supplementary Table 1.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 5. Definitions of outcome events

Outcome event	Definition of outcome event
	Primary endpoints
Stroke	
Ischemic stroke / haemorrhagic infarction	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale[1], and new (haemorrhagic) infarction on CT or MRI <2 weeks after stroke
Cerebral haemorrhage	Cerebral haemorrhage confirmed with CT, MRI or surgery
Subarachnoid haemorrhage	Subarachnoid haemorrhage confirmed with CT, MRI or surgery
Type not determined	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale, but no brain imaging performed
Retinal syndromes	
Infarction	Associated clinical symptoms, typical fundus changes and/or vision loss, scotoma on perimetry
Haemorrhage	Associated clinical symptoms, typical fundus changes and vision loss
Myocardial infarction	The assessment includes: chest pain >30 minutes, elevated cardiac enzymes, characteristic ECG-changes
STEMI	Acute chest pain with persistent (>20 minutes) ST-elevation
NSTEMI	Acute chest pain without ST-elevation, with elevated troponin
Intervention-related myocardial infarction	New Q wave and elevated troponin <7 days after any intervention (for PCI >3x, for CABG >5x)
Probable myocardial infarction	Typical pain, persistent STT-changes, no documented course of cardiac enzymes
Heart failure	≥2 of the following: dyspnoea, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, exercise intolerance, pulmonary oedema, increased central venous pressure, third heart tone, hepatojugular reflux, altered hemodynamics, peripheral oedema, cardiomegaly; and (intensified) treatment with loop diuretics or intravenous vasoactive inotropic agents Classified as: systolic heart failure (at least moderate left ventricle dysfunction or LVEF <40%) or heart failure with preserved ejection fraction, due to coronary disease, valve disease or other causes
Rupture of abdominal aortic aneurysm	Rupture abdominal aortic aneurysm, proven by ultrasound, CT or laparotomy
Renal disease	
End-stage renal disease	CKD stage 5 (i.e. persisting eGFR <15ml/min/1.73 m^2 for >3 months and/or need for renal replacement therapy (chronic dialysis or renal transplantation))

Acute renal insufficiency – temporary renal replacement therapy	Acute kidney injury requiring temporary renal replacement therapy
Acute renal insufficiency – no renal replacement therapy	Acute kidney injury KDIGO stage 3 (i.e. serum creatinine 3 times baseline creatinine and/or serum creatinine ≥354 µmol/L)
Bleeding	Bleeding requiring outpatient treatment or (prolonged) hospitalization
Major bleeding	*ISTH definition:* fatal bleeding and/or bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular causing compartment syndrome), bleeding causing Hb level drop of ≥1.24 mmol/L or leading to transfusion of ≥2 units of blood[4] *BARC type 3:* overt bleeding with Hb level drop of ≥1.86 mmol/L, leading to transfusion, cardiac tamponade, surgical intervention for control or intravenous vasoactive agents, or located intracranial or intraocular compromising vision *BARC type 5:* fatal bleeding[5]
Diabetes	Self-reported diagnosis, confirmed and classified based on a questionnaire. If necessary, additional information is requested from the general practitioner or looked up in the electronic health record.
DM type 1	Insulin needed immediately at onset and absence of oral glucose lowering medication. Supportive but not mandatory: ≤25 years of age, BMI <25 kg/m^2, presence of anti-GAD antibodies
DM type 2	Diagnosed between age 35 and 40 and BMI >33 kg/m^2 or diagnosed after age 40 and BMI >27 kg/m^2
Dementia	Self-reported diagnosis, confirmed and classified based on a questionnaire. Classified as: Alzheimer's disease; vascular dementia; a mix of Alzheimer's disease and vascular dementia; Lewy Body dementia; or frontotemporal dementia.
Vascular mortality	
Fatal cerebral infarction	Cerebral infarction leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal cerebral haemorrhage	Cerebral haemorrhage leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal stroke - type not determined	Stroke without radiological confirmation leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without stroke)
Fatal myocardial infarction	Documented myocardial infarction followed by death (>1 hour after onset of symptoms)
Fatal heart failure	Heart failure leading to death

Fatal rupture abdominal aortic aneurysm	Rupture abdominal aortic aneurysm followed by death
Fatal bleeding	Major bleeding leading to death
Sudden death	Witnessed death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Other	Death without apparent cause in case of cardiovascular history, terminal renal insufficiency, dementia (unless clearly non-vascular), pulmonary haemorrhage*
Non-vascular mortality	Death caused by malignancy, infection, unnatural death or other
All-cause mortality	Death from any cause
	Secondary endpoints
Amputation	Any amputation of a toe or part of the foot or leg due to chronic ischemia. *Excluding:* traumatic amputations, amputation due to sepsis, amputation of fingers.
Vascular intervention†	Percutaneous coronary intervention; coronary artery bypass grafting; carotid endarterectomy, angioplasty or stenting; vertebral artery angioplasty or stenting; vascular surgery or percutaneous transluminal angioplasty of the aorta(bifurcation), iliac arteries, femoral and crural arteries; vascular intervention because of abdominal angina; LVAD. Angioplasty and stenting of other arteries are registered as well.
Vascular intervention of an intracranial aneurysm	Coiling or clipping of an intracranial aneurysm

* In accordance with Antiplatelets Trialists' Collaboration, Lancet 2002
† Excluding interventions already planned before or at inclusion, but including re-interventions and complications of an intervention already planned before or at inclusion.

Anti-GAD, antibodies to glutamic acid decarboxylase; BARC; Bleeding Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; KDIGO, Kidney Disease Improving Global Outcomes; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Supplementary Table 6. Substudies of UCC-SMART

Substudy	Period in which the patients were included	N	Aim	Key publications	Additional measurements within substudy
ARTEMIS *(ARTErial calcifications of the Media and Intima in SMART)*	2015 - 2017	520	1) To determine whether intima and media calcification differ in their respective associated CVD risks. 2) To elucidate which risk factors and mechanisms lead to the development of these respective types of calcification and in turn to cardiovascular disease	- Zwakenberg, 2020, PloS One[6] - Hoek, 2021, Atherosclerosis[7]	Technique: unenhanced thin-slice CT-scan of the legs (femoral head to feet) Measurement: calcification in the femoral and crural arteries scored as absent, predominant intimal arterial calcification, predominant medial arterial calcification or indistinguishable; calcification volume.
Athero-Express *Added to UCC-SMART study in June 2022*	2002 - present	Patients undergoing a femoral or carotid endarterectomy	To investigate the value of plaque characteristics in relation to cardiovascular outcomes	Verhoeven, 2004, Eur J Epidemiology[8]	During surgery, the atherosclerotic plaque is collected and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells
BEST *(BEtter risk factor treatment with STructured agreement)* RCT	2004 - 2006	197 patients with at least 2 modifiable risk factors	To investigate whether a clearly written agreement on risk factor management between general practitioners and hospital improved the vascular risk profile of high-risk patients compared with usual care after 1 year	Brouwer, B.G. 2008. SMART risk factor screening in patients at high vascular risk. Utrecht University, Utrecht[9]	NA
Brown adipose tissue	2014 – 2016	50 patients with clinically manifest CVD	1) To evaluate and optimize a protocol for quantifying brown adipose tissue with MRI and to assess BAT volume per patient. 2) To evaluate the reproducibility of MRI by determining inter-scan, intra-observer and inter-observer variability in BAT volume	- Franssens, 2016, NMR Biomed[10] - Franssens, 2017, J Magn. Reson. Imaging[11]	Technique: 1.5T water-fat MRI of supraclavicular and subcutaneous adipose tissue Measurement: fat signal fraction value, representative of the amount of triglycerides, intracellular water content and capillary density, of supraclavicular and subcutaneous adipose tissue

DISH *(Diffuse idiopathic skeletal hyperostosis)*	1996 – 2018	4,791 (all patients from SMART with chest X-ray within 3 months of inclusion)	N.A.	- Harlianto, 2021, Rheumatology[12] - Harlianto, 2021, J. Pers. Med.[13]	*Technique: Chest X-ray within three months of inclusions (if available in routine clinical care)* Measurement: X-rays were scored for DISH using the Resnick criteria.[14] DISH is classified following the presence of ossification of at least four contiguous vertebrae; (relative) preservation of the intervertebral disc height; and the absence of apophyseal joint bony ankylosis or sacroiliac joint erosion. Thoracic aortic calcification subjective score as absent, mild, moderate and severe.
IRIS *(Internet-based vascular Risk factor Intervention and Self-management)* RCT	2008 - 2010	330 patients with a recent clinical manifestation of atherosclerosis of CAD, CeVD or PAD and with ≥ 2 treatable risk factors not at goal (from UMC Utrecht + Rijnstate)	1) To evaluate whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease. 2) To evaluate whether an internet-based vascular risk factor management program for reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease is cost-effective.	- Vernooij, 2012, BMJ[15] - Greving, 2015, BMJ Open[16]	NA
RULE *(Risk management in Utrecht and*	2005 - 2007	604 patients with CAD, CeVD, PAD or T2DM from	To assess risk factor status after referral in patients with established vascular disease or type 2 diabetes who took part in the	Brouwer, 2010, J of Int Med[17]	NA

Leiden Evaluation study) Two-centre parallel-group comparative investigation		UMC Utrecht (+ 566 patients from LUMC)	multidisciplinary hospital-based vascular screening program SMART, compared with a group who did not participate in such a program		
Small aneurysms trial (AAA)	1996 - 2005	230 patients with an initial AAA diameter of 30-55mm, who were examined by ≥ 2 AAA diameter measurements and with ≥ 6 months of FU	To estimate overall rupture rates of small AAAs and to investigate a predefined set of demographic characteristics and cardiovascular risk factors for association with AAA growth	Schlosser, 2008, J Vasc Surg[18]	Technique: Ultrasound scanning of the aorta Measurement: AAA diameter and change with initial AAA diameter
SMART-2	2007 - present	1794 patients with a history of CVD or diabetes, a median of 9.9 years after inclusion in UCC-SMART	To study the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment in the past		NA
SMART HEART	1996 - 2006	536 patients with ≥ 3 years hypertension, but free of known coronary or valvular disease	To detect patient characteristics related to the development of LVH with special focus on the detection of SNPs that confer an increased susceptibility for the development of LVH, and thus, heart failure	- Meijs, 2007, Neth Heart J[19] - Meijs, 2009, Eur J Prev Cardiol[20] - Vernooij, 2012, Am J Cardiol[21] - De Beus, 2015, Eur J Clin Invest[22]	Technique: 1.5T cardiac MRI and delayed-enhancement cardiac MRI Measurement: LV mass, LV-end diastolic and end-systolic volumes and left atrial volumes; areas of hyperintense myocardium classified as myocardial scar tissue (used to assess the presence of unrecognized

					myocardial infarction). Infarct size was quantified as scar mass relative to LV mass.
SMART Inform Three-armed hypothesis-blinded RCT	2017 - 2018	303 patients with stable CVD and using a statin	To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use in patients with stable CVD compared with standard (non-personalized) therapy-effects	Jaspers, 2021, BMJ Open[23]	NA
SMART-Junior	Questionnaires sent between 2009-2013 to patients who were included between 2001 and 2012	4,270 (10,564 children)	1) To investigate the presence of cardiovascular risk factors and vascular disease in offspring of patients participating in the SMART cohort. 2) To identify a risk profile of the parent prognostic for the development of traditional cardiovascular risk factors or cardiovascular events in their children.	- Weijmans, 2015, Int J Cardiol[24] - Weijmans, 2015, Am Heart J[25]	- Questions about CV risk factors (incl. dates of risk factor diagnoses): presence of diabetes, hypertension, hypercholesterolemia, smoking behaviour and present weight of the offspring - Questions about CVD (incl. dates of occurrence): whether offspring had experienced MI, PCI, CABG, stroke, PAD, or AAA.
SMART-MR and SMART Medea	2001 - 2005 1st follow-up: 2006-2009 2nd follow-up: 2013-2017	1,309	To investigate brain changes using 1.5T MRI in patients with symptomatic atherosclerotic disease (and 7T MRI in follow-up from 2013-2017)	- Geerlings, 2010, Atherosclerosis[26] - Muller, 2011, Ann Neurol[27] - Conijn, 2011, Stroke[28] - Kloppenborg, 2012, Neurology[29] - Jochemsen 2013, JAMA Neurology[30] - Van der Veen, 2015, Stroke[31] - Zwartbol, 2019, Stroke[32]	<u>Technique:</u> - 1.5T brain MRI - 7T brain MRI <u>Measurement:</u> - Total cerebral blood flow (mL/min per 100 mL brain parenchymal volume) - White matter lesions: volume (mL), shape (using the concavity index and fractal dimension[35]) and location were scored - Brain parenchymal fraction (% of intracranial volume (ICV) that is occupied by

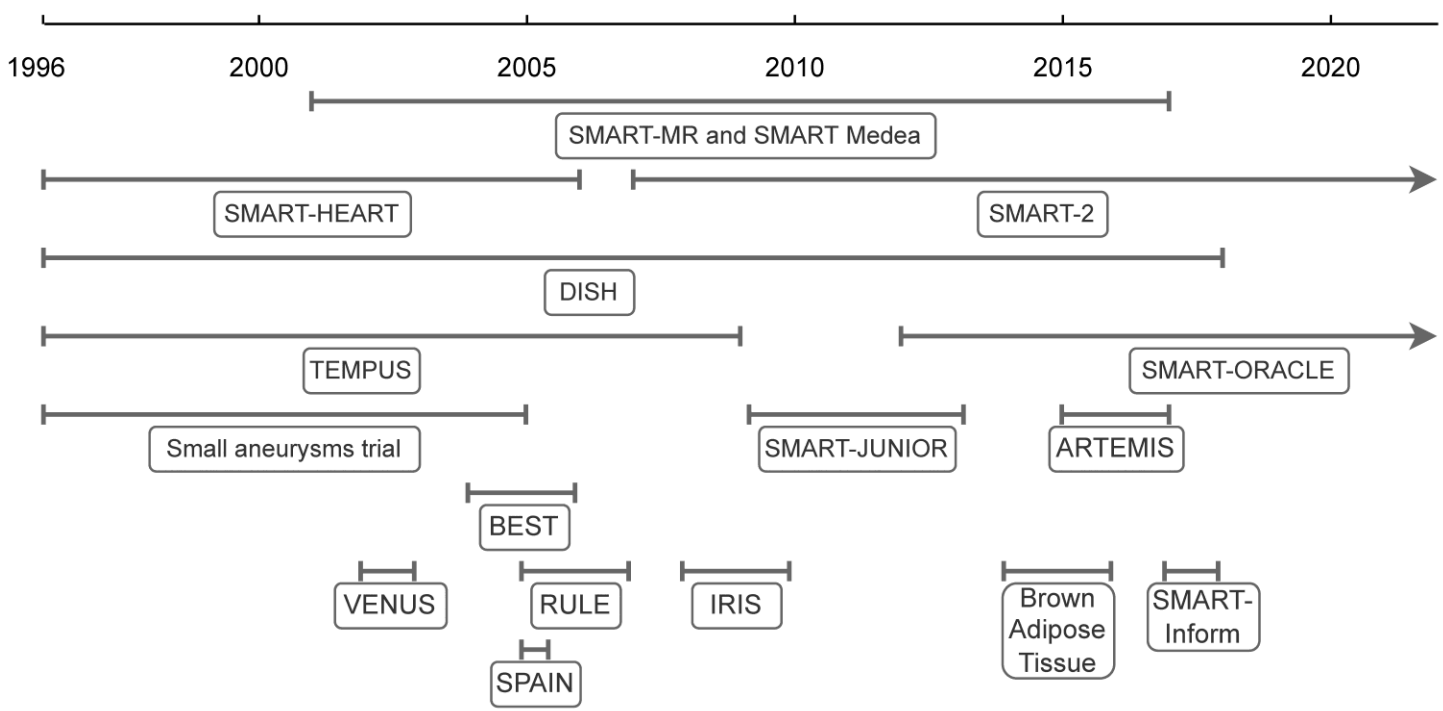
				- Ghaznawi 2021, Neurology[33] - Rissanen, 2021, Neurology[34]	brain tissue), an indicator for global brain atrophy - Ventricular enlargement (% of ventricular volume of the total ICV), an indicator for subcortical brain atrophy - Cortical gray matter fraction (% cortical gray matter volume of the total ICV), an indicator of cortical brain atrophy - Infarcts: location, affected flow territory and type were scored
					<u>Neuropsychological assessment (from 2003):</u> - 15-learning word test[36] - Rey-Osterrieth Complex Figure test[37] - Visual Elevator test[38] - Brixton Spatial Anticipation test[39] - Verbal Fluency test (letter)[40] - Dutch version of the National Adult Reading test[41] <u>From 2006:</u> - MMSE[42] - Verbal Fluency test (animals)[40] - Digit Symbol Substitution Test[43] - Forward Digit Span and Backward Digit Span[44]
SMART-ORACLE *(Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk*	2012 - present	1.182 (until Dec 2021; ongoing) patients with a history of symptomatic vascular	1) To determine whether there is additional value of performing CAC score, CTCA, total aorta calcification, burden as compared to traditional risk factors in the risk stratification in predicting any cardiovascular event. 2) To	- Franssens, 2017, Eur J of Prev Cardiol[45] - Van 't Klooster, 2020, IJC Heart & Vasculature[46]	<u>Technique:</u> Cardiac non-contrast enhanced CT and CTA of the heart and the carotids to the circle of Willis

for a cardiovascular event)		disease, T2DM or hypertension	estimate the additional value of CTCA and CAC score on top of traditional risk factors in predicting cardiac events. 3) To determine the value of soft plaque burden in the carotid and coronary arteries in predicting acute vascular events		Measurement: - Radiodensity and volume of epicardial adipose tissue - Coronary artery calcium (scored using the Agatston method[47]) - Calcifications on heart valves and in the thoracic aorta (quantified using a pseudo-mass score: mean calcium houndsfield units × region of interest volume) - CAD-RADS[48] - Carotid stenosis
SPAIN *(Selfmanagement of vascular Patients Activated by Internet and Nurses)*	2005	50 patients with computer facilities	1) To evaluate the feasibility of an Internet-based vascular risk reduction program in terms of accessibility, frequency and pattern of use of an individualized website for patients with a recent clinical manifestation of arterial disease. 2) To evaluate whether the use was related to a change in vascular risk factors after 6 months	Goessens, 2008, Patient education and counseling[49]	NA
TEMPUS *(The Evening versus Morning Polypill Utilization Study)* Randomized open blinded endpoint crossover trial	1996 - 2009. Patients were screened between 2012 - 2013	78 patients with established CVD or those at intermediate to high risk of CVD with indication for the use of cardiovascular medication, according to the current	1) To assess whether there is a difference in the morning or evening administration of a cardiovascular polypill, an FDC formulation containing aspirin, simvastatin, lisinopril and hydrochlorothiazide, on LDL-C and mean 24-hour systolic BP levels in individuals at high risk of cardiovascular disease. 2) To assess the effect of the polypill on LDL-C, ambulatory BP, anti-platelet function, adherence and patients'	- Lafeber, 2014, Eur J Prev Cardiol[50] - Lafeber, 2014, Int J Cardiol[51]	At baseline and at the end of each treatment period: medical history, anthropometric parameters, laboratory blood tests, office BP, 24-hour ambulatory BP monitoring, platelet function, pulse wave analysis, adherence to therapy, and questionnaires

		Dutch guidelines	preference as compared to the administration of the individual, identically dosed components of the polypill administered at different times of the day, as is currently recommended in clinical care.		
VENUS *(Vascular prEvention by NUrses Study)* RCT	Patients included between May 2002 and October 2003	236 patients with ≥ 2 modifiable risk factors	To investigate whether risk factor management in the hospital improved with nurse practitioner care plus usual care compared with usual care	- Goessens, 2006, Eur J Cardiovasc Prev Rehabil[52] - Sol, 2009, Eur J C Nurse[53]	Questionnaire about social support using a social support questionnaire for Dutch CHD patients: - Structural support: whether they have a spouse and whether they have someone they could turn to about their health problems - Functional support: statements about active involvement, protective buffering and overprotection.

AAA, aortic abdominal aneurysm; BAT, brown adipose tissue; BP, blood pressure; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease, CAD-RADS, CAD-reporting and data system, CeVD, cerebrovascular disease; CHD, coronary heart disease; CT, computed tomography; CTA, CT angiography; CTCA, CT coronary angiography; CV, cardiovascular; CVD, cardiovascular disease; DISH, diffuse idiopathic skeletal hyperostosis; FDC, fixed dose combination; FU, follow-up; LDL-c, low-density lipoprotein cholesterol; LUMC, Leiden University Medical Center; LV, left ventricle; LVH, left ventricle hypertrophy; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SMART, Second Manifestations of Arterial Disease; SNP; single nucleotide polymorphism; T2DM, type 2 diabetes mellitus; UCC-SMART, Utrecht Cardiovascular Cohort–SMART; UMC, University Medical Center

Supplemental Figure 1. Timeline of substudies of UCC-SMART



1.5T brain MRIs have been performed between 2001 and 2005. Follow-up of 1.5T MRI was performed between 2006 and 2009 and from 2013 to 2017. During the second follow-up, a 7T brain MRI was added in a subsample. A detailed overview of the substudies is provided in Supplementary Table 5.

ARTEMIS, ARTErial calcifications of the Media and Intima in SMART (Second Manifestations of Arterial Disease)[6]; BEST, BEtter risk factor treatment with STructured agreement[9]; Brown Adipose Tissue[10]; DISH, Diffuse idiopathic skeletal hyperostosis[12]; IRIS, Internet-based vascular Risk factor Intervention and Self-management[15]; RULE, Risk management in Utrecht and Leiden Evaluation study[17]; SMART HEART[19]; SMART Inform[23]; SMART-JUNIOR[24]; SMART-MR[26]; ORACLE; Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk for a cardiovascular event[45]; SPAIN, Self-management of vascular Patients Activated by Internet and Nurses[49]; TEMPUS, The Evening versus Morning Polypill Utilization Study[50]; VENUS, Vascular prEvention by NUrses Study[52].

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1+3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6+11-12
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-11
Bias	9	Describe any efforts to address potential sources of bias	6-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	16-17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	16-17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Cardiovascular medicine, Diabetes and endocrinology, Epidemiology
Keywords:	Vascular medicine < INTERNAL MEDICINE, EPIDEMIOLOGY, PREVENTIVE MEDICINE, General diabetes < DIABETES & ENDOCRINOLOGY

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Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

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Abstract

Purpose: The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study is an ongoing prospective single-center cohort study with the aim to assess important determinants and the prognosis of cardiovascular disease progression. This article provides an update of the rationale, design, included patients, measurements and findings from the start in 1996 to date.

Participants: The UCC-SMART study includes patients aged 18-90 years referred to the University Medical Center (UMC) Utrecht, the Netherlands, for management of cardiovascular disease (CVD) or severe cardiovascular risk factors. Since September 1996, a total of 14,830 patients has been included. Upon inclusion, patients undergo a standardized screening program, including questionnaires, vital signs, laboratory measurements, an electrocardiogram, vascular ultrasound of carotid arteries and aorta, ankle-brachial index and ultrasound measurements of adipose tissue, kidney size and intima media thickness. Outcomes of interest are collected through annual questionnaires and adjudicated by an endpoint committee.

Findings to date: By May 2022, the included patients contributed to a total follow-up time of over 134,000 person-years. During follow-up, 2,259 patients suffered a vascular endpoint (including non-fatal myocardial infarction, non-fatal stroke and vascular death) and 2,794 all-cause deaths, 943 incident cases of diabetes and 2,139 incident cases of cancer were observed up until January 2020. The UCC-SMART cohort contributed to over 350 articles published in peer-reviewed journals, including prediction models recommended by the 2021 ESC CVD prevention guidelines.

Future plans: The UCC-SMART study guarantees an infrastructure for research in patients at high cardiovascular risk. The cohort will continue to include about 600 patients yearly and follow-up will be ongoing to ensure an up-to-date cohort in accordance with current health care and scientific knowledge. In the near future, UCC-SMART will be enriched by echocardiography, and a food frequency questionnaire at baseline enabling the assessment of associations between nutrition and CVD and diabetes.

Strengths and limitations

- The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial disease (UCC-SMART) study is an ongoing cohort of almost 15,000 patients with various manifestations of CVD and cardiovascular risk factors
- The UCC-SMART study covers a long follow-up duration and prospectively captures extensive outcome data in a high cardiovascular risk population
- The use of a standardized screening program that includes baseline characteristics, physical examination, laboratory testing and non-invasive imaging provides an extended resource of data for research on cardiovascular disease epidemiology
- Limitations of the cohort include measurement of the determinants only at baseline for the majority of patients, and the sparse information on socioeconomic status

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, causing around one-third of all deaths globally in 2019.[1] Atherosclerosis, the dominant cause of CVD, is fuelled by multiple mutually reinforcing and co-existing risk factors. Because of the progressive nature of atherosclerosis, patients with established CVD are at high risk of recurrent CVD and mortality.[2,3] Treatment of cardiovascular risk factors is known to markedly reduce the risk of new cardiovascular events.[4,5] Slowing down the process of atherosclerosis by timely identification and treatment of cardiovascular risk factors is therefore of the utmost importance.

In 1996, the Second Manifestations of Arterial Disease (SMART) cohort study was set up enrolling patients newly referred to the University Medical Center (UMC) Utrecht with clinically manifest CVD or marked risk factors for atherosclerosis. The study was designed with the aim of determining the prevalence of concomitant atherosclerotic disease and risk factors, as well as studying the incidence of future cardiovascular events and its predictors. Furthermore, the SMART study contributes to the complete and protocolized multidisciplinary care of these high risk patients by integrating a standardized set of measurements into usual patient care. The rationale and design of the study were previously published in 1999[6], with the study containing around 600 patients at that time. In 2018, the name of SMART changed to Utrecht Cardiovascular Cohort (UCC)-SMART. By now, 26 years after enrolment of the first patient, many baseline measurements have been added, substudies have been initiated, the study has been linked to national registries and the data have been used in several large (inter)national collaborations. At the same time, demographic and guideline changes have led to differences in the baseline characteristics and absolute risk of the patients included in the cohort. The aim of the current article is to provide an update on the rationale, design, included patients, baseline measurements and follow-up to date.

Cohort description

The UCC-SMART-study is a single-centre prospective cohort study, ongoing in both inclusion and follow-up, in which patient care and scientific research concerning cardiovascular risk factors and disease are integrated. This is depicted in Figure 1 and discussed in more detail in the sections below.

