The Prospective Studies of Atherosclerosis (Proof-ATHERO) Consortium: Design and Rationale

Lena Tschiderer, Lisa Seekircher, Gerhard Klingenschmid, Raffaele Izzo, Damiano Baldassarre, Bernhard Iglseder, Laura Calabresi, Jing Liu, Jackie F Price, Jang-Ho Bae , Frank P Brouwers, Eric de Groot, Caroline Schmidt, Göran Bergström, Gülay Aşçi, Paolo Gresele, Shuhei Okazaki, Kostas Kapellas, Manuel F Landecho, Naveed Sattar, Stefan Agewall, Zhi-Yong Zou, Christopher D Byrne, Prabath W B Nanayakkara, Aikaterini Papagianni, Miles D Witham, Enrique Bernal, Robert Ekart, Michiel A van Agtmael, Mario F Neves, Eiichi Sato, Marat Ezhov, Matthew Walters, Michael H Olsen, Radojica Stolić, Dorota A Zozulińska-Ziółkiewicz, Markolf Hanefel, Daniel Staub, Michiaki Nagai, Pythia T Nieuwkerk, Menno V Huisman, Akihiko Kato, Hirokazu Honda, Grace Parraga, Dianna Magliano, Rafael Gabriel, Tatjana Rundek, Mark A Espeland, Stefan Kiechl, Johann Willeit, Lars Lind, Jean Philippe Empan, Eva Lonn, Tomi-Pekka Tuomainen, Alberico Catapano, Kuo-Liong Chien, Dirk Sander, Maryam Kavousi , Joline W J Beulens, Michiel L Bots, Michael J Sweeting, Matthias W Lorenz, Peter Willeit, Proof-ATHERO Study Group

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The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium: Design and rationale

Writing committee:
Lena Tschiderer[1]§, Lisa Seekircher[1]§, Gerhard Klingenschmid[1], Raffaele Izzo[2], Damiano Baldassarre[3,4], Bernhard Iglseder[5,6], Laura Calabresi[7], Jing Liu[8], Jackie F. Price[9], Jang-Ho Bae[10,11], Frank P. J. Brouwers[12], Eric de Groot[13], Caroline Schmidt[14], Paolo Gresele[15], Shuhei Okazaki[16], Kostas Kapellas[17], Manuel F. Landecho[18], Naveed Sattar[19], Stefan Agewall[20], Zhi-Yong Zou[21], Christopher D. Byrne[22], Prabath W. B. Nanayakkara[23], Aikaterini Papagianni[24], Miles D. Witham[25], Enrique Bernal[26], Robert Ekart[27], Michiel A. van Agtmael[28], Mario F. Neves[29], Eiichi Sato[30], Marat Ezhov[31], Matthew Walters[32], Michael H. Olsen[33], Radojica Stolić[34], Dorota A. Zozulińska-Ziółkiewicz[35], Markolf Hanefeld[36], Daniel Staub[37], Michiaki Nagai[38], Pythia T. Nieuwkerk[39], Menno V. Huisman[40], Akihiko Kato[41], Hirokazu Honda[42], Grace Parraga[43], Dianna Magliano[44], Rafael Gabriel[45], Tatjana Rundek[46], Mark A. Espeland[47], Stefan Kiechl[1], Johann Willeit[1], Lars Lind[48], Jean Philippe Empana[49], Eva Lonn[50,51], Tomi-Pekka Tuomainen[52], Alberico Catapano[7,53], Kuo-Liong Chien[54], Dirk Sander[55,56], Maryam Kavousi[57], Joline W. J. Beulens[58], Michiel L. Bots[59], Michael J. Sweeting[60,61], Matthias W. Lorenz[62], and Peter Willeit[1,61]* on behalf of the Proof-ATHERO Study Group.