Study population

Starting from September 1996, patients aged 18 to 80 years referred to the UMC Utrecht, the Netherlands, for management of CVD or severe risk factors for CVD, have been recruited. Patients with cerebrovascular disease (CeVD), coronary artery disease (CAD), abdominal aortic aneurysm (AAA), peripheral artery disease (PAD), renal artery stenosis or one or more of the following cardiovascular risk factors, if rated as severe, are eligible to be included: hypertension, hyperlipidaemia, diabetes mellitus, renal insufficiency and a positive family medical history. Patients with a chronic human immunodeficiency virus infection as a cardiovascular risk-increasing condition or with hypertensive pregnancy disorders have been included since 2007 and 2012, respectively. Definitions of the inclusion criteria are listed in Supplementary Table 1. If patients have a history of multiple vascular events or risk factors, the referral reason (usually the most recent event) is listed as the qualifying inclusion diagnosis and any comorbidities are also registered. Pregnant women, patients with a short life expectancy and those insufficiently fluent in Dutch are not eligible.

Qualifying patients with CVD and/or risk factors listed above are recruited upon their first visit to the outpatient clinics and hospital wards of the departments of vascular medicine, internal medicine, nephrology, neurology, cardiology, cardiac surgery, obstetrics and vascular surgery. From 2021 onwards, the outpatient clinic of the department of geriatric medicine has been added to this list and the maximum age to be eligible for inclusion has been raised from 80 to 90 years old. In case of a recent cardiovascular event or intervention as the reason for inclusion, patients are invited after discharge from the hospital. In such cases, baseline measurements are generally performed more than 30 days after the acute event. All qualifying patients receive written and oral information about study goals and methods and are included only after written informed consent to use their data for study goals, the reporting of incidental findings to their treating physician, indefinite period storage of blood samples for future research and follow-up through annual questionnaires. In addition, participants can opt in or out to the following items: retrieval of data from regional and national registries, use of their data in research collaborations with for-profit organizations, use of coded data and laboratory samples for research outside the European Union and possible future requests to participate in follow-up studies of UCC-

SMART. When patients do not consent to any of these additional items, they can still partake in the UCC-SMART study.

Baseline data collection

The screening program consists of questionnaires, physical examination, an electrocardiogram (ECG), blood, urine and radiology testing. Except for the questionnaires, to be filled out before the hospital visit, the diagnostic components of the program take place during a one-day visit. An overview of all the variables available in UCC-SMART is provided in Supplementary Table 2. Some measurements have only been collected for or starting from a certain time period (Figure 2 and Supplementary Table 3).

Health questionnaires

The questionnaires collect data on medical history including established CVD (CeVD, CAD, AAA and PAD as described in Supplementary Table 4), cardiovascular risk factors, symptoms of CVD (based on the Rose Angina Questionnaire[7]), medication use, family history and lifestyle. For women, a question on the age at menopause (if applicable) is included as well. From 2002 onward, information on obstetric history has been collected including the number of full-term pregnancies, miscarriages (<14 weeks of gestation), preterm deliveries (14 – 32 weeks of gestation), birth weight and pregnancy complications. As of August 2022, a 160-item food frequency questionnaire (FFQ), validated in the Dutch population, has been added to the questionnaires.[8] Recently, these questionnaires have also been sent to people who were included in the UCC-SMART study before August 2022. The results of the questionnaires will follow in 2023.

Physical examination

Anthropometric measurements are taken by trained (research) nurses and include body height in centimetres, weight in kilograms and waist and hip circumference in centimetres with patients wearing light clothing and no shoes. Weight and length are used to calculate body mass index in kg/m^2. Waist circumference is measured horizontally at the midpoint between the iliac crest and lower costal margin and hip circumference is taken at the maximum horizontal circumference around the gluteal muscles.

The mean of two measurements is calculated. If the two measurements differ by >2 cm, a third is taken and the mean of the closest two is calculated.

From 1996 up until 1999, office blood pressure was measured using a semiautomatic oscillometric device (Omega 1400; Invivo Research Laboratories Inc., Broken Arrow, OK, USA) every 4 minutes for a total of 25 minutes at the right brachial artery in supine position and the mean systolic (SBP) and diastolic blood pressure (DBP) were calculated. From April 1999 until 2015, using a non-random sphygmomanometer (Iso-Stabil 5; Speidel & Keller, Jungingen, Germany), 3 simultaneous measurements with an interval of 30 seconds were taken at both upper arms in upright position and the SBP and DBP of the last two measurements were calculated from the arm yielding the highest values. From 2015 onward, office blood pressure has been measured using an automatic oscillometric device (Microlife WatchBP Office AFIB; Microlife Corp, Widnau, Switzerland). The measurement is performed unattended, in triplicate with an interval of 30 seconds, at both upper arms in supine position after the patient has rested for 30 seconds. The measurements on the arm with the highest blood pressure are recorded and the mean SBP and DBP are calculated.

In order to calculate the ankle-brachial index (ABI), blood pressure measurements are taken at rest at both upper arms every two minutes whilst the blood pressure is measured at both lower legs. For this, a Falcon Quad 8 MHz Doppler probe (Viasonix, Ra'anana, Israel) is used at a 60° angle at the dorsal pedal and posterior tibial arteries. The ABI is defined for each leg as the highest SBP at the ankle divided by the highest brachial SBP.

Laboratory testing

On the day of screening, a venous blood sample is drawn after at least eight hours of fasting to measure glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, creaIk gatinine, and haemoglobin. Laboratory measurements of fasting insulin, C-reactive protein (CRP) and thyroid stimulating hormone (TSH) were added in 2003 and glycated haemoglobin (HbA1c) and apolipoprotein B (apoB) were added in 2006. Lastly, measurement of lipoprotein(a) was added in June 2020.

Glucose is measured using an enzymatic colorimetric assay (Beckman Coulter, Brea, CA, USA). Total cholesterol and triglycerides are measured using a commercial enzymatic dry chemistry kit

(Johnson & Johnson, New Brunswick, NJ, USA) and HDL-C with a commercial enzymatic kit (Boehringer, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) is calculated using the Friedewald formula up to a plasma triglyceride level of 9 mmol/L.[9] Estimated glomerular filtration rate (eGFR) is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[10] Spectrophotometry (Abbott Diagnostics, Santa Clara, CA, USA) is used to determine haemoglobin levels. CRP in plasma was initially determined using immunonephelometry (Nephelometer Analyzer BN II, Siemens, The Hague, The Netherlands) and from 2013 in heparin plasma on an AU5811 routine chemistry analyser using turbidimetry (Beckman Coulter, Brea, CA, USA). These types of measurements are strongly correlated (r = 0.99) and can therefore be pooled for analyses.[11] Before November 2006, TSH was quantified using a third-generation assay on a Centaur analyser (Bayer, Germany). Since December 2006, TSH has been measured by a third-generation assay on a DXi analyser (Beckman Coulter, Woerden, The Netherlands). Correlation between the two analysers is r = 0.9991 (n = 69), with an intercept of –0.05 mU/L (95%CI -0.22-0.12) and a slope of 1.04 (95%CI 1.029–1.052) (range 0–95 mU/L). ApoB and lipoprotein(a) are measured using nephelometry (Atellica Neph 630, Siemens, The Hague, The Netherlands). A morning-void urine sample is collected to determine urine albumin, creatinine, sodium and potassium levels. Urine albumin is measured using immunoturbidimetric assays. Ion selective electrode (Beckman Coulter, Brea, CA, USA) is used to determine urine sodium and potassium levels. DNA can be isolated from 10 mL of EDTA-augmented blood stored at -80° for genotyping.

Radiology testing

Non-invasive vascular imaging testing is performed by specially trained ultrasound technicians. Duplex examination of the carotid arteries is conducted to assess possible stenosis using peak systolic velocity measurements at the brachiocephalic trunk, carotid arteries (mid- and distal common, external and proximal and distal internal) and vertebral arteries (proximal and distal). Measurements are performed using an EPIQ-7 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands). In case of abnormal signals and/or retrograde flow in the vertebral arteries, the proximal subclavian arteries are evaluated in search of severe stenosis or occlusion. For research purposes, intima-media-thickness

(IMT) of the carotid arteries is measured using a linear array transducer. With the patient lying down and the head turned 45° away from the side investigated, the ultrasound frame yielding an optimal longitudinal picture of the common carotid arterial wall is frozen at the time of the R-peak of ECG recording. Over a length of 1 cm starting from the carotid bulb towards proximal direction, the arterial wall thickness is measured from the lumen-intima interface to the media-adventitia interface. The mean of measurements in anterolateral, lateral and posterolateral direction is calculated.

Abdominal ultrasound examination is performed using the same ultrasound machine to obtain the maximal anterior-posterior diameter of the juxtarenal and infrarenal abdominal aorta and kidney length and volume. As of January 2000, visceral and subcutaneous adipose tissue measurements were added. The amount of subcutaneous fat is estimated by the distance from the linea alba to the skin. Visceral adipose tissue thickness is measured as the distance between the lumbar spine and the peritoneum. Measurements are taken at the end of a quiet expiration on a frozen ultrasound frame at three points on the imaginary transversal line halfway between the iliac crest and lower costal margin: at the midsternal line and 10 cm to the left and right on the transversal line. Each measurement is taken three times and then the mean of the measurements is recorded as the actual thickness. Ultrasonography has been proven a suitable technique to measure intra-abdominal adipose tissue with good reproducibility.[12,13] Moreover, from September 1998 on, a protocolized 12-lead resting ECG has been recorded.

In the near future, echocardiography will be added to the UCC-SMART program to facilitate research on the presence of heart failure at baseline. Echocardiography will be performed using a Philips Affiniti 70 ultrasound machine (Philips Medical Systems, Andover, MA, USA) by using a specific protocol involving 2-dimensional (2D), M-mode, Doppler, tissue Doppler and 2D speckle tracking (STE) imaging in accordance with the European Association of Cardiovascular Imaging 2016 recommendations for chamber quantification.[14] In particular, left ventricular dimensions will be measured in order to calculate the left ventricular mass index.[15] Left ventricular ejection fraction will be assessed quantitatively, preferably with automated three-dimensional imaging or alternatively with the Simpsons biplane method. Left atrial maximal volume and right ventricular dimensions and function will be measured as recommended.[14] Multiple parameters of left ventricular diastolic function will be

assessed, including pulsed-wave Doppler of the mitral inflow and tissue Doppler imaging of the mitral annulus motion. Left ventricular diastolic function will be evaluated according to current diagnostic algorithms.[16] A minimal of three sequential complexes will be recorded. Standard image analysis will then be performed off-line in accordance with clinical guidelines using Philips IntelliSpace Cardiovascular software and will include 2D STE analysis of the left ventricle and left atrium.

Treatment recommendation

After completion of the screening, the findings are assessed by a multidisciplinary team of two medical specialists (internist, cardiologist, neurologist or vascular surgeon). A treatment recommendation is formulated based on current applicable guidelines, according to which patients are already treated by their general practitioner or medical specialist. The screening results and treatment recommendation are reported in a medical letter which is sent to the treating specialist and general practitioner. Patients receive a summary of relevant findings and recommendations.

Incidental medical findings during the screening are reported to one of the study physicians and if needed, discussed with specialists from the multidisciplinary team. The findings are added to the medical record and sent to the treating specialist or general practitioner for further action.

Follow-up

Patients receive annual questionnaires with questions on hospital admissions and outpatient clinic visits, regardless of whether they are still under the care of the UMC Utrecht. In case patients no longer wish to complete the questionnaires, they are asked if they consent to collection of information from their general practitioner. When the replies indicate possible outcome events, additional information is collected through hospital discharge letters and relevant laboratory and radiology examinations. Clinical events of interest include stroke, myocardial infarction, heart failure, AAA rupture, renal insufficiency, vascular interventions, bleeding, diabetes and vascular and non-vascular mortality as defined in Supplementary Table 5. Incident type 2 diabetes has been assessed since July 2006. To assess incident diabetes between 1996 and 2006, a questionnaire was sent to all patients without diabetes at baseline who were included before July 2006. Incident heart failure has been assessed since October 2011. Three

members from the endpoint committee independently judge reported events. The endpoint committee consists of medical specialists from the recruiting departments. If all three physicians judge differently, the event is discussed with two other physicians from the committee to reach consensus. Secondary outcomes are adjudicated by trained research nurses. As of 2021, diagnoses of dementia and mild cognitive impairment have been added to the annual questionnaire as self-reported diagnoses.

Data quality and management

Data collected in the UCC-SMART program is stored in the electronic medical record of the UMC Utrecht. Blood samples (serum, citrate plasma, EDTA plasma and erythrocytes concentrate aliquots) are stored at -80°C according to the Biobanks Regulations to be found at the UMC Utrecht website (https://www.umcutrecht.nl/nl/centrale-biobank). The central biobank of the UMC Utrecht is ISO9001 certified (certificate number 2175592). Release of material for future research is reviewed by the UMC Utrecht Biobanks Review Committee.

Recorded data is downloaded from the electronic medical record and pseudonymized by the data manager who holds the encryption key, only to be accessed after permission of the principal investigator. The UCC-SMART study group periodically performs quality checks for missing values and inconsistencies compared to source documents, or values outside of the range deemed likely.

Patient and public involvement

Patients were not involved in the study design. Their experiences of burden and required time are considered in the implementation of new components in the program. Relevant findings of the UCC-SMART screening program and corresponding recommendations are sent to the patients. In addition, patients regularly receive a newsletter containing up-to-date facts and figures of the UCC-SMART study and substudies and findings of publications using UCC-SMART data. The UMC Utrecht policies are in line with open science, for opening up the research agenda to societal stakeholders, open research data and open access publications.

Linkage to other registries

Data in the UCC-SMART study can be enriched by collecting data from various registries and organizations, for example to obtain additional information on outcomes and medication use. Some examples of these linkages are described below.

Netherlands Cancer Registry

CVD and cancer share many risk factors and pathophysiological mechanisms, including body fat distribution, diet, physical inactivity, smoking, chronic inflammation burden, and oxidative stress.[17] To evaluate the relation between several cardiovascular risk factors and the risk of cancer, the UCC-SMART cohort has been linked to the *Netherlands Comprehensive Cancer Organisation* (IKNL), a nationwide registry receiving notifications of all new cancer diagnoses. By linking the cohort to the national cancer registry repeatedly, with the most recent linkage taking place in 2022, information on cancer incidence and details of cancer types and histopathology was obtained.

Central Agency for Statistics (CBS) Netherlands

The UCC-SMART cohort can be linked to the *Central Agency for Statistics* (CBS), also known as *Statistic Netherlands*, which contains data on ICD-10 coded diagnoses and hospital admissions since 1996. This allows for, amongst others, collection of endpoints that are not regularly collected in UCC-SMART or have been collected from a later time point, such as heart failure diagnoses. The CBS collects data from all hospitals in the Netherlands and from general practitioner practices affiliated with 'Nivel' healthcare registration, which are a good reflection of the Dutch population.[18,19]

Utrecht Patient Oriented Database (UPOD)

The UCC-SMART cohort can be linked to UPOD[20], a database containing electronic patient data from routine clinical care in the UMC Utrecht. This database has been collecting patient characteristics, medication orders, laboratory test results, hospital discharge diagnoses and medical procedures since 2000, enabling the addition of baseline and follow-up information to the UCC-SMART study.

Consortia

The data collected in UCC-SMART is added to several consortia such as a genetics consortium (GENIUS-CHD[21] on genetics of subsequent coronary heart disease), the Netherlands consortium of dementia cohorts and the Chronic Kidney Disease Prognosis Consortium[22].

Dutch Foundation for Pharmaceutical Statistics

A future plan is to obtain information on medication use during follow-up by linking the UCC-SMART cohort to the *Dutch Foundation for Pharmaceutical Statistics* (*Stichting Farmaceutische Kengetallen* [SFK]). This foundation obtains data from over 97% of the community pharmacies in the Netherlands.[23]

Substudies

SMART-2

Patients with a history of CVD or diabetes are invited to participate in the SMART-2 substudy. In this study, the baseline measurements of UCC-SMART are repeated in order to investigate the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment. Until May 2022, 2,313 patients have participated in SMART-2 after a median of 9.9 years (IQR 9.2 – 10.8) since their inclusion in UCC-SMART. As with UCC-SMART, the findings of SMART-2 with an accompanying treatment recommendation are communicated to the patient, his or her treating medical specialist and general practitioner.

SMART-ORACLE

SMART-ORACLE aims to determine the additional value of contrast-enhanced computed tomography (CT) of the coronary and carotid arteries on top of traditional cardiovascular risk factors in patients with a history of CVD, diabetes or hypertension.[24] The study is still ongoing and has currently been conducted in 1,252 patients.

SMART-MR and SMART Medea

SMART-MR and SMART Medea target the investigation of brain changes in patients with CVD using 1.5T magnetic resonance imaging (MRI) (and 7T MRI in a subset of patients).[25,26] This study was conducted in 1,309 patients. Amongst others, measurements of the total cerebral blood flow have been performed and characteristics of white matter lesions and microbleeds have been mapped.

Athero-Express

In May 2022, the Athero-Express biobank and study cohort have been incorporated into the UCC-SMART study.[27] The objective of Athero-Express is to investigate the value of plaque characteristics in relation to long term cardiovascular events. This ongoing prospective study, initiated in April 2002, includes patients undergoing femoral or carotid endarterectomy. During surgery, the atherosclerotic plaque is harvested and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells.

Other substudies

Several other substudies have been carried out within the UCC-SMART cohort, providing additional information and parameters for subsets of patients (Supplementary Table 6). As part of **SMART-Junior**, additional questionnaires have been sent to 4,270 patients in order to investigate the presence of cardiovascular risk factors and CVD in their offspring.[28] In **DISH**, diffuse idiopathic skeletal hyperostosis was scored on chest X-rays of 4,791 patients, performed in the context of health care, using the Resnick criteria.[29,30] **SMART-HEART** aimed to detect patient characteristics related to the development of left ventricle hypertrophy using 1.5T cardiac MRI in 536 patients with hypertension, but free of known coronary or valvular disease.[31] In order to determine whether intima and media calcification differ in their associated CVD risks and to elucidate which risk factors lead to the development of those types of calcification, CT-scans of the femoral head to the feet have been performed in 520 patients as part of **ARTEMIS**.[32] The aim of the **Small aneurysms trial** was to estimate the overall rupture rates of small AAAs and to investigate demographic characteristics and cardiovascular risk factors for association with AAA growth using ultrasound scanning of the aorta in 230 patients with an initial AAA diameter of 30-55 mm.[33] In **Brown adipose tissue**, supraclavicular

and subcutaneous adipose tissue fat-signal-fractions were assessed in 50 patients with CVD using 1.5T water-fat MRI.[34] **SPAIN** evaluated the feasibility of a web-based coaching program for vascular risk factor treatment, described the patterns of use of this program and measured changes in risk factors in 50 patients with CVD.[35] **RULE** investigated the impact of the UCC-SMART study compared to usual care on cardiovascular risk factors in 604 patients with CVD or type 2 diabetes.[36]

A few clinical trials have been conducted within the UCC-SMART study. **TEMPUS** was a randomized crossover trial in 78 patients that investigated the effects of a cardiovascular polypill on LDL-C, ambulatory blood pressure and adherence as compared to the administration of the individual, identically dosed components of the polypill.[37] **SMART-Inform** was a three-armed randomized controlled trial (RCT) in 303 patients using a statin with CVD.[38] The aim was to determine whether communicating personalized statin therapy-effects leads to lower decisional conflicts associated with statin use compared with standardized (non-personalized) therapy-effects. **BEST** was an RCT investigating whether a clearly written agreement on risk factor management between general practitioners and hospitals improved the vascular risk profile of 197 patients compared with usual care.[39] Another RCT was **VENUS**, which included 236 patients with ≥2 modifiable risk factors, investigating whether risk factor management in the hospital improved with nurse practitioner care on top of usual care compared with usual care alone.[40] Lastly, **IRIS** was an RCT that evaluated whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in 330 patients with CVD.[41] A timeline showing the different substudies is presented in Supplementary Figure 1.

Characteristics of the study population

By May 2022, a total of 14,830 patients has been included (Figure 3). Of those, 3,294 patients died and 89% (n = 10,219) of the surviving patients are still being followed up. Reasons for follow-up to end in surviving patients include withdrawal of participation in further follow-up (80%) or being unreachable for further questionnaires (20%). The median follow-up time of these patients without complete follow-up data is 7.4 years (IQR 3.9 - 11.4). Figure 4 shows the numbers and distribution of the reasons for inclusion. The most common inclusion diagnosis was CAD (n = 4,729), followed by hypertension (n =

2,344) and CeVD (n = 2,276). PAD was the enrolment diagnosis in 1,173 patients and AAA in 369 patients. Hyperlipidaemia was the inclusion diagnosis in 1,433 patients and diabetes mellitus in 730 patients.

Patient characteristics, medication use and measurements at baseline are listed in Table 1. This table is stratified for medical history at baseline, with the items of medical history either being the inclusion diagnosis or a comorbidity. This means that patients may fall within more than one category as listed in Table 1. The majority of patients included in the cohort is male (65%), especially among the subgroup of patients with established CVD (73% male). The mean age of the total population is 56.8 ±12.5 years. In total, 2,608 individuals (18%) had diabetes and 9,633 individuals (65%) had established CVD at baseline. Of these CVD patients, 1,399 (15%) had polyvascular disease, i.e. multiple vascular beds (cerebral, coronary, abdominal aorta or lower extremity) being affected. The proportion of missing variables is less than 3% for all variables, except for adipose tissue measurements on ultrasound (3.6%), albuminuria (4.7%) and CRP level (9.0%). Vascular screening indicated significant carotid artery stenosis (>50% stenosis) in 526 (4%) patients, AAA in 188 (1%) patients and low ABI (≤0.9) in 829 (6%) patients who were not previously diagnosed with CeVD, AAA or PAD, respectively. Of the 3,095 patients with established CVD included between 2012 and 2022 (to account for applicable guidelines), 2,075 (67%) had a SBP <140 mmHg, 753 (25%) had an LDL-C ≤1.8 mmol/L and 2,737 patients (88%) were using antithrombotic agents at baseline. Baseline characteristics of patients with complete follow-up data available were comparable to the characteristics of patients who withdrew from or were unreachable for further follow-up (Supplementary Table 7).

Table 1. Baseline characteristics stratified for medical history

	History of CVD				Cardiovascular risk factors			
	Cerebrovascular disease	Coronary artery disease	Abdominal aortic aneurysm	Peripheral artery disease	Hypertension	Hyperlipidaemia	Diabetes mellitus (type 1 + 2)	Renal insufficiency
Number of patients	2801	5999	767	1646	8228	12972	2608	1118
Medical history[a]								
Cerebrovascular disease	2801 (100)	553 (9)	117 (15)	209 (13)	1655 (20)	2492 (19)	442 (17)	248 (22)
Coronary artery disease	553 (20)	5999 (100)	322 (42)	433 (26)	3192 (39)	5762 (44)	1131 (43)	497 (44)
Abdominal aortic aneurysm	117 (4)	322 (5)	767 (100)	134 (8)	466 (6)	693 (5)	114 (4)	151 (14)
Peripheral artery disease	209 (7)	433 (7)	134 (17)	1646 (100)	906 (11)	1492 (12)	328 (13)	205 (18)
Hypertension	1655 (60)	3192 (54)	466 (62)	906 (57)	8228 (100)	7285 (57)	1736 (68)	902 (82)
Hyperlipidaemia	2492 (90)	5762 (96)	693 (91)	1492 (92)	7285 (90)	12972 (100)	2275 (88)	1016 (92)
Diabetes mellitus	442 (16)	1131 (19)	114 (15)	328 (20)	1736 (21)	2275 (18)	2608 (100)	365 (33)
Health questionnaire								
Age (years)	60 ± 11	62 ± 10	65 ± 9	60 ± 11	59 ± 12	58 ± 12	59 ± 12	63 ± 11
Male sex	1744 (62)	4849 (81)	636 (83)	1100 (67)	5174 (63)	8699 (67)	1815 (70)	911 (82)
Previous or current smoking	2106 (76)	4511 (75)	661 (86)	1473 (90)	5697 (69)	9265 (72)	1865 (72)	847 (76)
Packyears in (former) smokers	20.2 (9.4 – 35.1)	20.7 (9.4 – 33.6)	28.0 (13.8 – 42.3)	27.9 (14.6 – 40.6)	18.9 (8.3 – 33.3)	18.9 (8.8 – 32.5)	21.0 (9.5 – 36.2)	22.8 (10.5 – 37.8)
Current alcohol use	1484 (53)	3641 (61)	368 (48)	770 (47)	4787 (58)	7584 (59)	1229 (47)	511 (46)
Highest level of education								
- Primary/secondary school	554 (31)	1248 (29)	128 (34)	315 (40)	1764 (31)	2569 (29)	553 (35)	210 (32)
- Vocational school	631 (35)	1466 (35)	117 (31)	236 (30)	1824 (32)	2891 (33)	519 (33)	223 (34)
- University (of applied science)	560 (31)	1415 (33)	125 (33)	196 (25)	1914 (34)	3031 (35)	422 (27)	194 (30)
Exercise (METh/week)	0.0 (0.0 – 10.5)	0.0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)	0 (0.0 – 11.0)	0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)
Medication use								
Lipid-lowering therapy	1682 (60)	4995 (83)	417 (54)	849 (52)	4720 (57)	8253 (64)	1664 (64)	678 (61)
Antihypertensive therapy	1724 (62)	5409 (90)	545 (71)	912 (55)	7130 (87)	9080 (70)	1980 (76)	965 (86)

Platelet inhibitors	2062 (74)	5263 (88)	450 (59)	987 (60)	4532 (55)	7694 (59)	1453 (56)	640 (57)
Oral anticoagulant therapy	311 (11)	821 (14)	123 (16)	234 (14)	743 (9)	1188 (9)	271 (10)	182 (16)
Glucose lowering therapy	287 (10)	757 (13)	67 (9)	189 (11)	1176 (14)	1475 (11)	1621 (62)	216 (19)
Anthropometric measurements								
Systolic blood pressure (mmHg)	141 ± 22	137 ± 20	142 ± 20	144 ± 21	150 ± 23	140 ± 22	144 ± 21	150 ± 24
Diastolic blood pressure (mmHg)	82 ± 12	80 ± 11	83 ± 12	81 ± 11	87 ± 14	83 ± 13	82 ± 12	85 ± 14
Ankle-brachial index ≤0.9	398 (14)	680 (11)	165 (22)	1063 (66)	1195 (15)	1751 (14)	434 (17)	283 (26)
Body mass index (kg/m^2)	26.6 ± 4.2	27.3 ± 4.0	26.4 ± 3.8	26.3 ± 4.3	27.6 ± 4.6	27.0 ± 4.3	28.7 ± 5.0	27 ± 4
Waist circumference (cm)	93.7 ± 12.9	97.4 ± 11.6	97.6 ± 12.1	95.0 ± 12.5	96.4 ± 13.3	95.1 ± 12.7	100.7 ± 13.7	98.9 ± 12.5
Hip circumference (cm)	103.6 ± 8.7	104.2 ± 7.6	103.8 ± 7.8	103.0 ± 8.7	105.1 ± 9.2	104.1 ± 8.5	106.3 ± 9.8	104.4 ± 8.4
Visceral fat (cm)	8.6 ± 2.6	9.3 ± 2.6	9.5 ± 2.6	9.2 ± 2.7	9.0 ± 2.8	8.8 ± 2.7	10.1 ± 2.9	9.9 ± 2.8
Subcutaneous fat (cm)	2.5 ± 1.2	2.4 ± 1.2	2.2 ± 1.1	2.4 ± 1.5	2.6 ± 1.4	2.5 ± 1.3	2.4 ± 1.4	2.2 ± 1.4
Carotid artery stenosis	652 (24)	443 (8)	84 (11)	255 (16)	77 (10)	1104 (9)	283 (11)	181 (16)
cIMT (mm)	0.9 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)
Aortic aneurysm	81 (3)	244 (4)	307 (41)	72 (4)	289 (4)	458 (4)	61 (2)	108 (10)
Kidney size (cm)	11.1 ± 1.0	11.3 ± 1.0	11.3 ± 1.0	11.2 ± 1.1	11.2 ± 1.0	11.2 ± 1.0	11.5 ± 1.0	10.9 ± 1.3
Laboratory measurements								
Haemoglobin (mmol/L)	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.9 ± 0.9	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.5 ± 1.0
Total cholesterol (mmol/L)	4.9 ± 1.2	4.5 ± 1.1	5.1 ± 1.3	5.3 ± 1.3	5.0 ± 1.3	5.1 ± 1.4	4.7 ± 1.3	5.0 ± 1.4
LDL-C (mmol/L)	2.9 ± 1.1	2.6 ± 0.9	3.1 ± 1.1	3.2 ± 1.1	2.9 ± 1.1	3.1 ± 1.2	2.7 ± 1.0	2.9 ± 1.1
HDL-C (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Apolipoprotein B (g/L)	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
Triglycerides (mmol/L)	1.3 (0.9 – 1.9)	1.4 (1.0 – 2.0)	1.5 (1.1 – 2.1)	1.5 (1.1 – 2.3)	1.4 (1.0 – 2.1)	1.4 (1.0 – 2.1)	1.6 (1.1 – 2.4)	1.7 (1.2 – 2.5)
HbA1c (mmol/mol)	38 (36 – 42)	39 (36 – 43)	39 (36 – 43)	40 (37 – 48)	39 (36 – 44)	38 (36 – 43)	52 (45 – 62)	41 (37 – 52)
Fasting glucose (mmol/L)	5.7 (5.3 – 6.3)	5.9 (5.4 – 6.6)	5.8 (5.4 – 6.5)	5.8 (5.3 – 6.7)	5.8 (5.4 – 6.6)	5.8 (5.3 – 6.4)	8.1 (6.9 – 10.0)	6.0 (5.5 – 7.2)
eGFR (mL/min/1.73 m^2)	48 ± 40	63 ± 34	58 ± 32	51 ± 40	49 ± 40	54 ± 40	55 ± 41	40 ± 26
Albuminuria (mg/L)	10.0 (6.0 – 24.1)	9.0 (6.0 – 20.0)	12.9 (8.0 – 39.9)	11.0 (7.0 – 32.0)	11.0 (7.0 – 29.0)	9.0 (6.0 – 22.0)	14.0 (8.0 – 41.0)	82.0 (16.0 – 257.6)
CRP (mg/L)	2.1 (1.0 – 4.5)	1.9 (1.0 – 4.0)	3.3 (1.6 – 6.9)	3.1 (1.4 – 6.3)	2.2 (1.0 – 4.7)	2.0 (1.0 – 4.2)	2.4 (1.1 – 5.1)	3.2 (1.5 – 7.2)
TSH (mU/L)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.8 (1.2 – 2.6)	1.8 (1.2 – 2.5)	1.9 (1.3 – 2.7)	1.8 (1.3 – 2.7)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

[a] Based on inclusion diagnosis, items of the health questionnaire and/or measurements at baseline:

Cerebrovascular disease: history of stroke, carotid surgery or percutaneous transluminal angioplasty;

Coronary artery disease: history of myocardial infarction, cardiac arrest, coronary bypass surgery or percutaneous transluminal coronary angioplasty;

Abdominal aortic aneurysm: history of abdominal aortic aneurysm, transluminal or surgical treatment of abdominal aortic aneurysm;

Peripheral artery disease: history of amputation of (part of) lower limb, lower limb peripheral artery surgery or percutaneous transluminal angioplasty;

Hypertension: treatment with antihypertensive drugs or blood pressure ≥160/95 mmHg at baseline measurement;

Hyperlipidaemia: treatment with lipid-lowering agents, total cholesterol ≥5 mmol/L or LDL-cholesterol ≥3.2 mmol/L at baseline measurement;

Diabetes mellitus: treatment with antidiabetic agents, fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥11.1 mmol/L at baseline measurement;

Renal insufficiency: creatinine >120 mmol/L and/or microprotein/creatinine ratio in urine >20.

Cut-off values applied at the start of UCC-SMART study, please note target values have changed over time and continuous variable are available.

cIMT, carotid intima media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; TSH: thyroid stimulation hormone.

Findings to date

The findings of this section are reported for patients included up to January 2020 (n = 13,898), because the collection and processing of outcome events has been completed up until this date. These patients contributed to a total follow-up time of 134,439 person-years. Median follow-up time was 9.2 years (interquartile range 4.8 – 14.1 years). During follow-up, 2,259 (16%) patients suffered a first combined major cardiovascular endpoint (including non-fatal myocardial infarction, non-fatal stroke or cardiovascular death). Furthermore, there were 943 (7%) cases of incident diabetes, 105 (1%) cases of end-stage kidney disease, 161 (1%) cases of heart failure and 434 (3%) cases of major bleeding. A total of 3,264 (23%) patients underwent a vascular intervention during follow-up. Of patients with established CVD, 1,906 patients (21%) suffered the combined vascular endpoint mentioned above as subsequent event, whereas 353 patients (7%) with severe risk factors without prior CVD experienced this combined outcome as their first ever event. Of the 2,450 individuals with diabetes at baseline, 568 (23%) individuals suffered the combined vascular endpoint. Corresponding incidence rates are 21.2 per 1000 person years for patients with established CVD and 8.2 per 1000 person years for patients without a history of CVD. Numbers and observed incidence rates of all specific outcome events of interest are listed in Table 2. Through linkage with the Dutch National Cancer Registry, a total of 2,139 patients (15%) was diagnosed with cancer during follow-up. This includes 414 diagnoses of lung cancer, 354 of prostate cancer, 294 of intestinal cancer and 163 of breast cancer as most common diagnoses.

456 *Table 2. Number and incidence rates of outcome events from 1996 to 2020*

Outcome event	Number of first events	Person-years of follow-up	Incidence rate per 1,000 person-years
Non-fatal stroke	613	131,684	4.66
Ischemic stroke	502	132,042	3.80
Haemorrhagic infarction	20	134,362	0.15
Intracerebral haemorrhage	66	134,285	0.49
Subarachnoid haemorrhage	17	134,322	0.13
Type not determined	8	134,430	0.06
Retinal syndromes	16	134,338	0.12
Infarction	13	134,353	0.10
Haemorrhage	3	134,424	0.02
Non-fatal myocardial infarction	793	130,065	6.10
Heart failure	161	134,075	1.20
Systolic heart failure, due to	115	134,203	0.86
coronary disease	85	134,266	0.63
valve disorders	11	134,425	0.08
other causes	19	134,390	0.14
HFpEF, due to	46	134,311	0.34
coronary disease	15	134,390	0.11
valve disorders	8	134,418	0.06
other causes	23	134,381	0.17
Non-fatal rupture AAA	5	139,895	0.04
End-stage kidney disease	105	134,118	0.78
Vascular intervention	3,264	110,154	29.6
Heart	1606	121,936	13.2
Carotid or intracranial arteries	240	132,611	1.81
Aorta	439	131,553	3.34
Peripheral arteries	953	127,914	7.45
Renal artery	62	133,970	0.46
Major bleeding			
ISTH major bleeding	434	129,804	3.34
BARC 3 or 5 bleeding	457	132,497	3.45
Incident diabetes	943	124,310	7.59
Type 1 diabetes	1	131,417	0.01
Type 2 diabetes	942	124,330	7.58

Vascular mortality	1,267	134,439	9.42
Fatal cerebral infarction	85		0.63
Fatal cerebral haemorrhage	65		0.48
Fatal stroke – type not determined	21		0.16
Fatal myocardial infarction	63		0.47
Fatal heart failure	198		1.47
Fatal rupture AAA	29		0.22
Sudden death	401		2.98
Other	405		3.01
Non-vascular mortality	1317	134,439	9.80
Fatal malignancy	800		5.95
Fatal infection	169		1.26
Unnatural death	58		0.43
Other	290		2.16
All-cause mortality	2,794	134,439	20.78
Malignancy[a]	2,139	127,514	16.77
Lung	414		3.25
Prostate	354		2.78
Breast	163		1.28
Intestinal	294		2.31
Other	914		7.17

[a] Other subtypes of cancer in the dataset include cancer of the lip, oral cavity or pharynx; oesophagus; stomach; liver, intrahepatic bile ducts, or gallbladder; pancreas; respiratory tract; thymus; bone or articular cartilage of limb; melanoma; mesothelial or soft tissue; vulva or vagina; cervix uteri or corpus uteri; ovary; penis or testes; kidney, renal pelvis or ureter; bladder; eye, brain, and other parts of the central nervous system; thyroid gland; lymphatic/hematopoietic.

AAA, abdominal aortic aneurysm; BARC, Bleeding Academic Research Consortium; HFpEF, heart failure with preserved ejection fraction; ISTH, International Society on Thrombosis and Haemostasis.

The large database of observational data has been used for over 350 etiological and prognostic studies so far, and the coverage of a wide age range and long follow-up provides opportunity to develop and validate prediction models. This has been done with the SMART risk score[42,43], the SMART-REACH lifetime model for patients with previous CVD[3] and the DIAL lifetime model[44] for patients with type 2 diabetes (to be found at https://u-prevent.com and the ESC 'CVD risk calculation'-app). These estimates serve clinical practice by providing insight into risk and thus supporting patient education and shared decision making. Moreover, routinely collection of patient data allows for embedding clinical trials within the cohort, as has been done with, amongst others, TEMPUS[37] and SMART-Inform[38].

The vascular screening in the UCC-SMART study is a structured uniform program to detect risk factors and asymptomatic atherosclerosis and provides a basis for optimizing treatment of high-risk patients. In a previous study comparing the UCC-SMART screening program to usual care in another university hospital in the Netherlands, a beneficial effect of the screening program on SBP and LDL-C was seen.[36] Previous research on screening programs in the general population shows improvement of cardiovascular risk factors and detection of patients at risk, but conflicting results are found on mortality and cardiovascular events.[2,45] In a population at risk (e.g. with hypertension or diabetes), the beneficial effect of cardiovascular screening is more pronounced.[2,46] In addition, a higher baseline achievement of secondary prevention targets is associated with improved cardiovascular health outcomes in patients with established CVD and type 2 diabetes.[47]

Strengths and limitations

The UCC-SMART study is a unique ongoing prospective cohort study in over 14,000 patients with a history of various manifestations of CVD or severe cardiovascular risk factors, providing a large up-to-date cohort of a population at high cardiovascular risk. Collecting diverse outcome events in this population allows for research on risk factors for different manifestations of CVD and incident diabetes. Linkage to multiple registries facilitates the investigation of relationships between cardiovascular risk factors and diseases and other conditions such as cancer and dementia. By the integration of health care and scientific research, patient care becomes more complete and data already to be collected for patient

care is used to increase knowledge of CVD, whilst the additive burden for participating patients is limited.

The main strengths of the UCC-SMART cohort include the large size, its capture of a high-risk population with various CVD manifestations and risk factors with few exclusion criteria, the use of a standardized diagnostic protocol, the long follow-up duration and the comprehensive capture of a wide range of data. Because inclusion of patients is still ongoing, the UCC-SMART cohort provides a good representation of the past and current population of patients at high cardiovascular risk. Due to the high risk study population, the prevalence and incidence of the main outcome variables are higher than in the general population, thereby increasing the power to study these outcomes. Furthermore, all outcome events are adjudicated independently by three physicians of the endpoint committee, reducing the risk of misclassification. The proportion of missing data is small, possibly explained by the protocolized screening program taking place in one day. The substudies provide additional information on specific cardiovascular risk factors (e.g. parental history of CVD[48], characteristics related to left ventricle hypertrophia[31], and the presence of diffuse idiopathic skeletal hyperostosis[49]), manifestations of atherosclerosis (e.g. brain changes on MRI[25] and cognitive decline[26]), and other important aspects in cardiovascular risk management (e.g. the effect of a cardiovascular polypill[50]).

Limitations also need to be considered. Due to the prospective observational design, for the majority of the patients, risk factors and medication use are only recorded at baseline and may have changed during follow-up. This could be reflected by the finding of this article that not all patients with CVD meet treatment goals for modifiable risk factors at baseline. Since patients are included several weeks to months after an index CVD event, risk factors are likely to be further optimized during this period after baseline examination. For a subset of patients with CVD or diabetes, a repeat of the baseline measurements after a median of 9.9 years is indeed available, allowing for investigating the course of atherosclerosis over time. Furthermore, in 10.6% of the included patients, follow-up ended due to either withdrawal of participation in further follow-up (8.5%) or being unreachable for further questionnaires (2.1%). Yet, the median follow-up time for these patients is 7.4 years, so those patients still contribute to a fair amount of patient-years. In addition, because UCC-SMART is a single-center study in a university hospital, it can be disputed whether it represents the general high risk population and patients

with established CVD. The UMC Utrecht provides care to nationwide patients referred for complex and specialized care, but also to patients referred by general practitioners from the region. Patients included in UCC-SMART correspond to patients with severe cardiovascular risk factors or established CVD from the general population. As reflected by the inclusion criteria, the UCC-SMART study does not include patients requiring highly specialized care (including heart transplantation and rare causes of vascular disease). Lastly, except for information on education level, the database does not contain extensive information on socioeconomic status.

In conclusion, we have provided an updated extensive overview of the design of the UCC-SMART study as well as an overview of the findings to date. This underlines the value of the UCC-SMART study as a basis for contemporary and future epidemiologic research in CVD using a well-characterized high risk cardiovascular population with long-term follow-up. A future goal is to make the UCC-SMART data Findable, Accessible, Interoperable and Reusable (FAIR).[51]

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Contributors

F.L.J.V., J.W., S.H.J.H., M.C.C. and M.A.G.H. contributed to the conception and design of the work. M.A.G.H. and M.C.C. drafted the manuscript and contributed equally to this paper. M.C.C., M.A.G.H.,

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

The study is in accordance with the Helsinki declaration and the Good Clinical Practice guidelines, and is approved by the ethics committee of the UMC Utrecht in 1996, 2014 and 2022 (reference number 22-088).

Data availability statement

The UCC-SMART study group directs the academic focus of research using the UCC-SMART data and consists of members from both epidemiological and clinical cardiovascular research. Datasets are provided to interested researchers after approval of request by the UCC-SMART study group. Access to the data request module can be applied for via ucc-smart@umcutrecht.nl.

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Figure legends

Figure 1. Course of the UCC-SMART study

ECG, electrocardiogram; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease; UMC Utrecht, University Medical Centre Utrecht

Figure 2. Timeline of measurements collected for or starting from a certain period

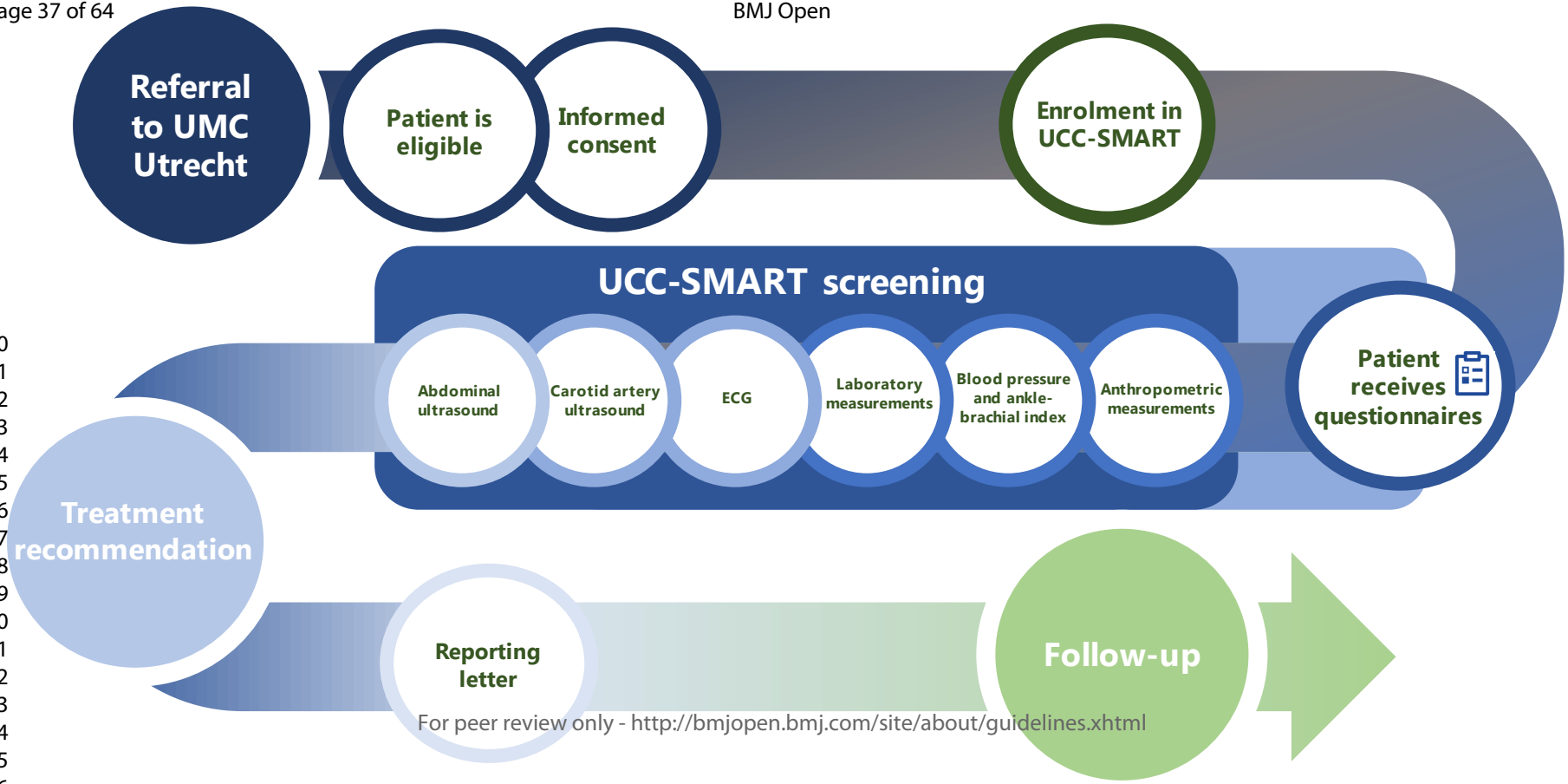
ACE, angiotensin converting enzyme; apoB, apolipoprotein B; CAC, coronary artery calcium; CRP, C-reactive protein; CT, computerized tomography; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; Lp(a), lipoprotein a; MRI, magnetic resonance imaging; T, Tesla; TSH, thyroid stimulating hormone

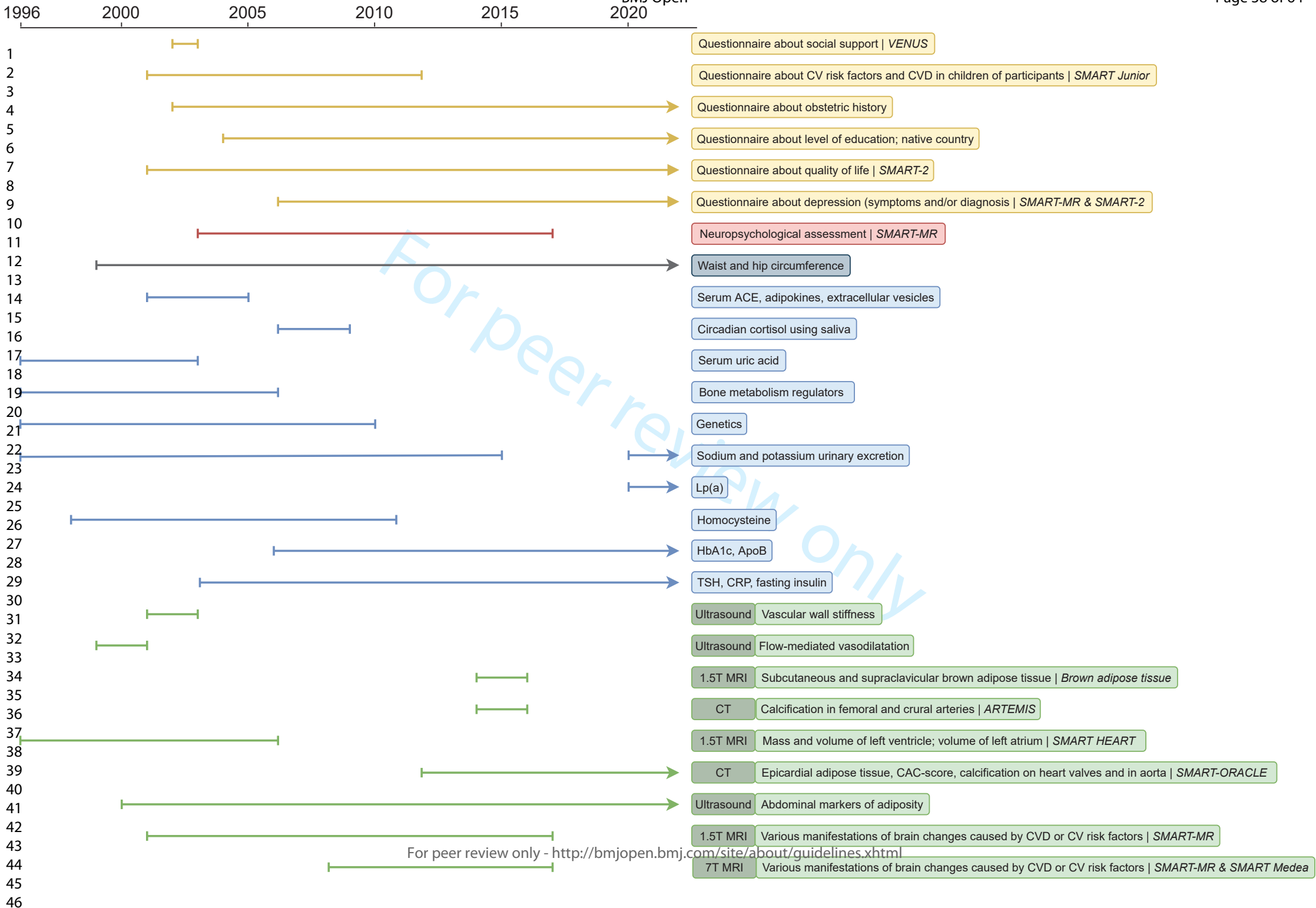
Figure 3. Cumulative number of patients over time

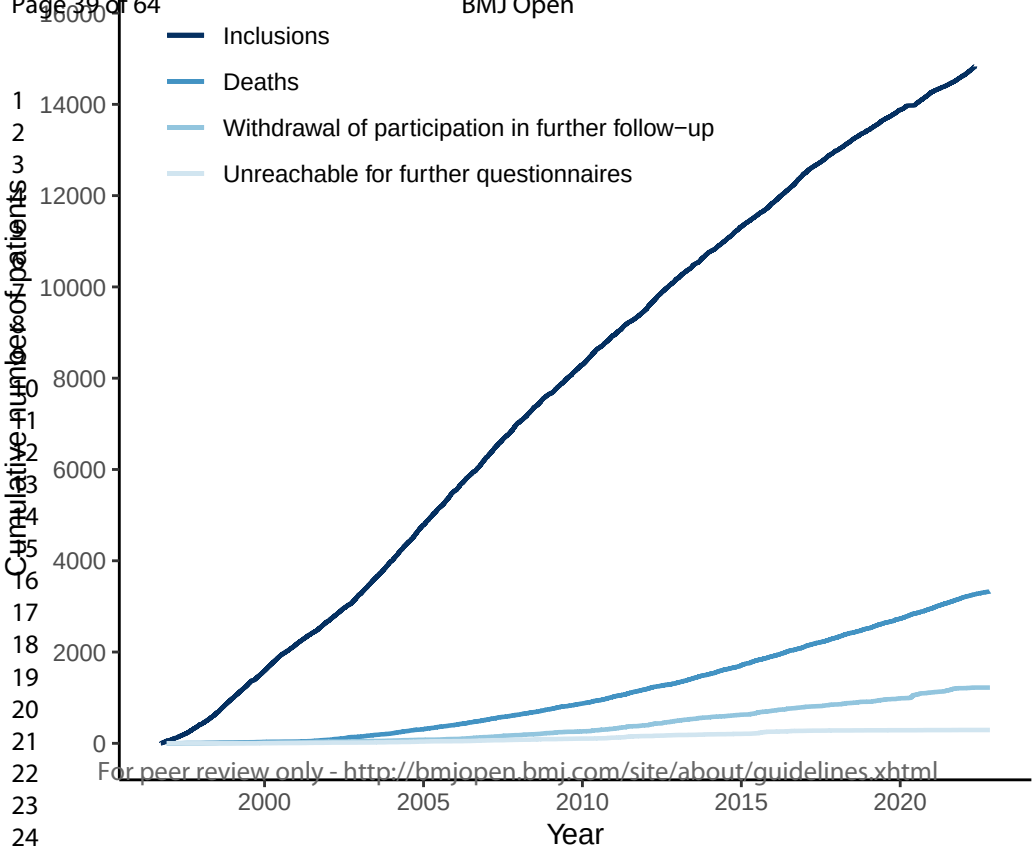
Inclusion in the UCC-SMART study started in September 1996.