[1]Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria; [2]Department of Advanced Biochemical Sciences, Federico II University, Naples, Italy; [3]Department of Medical Biotechnology and Translational Medicine, University of Milan, Milan, Italy; [4]Centro Cardiologico Monzino IRCCS, Milan, Italy; [5]Department of Geriatric Medicine, Gemeinnützige Salzburger Landeskliniken Betriebsgesellschaft GmbH Christian-Doppler-Klinik, Salzburg, Austria; [6]Department of Geriatric Medicine, Paracelsus Medical University, Salzburg, Austria; [7]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [8]Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [9]Usher Institute, University of Edinburgh, Edinburgh, UK; [10]Heart Center, Konyang University Hospital, Daejeon, Korea; [11]Department of Cardiology, Konyang University College of Medicine, Daejeon, Korea; [12]Department of Cardiology, Haga Teaching Hospital, the Hague, the Netherlands; [13]Imagelabonline & Cardiovascular, Eindhoven and Lunteren, the Netherlands; [14]Wallenberg Laboratory for Cardiovascular Research, University of Gothenburg, Gothenburg, Sweden; [15]Division of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [16]Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan; [17]Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, SA, Australia; [18]Department of Internal Medicine, University Clinic of Navarra, Navarra, Spain; [19]BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, UK; [20]Oslo University Hospital Ullevål and Institute of Clinical Sciences, University of Oslo, Oslo, Norway; [21]Institute of Child and Adolescent Health, School of Public Health, Peking University, Beijing, China; [22]Human Development and Health Academic Unit, Faculty of Medicine, The Institute of Developmental Sciences, University of Southampton - Southampton General Hospital, Southampton, UK; [23]Department of Clinical Neurophysiology, Amsterdam UMC, Amsterdam, the Netherlands; [24]University Department of Nephrology, Hippokration General Hospital, Thessaloniki, Greece; [25]AGE Research Group, NIHR Newcastle Biomedical Research Centre, Newcastle University and Newcastle-upon-Tyne Hospitals Trust, Newcastle, UK; [26]Infectious Diseases Unit, Reina Sofia Hospital, Murcia, Spain; [27]Department of Dialysis, University

Medical Centre Maribor, Maribor, Slovenia; [28]Department of Internal Medicine, Amsterdam UMC- Location Vumc, Amsterdam, the Netherlands; [29]Department of Clinical Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil; [30]Division of Nephrology, Shinmatsudo Central General Hospital, Chiba, Japan; [31]Laboratory of Lipid Disorders, National Medical Research Center of Cardiology, Moscow, Russia; [32]School of Medicine, Dentistry and Nursing, University of Glasgow, Glasgow, UK; [33]Department of Internal Medicine, Holbaek Hospital, University of Southern Denmark, Odense, Denmark; [34]Department of Internal Medicine, Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia; [35]Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznan, Poland; [36]Center for Clinical Studies, Technical University Dresden, Dresden, Germany; [37]Department of Angiology, University Hospital Basel, Basel, Switzerland; [38]Department of Internal Medicine, General Medicine and Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan; [39]Department of Medical Psychology, Amsterdam UMC- Location AMC, Amsterdam, the Netherlands; [40]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands; [41]Blood Purification Unit, Hamamatsu University Hospital, Hamamatsu, Japan; [42]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [43]Department of Medical Biophysics, Western University, London, Canada; [44]Department of Epidemiology and Preventive Medicine, Monash University, Alfred Hospital, Melbourne, Australia; [45]National School of Public Health, Instituto de Salud Carlos III, Madrid, Spain; [46]Department of Neurology, University of Miami Miller School of Medicine, Miami, USA; [47]Department of Biostatistical Sciences, Wake Forest School of Medicine, Winston-Salem, NC, USA; [48]Department of Medicine, Uppsala University, Uppsala, Sweden; [49]Paris Cardiovascular Research Centre (PARCC), University Paris Descartes, Paris, France; [50]Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [51]Hamilton General Hospital, Hamilton, Ontario, Canada; [52]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; [53]IRCCS Multimedica, Milan, Italy; [54]Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan; [55]Department of Neurology, Benedictus Hospital Tutzing & Feldafing, Feldafing, Germany; [56]Department of Neurology, Technische Universität München, Munich, Germany; [57]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands; [58]Department of Epidemiology & Biostatistics, Amsterdam UMC- Location Vumc, Amsterdam, the Netherlands; [59]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [60]Department of Health Sciences, University of Leicester, Leicester, UK; [61]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [62]Department of Neurology, Goethe University, Frankfurt am Main, Germany

§Authors contributed equally to this article.