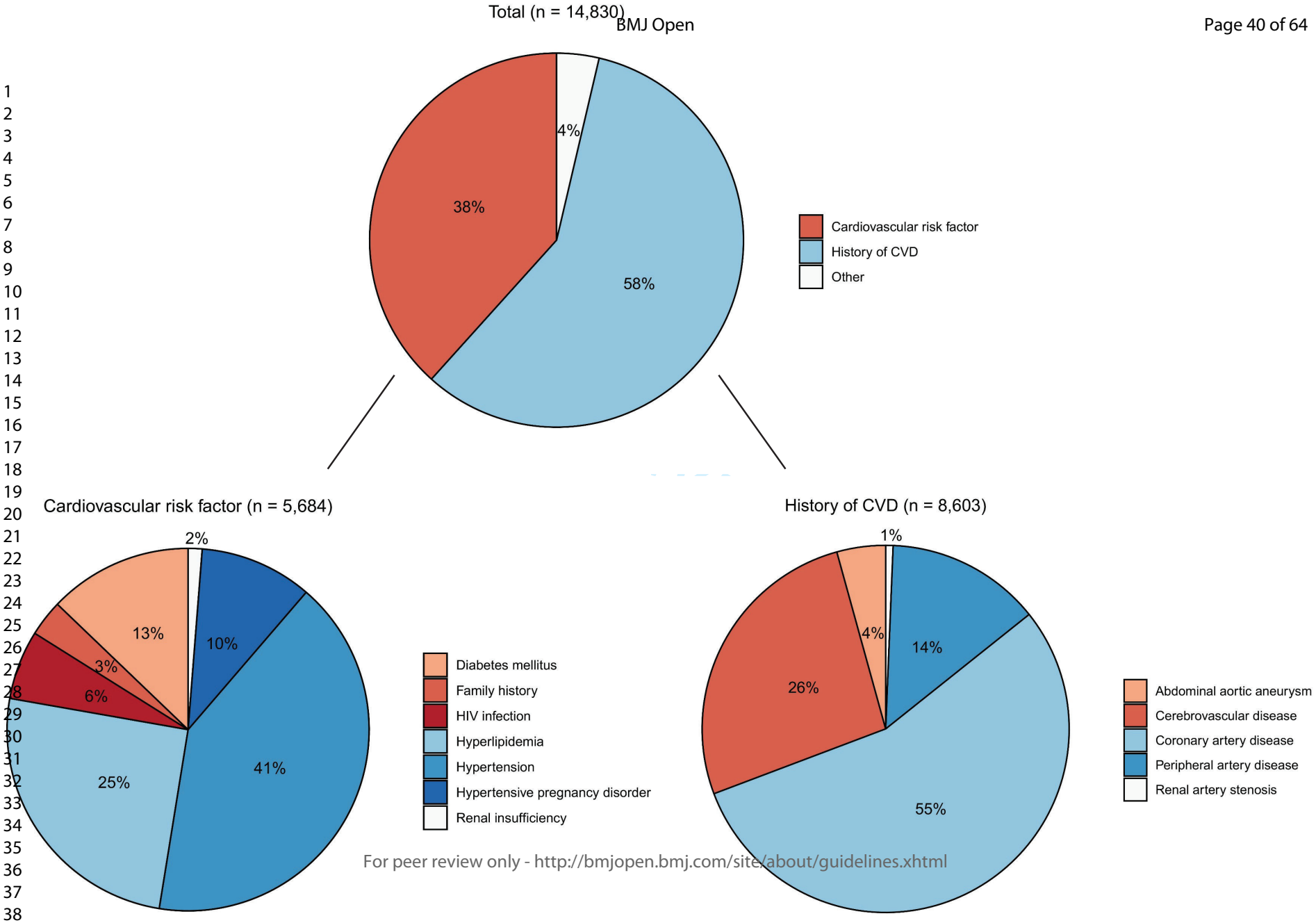
Figure 4. Distribution of inclusion diagnoses

CVD, cardiovascular disease; HIV, human immunodeficiency virus









Supplementary material

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

Content list

Supplementary Table 1. Inclusion criteria and exclusion criteria

Inclusion criteria	Definition
One or more of the following cardiovascular diseases or risk factors:	
Cardiovascular disease	
Transient ischemic attack	Sudden onset, ≤24 hours of: *carotid:* temporary motor weakness in one half of the body, language disorder, blindness in one eye *vertebrobasilar*: ≥2 simultaneously: bilateral motor weakness or paraesthesia, dizziness, diplopia, dysphagia, ataxia, dysarthria *unknown vascular region:* hemianopia, dysarthria
Cerebral infarction	Criteria as for TIA, but duration of >24 hours
Subarachnoid haemorrhage	Sudden headache and (temporary) loss of consciousness, often accompanied by neck stiffness, nausea and vomiting, with blood in basal cisterns confirmed by CT or xantochromia in cerebrospinal fluid
Carotid artery stenosis	Duplex ultrasound confirmed stenosis or occlusion of ≥1 carotid artery with diameter reduction ≥50%
Ischemic retinal syndrome	Visual field defect diagnosed as retinal syndrome by ophthalmologist
Angina pectoris	Chest pain with proven stenosis on coronary angiogram
Myocardial infarction	≥2 of following: - Chest pain >20 minutes, not relieved by nitrates; - ST elevation >1 mm in 2 contiguous ECG leads, or left bundle branch block; - Troponin levels >60 ng/L with rise and fall pattern*
Coronary syndrome requiring PCI or CABG	
Abdominal aortic aneurysm	Ultrasound confirmed local dilatation of abdominal aorta with anterior-posterior diameter ≥3 cm and/or distal-proximal ratio of >1,5
Renal artery stenosis	Stenosis of ≥1 renal artery with lumen narrowing ≥50%, caused by atherosclerosis
Peripheral artery disease of the lower limbs	Fontaine classification: - Fontaine II: intermittent claudication: pain (or other symptoms) in one or both legs after certain walking distance, disappearing at rest; - Fontaine III: rest/nocturnal pain; - Fontaine IV: ischemic ulceration, necrosis or gangrene; confirmed by ABI ≤0.90 at rest and/or ≥20% post-exercise decrease
Cardiovascular risk factors	
Hypertension	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hypertension, target organ damage, medical or family history
Hyperlipidaemia	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hyperlipidaemia, suspected lipid metabolism disorder, medical or family history

Diabetes mellitus	Fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or use of oral antidiabetic agents or insulin
Renal insufficiency	Serum creatinine >120 µmol/L
HIV infection	Chronic infection with human immunodeficiency virus
Family medical history	Positive family history for premature cardiovascular disease in 1st degree relatives
Pre-eclampsia†	Gestational hypertension accompanied by proteinuria, other maternal organ dysfunction or uteroplacental dysfunction
HELLP syndrome†	Haemolysis, elevated liver enzymes, low platelets as a manifestation of pre-eclampsia
Placental abruption†	Gestational hypertension accompanied by placental abruption as an effect of uteroplacental insufficiency
Intrauterine growth restriction†	Gestational hypertension accompanied by fetal growth restriction as an effect of uteroplacental insufficiency
Remaining inclusion criteria	
18 – 90 years of age	
Independent in most daily activities	Rankin scale ≤3[1]
Exclusion criteria	
Pregnancy	
Short life expectancy (per judgement of the treating physician)	
Insufficient understanding and expression of the Dutch language	
No informed consent	
Follow-up impossible	

* In earlier years of the UCC-SMART study, this laboratory item was defined as CK elevation of ≥2x upper limit and MB-fraction >5% of total CK level.
† Hypertensive pregnancy complications are based on the ISSHP criteria[2]

ABI, ankle-brachial index; CABG, coronary artery bypass grafting; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; HELLP, haemolysis, elevated liver enzymes and low platelets; HIV, human immunodeficiency virus; ISSHP, International Society for the Study of Hypertension in Pregnancy; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 2. Variables available in UCC-SMART

Health questionnaire	Medication use	Physical examination	Radiology measurements	Laboratory measurements
Medical history	Statins	Weight (kg)	Visceral fat (cm)	Haemoglobin (mmol/L)
Age (years)	Ezetimibe	Height (m)	Subcutaneous fat (cm)	Haematocrit (%)
Sex	Fibrates	Blood pressure (mmHg)	Carotid artery stenosis (%)	Total cholesterol (mmol/L)
Smoking and pack years	Thiazide diuretics	Ankle-brachial index	Carotid intima thickness (mm)	LDL-C (mmol/L)
Alcohol use and number of units	Loop diuretics	Body mass index (kg/m^2)	Aortic artery diameter (cm)	HDL-C (mmol/L)
Level of education	Potassium saving diuretics	Waist circumference (cm)	Kidney size and volume (cm; mL)	Apolipoprotein B (g/L)
Country of birth	ACE-inhibitors	Hip circumference (cm)	Electrocardiography	Triglycerides (mmol/L)
Quality of life*	Angiotensin II-receptor blockers		Echocardiography†	HbA1c (%)
Exercise (MET-hours per week)	Aldosterone antagonists			Fasting glucose (mmol/L)
	Beta-blockers			Fasting insulin (mU/L)
	Calcium antagonists			Creatinine (µmol/L)
	Alpha blockers			eGFR (ml/min/1.73 m^2)
	Central acting antihypertensives			Albuminuria (mg/L)
	Direct vasodilators			Albumin-to-creatinine ratio
	Aspirin			CRP (mg/L)
	Clopidogrel			TSH (mU/L)
	Dipyridamole			Lp(a)
	DOAC			Urine sodium
	Vitamin K antagonists			Urine potassium
	LMWH			
	Oral glucose-lowering therapy			
	Insulin			
	Antidepressants			
	Benzodiazepines			

* Based on EQ-5D questionnaire

† Echocardiography will be added to the UCC-SMART program in the near future

ACE, angiotensin converting enzyme; CRP, C-reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low molecular weight heparin; Lp(a), lipoprotein(a); MET, metabolic equivalent of task; TSH, thyroid stimulating hormone; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Diseas

Supplementary Table 3. Measurements that have been performed in the past

Vascular wall stiffness was determined from 2001 until 2003 using the Wall Track System that captures vascular diameter changes using radio-frequent signals. At the first signal, the position of the anterior and posterior vascular wall of the common carotid artery are marked at 2 cm proximal to the carotid bulb. Then, for five times on both the left and right side, changes in arterial diameter (ΔD) and end-diastolic diameter (D_d) are registered during four seconds, and the mean is calculated. Carotid distension is defined as the change in artery diameter in systole relative to diastolic diameter. Other stiffness indices include β stiffness index ($\ln(SBP/DBP)/(\Delta D/D_d)$), compliance coefficient ($(\pi \times D_d \times \Delta D)/2 \times$pulse pressure), distensibility coefficient ($(2 \times \Delta D/D_d)$/pulse pressure), Peterson's modulus (pressure change required for theoretical 100% increase in diameter) and Young's elastic modulus (pressure per mm^2 required for theoretical 100% extension).
Flow-mediated vasodilatation (FMD) was assessed temporarily starting from March 1999. Here, the Wall Track System described above was used to capture the diameter of the brachial artery in the elbow crease. Following 3 baseline readings, new measurements were taken every 30 seconds for 5 minutes: first after a blood pressure cuff at the forearm was inflated to 100 mmHg above SBP for 4 minutes, and then after sublingual administration of 400 µg of nitroglycerin. Endothelial function was defined as the proportional increase of diameter after nitrate and the baseline-adjusted maximal diameter following ischemia. This examination was stopped in June 2001, since analysis in the first 400 patients showed this measurement was not related to other known measures of atherosclerosis.
Quality of life information was collected through questionnaires based on the 36-Item Short Form Health Survey (SF-36)[3], sent to participants from 2001 until 2019. This quality of life assessment contains scales for 1) limitations in physical activities; 2) limitations in social activities; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality and 8) general health perceptions.
Homocysteine was measured from 1998 until 2011 in fasting blood samples by high performance liquid chromatography with fluorescence detection. Up until 2000, a methionine loading test was performed in patients younger than 50 years. Plasma homocysteine was measured six hours after oral administration of 100mg methionine per kilogram bodyweight.

DBP, diastolic blood pressure; SBP; systolic blood pressure

Supplementary Table 4. Definitions of established cardiovascular disease

Cardiovascular disease	Definition of cardiovascular disease*
Cerebrovascular disease	TIA, cerebral infarction, ischemic retinal syndrome, carotid surgery or angioplasty in medical history
Coronary artery disease	Myocardial infarction, angina pectoris, ≥ 1 vessel disease on coronary angiography, PCI or CABG in medical history
Abdominal aortic aneurysm	Abdominal aortic aneurysm, surgical or endovascular treatment of abdominal aortic aneurysm in medical history
Peripheral artery disease	Fontaine classification ≥ II, amputation, vascular surgery or angioplasty in medical history

* Definitions of these items are listed in Supplementary Table 1.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 5. Definitions of outcome events

Outcome event	Definition of outcome event
	Primary endpoints
Stroke	
Ischemic stroke / haemorrhagic infarction	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale[1], and new (haemorrhagic) infarction on CT or MRI <2 weeks after stroke
Cerebral haemorrhage	Cerebral haemorrhage confirmed with CT, MRI or surgery
Subarachnoid haemorrhage	Subarachnoid haemorrhage confirmed with CT, MRI or surgery
Type not determined	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale, but no brain imaging performed
Retinal syndromes	
Infarction	Associated clinical symptoms, typical fundus changes and/or vision loss, scotoma on perimetry
Haemorrhage	Associated clinical symptoms, typical fundus changes and vision loss
Myocardial infarction	The assessment includes: chest pain >30 minutes, elevated cardiac enzymes, characteristic ECG-changes
STEMI	Acute chest pain with persistent (>20 minutes) ST-elevation
NSTEMI	Acute chest pain without ST-elevation, with elevated troponin
Intervention-related myocardial infarction	New Q wave and elevated troponin <7 days after any intervention (for PCI >3x, for CABG >5x)
Probable myocardial infarction	Typical pain, persistent STT-changes, no documented course of cardiac enzymes
Heart failure	≥2 of the following: dyspnoea, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, exercise intolerance, pulmonary oedema, increased central venous pressure, third heart tone, hepatojugular reflux, altered hemodynamics, peripheral oedema, cardiomegaly; and (intensified) treatment with loop diuretics or intravenous vasoactive inotropic agents Classified as: systolic heart failure (at least moderate left ventricle dysfunction or LVEF <40%) or heart failure with preserved ejection fraction, due to coronary disease, valve disease or other causes
Rupture of abdominal aortic aneurysm	Rupture abdominal aortic aneurysm, proven by ultrasound, CT or laparotomy
Renal disease	
End-stage renal disease	CKD stage 5 (i.e. persisting eGFR <15ml/min/1.73 m^2 for >3 months and/or need for renal replacement therapy (chronic dialysis or renal transplantation))

Acute renal insufficiency – temporary renal replacement therapy	Acute kidney injury requiring temporary renal replacement therapy
Acute renal insufficiency – no renal replacement therapy	Acute kidney injury KDIGO stage 3 (i.e. serum creatinine 3 times baseline creatinine and/or serum creatinine ≥354 µmol/L)
Bleeding	Bleeding requiring outpatient treatment or (prolonged) hospitalization
Major bleeding	*ISTH definition:* fatal bleeding and/or bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular causing compartment syndrome), bleeding causing Hb level drop of ≥1.24 mmol/L or leading to transfusion of ≥2 units of blood[4] *BARC type 3:* overt bleeding with Hb level drop of ≥1.86 mmol/L, leading to transfusion, cardiac tamponade, surgical intervention for control or intravenous vasoactive agents, or located intracranial or intraocular compromising vision *BARC type 5:* fatal bleeding[5]
Diabetes	Self-reported diagnosis, confirmed and classified based on a questionnaire. If necessary, additional information is requested from the general practitioner or looked up in the electronic health record.
DM type 1	Insulin needed immediately at onset and absence of oral glucose lowering medication. Supportive but not mandatory: ≤25 years of age, BMI <25 kg/m^2, presence of anti-GAD antibodies
DM type 2	Diagnosed between age 35 and 40 and BMI >33 kg/m^2 or diagnosed after age 40 and BMI >27 kg/m^2
Dementia	Self-reported diagnosis, confirmed and classified based on a questionnaire. Classified as: Alzheimer's disease; vascular dementia; a mix of Alzheimer's disease and vascular dementia; Lewy Body dementia; or frontotemporal dementia.
Vascular mortality	
Fatal cerebral infarction	Cerebral infarction leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal cerebral haemorrhage	Cerebral haemorrhage leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal stroke - type not determined	Stroke without radiological confirmation leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without stroke)
Fatal myocardial infarction	Documented myocardial infarction followed by death (>1 hour after onset of symptoms)

Fatal heart failure	Heart failure leading to death
Fatal rupture abdominal aortic aneurysm	Rupture abdominal aortic aneurysm followed by death
Fatal bleeding	Major bleeding leading to death
Sudden death	Witnessed death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Other	Death without apparent cause in case of cardiovascular history, terminal renal insufficiency, dementia (unless clearly non-vascular), pulmonary haemorrhage*
Non-vascular mortality	Death caused by malignancy, infection, unnatural death or other
All-cause mortality	Death from any cause
	Secondary endpoints
Amputation	Any amputation of a toe or part of the foot or leg due to chronic ischemia. *Excluding:* traumatic amputations, amputation due to sepsis, amputation of fingers.
Vascular intervention†	Percutaneous coronary intervention; coronary artery bypass grafting; carotid endarterectomy, angioplasty or stenting; vertebral artery angioplasty or stenting; vascular surgery or percutaneous transluminal angioplasty of the aorta(bifurcation), iliac arteries, femoral and crural arteries; vascular intervention because of abdominal angina; LVAD. Angioplasty and stenting of other arteries are registered as well.
Vascular intervention of an intracranial aneurysm	Coiling or clipping of an intracranial aneurysm

* In accordance with Antiplatelets Trialists' Collaboration, Lancet 2002
† Excluding interventions already planned before or at inclusion, but including re-interventions and complications of an intervention already planned before or at inclusion.

Anti-GAD, antibodies to glutamic acid decarboxylase; BARC; Bleeding Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; KDIGO, Kidney Disease Improving Global Outcomes; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Supplementary Table 6. Substudies of UCC-SMART

Substudy	Period in which the patients were included	N	Aim	Key publications	Additional measurements within substudy
ARTEMIS *(ARTErial calcifications of the Media and Intima in SMART)*	2015 - 2017	520	1) To determine whether intima and media calcification differ in their respective associated CVD risks. 2) To elucidate which risk factors and mechanisms lead to the development of these respective types of calcification and in turn to cardiovascular disease	- Zwakenberg, 2020, PloS One[6] - Hoek, 2021, Atherosclerosis[7]	Technique: unenhanced thin-slice CT-scan of the legs (femoral head to feet) Measurement: calcification in the femoral and crural arteries scored as absent, predominant intimal arterial calcification, predominant medial arterial calcification or indistinguishable; calcification volume.
Athero-Express *Added to UCC-SMART study in June 2022*	2002 - present	Patients undergoing a femoral or carotid endarterectomy	To investigate the value of plaque characteristics in relation to cardiovascular outcomes	Verhoeven, 2004, Eur J Epidemiology[8]	During surgery, the atherosclerotic plaque is collected and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells
BEST *(BEtter risk factor treatment with STructured agreement)* RCT	2004 - 2006	197 patients with at least 2 modifiable risk factors	To investigate whether a clearly written agreement on risk factor management between general practitioners and hospital improved the vascular risk profile of high-risk patients compared with usual care after 1 year	Brouwer, B.G. 2008. SMART risk factor screening in patients at high vascular risk. Utrecht University, Utrecht[9]	NA
Brown adipose tissue	2014 – 2016	50 patients with clinically manifest CVD	1) To evaluate and optimize a protocol for quantifying brown adipose tissue with MRI and to assess BAT volume per patient. 2) To evaluate the reproducibility of MRI by determining inter-scan, intra-observer and inter-observer variability in BAT volume	- Franssens, 2016, NMR Biomed[10] - Franssens, 2017, J Magn. Reson. Imaging[11]	Technique: 1.5T water-fat MRI of supraclavicular and subcutaneous adipose tissue Measurement: fat signal fraction value, representative of the amount of triglycerides, intracellular water content and capillary

					density, of supraclavicular and subcutaneous adipose tissue
DISH *(Diffuse idiopathic skeletal hyperostosis)*	1996 – 2018	4,791 (all patients from SMART with chest X-ray within 3 months of inclusion)	N.A.	- Harlianto, 2021, Rheumatology[12] - Harlianto, 2021, J. Pers. Med.[13]	*Technique: Chest X-ray within three months of inclusions (if available in routine clinical care)*
					Measurement: X-rays were scored for DISH using the Resnick criteria.[14] DISH is classified following the presence of ossification of at least four contiguous vertebrae; (relative) preservation of the intervertebral disc height; and the absence of apophyseal joint bony ankylosis or sacroiliac joint erosion. Thoracic aortic calcification subjective score as absent, mild, moderate and severe.
IRIS *(Internet-based vascular Risk factor Intervention and Self-management)* RCT	2008 - 2010	330 patients with a recent clinical manifestation of atherosclerosis of CAD, CeVD or PAD and with ≥ 2 treatable risk factors not at goal (from UMC Utrecht + Rijnstate)	1) To evaluate whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease. 2) To evaluate whether an internet-based vascular risk factor management program for reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease is cost-effective.	- Vernooij, 2012, BMJ[15] - Greving, 2015, BMJ Open[16]	NA

RULE *(Risk management in Utrecht and Leiden Evaluation study)* Two-centre parallel-group comparative investigation	2005 - 2007	604 patients with CAD, CeVD, PAD or T2DM from UMC Utrecht (+ 566 patients from LUMC)	To assess risk factor status after referral in patients with established vascular disease or type 2 diabetes who took part in the multidisciplinary hospital-based vascular screening program SMART, compared with a group who did not participate in such a program	Brouwer, 2010, J of Int Med[17]	NA
Small aneurysms trial (AAA)	1996 - 2005	230 patients with an initial AAA diameter of 30-55mm, who were examined by ≥ 2 AAA diameter measurements and with ≥ 6 months of FU	To estimate overall rupture rates of small AAAs and to investigate a predefined set of demographic characteristics and cardiovascular risk factors for association with AAA growth	Schlosser, 2008, J Vasc Surg[18]	<u>Technique:</u> Ultrasound scanning of the aorta <u>Measurement:</u> AAA diameter and change with initial AAA diameter
SMART-2	2007 - present	1794 patients with a history of CVD or diabetes, a median of 9.9 years after inclusion in UCC-SMART	To study the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment in the past		NA
SMART HEART	1996 - 2006	536 patients with ≥ 3 years hypertension, but free of known coronary or	To detect patient characteristics related to the development of LVH with special focus on the detection of SNPs that confer an increased susceptibility for the development of LVH, and thus, heart failure	- Meijs, 2007, Neth Heart J[19] - Meijs, 2009, Eur J Prev Cardiol[20] - Vernooij, 2012, Am J Cardiol[21]	<u>Technique:</u> 1.5T cardiac MRI and delayed-enhancement cardiac MRI <u>Measurement:</u> LV mass, LV-end diastolic and end-systolic volumes and left atrial volumes; areas of hyperintense myocardium

		valvular disease		- De Beus, 2015, Eur J Clin Invest[22]	classified as myocardial scar tissue (used to assess the presence of unrecognized myocardial infarction). Infarct size was quantified as scar mass relative to LV mass.
SMART Inform Three-armed hypothesis-blinded RCT	2017 - 2018	303 patients with stable CVD and using a statin	To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use in patients with stable CVD compared with standard (non-personalized) therapy-effects	Jaspers, 2021, BMJ Open[23]	NA
SMART-Junior	Questionnaires sent between 2009-2013 to patients who were included between 2001 and 2012	4,270 (10,564 children)	1) To investigate the presence of cardiovascular risk factors and vascular disease in offspring of patients participating in the SMART cohort. 2) To identify a risk profile of the parent prognostic for the development of traditional cardiovascular risk factors or cardiovascular events in their children.	- Weijmans, 2015, Int J Cardiol[24] - Weijmans, 2015, Am Heart J[25]	- Questions about CV risk factors (incl. dates of risk factor diagnoses): presence of diabetes, hypertension, hypercholesterolemia, smoking behaviour and present weight of the offspring - Questions about CVD (incl. dates of occurrence): whether offspring had experienced MI, PCI, CABG, stroke, PAD, or AAA.
SMART-MR and SMART Medea	2001 - 2005 1st follow-up: 2006-2009 2nd follow-up: 2013-2017	1,309	To investigate brain changes using 1.5T MRI in patients with symptomatic atherosclerotic disease (and 7T MRI in follow-up from 2013-2017)	- Geerlings, 2010, Atherosclerosis[26] - Muller, 2011, Ann Neurol[27] - Conijn, 2011, Stroke[28] - Kloppenborg, 2012, Neurology[29] - Jochemsen 2013, JAMA Neurology[30] - Van der Veen, 2015, Stroke[31]	<u>Technique:</u> - 1.5T brain MRI - 7T brain MRI <u>Measurement:</u> - Total cerebral blood flow (mL/min per 100 mL brain parenchymal volume) - White matter lesions: volume (mL), shape (using the concavity index and fractal dimension[35]) and location were scored

				- Zwartbol, 2019, Stroke[32] - Ghaznawi 2021, Neurology[33] - Rissanen, 2021, Neurology[34]	- Brain parenchymal fraction (% of intracranial volume (ICV) that is occupied by brain tissue), an indicator for global brain atrophy - Ventricular enlargement (% of ventricular volume of the total ICV), an indicator for subcortical brain atrophy - Cortical gray matter fraction (% cortical gray matter volume of the total ICV), an indicator of cortical brain atrophy - Infarcts: location, affected flow territory and type were scored
					<u>Neuropsychological assessment (from 2003):</u> - 15-learning word test[36] - Rey-Osterrieth Complex Figure test[37] - Visual Elevator test[38] - Brixton Spatial Anticipation test[39] - Verbal Fluency test (letter)[40] - Dutch version of the National Adult Reading test[41] <u>From 2006:</u> - MMSE[42] - Verbal Fluency test (animals)[40] - Digit Symbol Substitution Test[43] - Forward Digit Span and Backward Digit Span[44]
SMART-ORACLE *(Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk*	2012 - present	1.182 (until Dec 2021; ongoing) patients with a history of symptomatic vascular	1) To determine whether there is additional value of performing CAC score, CTCA, total aorta calcification, burden as compared to traditional risk factors in the risk stratification in predicting any cardiovascular event. 2) To	- Franssens, 2017, Eur J of Prev Cardiol[45] - Van 't Klooster, 2020, IJC Heart & Vasculature[46]	<u>Technique:</u> Cardiac non-contrast enhanced CT and CTA of the heart and the carotids to the circle of Willis

for a cardiovascular event)		disease, T2DM or hypertension	estimate the additional value of CTCA and CAC score on top of traditional risk factors in predicting cardiac events. 3) To determine the value of soft plaque burden in the carotid and coronary arteries in predicting acute vascular events		Measurement: - Radiodensity and volume of epicardial adipose tissue - Coronary artery calcium (scored using the Agatston method[47]) - Calcifications on heart valves and in the thoracic aorta (quantified using a pseudo-mass score: mean calcium houndsfield units × region of interest volume) - CAD-RADS[48] - Carotid stenosis
SPAIN *(Selfmanagement of vascular Patients Activated by Internet and Nurses)*	2005	50 patients with computer facilities	1) To evaluate the feasibility of an Internet-based vascular risk reduction program in terms of accessibility, frequency and pattern of use of an individualized website for patients with a recent clinical manifestation of arterial disease. 2) To evaluate whether the use was related to a change in vascular risk factors after 6 months	Goessens, 2008, Patient education and counseling[49]	NA
TEMPUS *(The Evening versus Morning Polypill Utilization Study)* Randomized open blinded endpoint crossover trial	1996 - 2009. Patients were screened between 2012 - 2013	78 patients with established CVD or those at intermediate to high risk of CVD with indication for the use of cardiovascular medication, according to the current	1) To assess whether there is a difference in the morning or evening administration of a cardiovascular polypill, an FDC formulation containing aspirin, simvastatin, lisinopril and hydrochlorothiazide, on LDL-C and mean 24-hour systolic BP levels in individuals at high risk of cardiovascular disease. 2) To assess the effect of the polypill on LDL-C, ambulatory BP, anti-platelet function, adherence and patients'	- Lafeber, 2014, Eur J Prev Cardiol[50] - Lafeber, 2014, Int J Cardiol[51]	At baseline and at the end of each treatment period: medical history, anthropometric parameters, laboratory blood tests, office BP, 24-hour ambulatory BP monitoring, platelet function, pulse wave analysis, adherence to therapy, and questionnaires

		Dutch guidelines	preference as compared to the administration of the individual, identically dosed components of the polypill administered at different times of the day, as is currently recommended in clinical care.		
VENUS *(Vascular prEvention by NUrses Study)* RCT	Patients included between May 2002 and October 2003	236 patients with ≥ 2 modifiable risk factors	To investigate whether risk factor management in the hospital improved with nurse practitioner care plus usual care compared with usual care	- Goessens, 2006, Eur J Cardiovasc Prev Rehabil[52] - Sol, 2009, Eur J C Nurse[53]	Questionnaire about social support using a social support questionnaire for Dutch CHD patients: - Structural support: whether they have a spouse and whether they have someone they could turn to about their health problems - Functional support: statements about active involvement, protective buffering and overprotection.

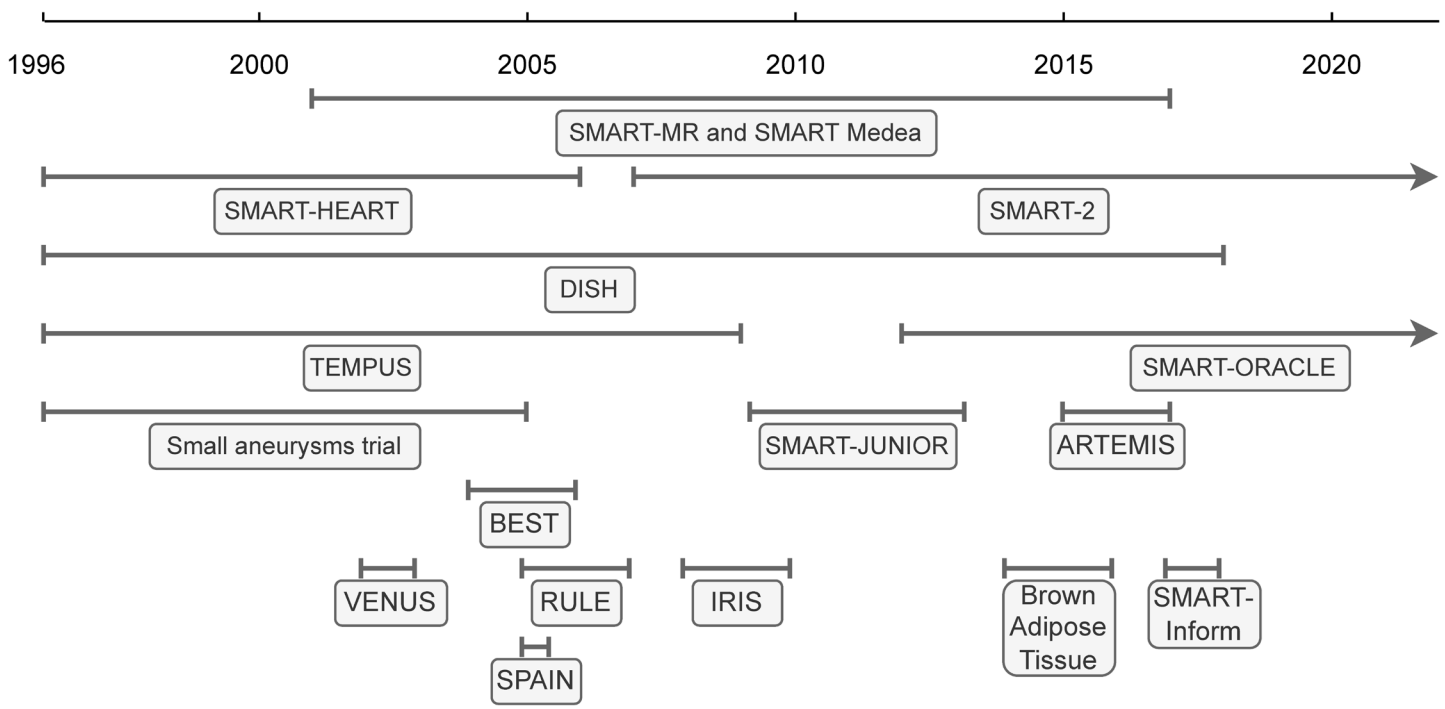
AAA, aortic abdominal aneurysm; BAT, brown adipose tissue; BP, blood pressure; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease, CAD-RADS, CAD-reporting and data system, CeVD, cerebrovascular disease; CHD, coronary heart disease; CT, computed tomography; CTA, CT angiography; CTCA, CT coronary angiography; CV, cardiovascular; CVD, cardiovascular disease; DISH, diffuse idiopathic skeletal hyperostosis; FDC, fixed dose combination; FU, follow-up; LDL-c, low-density lipoprotein cholesterol; LUMC, Leiden University Medical Center; LV, left ventricle; LVH, left ventricle hypertrophy; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SMART, Second Manifestations of Arterial Disease; SNP; single nucleotide polymorphism; T2DM, type 2 diabetes mellitus; UCC-SMART, Utrecht Cardiovascular Cohort–SMART; UMC, University Medical Center

Supplementary Table 7. Baseline characteristics of participants with complete follow-up and participants without complete follow-up

	Participants with complete follow-up (n = 13,284)	Participants without complete follow-up (n = 1,546)
Age (years)	57 ± 12	55 ± 14
Male sex	8,736 (66)	894 (57)
Previous or current smoking	9,285 (70)	1,065 (69)
Established cardiovascular disease	8,270 (65)	913 (59)
Diabetes mellitus	2,272 (17)	336 (22)
Lipid-lowering therapy	7,529 (57)	724 (47)
Antihypertensive therapy	9,053 (68)	977 (63)
Oral anticoagulant therapy	1,145 (9)	121 (8)
Systolic blood pressure (mmHg)	140 ± 22	144 ± 23
Diastolic blood pressure (mmHg)	83 ± 13	84 ± 13
Body mass index (kg/m^2)	26.9 ± 4.4	27.1 ± 4.8
Non-HDL-cholesterol (mmol/L)	3.8 ± 1.3	4.0 ± 1.5
eGFR (ml/min/1.73 m^2)	53 ± 41	48 ± 43
HbA1c (mmol/mol)	38 (36 - 42)	40 (36 - 48)
CRP (mg/L)	2.0 (1.0 - 4.3)	2.2 (1.0 - 4.4)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

Supplemental Figure 1. Timeline of substudies of UCC-SMART



1.5T brain MRIs have been performed between 2001 and 2005. Follow-up of 1.5T MRI was performed between 2006 and 2009 and from 2013 to 2017. During the second follow-up, a 7T brain MRI was added in a subsample. A detailed overview of the substudies is provided in Supplementary Table 5.

ARTEMIS, ARTErial calcifications of the Media and Intima in SMART (Second Manifestations of Arterial Disease)[6]; BEST, BEtter risk factor treatment with STructured agreement[9]; Brown Adipose Tissue[10]; DISH, Diffuse idiopathic skeletal hyperostosis[12]; IRIS, Internet-based vascular Risk factor Intervention and Self-management[15]; RULE, Risk management in Utrecht and Leiden Evaluation study[17]; SMART HEART[19]; SMART Inform[23]; SMART-JUNIOR[24]; SMART-MR[26]; ORACLE; Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk for a cardiovascular event[45]; SPAIN,

Self-management of vascular Patients Activated by Internet and Nurses[49]; TEMPUS, The Evening versus Morning Polypill Utilization Study[50]; VENUS, Vascular prEvention by NUrses Study[52].

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1+3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5+6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6+11-12
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-12
Bias	9	Describe any efforts to address potential sources of bias	6-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	16-17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	16-17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25-26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	25
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

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Primary Subject Heading:	Cardiovascular medicine
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Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

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Abstract

Purpose: The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study is an ongoing prospective single-center cohort study with the aim to assess important determinants and the prognosis of cardiovascular disease progression. This article provides an update of the rationale, design, included patients, measurements and findings from the start in 1996 to date.

Participants: The UCC-SMART study includes patients aged 18-90 years referred to the University Medical Center (UMC) Utrecht, the Netherlands, for management of cardiovascular disease (CVD) or severe cardiovascular risk factors. Since September 1996, a total of 14,830 patients has been included. Upon inclusion, patients undergo a standardized screening program, including questionnaires, vital signs, laboratory measurements, an electrocardiogram, vascular ultrasound of carotid arteries and aorta, ankle-brachial index and ultrasound measurements of adipose tissue, kidney size and intima media thickness. Outcomes of interest are collected through annual questionnaires and adjudicated by an endpoint committee.

Findings to date: By May 2022, the included patients contributed to a total follow-up time of over 134,000 person-years. During follow-up, 2,259 patients suffered a vascular endpoint (including non-fatal myocardial infarction, non-fatal stroke and vascular death) and 2,794 all-cause deaths, 943 incident cases of diabetes and 2,139 incident cases of cancer were observed up until January 2020. The UCC-SMART cohort contributed to over 350 articles published in peer-reviewed journals, including prediction models recommended by the 2021 ESC CVD prevention guidelines.

Future plans: The UCC-SMART study guarantees an infrastructure for research in patients at high cardiovascular risk. The cohort will continue to include about 600 patients yearly and follow-up will be ongoing to ensure an up-to-date cohort in accordance with current health care and scientific knowledge. In the near future, UCC-SMART will be enriched by echocardiography, and a food frequency questionnaire at baseline enabling the assessment of associations between nutrition and CVD and diabetes.

Strengths and limitations

- The Utrecht Cardiovascular Cohort – Second Manifestations of Arterial disease (UCC-SMART) study is an ongoing cohort of almost 15,000 patients with various manifestations of CVD and cardiovascular risk factors
- The UCC-SMART study covers a long follow-up duration and prospectively captures extensive outcome data in a high cardiovascular risk population
- The use of a standardized screening program that includes baseline characteristics, physical examination, laboratory testing and non-invasive imaging provides an extended resource of data for research on cardiovascular disease epidemiology
- Limitations of the cohort include measurement of the determinants only at baseline for the majority of patients, and the sparse information on socioeconomic status

Introduction

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, causing around one-third of all deaths globally in 2019.[1] Atherosclerosis, the dominant cause of CVD, is fuelled by multiple mutually reinforcing and co-existing risk factors. Because of the progressive nature of atherosclerosis, patients with established CVD are at high risk of recurrent CVD and mortality.[2,3] Treatment of cardiovascular risk factors is known to markedly reduce the risk of new cardiovascular events.[4,5] Slowing down the process of atherosclerosis by timely identification and treatment of cardiovascular risk factors is therefore of the utmost importance.

In 1996, the Second Manifestations of Arterial Disease (SMART) cohort study was set up enrolling patients newly referred to the University Medical Center (UMC) Utrecht with clinically manifest CVD or marked risk factors for atherosclerosis. The study was designed with the aim of determining the prevalence of concomitant atherosclerotic disease and risk factors, as well as studying the incidence of future cardiovascular events and its predictors. Furthermore, the SMART study contributes to the complete and protocolized multidisciplinary care of these high risk patients by integrating a standardized set of measurements into usual patient care. The rationale and design of the study were previously published in 1999[6], with the study containing around 600 patients at that time. In 2018, the name of SMART changed to Utrecht Cardiovascular Cohort (UCC)-SMART. By now, 26 years after enrolment of the first patient, many baseline measurements have been added, substudies have been initiated, the study has been linked to national registries and the data have been used in several large (inter)national collaborations. At the same time, demographic and guideline changes have led to differences in the baseline characteristics and absolute risk of the patients included in the cohort. The aim of the current article is to provide an update on the rationale, design, included patients, baseline measurements and follow-up to date.

Cohort description

The UCC-SMART-study is a single-centre prospective cohort study, ongoing in both inclusion and follow-up, in which patient care and scientific research concerning cardiovascular risk factors and disease are integrated. This is depicted in Figure 1 and discussed in more detail in the sections below.

Study population

Starting from September 1996, patients aged 18 to 80 years referred to the UMC Utrecht, the Netherlands, for management of CVD or severe risk factors for CVD, have been recruited. Patients with cerebrovascular disease (CeVD), coronary artery disease (CAD), abdominal aortic aneurysm (AAA), peripheral artery disease (PAD), renal artery stenosis or one or more of the following cardiovascular risk factors, if rated as severe, are eligible to be included: hypertension, hyperlipidaemia, diabetes mellitus, renal insufficiency and a positive family medical history. Patients with a chronic human immunodeficiency virus infection as a cardiovascular risk-increasing condition or with hypertensive pregnancy disorders have been included since 2007 and 2012, respectively. Definitions of the inclusion criteria are listed in Supplementary Table 1. If patients have a history of multiple vascular events or risk factors, the referral reason (usually the most recent event) is listed as the qualifying inclusion diagnosis and any comorbidities are also registered. Pregnant women, patients with a short life expectancy and those insufficiently fluent in Dutch are not eligible.

Qualifying patients with CVD and/or risk factors listed above are recruited upon their first visit to the outpatient clinics and hospital wards of the departments of vascular medicine, internal medicine, nephrology, neurology, cardiology, cardiac surgery, obstetrics and vascular surgery. From 2021 onwards, the outpatient clinic of the department of geriatric medicine has been added to this list and the maximum age to be eligible for inclusion has been raised from 80 to 90 years old. In case of a recent cardiovascular event or intervention as the reason for inclusion, patients are invited after discharge from the hospital. In such cases, baseline measurements are generally performed more than 30 days after the acute event. All qualifying patients receive written and oral information about study goals and methods and are included only after written informed consent to use their data for study goals, the reporting of incidental findings to their treating physician, indefinite period storage of blood samples for future research and follow-up through annual questionnaires. In addition, participants can opt in or out to the following items: retrieval of data from regional and national registries, use of their data in research collaborations with for-profit organizations, use of coded data and laboratory samples for research outside the European Union and possible future requests to participate in follow-up studies of UCC-

SMART. When patients do not consent to any of these additional items, they can still partake in the UCC-SMART study.

Baseline data collection

The screening program consists of questionnaires, physical examination, an electrocardiogram (ECG), blood, urine and radiology testing. Except for the questionnaires, to be filled out before the hospital visit, the diagnostic components of the program take place during a one-day visit. An overview of all the variables available in UCC-SMART is provided in Supplementary Table 2. Some measurements have only been collected for or starting from a certain time period (Figure 2 and Supplementary Table 3).

Health questionnaires

The questionnaires collect data on medical history including established CVD (CeVD, CAD, AAA and PAD as described in Supplementary Table 4), cardiovascular risk factors, symptoms of CVD (based on the Rose Angina Questionnaire[7]), medication use, family history and lifestyle. For women, a question on the age at menopause (if applicable) is included as well. From 2002 onward, information on obstetric history has been collected including the number of full-term pregnancies, miscarriages (<14 weeks of gestation), preterm deliveries (14 – 32 weeks of gestation), birth weight and pregnancy complications. As of August 2022, a 160-item food frequency questionnaire (FFQ), validated in the Dutch population, has been added to the questionnaires.[8] Recently, these questionnaires have also been sent to people who were included in the UCC-SMART study before August 2022. The results of the questionnaires will follow in 2023.

Physical examination

Anthropometric measurements are taken by trained (research) nurses and include body height in centimetres, weight in kilograms and waist and hip circumference in centimetres with patients wearing light clothing and no shoes. Weight and length are used to calculate body mass index in kg/m^2. Waist circumference is measured horizontally at the midpoint between the iliac crest and lower costal margin and hip circumference is taken at the maximum horizontal circumference around the gluteal muscles.

The mean of two measurements is calculated. If the two measurements differ by >2 cm, a third is taken and the mean of the closest two is calculated.

From 1996 up until 1999, office blood pressure was measured using a semiautomatic oscillometric device (Omega 1400; Invivo Research Laboratories Inc., Broken Arrow, OK, USA) every 4 minutes for a total of 25 minutes at the right brachial artery in supine position and the mean systolic (SBP) and diastolic blood pressure (DBP) were calculated. From April 1999 until 2015, using a non-random sphygmomanometer (Iso-Stabil 5; Speidel & Keller, Jungingen, Germany), 3 simultaneous measurements with an interval of 30 seconds were taken at both upper arms in upright position and the SBP and DBP of the last two measurements were calculated from the arm yielding the highest values. From 2015 onward, office blood pressure has been measured using an automatic oscillometric device (Microlife WatchBP Office AFIB; Microlife Corp, Widnau, Switzerland). The measurement is performed unattended, in triplicate with an interval of 30 seconds, at both upper arms in supine position after the patient has rested for 30 seconds. The measurements on the arm with the highest blood pressure are recorded and the mean SBP and DBP are calculated.

In order to calculate the ankle-brachial index (ABI), blood pressure measurements are taken at rest at both upper arms every two minutes whilst the blood pressure is measured at both lower legs. For this, a Falcon Quad 8 MHz Doppler probe (Viasonix, Ra'anana, Israel) is used at a 60° angle at the dorsal pedal and posterior tibial arteries. The ABI is defined for each leg as the highest SBP at the ankle divided by the highest brachial SBP.

Laboratory testing

On the day of screening, a venous blood sample is drawn after at least eight hours of fasting to measure glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, creatinine, and haemoglobin. Laboratory measurements of fasting insulin, C-reactive protein (CRP) and thyroid stimulating hormone (TSH) were added in 2003 and glycated haemoglobin (HbA1c) and apolipoprotein B (apoB) were added in 2006. Lastly, measurement of lipoprotein(a) was added in June 2020.

Glucose is measured using an enzymatic colorimetric assay (Beckman Coulter, Brea, CA, USA). Total cholesterol and triglycerides are measured using a commercial enzymatic dry chemistry kit

(Johnson & Johnson, New Brunswick, NJ, USA) and HDL-C with a commercial enzymatic kit (Boehringer, Mannheim, Germany). Low-density lipoprotein cholesterol (LDL-C) is calculated using the Friedewald formula up to a plasma triglyceride level of 9 mmol/L.[9] Estimated glomerular filtration rate (eGFR) is calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[10] Spectrophotometry (Abbott Diagnostics, Santa Clara, CA, USA) is used to determine haemoglobin levels. CRP in plasma was initially determined using immunonephelometry (Nephelometer Analyzer BN II, Siemens, The Hague, The Netherlands) and from 2013 in heparin plasma on an AU5811 routine chemistry analyser using turbidimetry (Beckman Coulter, Brea, CA, USA). These types of measurements are strongly correlated (r = 0.99) and can therefore be pooled for analyses.[11] Before November 2006, TSH was quantified using a third-generation assay on a Centaur analyser (Bayer, Germany). Since December 2006, TSH has been measured by a third-generation assay on a DXi analyser (Beckman Coulter, Woerden, The Netherlands). Correlation between the two analysers is r = 0.9991 (n = 69), with an intercept of –0.05 mU/L (95%CI -0.22-0.12) and a slope of 1.04 (95%CI 1.029–1.052) (range 0–95 mU/L). ApoB and lipoprotein(a) are measured using nephelometry (Atellica Neph 630, Siemens, The Hague, The Netherlands). A morning-void urine sample is collected to determine urine albumin, creatinine, sodium and potassium levels. Urine albumin is measured using immunoturbidimetric assays. Ion selective electrode (Beckman Coulter, Brea, CA, USA) is used to determine urine sodium and potassium levels. DNA can be isolated from 10 mL of EDTA-augmented blood stored at -80° for genotyping.

Radiology testing

Non-invasive vascular imaging testing is performed by specially trained ultrasound technicians. Duplex examination of the carotid arteries is conducted to assess possible stenosis using peak systolic velocity measurements at the brachiocephalic trunk, carotid arteries (mid- and distal common, external and proximal and distal internal) and vertebral arteries (proximal and distal). Measurements are performed using an EPIQ-7 ultrasound machine (Philips Medical Systems, Eindhoven, The Netherlands). In case of abnormal signals and/or retrograde flow in the vertebral arteries, the proximal subclavian arteries are evaluated in search of severe stenosis or occlusion. For research purposes, intima-media-thickness

(IMT) of the carotid arteries is measured using a linear array transducer. With the patient lying down and the head turned 45° away from the side investigated, the ultrasound frame yielding an optimal longitudinal picture of the common carotid arterial wall is frozen at the time of the R-peak of ECG recording. Over a length of 1 cm starting from the carotid bulb towards proximal direction, the arterial wall thickness is measured from the lumen-intima interface to the media-adventitia interface. The mean of measurements in anterolateral, lateral and posterolateral direction is calculated.

Abdominal ultrasound examination is performed using the same ultrasound machine to obtain the maximal anterior-posterior diameter of the juxtarenal and infrarenal abdominal aorta and kidney length and volume. As of January 2000, visceral and subcutaneous adipose tissue measurements were added. The amount of subcutaneous fat is estimated by the distance from the linea alba to the skin. Visceral adipose tissue thickness is measured as the distance between the lumbar spine and the peritoneum. Measurements are taken at the end of a quiet expiration on a frozen ultrasound frame at three points on the imaginary transversal line halfway between the iliac crest and lower costal margin: at the midsternal line and 10 cm to the left and right on the transversal line. Each measurement is taken three times and then the mean of the measurements is recorded as the actual thickness. Ultrasonography has been proven a suitable technique to measure intra-abdominal adipose tissue with good reproducibility.[12,13] Moreover, from September 1998 on, a protocolized 12-lead resting ECG has been recorded.

In the near future, echocardiography will be added to the UCC-SMART program to facilitate research on the presence of heart failure at baseline. Echocardiography will be performed using a Philips Affiniti 70 ultrasound machine (Philips Medical Systems, Andover, MA, USA) by using a specific protocol involving 2-dimensional (2D), M-mode, Doppler, tissue Doppler and 2D speckle tracking (STE) imaging in accordance with the European Association of Cardiovascular Imaging 2016 recommendations for chamber quantification.[14] In particular, left ventricular dimensions will be measured in order to calculate the left ventricular mass index.[15] Left ventricular ejection fraction will be assessed quantitatively, preferably with automated three-dimensional imaging or alternatively with the Simpsons biplane method. Left atrial maximal volume and right ventricular dimensions and function will be measured as recommended.[14] Multiple parameters of left ventricular diastolic function will be

assessed, including pulsed-wave Doppler of the mitral inflow and tissue Doppler imaging of the mitral annulus motion. Left ventricular diastolic function will be evaluated according to current diagnostic algorithms.[16] A minimal of three sequential complexes will be recorded. Standard image analysis will then be performed off-line in accordance with clinical guidelines using Philips IntelliSpace Cardiovascular software and will include 2D STE analysis of the left ventricle and left atrium.

Treatment recommendation

After completion of the screening, the findings are assessed by a multidisciplinary team of two medical specialists (internist, cardiologist, neurologist or vascular surgeon). A treatment recommendation is formulated based on current applicable guidelines, according to which patients are already treated by their general practitioner or medical specialist. The screening results and treatment recommendation are reported in a medical letter which is sent to the treating specialist and general practitioner. Patients receive a summary of relevant findings and recommendations.

Incidental medical findings during the screening are reported to one of the study physicians and if needed, discussed with specialists from the multidisciplinary team. The findings are added to the medical record and sent to the treating specialist or general practitioner for further action.

Follow-up

Patients receive annual questionnaires with questions on hospital admissions and outpatient clinic visits, regardless of whether they are still under the care of the UMC Utrecht. In case patients no longer wish to complete the questionnaires, they are asked if they consent to collection of information from their general practitioner. When the replies indicate possible outcome events, additional information is collected through hospital discharge letters and relevant laboratory and radiology examinations. Clinical events of interest include stroke, myocardial infarction, heart failure, AAA rupture, renal insufficiency, vascular interventions, bleeding, diabetes and vascular and non-vascular mortality as defined in Supplementary Table 5. Incident type 2 diabetes has been assessed since July 2006. To assess incident diabetes between 1996 and 2006, a questionnaire was sent to all patients without diabetes at baseline who were included before July 2006. Incident heart failure has been assessed since October 2011. Three

members from the endpoint committee independently judge reported events. The endpoint committee consists of medical specialists from the recruiting departments. If all three physicians judge differently, the event is discussed with two other physicians from the committee to reach consensus. Secondary outcomes are adjudicated by trained research nurses. As of 2021, diagnoses of dementia and mild cognitive impairment have been added to the annual questionnaire as self-reported diagnoses.

Data quality and management

Data collected in the UCC-SMART program is stored in the electronic medical record of the UMC Utrecht. Blood samples (serum, citrate plasma, EDTA plasma and erythrocytes concentrate aliquots) are stored at -80°C according to the Biobanks Regulations to be found at the UMC Utrecht website (https://www.umcutrecht.nl/nl/centrale-biobank). The central biobank of the UMC Utrecht is ISO9001 certified (certificate number 2175592). Release of material for future research is reviewed by the UMC Utrecht Biobanks Review Committee.

Recorded data is downloaded from the electronic medical record and pseudonymized by the data manager who holds the encryption key, only to be accessed after permission of the principal investigator. The UCC-SMART study group periodically performs quality checks for missing values and inconsistencies compared to source documents, or values outside of the range deemed likely.

Patient and public involvement

Patients were not involved in the study design. Their experiences of burden and required time are considered in the implementation of new components in the program. Relevant findings of the UCC-SMART screening program and corresponding recommendations are sent to the patients. In addition, patients regularly receive a newsletter containing up-to-date facts and figures of the UCC-SMART study and substudies and findings of publications using UCC-SMART data. The UMC Utrecht policies are in line with open science, for opening up the research agenda to societal stakeholders, open research data and open access publications.

Linkage to other registries

Data in the UCC-SMART study can be enriched by collecting data from various registries and organizations, for example to obtain additional information on outcomes and medication use. Some examples of these linkages are described below.

Netherlands Cancer Registry

CVD and cancer share many risk factors and pathophysiological mechanisms, including body fat distribution, diet, physical inactivity, smoking, chronic inflammation burden, and oxidative stress.[17] To evaluate the relation between several cardiovascular risk factors and the risk of cancer, the UCC-SMART cohort has been linked to the *Netherlands Comprehensive Cancer Organisation* (IKNL), a nationwide registry receiving notifications of all new cancer diagnoses. By linking the cohort to the national cancer registry repeatedly, with the most recent linkage taking place in 2022, information on cancer incidence and details of cancer types and histopathology was obtained.

Central Agency for Statistics (CBS) Netherlands

The UCC-SMART cohort can be linked to the *Central Agency for Statistics* (CBS), also known as *Statistic Netherlands*, which contains data on ICD-10 coded diagnoses and hospital admissions since 1996. This allows for, amongst others, collection of endpoints that are not regularly collected in UCC-SMART or have been collected from a later time point, such as heart failure diagnoses. The CBS collects data from all hospitals in the Netherlands and from general practitioner practices affiliated with 'Nivel' healthcare registration, which are a good reflection of the Dutch population.[18,19]

Utrecht Patient Oriented Database (UPOD)

The UCC-SMART cohort can be linked to UPOD[20], a database containing electronic patient data from routine clinical care in the UMC Utrecht. This database has been collecting patient characteristics, medication orders, laboratory test results, hospital discharge diagnoses and medical procedures since 2000, enabling the addition of baseline and follow-up information to the UCC-SMART study.

Consortia

The data collected in UCC-SMART is added to several consortia such as a genetics consortium (GENIUS-CHD[21] on genetics of subsequent coronary heart disease), the Netherlands consortium of dementia cohorts and the Chronic Kidney Disease Prognosis Consortium[22].

Dutch Foundation for Pharmaceutical Statistics

A future plan is to obtain information on medication use during follow-up by linking the UCC-SMART cohort to the *Dutch Foundation for Pharmaceutical Statistics* (*Stichting Farmaceutische Kengetallen* [SFK]). This foundation obtains data from over 97% of the community pharmacies in the Netherlands.[23]

Substudies

SMART-2

Patients with a history of CVD or diabetes are invited to participate in the SMART-2 substudy. In this study, the baseline measurements of UCC-SMART are repeated in order to investigate the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment. Until May 2022, 2,313 patients have participated in SMART-2 after a median of 9.9 years (IQR 9.2 – 10.8) since their inclusion in UCC-SMART. As with UCC-SMART, the findings of SMART-2 with an accompanying treatment recommendation are communicated to the patient, his or her treating medical specialist and general practitioner.

SMART-ORACLE

SMART-ORACLE aims to determine the additional value of contrast-enhanced computed tomography (CT) of the coronary and carotid arteries on top of traditional cardiovascular risk factors in patients with a history of CVD, diabetes or hypertension.[24] The study is still ongoing and has currently been conducted in 1,252 patients.

SMART-MR and SMART Medea

SMART-MR and SMART Medea target the investigation of brain changes in patients with CVD using 1.5T magnetic resonance imaging (MRI) (and 7T MRI in a subset of patients).[25,26] This study was conducted in 1,309 patients. Amongst others, measurements of the total cerebral blood flow have been performed and characteristics of white matter lesions and microbleeds have been mapped.

Athero-Express

In May 2022, the Athero-Express biobank and study cohort have been incorporated into the UCC-SMART study.[27] The objective of Athero-Express is to investigate the value of plaque characteristics in relation to long term cardiovascular events. This ongoing prospective study, initiated in April 2002, includes patients undergoing femoral or carotid endarterectomy. During surgery, the atherosclerotic plaque is harvested and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells.

Other substudies

Several other substudies have been carried out within the UCC-SMART cohort, providing additional information and parameters for subsets of patients (Supplementary Table 6). As part of **SMART-Junior**, additional questionnaires have been sent to 4,270 patients in order to investigate the presence of cardiovascular risk factors and CVD in their offspring.[28] In **DISH**, diffuse idiopathic skeletal hyperostosis was scored on chest X-rays of 4,791 patients, performed in the context of health care, using the Resnick criteria.[29,30] **SMART-HEART** aimed to detect patient characteristics related to the development of left ventricle hypertrophy using 1.5T cardiac MRI in 536 patients with hypertension, but free of known coronary or valvular disease.[31] In order to determine whether intima and media calcification differ in their associated CVD risks and to elucidate which risk factors lead to the development of those types of calcification, CT-scans of the femoral head to the feet have been performed in 520 patients as part of **ARTEMIS**.[32] The aim of the **Small aneurysms trial** was to estimate the overall rupture rates of small AAAs and to investigate demographic characteristics and cardiovascular risk factors for association with AAA growth using ultrasound scanning of the aorta in 230 patients with an initial AAA diameter of 30-55 mm.[33] In **Brown adipose tissue**, supraclavicular

and subcutaneous adipose tissue fat-signal-fractions were assessed in 50 patients with CVD using 1.5T water-fat MRI.[34] **SPAIN** evaluated the feasibility of a web-based coaching program for vascular risk factor treatment, described the patterns of use of this program and measured changes in risk factors in 50 patients with CVD.[35] **RULE** investigated the impact of the UCC-SMART study compared to usual care on cardiovascular risk factors in 604 patients with CVD or type 2 diabetes.[36]

A few clinical trials have been conducted within the UCC-SMART study. **TEMPUS** was a randomized crossover trial in 78 patients that investigated the effects of a cardiovascular polypill on LDL-C, ambulatory blood pressure and adherence as compared to the administration of the individual, identically dosed components of the polypill.[37] **SMART-Inform** was a three-armed randomized controlled trial (RCT) in 303 patients using a statin with CVD.[38] The aim was to determine whether communicating personalized statin therapy-effects leads to lower decisional conflicts associated with statin use compared with standardized (non-personalized) therapy-effects. **BEST** was an RCT investigating whether a clearly written agreement on risk factor management between general practitioners and hospitals improved the vascular risk profile of 197 patients compared with usual care.[39] Another RCT was **VENUS**, which included 236 patients with ≥2 modifiable risk factors, investigating whether risk factor management in the hospital improved with nurse practitioner care on top of usual care compared with usual care alone.[40] Lastly, **IRIS** was an RCT that evaluated whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in 330 patients with CVD.[41] A timeline showing the different substudies is presented in Supplementary Figure 1.

Characteristics of the study population

By May 2022, a total of 14,830 patients has been included (Figure 3). Of those, 3,294 patients died and 89% (n = 10,219) of the surviving patients are still being followed up. Reasons for follow-up to end in surviving patients include withdrawal of participation in further follow-up (80%) or being unreachable for further questionnaires (20%). The median follow-up time of these patients without complete follow-up data is 7.4 years (IQR 3.9 - 11.4). Figure 4 shows the numbers and distribution of the reasons for inclusion. The most common inclusion diagnosis was CAD (n = 4,729), followed by hypertension (n =

2,344) and CeVD (n = 2,276). PAD was the enrolment diagnosis in 1,173 patients and AAA in 369 patients. Hyperlipidaemia was the inclusion diagnosis in 1,433 patients and diabetes mellitus in 730 patients.

Patient characteristics, medication use and measurements at baseline are listed in Table 1. This table is stratified for medical history at baseline, with the items of medical history either being the inclusion diagnosis or a comorbidity. This means that patients may fall within more than one category as listed in Table 1. The majority of patients included in the cohort is male (65%), especially among the subgroup of patients with established CVD (73% male). The mean age of the total population is 56.8 ±12.5 years. In total, 2,608 individuals (18%) had diabetes and 9,633 individuals (65%) had established CVD at baseline. Of these CVD patients, 1,399 (15%) had polyvascular disease, i.e. multiple vascular beds (cerebral, coronary, abdominal aorta or lower extremity) being affected. The proportion of missing variables is less than 3% for all variables, except for adipose tissue measurements on ultrasound (3.6%), albuminuria (4.7%) and CRP level (9.0%). Vascular screening indicated significant carotid artery stenosis (>50% stenosis) in 526 (4%) patients, AAA in 188 (1%) patients and low ABI (≤0.9) in 829 (6%) patients who were not previously diagnosed with CeVD, AAA or PAD, respectively. Of the 3,095 patients with established CVD included between 2012 and 2022 (to account for applicable guidelines), 2,075 (67%) had a SBP <140 mmHg, 753 (25%) had an LDL-C ≤1.8 mmol/L and 2,737 patients (88%) were using antithrombotic agents at baseline. Baseline characteristics of patients with complete follow-up data available were comparable to the characteristics of patients who withdrew from or were unreachable for further follow-up (Supplementary Table 7).

Table 1. Baseline characteristics stratified for medical history

	History of CVD				Cardiovascular risk factors			
	Cerebrovascular disease	Coronary artery disease	Abdominal aortic aneurysm	Peripheral artery disease	Hypertension	Hyperlipidaemia	Diabetes mellitus (type 1 + 2)	Renal insufficiency
Number of patients	2801	5999	767	1646	8228	12972	2608	1118
Medical history[a]								
Cerebrovascular disease	2801 (100)	553 (9)	117 (15)	209 (13)	1655 (20)	2492 (19)	442 (17)	248 (22)
Coronary artery disease	553 (20)	5999 (100)	322 (42)	433 (26)	3192 (39)	5762 (44)	1131 (43)	497 (44)
Abdominal aortic aneurysm	117 (4)	322 (5)	767 (100)	134 (8)	466 (6)	693 (5)	114 (4)	151 (14)
Peripheral artery disease	209 (7)	433 (7)	134 (17)	1646 (100)	906 (11)	1492 (12)	328 (13)	205 (18)
Hypertension	1655 (60)	3192 (54)	466 (62)	906 (57)	8228 (100)	7285 (57)	1736 (68)	902 (82)
Hyperlipidaemia	2492 (90)	5762 (96)	693 (91)	1492 (92)	7285 (90)	12972 (100)	2275 (88)	1016 (92)
Diabetes mellitus	442 (16)	1131 (19)	114 (15)	328 (20)	1736 (21)	2275 (18)	2608 (100)	365 (33)
Health questionnaire								
Age (years)	60 ± 11	62 ± 10	65 ± 9	60 ± 11	59 ± 12	58 ± 12	59 ± 12	63 ± 11
Male sex	1744 (62)	4849 (81)	636 (83)	1100 (67)	5174 (63)	8699 (67)	1815 (70)	911 (82)
Previous or current smoking	2106 (76)	4511 (75)	661 (86)	1473 (90)	5697 (69)	9265 (72)	1865 (72)	847 (76)
Packyears in (former) smokers	20.2 (9.4 – 35.1)	20.7 (9.4 – 33.6)	28.0 (13.8 – 42.3)	27.9 (14.6 – 40.6)	18.9 (8.3 – 33.3)	18.9 (8.8 – 32.5)	21.0 (9.5 – 36.2)	22.8 (10.5 – 37.8)
Current alcohol use	1484 (53)	3641 (61)	368 (48)	770 (47)	4787 (58)	7584 (59)	1229 (47)	511 (46)
Highest level of education								
- Primary/secondary school	554 (31)	1248 (29)	128 (34)	315 (40)	1764 (31)	2569 (29)	553 (35)	210 (32)
- Vocational school	631 (35)	1466 (35)	117 (31)	236 (30)	1824 (32)	2891 (33)	519 (33)	223 (34)
- University (of applied science)	560 (31)	1415 (33)	125 (33)	196 (25)	1914 (34)	3031 (35)	422 (27)	194 (30)
Exercise (METh/week)	0.0 (0.0 – 10.5)	0.0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)	0 (0.0 – 11.0)	0 (0.0 – 12.0)	0 (0.0 – 6.0)	0 (0.0 – 5.5)
Medication use								
Lipid-lowering therapy	1682 (60)	4995 (83)	417 (54)	849 (52)	4720 (57)	8253 (64)	1664 (64)	678 (61)
Antihypertensive therapy	1724 (62)	5409 (90)	545 (71)	912 (55)	7130 (87)	9080 (70)	1980 (76)	965 (86)

Platelet inhibitors	2062 (74)	5263 (88)	450 (59)	987 (60)	4532 (55)	7694 (59)	1453 (56)	640 (57)
Oral anticoagulant therapy	311 (11)	821 (14)	123 (16)	234 (14)	743 (9)	1188 (9)	271 (10)	182 (16)
Glucose lowering therapy	287 (10)	757 (13)	67 (9)	189 (11)	1176 (14)	1475 (11)	1621 (62)	216 (19)
Anthropometric measurements								
Systolic blood pressure (mmHg)	141 ± 22	137 ± 20	142 ± 20	144 ± 21	150 ± 23	140 ± 22	144 ± 21	150 ± 24
Diastolic blood pressure (mmHg)	82 ± 12	80 ± 11	83 ± 12	81 ± 11	87 ± 14	83 ± 13	82 ± 12	85 ± 14
Ankle-brachial index ≤0.9	398 (14)	680 (11)	165 (22)	1063 (66)	1195 (15)	1751 (14)	434 (17)	283 (26)
Body mass index (kg/m^2)	26.6 ± 4.2	27.3 ± 4.0	26.4 ± 3.8	26.3 ± 4.3	27.6 ± 4.6	27.0 ± 4.3	28.7 ± 5.0	27 ± 4
Waist circumference (cm)	93.7 ± 12.9	97.4 ± 11.6	97.6 ± 12.1	95.0 ± 12.5	96.4 ± 13.3	95.1 ± 12.7	100.7 ± 13.7	98.9 ± 12.5
Hip circumference (cm)	103.6 ± 8.7	104.2 ± 7.6	103.8 ± 7.8	103.0 ± 8.7	105.1 ± 9.2	104.1 ± 8.5	106.3 ± 9.8	104.4 ± 8.4
Visceral fat (cm)	8.6 ± 2.6	9.3 ± 2.6	9.5 ± 2.6	9.2 ± 2.7	9.0 ± 2.8	8.8 ± 2.7	10.1 ± 2.9	9.9 ± 2.8
Subcutaneous fat (cm)	2.5 ± 1.2	2.4 ± 1.2	2.2 ± 1.1	2.4 ± 1.5	2.6 ± 1.4	2.5 ± 1.3	2.4 ± 1.4	2.2 ± 1.4
Carotid artery stenosis	652 (24)	443 (8)	84 (11)	255 (16)	77 (10)	1104 (9)	283 (11)	181 (16)
cIMT (mm)	0.9 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)	0.9 (0.8 – 1.1)	0.8 (0.7 – 1.0)	0.8 (0.7 – 1.0)	0.9 (0.7 – 1.0)	0.9 (0.8 – 1.1)
Aortic aneurysm	81 (3)	244 (4)	307 (41)	72 (4)	289 (4)	458 (4)	61 (2)	108 (10)
Kidney size (cm)	11.1 ± 1.0	11.3 ± 1.0	11.3 ± 1.0	11.2 ± 1.1	11.2 ± 1.0	11.2 ± 1.0	11.5 ± 1.0	10.9 ± 1.3
Laboratory measurements								
Haemoglobin (mmol/L)	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.9 ± 0.9	8.9 ± 0.8	8.9 ± 0.8	8.8 ± 0.9	8.5 ± 1.0
Total cholesterol (mmol/L)	4.9 ± 1.2	4.5 ± 1.1	5.1 ± 1.3	5.3 ± 1.3	5.0 ± 1.3	5.1 ± 1.4	4.7 ± 1.3	5.0 ± 1.4
LDL-C (mmol/L)	2.9 ± 1.1	2.6 ± 0.9	3.1 ± 1.1	3.2 ± 1.1	2.9 ± 1.1	3.1 ± 1.2	2.7 ± 1.0	2.9 ± 1.1
HDL-C (mmol/L)	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.4	1.3 ± 0.4	1.2 ± 0.3	1.2 ± 0.4
Apolipoprotein B (g/L)	0.8 ± 0.3	0.8 ± 0.2	0.9 ± 0.2	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3	0.9 ± 0.3
Triglycerides (mmol/L)	1.3 (0.9 – 1.9)	1.4 (1.0 – 2.0)	1.5 (1.1 – 2.1)	1.5 (1.1 – 2.3)	1.4 (1.0 – 2.1)	1.4 (1.0 – 2.1)	1.6 (1.1 – 2.4)	1.7 (1.2 – 2.5)
HbA1c (mmol/mol)	38 (36 – 42)	39 (36 – 43)	39 (36 – 43)	40 (37 – 48)	39 (36 – 44)	38 (36 – 43)	52 (45 – 62)	41 (37 – 52)
Fasting glucose (mmol/L)	5.7 (5.3 – 6.3)	5.9 (5.4 – 6.6)	5.8 (5.4 – 6.5)	5.8 (5.3 – 6.7)	5.8 (5.4 – 6.6)	5.8 (5.3 – 6.4)	8.1 (6.9 – 10.0)	6.0 (5.5 – 7.2)
eGFR (mL/min/1.73 m^2)	48 ± 40	63 ± 34	58 ± 32	51 ± 40	49 ± 40	54 ± 40	55 ± 41	40 ± 26
Albuminuria (mg/L)	10.0 (6.0 – 24.1)	9.0 (6.0 – 20.0)	12.9 (8.0 – 39.9)	11.0 (7.0 – 32.0)	11.0 (7.0 – 29.0)	9.0 (6.0 – 22.0)	14.0 (8.0 – 41.0)	82.0 (16.0 – 257.6)
CRP (mg/L)	2.1 (1.0 – 4.5)	1.9 (1.0 – 4.0)	3.3 (1.6 – 6.9)	3.1 (1.4 – 6.3)	2.2 (1.0 – 4.7)	2.0 (1.0 – 4.2)	2.4 (1.1 – 5.1)	3.2 (1.5 – 7.2)
TSH (mU/L)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.7 (1.2 – 2.5)	1.8 (1.2 – 2.6)	1.8 (1.2 – 2.5)	1.9 (1.3 – 2.7)	1.8 (1.3 – 2.7)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

[a] Based on inclusion diagnosis, items of the health questionnaire and/or measurements at baseline:

Cerebrovascular disease: history of stroke, carotid surgery or percutaneous transluminal angioplasty;

Coronary artery disease: history of myocardial infarction, cardiac arrest, coronary bypass surgery or percutaneous transluminal coronary angioplasty;

Abdominal aortic aneurysm: history of abdominal aortic aneurysm, transluminal or surgical treatment of abdominal aortic aneurysm;

Peripheral artery disease: history of amputation of (part of) lower limb, lower limb peripheral artery surgery or percutaneous transluminal angioplasty;

Hypertension: treatment with antihypertensive drugs or blood pressure ≥160/95 mmHg at baseline measurement;

Hyperlipidaemia: treatment with lipid-lowering agents, total cholesterol ≥5 mmol/L or LDL-cholesterol ≥3.2 mmol/L at baseline measurement;

Diabetes mellitus: treatment with antidiabetic agents, fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥11.1 mmol/L at baseline measurement;

Renal insufficiency: creatinine >120 mmol/L and/or microprotein/creatinine ratio in urine >20.

Cut-off values applied at the start of UCC-SMART study, please note target values have changed over time and continuous variable are available.

cIMT, carotid intima media thickness; CRP, C-reactive protein; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MET, metabolic equivalent of task; TSH: thyroid stimulation hormone.

Findings to date

The findings of this section are reported for patients included up to January 2020 (n = 13,898), because the collection and processing of outcome events has been completed up until this date. These patients contributed to a total follow-up time of 134,439 person-years. Median follow-up time was 9.2 years (interquartile range 4.8 – 14.1 years). During follow-up, 2,259 (16%) patients suffered a first combined major cardiovascular endpoint (including non-fatal myocardial infarction, non-fatal stroke or cardiovascular death). Furthermore, there were 943 (7%) cases of incident diabetes, 105 (1%) cases of end-stage kidney disease, 161 (1%) cases of heart failure and 434 (3%) cases of major bleeding. A total of 3,264 (23%) patients underwent a vascular intervention during follow-up. Of patients with established CVD, 1,906 patients (21%) suffered the combined vascular endpoint mentioned above as subsequent event, whereas 353 patients (7%) with severe risk factors without prior CVD experienced this combined outcome as their first ever event. Of the 2,450 individuals with diabetes at baseline, 568 (23%) individuals suffered the combined vascular endpoint. Corresponding incidence rates are 21.2 per 1000 person years for patients with established CVD and 8.2 per 1000 person years for patients without a history of CVD. Numbers and observed incidence rates of all specific outcome events of interest are listed in Table 2. Through linkage with the Dutch National Cancer Registry, a total of 2,139 patients (15%) was diagnosed with cancer during follow-up. This includes 414 diagnoses of lung cancer, 354 of prostate cancer, 294 of intestinal cancer and 163 of breast cancer as most common diagnoses.

456 *Table 2. Number and incidence rates of outcome events from 1996 to 2020*

Outcome event	Number of first events	Person-years of follow-up	Incidence rate per 1,000 person-years
Non-fatal stroke	613	131,684	4.66
Ischemic stroke	502	132,042	3.80
Haemorrhagic infarction	20	134,362	0.15
Intracerebral haemorrhage	66	134,285	0.49
Subarachnoid haemorrhage	17	134,322	0.13
Type not determined	8	134,430	0.06
Retinal syndromes	16	134,338	0.12
Infarction	13	134,353	0.10
Haemorrhage	3	134,424	0.02
Non-fatal myocardial infarction	793	130,065	6.10
Heart failure	161	134,075	1.20
Systolic heart failure, due to	115	134,203	0.86
coronary disease	85	134,266	0.63
valve disorders	11	134,425	0.08
other causes	19	134,390	0.14
HFpEF, due to	46	134,311	0.34
coronary disease	15	134,390	0.11
valve disorders	8	134,418	0.06
other causes	23	134,381	0.17
Non-fatal rupture AAA	5	139,895	0.04
End-stage kidney disease	105	134,118	0.78
Vascular intervention	3,264	110,154	29.6
Heart	1606	121,936	13.2
Carotid or intracranial arteries	240	132,611	1.81
Aorta	439	131,553	3.34
Peripheral arteries	953	127,914	7.45
Renal artery	62	133,970	0.46
Major bleeding			
ISTH major bleeding	434	129,804	3.34
BARC 3 or 5 bleeding	457	132,497	3.45
Incident diabetes	943	124,310	7.59
Type 1 diabetes	1	131,417	0.01
Type 2 diabetes	942	124,330	7.58

Vascular mortality	1,267	134,439	9.42
Fatal cerebral infarction	85		0.63
Fatal cerebral haemorrhage	65		0.48
Fatal stroke – type not determined	21		0.16
Fatal myocardial infarction	63		0.47
Fatal heart failure	198		1.47
Fatal rupture AAA	29		0.22
Sudden death	401		2.98
Other	405		3.01
Non-vascular mortality	1317	134,439	9.80
Fatal malignancy	800		5.95
Fatal infection	169		1.26
Unnatural death	58		0.43
Other	290		2.16
All-cause mortality	2,794	134,439	20.78
Malignancy[a]	2,139	127,514	16.77
Lung	414		3.25
Prostate	354		2.78
Breast	163		1.28
Intestinal	294		2.31
Other	914		7.17

[a] Other subtypes of cancer in the dataset include cancer of the lip, oral cavity or pharynx; oesophagus; stomach; liver, intrahepatic bile ducts, or gallbladder; pancreas; respiratory tract; thymus; bone or articular cartilage of limb; melanoma; mesothelial or soft tissue; vulva or vagina; cervix uteri or corpus uteri; ovary; penis or testes; kidney, renal pelvis or ureter; bladder; eye, brain, and other parts of the central nervous system; thyroid gland; lymphatic/hematopoietic.

AAA, abdominal aortic aneurysm; BARC, Bleeding Academic Research Consortium; HFpEF, heart failure with preserved ejection fraction; ISTH, International Society on Thrombosis and Haemostasis.

The large database of observational data has been used for over 350 etiological and prognostic studies so far, and the coverage of a wide age range and long follow-up provides opportunity to develop and validate prediction models. This has been done with the SMART risk score[42,43], the SMART-REACH lifetime model for patients with previous CVD[3] and the DIAL lifetime model[44] for patients with type 2 diabetes (to be found at https://u-prevent.com and the ESC 'CVD risk calculation'-app). These estimates serve clinical practice by providing insight into risk and thus supporting patient education and shared decision making. Moreover, routinely collection of patient data allows for embedding clinical trials within the cohort, as has been done with, amongst others, TEMPUS[37] and SMART-Inform[38].

The vascular screening in the UCC-SMART study is a structured uniform program to detect risk factors and asymptomatic atherosclerosis and provides a basis for optimizing treatment of high-risk patients. In a previous study comparing the UCC-SMART screening program to usual care in another university hospital in the Netherlands, a beneficial effect of the screening program on SBP and LDL-C was seen.[36] Previous research on screening programs in the general population shows improvement of cardiovascular risk factors and detection of patients at risk, but conflicting results are found on mortality and cardiovascular events.[2,45] In a population at risk (e.g. with hypertension or diabetes), the beneficial effect of cardiovascular screening is more pronounced.[2,46] In addition, a higher baseline achievement of secondary prevention targets is associated with improved cardiovascular health outcomes in patients with established CVD and type 2 diabetes.[47]

Strengths and limitations

The UCC-SMART study is a unique ongoing prospective cohort study in over 14,000 patients with a history of various manifestations of CVD or severe cardiovascular risk factors, providing a large up-to-date cohort of a population at high cardiovascular risk. Collecting diverse outcome events in this population allows for research on risk factors for different manifestations of CVD and incident diabetes. Linkage to multiple registries facilitates the investigation of relationships between cardiovascular risk factors and diseases and other conditions such as cancer and dementia. By the integration of health care and scientific research, patient care becomes more complete and data already to be collected for patient

care is used to increase knowledge of CVD, whilst the additive burden for participating patients is limited.

The main strengths of the UCC-SMART cohort include the large size, its capture of a high-risk population with various CVD manifestations and risk factors with few exclusion criteria, the use of a standardized diagnostic protocol, the long follow-up duration and the comprehensive capture of a wide range of data. Because inclusion of patients is still ongoing, the UCC-SMART cohort provides a good representation of the past and current population of patients at high cardiovascular risk. Due to the high risk study population, the prevalence and incidence of the main outcome variables are higher than in the general population, thereby increasing the power to study these outcomes. Furthermore, all outcome events are adjudicated independently by three physicians of the endpoint committee, reducing the risk of misclassification. The proportion of missing data is small, possibly explained by the protocolized screening program taking place in one day. The substudies provide additional information on specific cardiovascular risk factors (e.g. parental history of CVD[48], characteristics related to left ventricle hypertrophia[31], and the presence of diffuse idiopathic skeletal hyperostosis[49]), manifestations of atherosclerosis (e.g. brain changes on MRI[25] and cognitive decline[26]), and other important aspects in cardiovascular risk management (e.g. the effect of a cardiovascular polypill[50]).

Limitations also need to be considered. Due to the prospective observational design, for the majority of the patients, risk factors and medication use are only recorded at baseline and may have changed during follow-up. This could be reflected by the finding of this article that not all patients with CVD meet treatment goals for modifiable risk factors at baseline. Since patients are included several weeks to months after an index CVD event, risk factors are likely to be further optimized during this period after baseline examination. For a subset of patients with CVD or diabetes, a repeat of the baseline measurements after a median of 9.9 years is indeed available, allowing for investigating the course of atherosclerosis over time. Furthermore, in 10.6% of the included patients, follow-up ended due to either withdrawal of participation in further follow-up (8.5%) or being unreachable for further questionnaires (2.1%). Yet, the median follow-up time for these patients is 7.4 years, so those patients still contribute to a fair amount of patient-years. In addition, because UCC-SMART is a single-center study in a university hospital, it can be disputed whether it represents the general high risk population and patients

with established CVD. The UMC Utrecht provides care to nationwide patients referred for complex and specialized care, but also to patients referred by general practitioners from the region. Patients included in UCC-SMART correspond to patients with severe cardiovascular risk factors or established CVD from the general population. As reflected by the inclusion criteria, the UCC-SMART study does not include patients requiring highly specialized care (including heart transplantation and rare causes of vascular disease). Lastly, except for information on education level, the database does not contain extensive information on socioeconomic status.

In conclusion, we have provided an updated extensive overview of the design of the UCC-SMART study as well as an overview of the findings to date. This underlines the value of the UCC-SMART study as a basis for contemporary and future epidemiologic research in CVD using a well-characterized high risk cardiovascular population with long-term follow-up. A future goal is to make the UCC-SMART data Findable, Accessible, Interoperable and Reusable (FAIR).[51]

Collaboration

The UCC-SMART study group directs the academic focus of research using the UCC-SMART data and consists of staff members from both epidemiological and clinical departments. All data presented in this manuscript will be available upon reasonable request, and specific datasets will be compiled based on the research proposal. The data is to be used only for the purposes as described in the research proposal. Datasets are provided to interested researchers after approval of request by the UCC-SMART study group. Access to the data request module can be applied for via ucc-smart@umcutrecht.nl. We encourage collaborations within overarching cardiovascular topics in which datasets are combined.

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Contributors

F.L.J.V., J.W., S.H.J.H., M.C.C. and M.A.G.H. contributed to the conception and design of the work. M.A.G.H. and M.C.C. drafted the manuscript and contributed equally to this paper. M.C.C., M.A.G.H., S.H.J.H., F.W.A., G.J.B., M.L.B., M.J.C., J.A.N.D., M.H.E-V., M.I.G., P.A.J., N.K., J.K., A.T.L., M.G.M., B.M.M., H.M.N., C.O.-M., R.B.P., Y.M.R., M.S., M.T., A.V., M.C.V., J.W. and F.L.J.V contributed to the interpretation of data and critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Competing interests

None declared.

Patient consent for publication

Not applicable.

Ethics approval

The study is in accordance with the Helsinki declaration and the Good Clinical Practice guidelines, and is approved by the ethics committee of the UMC Utrecht in 1996, 2014 and 2022 (reference number 22-088).

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Figure legends

Figure 1. Course of the UCC-SMART study

ECG, electrocardiogram; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease; UMC Utrecht, University Medical Centre Utrecht

Figure 2. Timeline of measurements collected for or starting from a certain period

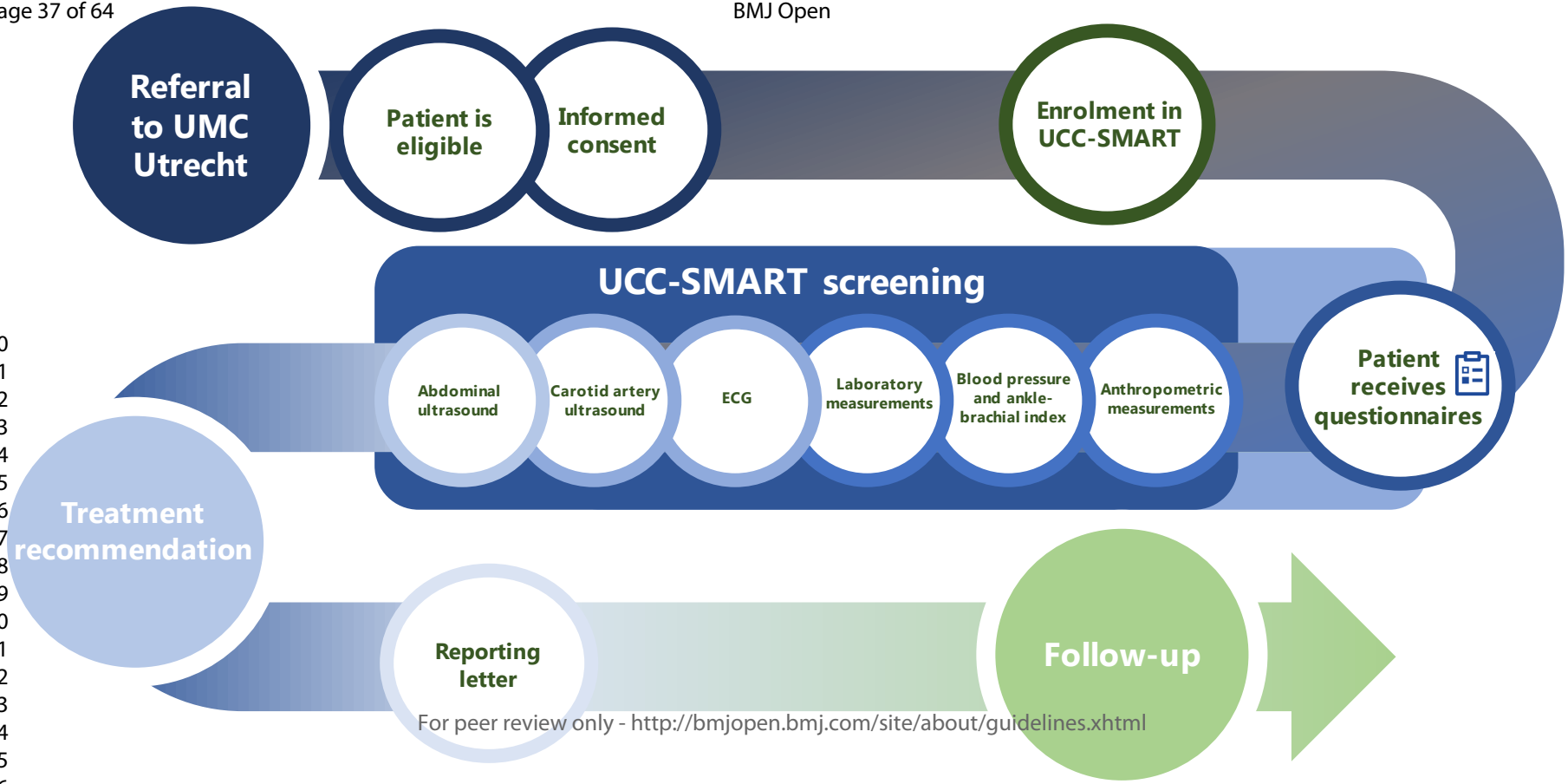
ACE, angiotensin converting enzyme; apoB, apolipoprotein B; CAC, coronary artery calcium; CRP, C-reactive protein; CT, computerized tomography; CV, cardiovascular; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; Lp(a), lipoprotein a; MRI, magnetic resonance imaging; T, Tesla; TSH, thyroid stimulating hormone

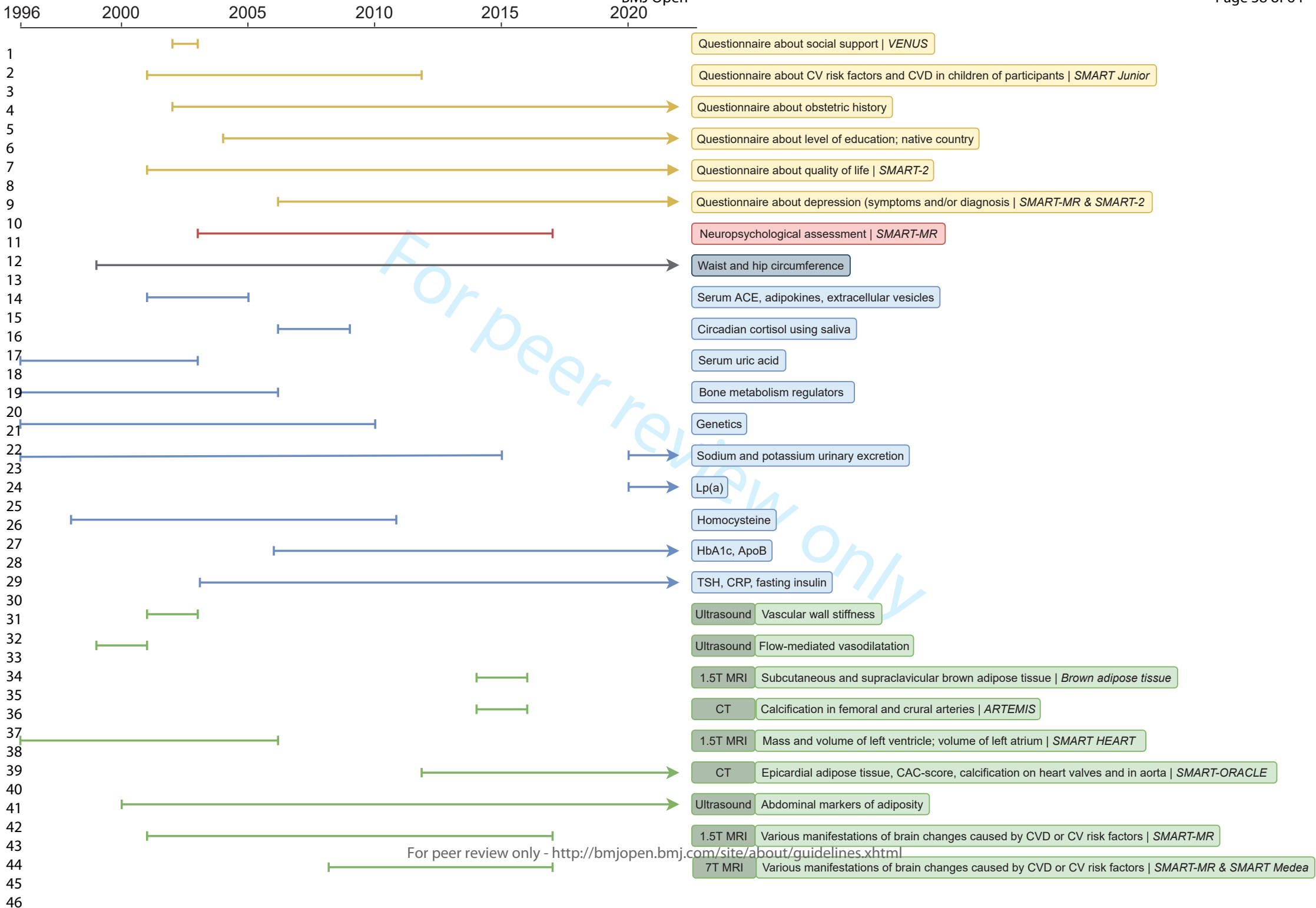
Figure 3. Cumulative number of patients over time

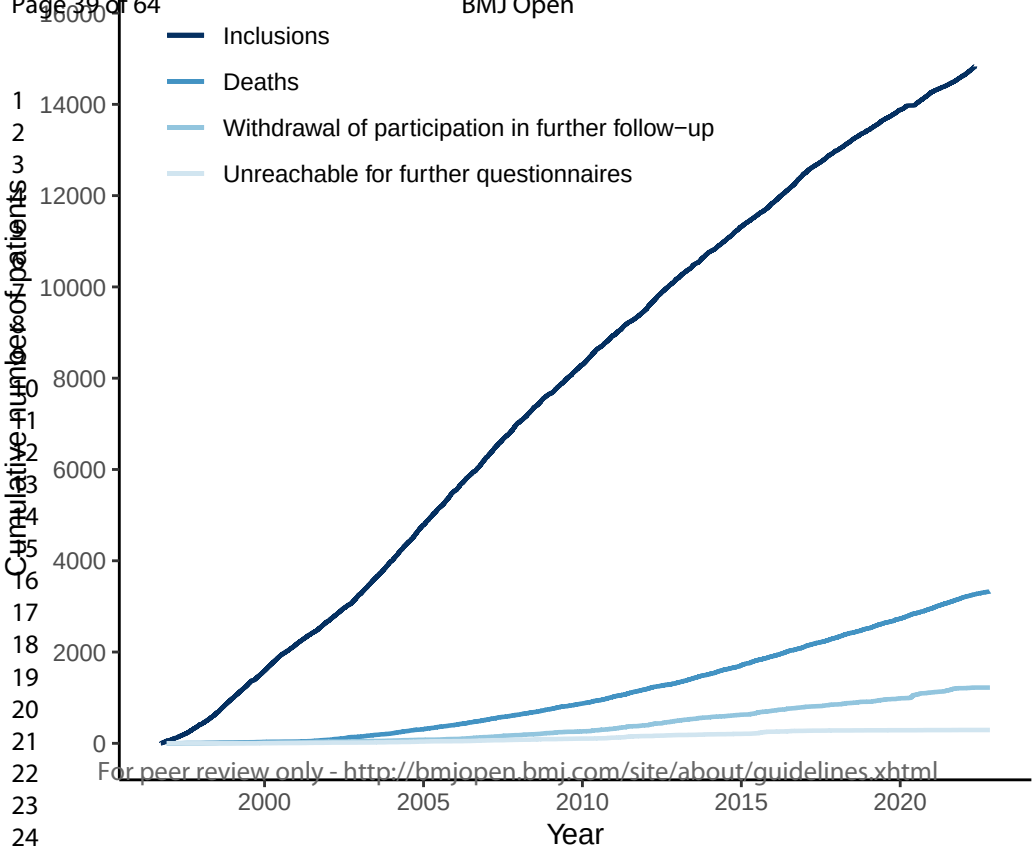
Inclusion in the UCC-SMART study started in September 1996.

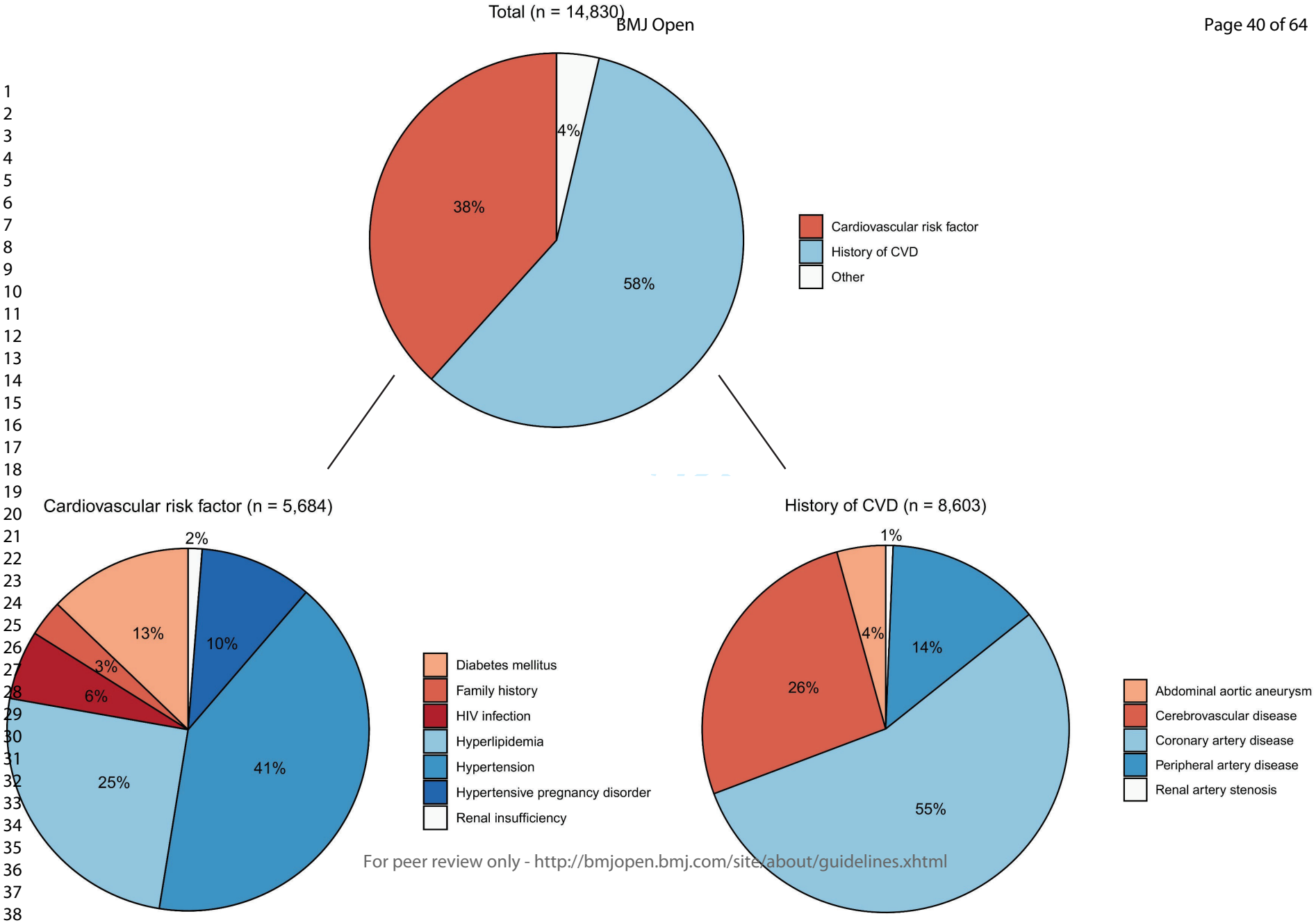
Figure 4. Distribution of inclusion diagnoses

CVD, cardiovascular disease; HIV, human immunodeficiency virus









Supplementary material

Cohort profile: the Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Disease (UCC-SMART) study – an ongoing prospective cohort study of patients at high cardiovascular risk in the Netherlands

Content list

Supplementary Table 1. Inclusion criteria and exclusion criteria

Inclusion criteria	Definition
One or more of the following cardiovascular diseases or risk factors:	
Cardiovascular disease	
Transient ischemic attack	Sudden onset, ≤24 hours of: *carotid:* temporary motor weakness in one half of the body, language disorder, blindness in one eye *vertebrobasilar*: ≥2 simultaneously: bilateral motor weakness or paraesthesia, dizziness, diplopia, dysphagia, ataxia, dysarthria *unknown vascular region:* hemianopia, dysarthria
Cerebral infarction	Criteria as for TIA, but duration of >24 hours
Subarachnoid haemorrhage	Sudden headache and (temporary) loss of consciousness, often accompanied by neck stiffness, nausea and vomiting, with blood in basal cisterns confirmed by CT or xantochromia in cerebrospinal fluid
Carotid artery stenosis	Duplex ultrasound confirmed stenosis or occlusion of ≥1 carotid artery with diameter reduction ≥50%
Ischemic retinal syndrome	Visual field defect diagnosed as retinal syndrome by ophthalmologist
Angina pectoris	Chest pain with proven stenosis on coronary angiogram
Myocardial infarction	≥2 of following: - Chest pain >20 minutes, not relieved by nitrates; - ST elevation >1 mm in 2 contiguous ECG leads, or left bundle branch block; - Troponin levels >60 ng/L with rise and fall pattern*
Coronary syndrome requiring PCI or CABG	
Abdominal aortic aneurysm	Ultrasound confirmed local dilatation of abdominal aorta with anterior-posterior diameter ≥3 cm and/or distal-proximal ratio of >1,5
Renal artery stenosis	Stenosis of ≥1 renal artery with lumen narrowing ≥50%, caused by atherosclerosis
Peripheral artery disease of the lower limbs	Fontaine classification: - Fontaine II: intermittent claudication: pain (or other symptoms) in one or both legs after certain walking distance, disappearing at rest; - Fontaine III: rest/nocturnal pain; - Fontaine IV: ischemic ulceration, necrosis or gangrene; confirmed by ABI ≤0.90 at rest and/or ≥20% post-exercise decrease
Cardiovascular risk factors	
Hypertension	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hypertension, target organ damage, medical or family history
Hyperlipidaemia	Estimated as severe risk factor by physician, based on e.g. difficult-to-control hyperlipidaemia, suspected lipid metabolism disorder, medical or family history

Diabetes mellitus	Fasting glucose ≥7.0 mmol/L, non-fasting glucose ≥11.1 mmol/L or use of oral antidiabetic agents or insulin
Renal insufficiency	Serum creatinine >120 µmol/L
HIV infection	Chronic infection with human immunodeficiency virus
Family medical history	Positive family history for premature cardiovascular disease in 1st degree relatives
Pre-eclampsia†	Gestational hypertension accompanied by proteinuria, other maternal organ dysfunction or uteroplacental dysfunction
HELLP syndrome†	Haemolysis, elevated liver enzymes, low platelets as a manifestation of pre-eclampsia
Placental abruption†	Gestational hypertension accompanied by placental abruption as an effect of uteroplacental insufficiency
Intrauterine growth restriction†	Gestational hypertension accompanied by fetal growth restriction as an effect of uteroplacental insufficiency
Remaining inclusion criteria	
18 – 90 years of age	
Independent in most daily activities	Rankin scale ≤3[1]
Exclusion criteria	
Pregnancy	
Short life expectancy (per judgement of the treating physician)	
Insufficient understanding and expression of the Dutch language	
No informed consent	
Follow-up impossible	

* In earlier years of the UCC-SMART study, this laboratory item was defined as CK elevation of ≥2x upper limit and MB-fraction >5% of total CK level.
† Hypertensive pregnancy complications are based on the ISSHP criteria[2]

ABI, ankle-brachial index; CABG, coronary artery bypass grafting; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; HELLP, haemolysis, elevated liver enzymes and low platelets; HIV, human immunodeficiency virus; ISSHP, International Society for the Study of Hypertension in Pregnancy; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 2. Variables available in UCC-SMART

Health questionnaire	Medication use	Physical examination	Radiology measurements	Laboratory measurements
Medical history	Statins	Weight (kg)	Visceral fat (cm)	Haemoglobin (mmol/L)
Age (years)	Ezetimibe	Height (m)	Subcutaneous fat (cm)	Haematocrit (%)
Sex	Fibrates	Blood pressure (mmHg)	Carotid artery stenosis (%)	Total cholesterol (mmol/L)
Smoking and pack years	Thiazide diuretics	Ankle-brachial index	Carotid intima thickness (mm)	LDL-C (mmol/L)
Alcohol use and number of units	Loop diuretics	Body mass index (kg/m^2)	Aortic artery diameter (cm)	HDL-C (mmol/L)
Level of education	Potassium saving diuretics	Waist circumference (cm)	Kidney size and volume (cm; mL)	Apolipoprotein B (g/L)
Country of birth	ACE-inhibitors	Hip circumference (cm)	Electrocardiography	Triglycerides (mmol/L)
Quality of life*	Angiotensin II-receptor blockers		Echocardiography†	HbA1c (%)
Exercise (MET-hours per week)	Aldosterone antagonists			Fasting glucose (mmol/L)
	Beta-blockers			Fasting insulin (mU/L)
	Calcium antagonists			Creatinine (µmol/L)
	Alpha blockers			eGFR (ml/min/1.73 m^2)
	Central acting antihypertensives			Albuminuria (mg/L)
	Direct vasodilators			Albumin-to-creatinine ratio
	Aspirin			CRP (mg/L)
	Clopidogrel			TSH (mU/L)
	Dipyridamole			Lp(a)
	DOAC			Urine sodium
	Vitamin K antagonists			Urine potassium
	LMWH			
	Oral glucose-lowering therapy			
	Insulin			
	Antidepressants			
	Benzodiazepines			

* Based on EQ-5D questionnaire

† Echocardiography will be added to the UCC-SMART program in the near future

ACE, angiotensin converting enzyme; CRP, C-reactive protein; DOAC, direct oral anticoagulant; eGFR, estimated glomerular filtration rate; HbA1c, glycosylated haemoglobin type A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LMWH, low molecular weight heparin; Lp(a), lipoprotein(a); MET, metabolic equivalent of task; TSH, thyroid stimulating hormone; UCC-SMART, Utrecht Cardiovascular Cohort – Second Manifestations of Arterial Diseas

Supplementary Table 3. Measurements that have been performed in the past

Vascular wall stiffness was determined from 2001 until 2003 using the Wall Track System that captures vascular diameter changes using radio-frequent signals. At the first signal, the position of the anterior and posterior vascular wall of the common carotid artery are marked at 2 cm proximal to the carotid bulb. Then, for five times on both the left and right side, changes in arterial diameter (ΔD) and end-diastolic diameter (D_d) are registered during four seconds, and the mean is calculated. Carotid distension is defined as the change in artery diameter in systole relative to diastolic diameter. Other stiffness indices include β stiffness index ($\ln(SBP/DBP)/(\Delta D/D_d)$), compliance coefficient ($(\pi \times D_d \times \Delta D)/2 \times$pulse pressure), distensibility coefficient ($(2 \times \Delta D/D_d)$/pulse pressure), Peterson's modulus (pressure change required for theoretical 100% increase in diameter) and Young's elastic modulus (pressure per mm^2 required for theoretical 100% extension).
Flow-mediated vasodilatation (FMD) was assessed temporarily starting from March 1999. Here, the Wall Track System described above was used to capture the diameter of the brachial artery in the elbow crease. Following 3 baseline readings, new measurements were taken every 30 seconds for 5 minutes: first after a blood pressure cuff at the forearm was inflated to 100 mmHg above SBP for 4 minutes, and then after sublingual administration of 400 µg of nitroglycerin. Endothelial function was defined as the proportional increase of diameter after nitrate and the baseline-adjusted maximal diameter following ischemia. This examination was stopped in June 2001, since analysis in the first 400 patients showed this measurement was not related to other known measures of atherosclerosis.
Quality of life information was collected through questionnaires based on the 36-Item Short Form Health Survey (SF-36)[3], sent to participants from 2001 until 2019. This quality of life assessment contains scales for 1) limitations in physical activities; 2) limitations in social activities; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) mental health; 6) limitations in usual role activities because of emotional problems; 7) vitality and 8) general health perceptions.
Homocysteine was measured from 1998 until 2011 in fasting blood samples by high performance liquid chromatography with fluorescence detection. Up until 2000, a methionine loading test was performed in patients younger than 50 years. Plasma homocysteine was measured six hours after oral administration of 100mg methionine per kilogram bodyweight.

DBP, diastolic blood pressure; SBP; systolic blood pressure

Supplementary Table 4. Definitions of established cardiovascular disease

Cardiovascular disease	Definition of cardiovascular disease*
Cerebrovascular disease	TIA, cerebral infarction, ischemic retinal syndrome, carotid surgery or angioplasty in medical history
Coronary artery disease	Myocardial infarction, angina pectoris, ≥ 1 vessel disease on coronary angiography, PCI or CABG in medical history
Abdominal aortic aneurysm	Abdominal aortic aneurysm, surgical or endovascular treatment of abdominal aortic aneurysm in medical history
Peripheral artery disease	Fontaine classification ≥ II, amputation, vascular surgery or angioplasty in medical history

* Definitions of these items are listed in Supplementary Table 1.
CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TIA, transient ischemic attack.

Supplementary Table 5. Definitions of outcome events

Outcome event	Definition of outcome event
	Primary endpoints
Stroke	
Ischemic stroke / haemorrhagic infarction	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale[1], and new (haemorrhagic) infarction on CT or MRI <2 weeks after stroke
Cerebral haemorrhage	Cerebral haemorrhage confirmed with CT, MRI or surgery
Subarachnoid haemorrhage	Subarachnoid haemorrhage confirmed with CT, MRI or surgery
Type not determined	>24 hours of associated clinical signs causing increased disability of ≥1 grade on modified Rankin scale, but no brain imaging performed
Retinal syndromes	
Infarction	Associated clinical symptoms, typical fundus changes and/or vision loss, scotoma on perimetry
Haemorrhage	Associated clinical symptoms, typical fundus changes and vision loss
Myocardial infarction	The assessment includes: chest pain >30 minutes, elevated cardiac enzymes, characteristic ECG-changes
STEMI	Acute chest pain with persistent (>20 minutes) ST-elevation
NSTEMI	Acute chest pain without ST-elevation, with elevated troponin
Intervention-related myocardial infarction	New Q wave and elevated troponin <7 days after any intervention (for PCI >3x, for CABG >5x)
Probable myocardial infarction	Typical pain, persistent STT-changes, no documented course of cardiac enzymes
Heart failure	≥2 of the following: dyspnoea, dyspnoea on exertion, paroxysmal nocturnal dyspnoea, orthopnoea, exercise intolerance, pulmonary oedema, increased central venous pressure, third heart tone, hepatojugular reflux, altered hemodynamics, peripheral oedema, cardiomegaly; and (intensified) treatment with loop diuretics or intravenous vasoactive inotropic agents Classified as: systolic heart failure (at least moderate left ventricle dysfunction or LVEF <40%) or heart failure with preserved ejection fraction, due to coronary disease, valve disease or other causes
Rupture of abdominal aortic aneurysm	Rupture abdominal aortic aneurysm, proven by ultrasound, CT or laparotomy
Renal disease	
End-stage renal disease	CKD stage 5 (i.e. persisting eGFR <15ml/min/1.73 m^2 for >3 months and/or need for renal replacement therapy (chronic dialysis or renal transplantation))

Acute renal insufficiency – temporary renal replacement therapy	Acute kidney injury requiring temporary renal replacement therapy
Acute renal insufficiency – no renal replacement therapy	Acute kidney injury KDIGO stage 3 (i.e. serum creatinine 3 times baseline creatinine and/or serum creatinine ≥354 µmol/L)
Bleeding	Bleeding requiring outpatient treatment or (prolonged) hospitalization
Major bleeding	*ISTH definition:* fatal bleeding and/or bleeding in critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, intramuscular causing compartment syndrome), bleeding causing Hb level drop of ≥1.24 mmol/L or leading to transfusion of ≥2 units of blood[4] *BARC type 3:* overt bleeding with Hb level drop of ≥1.86 mmol/L, leading to transfusion, cardiac tamponade, surgical intervention for control or intravenous vasoactive agents, or located intracranial or intraocular compromising vision *BARC type 5:* fatal bleeding[5]
Diabetes	Self-reported diagnosis, confirmed and classified based on a questionnaire. If necessary, additional information is requested from the general practitioner or looked up in the electronic health record.
DM type 1	Insulin needed immediately at onset and absence of oral glucose lowering medication. Supportive but not mandatory: ≤25 years of age, BMI <25 kg/m^2, presence of anti-GAD antibodies
DM type 2	Diagnosed between age 35 and 40 and BMI >33 kg/m^2 or diagnosed after age 40 and BMI >27 kg/m^2
Dementia	Self-reported diagnosis, confirmed and classified based on a questionnaire. Classified as: Alzheimer's disease; vascular dementia; a mix of Alzheimer's disease and vascular dementia; Lewy Body dementia; or frontotemporal dementia.
Vascular mortality	
Fatal cerebral infarction	Cerebral infarction leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal cerebral haemorrhage	Cerebral haemorrhage leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without infarction)
Fatal stroke - type not determined	Stroke without radiological confirmation leading to Rankin score 4 or 5 followed by death (reasonably plausible that patient would not have died without stroke)
Fatal myocardial infarction	Documented myocardial infarction followed by death (>1 hour after onset of symptoms)

Fatal heart failure	Heart failure leading to death
Fatal rupture abdominal aortic aneurysm	Rupture abdominal aortic aneurysm followed by death
Fatal bleeding	Major bleeding leading to death
Sudden death	Witnessed death occurring within 1 hour after onset of symptoms, or within 24 hours given convincing circumstantial evidence
Other	Death without apparent cause in case of cardiovascular history, terminal renal insufficiency, dementia (unless clearly non-vascular), pulmonary haemorrhage*
Non-vascular mortality	Death caused by malignancy, infection, unnatural death or other
All-cause mortality	Death from any cause
	Secondary endpoints
Amputation	Any amputation of a toe or part of the foot or leg due to chronic ischemia. *Excluding:* traumatic amputations, amputation due to sepsis, amputation of fingers.
Vascular intervention†	Percutaneous coronary intervention; coronary artery bypass grafting; carotid endarterectomy, angioplasty or stenting; vertebral artery angioplasty or stenting; vascular surgery or percutaneous transluminal angioplasty of the aorta(bifurcation), iliac arteries, femoral and crural arteries; vascular intervention because of abdominal angina; LVAD. Angioplasty and stenting of other arteries are registered as well.
Vascular intervention of an intracranial aneurysm	Coiling or clipping of an intracranial aneurysm

* In accordance with Antiplatelets Trialists' Collaboration, Lancet 2002
† Excluding interventions already planned before or at inclusion, but including re-interventions and complications of an intervention already planned before or at inclusion.

Anti-GAD, antibodies to glutamic acid decarboxylase; BARC; Bleeding Academic Research Consortium; BMI, body mass index; CABG, coronary artery bypass grafting; CKD, chronic kidney disease; CT, computed tomography; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; KDIGO, Kidney Disease Improving Global Outcomes; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction

Supplementary Table 6. Substudies of UCC-SMART

Substudy	Period in which the patients were included	N	Aim	Key publications	Additional measurements within substudy
ARTEMIS *(ARTErial calcifications of the Media and Intima in SMART)*	2015 - 2017	520	1) To determine whether intima and media calcification differ in their respective associated CVD risks. 2) To elucidate which risk factors and mechanisms lead to the development of these respective types of calcification and in turn to cardiovascular disease	- Zwakenberg, 2020, PloS One[6] - Hoek, 2021, Atherosclerosis[7]	Technique: unenhanced thin-slice CT-scan of the legs (femoral head to feet) Measurement: calcification in the femoral and crural arteries scored as absent, predominant intimal arterial calcification, predominant medial arterial calcification or indistinguishable; calcification volume.
Athero-Express *Added to UCC-SMART study in June 2022*	2002 - present	Patients undergoing a femoral or carotid endarterectomy	To investigate the value of plaque characteristics in relation to cardiovascular outcomes	Verhoeven, 2004, Eur J Epidemiology[8]	During surgery, the atherosclerotic plaque is collected and immunohistochemically stained in order to asses fat, collagen, macrophages and smooth muscle cells
BEST *(BEtter risk factor treatment with STructured agreement)* RCT	2004 - 2006	197 patients with at least 2 modifiable risk factors	To investigate whether a clearly written agreement on risk factor management between general practitioners and hospital improved the vascular risk profile of high-risk patients compared with usual care after 1 year	Brouwer, B.G. 2008. SMART risk factor screening in patients at high vascular risk. Utrecht University, Utrecht[9]	NA
Brown adipose tissue	2014 – 2016	50 patients with clinically manifest CVD	1) To evaluate and optimize a protocol for quantifying brown adipose tissue with MRI and to assess BAT volume per patient. 2) To evaluate the reproducibility of MRI by determining inter-scan, intra-observer and inter-observer variability in BAT volume	- Franssens, 2016, NMR Biomed[10] - Franssens, 2017, J Magn. Reson. Imaging[11]	Technique: 1.5T water-fat MRI of supraclavicular and subcutaneous adipose tissue Measurement: fat signal fraction value, representative of the amount of triglycerides, intracellular water content and capillary

					density, of supraclavicular and subcutaneous adipose tissue
DISH *(Diffuse idiopathic skeletal hyperostosis)*	1996 – 2018	4,791 (all patients from SMART with chest X-ray within 3 months of inclusion)	N.A.	- Harlianto, 2021, Rheumatology[12] - Harlianto, 2021, J. Pers. Med.[13]	*Technique: Chest X-ray within three months of inclusions (if available in routine clinical care)*
					Measurement: X-rays were scored for DISH using the Resnick criteria.[14] DISH is classified following the presence of ossification of at least four contiguous vertebrae; (relative) preservation of the intervertebral disc height; and the absence of apophyseal joint bony ankylosis or sacroiliac joint erosion. Thoracic aortic calcification subjective score as absent, mild, moderate and severe.
IRIS *(Internet-based vascular Risk factor Intervention and Self-management)* RCT	2008 - 2010	330 patients with a recent clinical manifestation of atherosclerosis of CAD, CeVD or PAD and with ≥ 2 treatable risk factors not at goal (from UMC Utrecht + Rijnstate)	1) To evaluate whether an internet-based vascular risk factor management program promoting self-efficacy on top of usual care is more effective than usual care alone in reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease. 2) To evaluate whether an internet-based vascular risk factor management program for reducing vascular risk factors in patients with a recent clinical manifestation of a vascular disease is cost-effective.	- Vernooij, 2012, BMJ[15] - Greving, 2015, BMJ Open[16]	NA

RULE *(Risk management in Utrecht and Leiden Evaluation study)* Two-centre parallel-group comparative investigation	2005 - 2007	604 patients with CAD, CeVD, PAD or T2DM from UMC Utrecht (+ 566 patients from LUMC)	To assess risk factor status after referral in patients with established vascular disease or type 2 diabetes who took part in the multidisciplinary hospital-based vascular screening program SMART, compared with a group who did not participate in such a program	Brouwer, 2010, J of Int Med[17]	NA
Small aneurysms trial (AAA)	1996 - 2005	230 patients with an initial AAA diameter of 30-55mm, who were examined by ≥ 2 AAA diameter measurements and with ≥ 6 months of FU	To estimate overall rupture rates of small AAAs and to investigate a predefined set of demographic characteristics and cardiovascular risk factors for association with AAA growth	Schlosser, 2008, J Vasc Surg[18]	<u>Technique:</u> Ultrasound scanning of the aorta <u>Measurement:</u> AAA diameter and change with initial AAA diameter
SMART-2	2007 - present	1794 patients with a history of CVD or diabetes, a median of 9.9 years after inclusion in UCC-SMART	To study the course of atherosclerosis and vascular risk factors over time, and to evaluate the effects of treatment in the past		NA
SMART HEART	1996 - 2006	536 patients with ≥ 3 years hypertension, but free of known coronary or	To detect patient characteristics related to the development of LVH with special focus on the detection of SNPs that confer an increased susceptibility for the development of LVH, and thus, heart failure	- Meijs, 2007, Neth Heart J[19] - Meijs, 2009, Eur J Prev Cardiol[20] - Vernooij, 2012, Am J Cardiol[21]	<u>Technique:</u> 1.5T cardiac MRI and delayed-enhancement cardiac MRI <u>Measurement:</u> LV mass, LV-end diastolic and end-systolic volumes and left atrial volumes; areas of hyperintense myocardium

		valvular disease		- De Beus, 2015, Eur J Clin Invest[22]	classified as myocardial scar tissue (used to assess the presence of unrecognized myocardial infarction). Infarct size was quantified as scar mass relative to LV mass.
SMART Inform Three-armed hypothesis-blinded RCT	2017 - 2018	303 patients with stable CVD and using a statin	To determine whether communicating personalized statin therapy-effects obtained by prognostic algorithm leads to lower decisional conflict associated with statin use in patients with stable CVD compared with standard (non-personalized) therapy-effects	Jaspers, 2021, BMJ Open[23]	NA
SMART-Junior	Questionnaires sent between 2009-2013 to patients who were included between 2001 and 2012	4,270 (10,564 children)	1) To investigate the presence of cardiovascular risk factors and vascular disease in offspring of patients participating in the SMART cohort. 2) To identify a risk profile of the parent prognostic for the development of traditional cardiovascular risk factors or cardiovascular events in their children.	- Weijmans, 2015, Int J Cardiol[24] - Weijmans, 2015, Am Heart J[25]	- Questions about CV risk factors (incl. dates of risk factor diagnoses): presence of diabetes, hypertension, hypercholesterolemia, smoking behaviour and present weight of the offspring - Questions about CVD (incl. dates of occurrence): whether offspring had experienced MI, PCI, CABG, stroke, PAD, or AAA.
SMART-MR and SMART Medea	2001 - 2005 1st follow-up: 2006-2009 2nd follow-up: 2013-2017	1,309	To investigate brain changes using 1.5T MRI in patients with symptomatic atherosclerotic disease (and 7T MRI in follow-up from 2013-2017)	- Geerlings, 2010, Atherosclerosis[26] - Muller, 2011, Ann Neurol[27] - Conijn, 2011, Stroke[28] - Kloppenborg, 2012, Neurology[29] - Jochemsen 2013, JAMA Neurology[30] - Van der Veen, 2015, Stroke[31]	<u>Technique:</u> - 1.5T brain MRI - 7T brain MRI <u>Measurement:</u> - Total cerebral blood flow (mL/min per 100 mL brain parenchymal volume) - White matter lesions: volume (mL), shape (using the concavity index and fractal dimension[35]) and location were scored

				- Zwartbol, 2019, Stroke[32] - Ghaznawi 2021, Neurology[33] - Rissanen, 2021, Neurology[34]	- Brain parenchymal fraction (% of intracranial volume (ICV) that is occupied by brain tissue), an indicator for global brain atrophy - Ventricular enlargement (% of ventricular volume of the total ICV), an indicator for subcortical brain atrophy - Cortical gray matter fraction (% cortical gray matter volume of the total ICV), an indicator of cortical brain atrophy - Infarcts: location, affected flow territory and type were scored
					<u>Neuropsychological assessment (from 2003):</u> - 15-learning word test[36] - Rey-Osterrieth Complex Figure test[37] - Visual Elevator test[38] - Brixton Spatial Anticipation test[39] - Verbal Fluency test (letter)[40] - Dutch version of the National Adult Reading test[41] <u>From 2006:</u> - MMSE[42] - Verbal Fluency test (animals)[40] - Digit Symbol Substitution Test[43] - Forward Digit Span and Backward Digit Span[44]
SMART-ORACLE *(Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk*	2012 - present	1.182 (until Dec 2021; ongoing) patients with a history of symptomatic vascular	1) To determine whether there is additional value of performing CAC score, CTCA, total aorta calcification, burden as compared to traditional risk factors in the risk stratification in predicting any cardiovascular event. 2) To	- Franssens, 2017, Eur J of Prev Cardiol[45] - Van 't Klooster, 2020, IJC Heart & Vasculature[46]	<u>Technique:</u> Cardiac non-contrast enhanced CT and CTA of the heart and the carotids to the circle of Willis

for a cardiovascular event)		disease, T2DM or hypertension	estimate the additional value of CTCA and CAC score on top of traditional risk factors in predicting cardiac events. 3) To determine the value of soft plaque burden in the carotid and coronary arteries in predicting acute vascular events		Measurement: - Radiodensity and volume of epicardial adipose tissue - Coronary artery calcium (scored using the Agatston method[47]) - Calcifications on heart valves and in the thoracic aorta (quantified using a pseudo-mass score: mean calcium houndsfield units × region of interest volume) - CAD-RADS[48] - Carotid stenosis
SPAIN *(Selfmanagement of vascular Patients Activated by Internet and Nurses)*	2005	50 patients with computer facilities	1) To evaluate the feasibility of an Internet-based vascular risk reduction program in terms of accessibility, frequency and pattern of use of an individualized website for patients with a recent clinical manifestation of arterial disease. 2) To evaluate whether the use was related to a change in vascular risk factors after 6 months	Goessens, 2008, Patient education and counseling[49]	NA
TEMPUS *(The Evening versus Morning Polypill Utilization Study)* Randomized open blinded endpoint crossover trial	1996 - 2009. Patients were screened between 2012 - 2013	78 patients with established CVD or those at intermediate to high risk of CVD with indication for the use of cardiovascular medication, according to the current	1) To assess whether there is a difference in the morning or evening administration of a cardiovascular polypill, an FDC formulation containing aspirin, simvastatin, lisinopril and hydrochlorothiazide, on LDL-C and mean 24-hour systolic BP levels in individuals at high risk of cardiovascular disease. 2) To assess the effect of the polypill on LDL-C, ambulatory BP, anti-platelet function, adherence and patients'	- Lafeber, 2014, Eur J Prev Cardiol[50] - Lafeber, 2014, Int J Cardiol[51]	At baseline and at the end of each treatment period: medical history, anthropometric parameters, laboratory blood tests, office BP, 24-hour ambulatory BP monitoring, platelet function, pulse wave analysis, adherence to therapy, and questionnaires

		Dutch guidelines	preference as compared to the administration of the individual, identically dosed components of the polypill administered at different times of the day, as is currently recommended in clinical care.		
VENUS *(Vascular prEvention by NUrses Study)* RCT	Patients included between May 2002 and October 2003	236 patients with ≥ 2 modifiable risk factors	To investigate whether risk factor management in the hospital improved with nurse practitioner care plus usual care compared with usual care	- Goessens, 2006, Eur J Cardiovasc Prev Rehabil[52] - Sol, 2009, Eur J C Nurse[53]	Questionnaire about social support using a social support questionnaire for Dutch CHD patients: - Structural support: whether they have a spouse and whether they have someone they could turn to about their health problems - Functional support: statements about active involvement, protective buffering and overprotection.

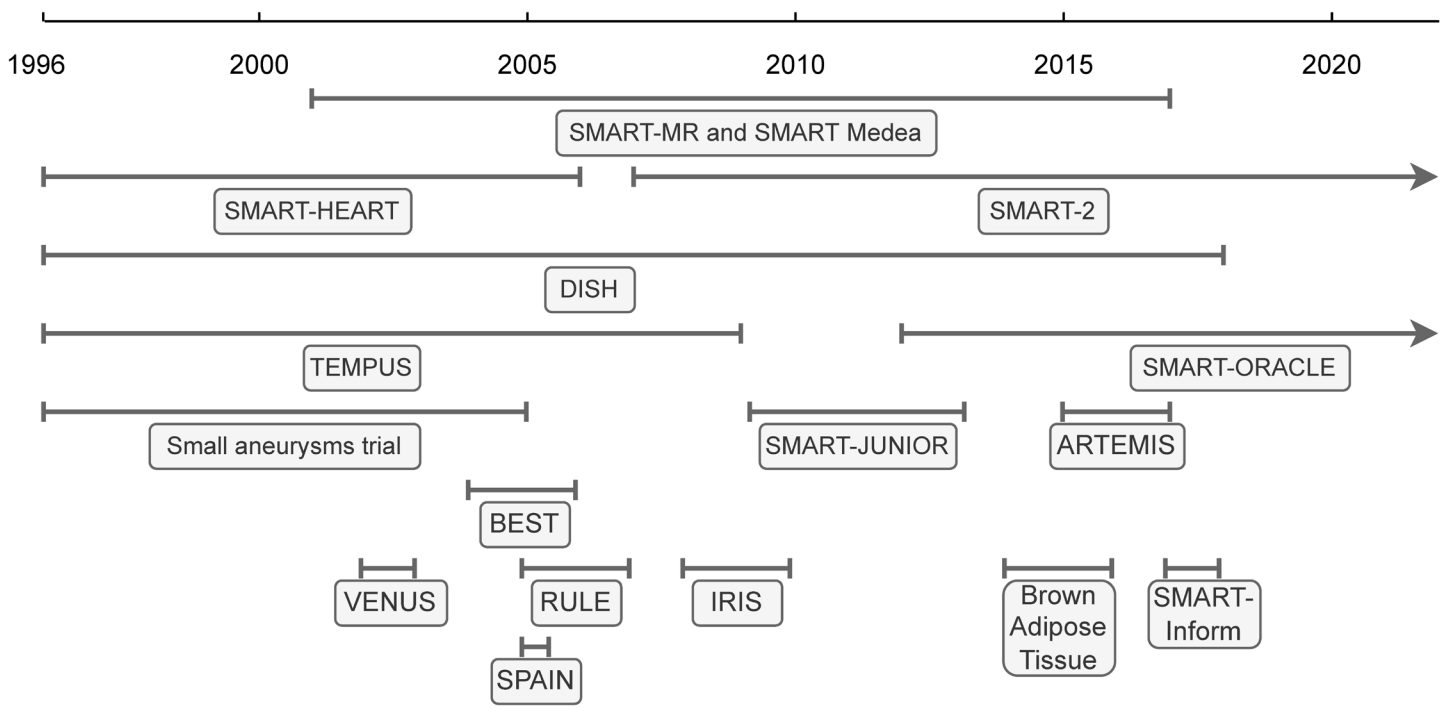
AAA, aortic abdominal aneurysm; BAT, brown adipose tissue; BP, blood pressure; CABG, coronary artery bypass grafting; CAC, coronary artery calcium; CAD, coronary artery disease, CAD-RADS, CAD-reporting and data system, CeVD, cerebrovascular disease; CHD, coronary heart disease; CT, computed tomography; CTA, CT angiography; CTCA, CT coronary angiography; CV, cardiovascular; CVD, cardiovascular disease; DISH, diffuse idiopathic skeletal hyperostosis; FDC, fixed dose combination; FU, follow-up; LDL-c, low-density lipoprotein cholesterol; LUMC, Leiden University Medical Center; LV, left ventricle; LVH, left ventricle hypertrophy; MI, myocardial infarction; MRI, magnetic resonance imaging; NA, not applicable; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SMART, Second Manifestations of Arterial Disease; SNP; single nucleotide polymorphism; T2DM, type 2 diabetes mellitus; UCC-SMART, Utrecht Cardiovascular Cohort–SMART; UMC, University Medical Center

Supplementary Table 7. Baseline characteristics of participants with complete follow-up and participants without complete follow-up

	Participants with complete follow-up (n = 13,284)	Participants without complete follow-up (n = 1,546)
Age (years)	57 ± 12	55 ± 14
Male sex	8,736 (66)	894 (57)
Previous or current smoking	9,285 (70)	1,065 (69)
Established cardiovascular disease	8,270 (65)	913 (59)
Diabetes mellitus	2,272 (17)	336 (22)
Lipid-lowering therapy	7,529 (57)	724 (47)
Antihypertensive therapy	9,053 (68)	977 (63)
Oral anticoagulant therapy	1,145 (9)	121 (8)
Systolic blood pressure (mmHg)	140 ± 22	144 ± 23
Diastolic blood pressure (mmHg)	83 ± 13	84 ± 13
Body mass index (kg/m^2)	26.9 ± 4.4	27.1 ± 4.8
Non-HDL-cholesterol (mmol/L)	3.8 ± 1.3	4.0 ± 1.5
eGFR (ml/min/1.73 m^2)	53 ± 41	48 ± 43
HbA1c (mmol/mol)	38 (36 - 42)	40 (36 - 48)
CRP (mg/L)	2.0 (1.0 - 4.3)	2.2 (1.0 - 4.4)

Data are presented as number (percentage), mean ± standard difference or median (interquartile range).

Supplemental Figure 1. Timeline of substudies of UCC-SMART



1.5T brain MRIs have been performed between 2001 and 2005. Follow-up of 1.5T MRI was performed between 2006 and 2009 and from 2013 to 2017. During the second follow-up, a 7T brain MRI was added in a subsample. A detailed overview of the substudies is provided in Supplementary Table 5.

ARTEMIS, ARTErial calcifications of the Media and Intima in SMART (Second Manifestations of Arterial Disease)[6]; BEST, BEtter risk factor treatment with STructured agreement[9]; Brown Adipose Tissue[10]; DISH, Diffuse idiopathic skeletal hyperostosis[12]; IRIS, Internet-based vascular Risk factor Intervention and Self-management[15]; RULE, Risk management in Utrecht and Leiden Evaluation study[17]; SMART HEART[19]; SMART Inform[23]; SMART-JUNIOR[24]; SMART-MR[26]; ORACLE; Optimizing Risk Assessment with CT-angiography or Calcium score in patients at high risk for a cardiovascular event[45]; SPAIN,

Self-management of vascular Patients Activated by Internet and Nurses[49]; TEMPUS, The Evening versus Morning Polypill Utilization Study[50]; VENUS, Vascular prEvention by NUrses Study[52].

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1+3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5+6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6+11-12
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-12
Bias	9	Describe any efforts to address potential sources of bias	6-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16-17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	16-17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	16-17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	25-26
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	25-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	25
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	27

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.