Short Title: Design and rationale of the Proof-ATHERO consortium

***Corresponding author:**
Peter Willeit, MD MPhil PhD, Department of Neurology, Medical University of Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria, Tel: +43 512 504-83493, Fax: +43 50 504-23852, E-mail: peter.willeit@i-med.ac.at

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Collaborators committee:

Maria V. Manzi[1], Costantino Mancusi[1], Helmuth Steinmetz[2], Matthias Sitzer[2,3], Mauro Amato[4], Fabrizio Veglia[4], Elena Tremoli[4], Samuela Castelnuovo[5], Dong Zhao[6], Miao Wang[6], Stela McLachlan[7], Moo-Sik Lee[8,9], Hyun-Woong Park[9], Salim Yusuf[10,11], Diederick E. Grobbee[12], Frank L. J. Visseren[13], John J. P. Kastelein[14], Wiek van Gilst[15], Folkert W. Asselbergs[16], Muriel P. C. Grooteman[17], Peter J. Blankestijn[18], Göran Bergström[19,20], Giuseppe Guglielmini[21], Rino Migliacci[22], Lena Bokemark[23], Kazuo Kitagawa[24], Michael Skilton[25], Lisa M. Jamieson[26], Oscar Beloqui[27], David Preiss[28], Philip C. Calder[29,30], Lokpal Bhatia[29,30], Pieter M. ter Wee[17], Chrystosomos Dimitriadis[31], Radovan Hojs[32,33], Sebastjan Bevc[32,33], Peter Reiss[34,35], Marit G. A. van Vonderen[36], Ana R. Cunha[37], Mayuko Amaha[38], Tsukasa Nakamura[38], Tatyana Balakhonova[39], Maya Safarova[40], Jesse Dawson[41], Peter Higgins[41], Kristian Wachtell[42], Sverre E. Kjeldsen[42], Aleksandar Jovanovic[43], Tatjana Lazarevic[44], Aleksandra Araszkiewicz[45], Aleksandra Uruska[45], Dariusz Naskręt[45], Beat Frauchiger[46], Heiko Uthoff[47], Kazuomi Kario[48], Satoshi Hoshide[48], Erik Stroes[14], Edith Beishuizen[49], Tadao Akizawa[50], Thapat Wannarong[51,52], Sophia Zoungas[53], John McNeil[53], Alfonsa Friera[54], Carmen Suarez[55], Femke Rutters[56], Petra Elders[57], Coen D. A. Stehouwer[58], Moise Desvarieux[59,60], Pierre Ducimetiere[61], Matthieu Plichart[62,63], Hertzel C. Gerstein[10,11], Ari Voutilainen[64], Jussi Kauhanen[64], Liliana Grigore[65], Giuseppe D. Norata[65,66], Ta-Chen Su[67], Pei-Chun Chen[68], Hung-Ju Lin[67], Holger Poppert[69], Horst Bickel[70], and M. Arfan Ikram[71].

[1]Department of Advanced Biochemical Sciences, Federico II University, Naples, Italy; [2]Department of Neurology, Goethe University, Frankfurt am Main, Germany; [3]Department of Neurology, Klinikum Herford, Herford, Germany; [4]Centro Cardiologico Monzino IRCCS, Milan, Italy; [5]Centro Dislipidemie, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [6]Department of Epidemiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, China; [7]Usher Institute, University of Edinburgh, Edinburgh, UK; [8]Department of Preventive Medicine, Konyang University, Daejeon, Korea; [9]College of Medicine, Konyang University Hospital, Daejeon, Korea; [10]Department of Medicine and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada; [11]Hamilton General Hospital, Hamilton, Ontario, Canada; [12]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands; [13]Department of Vascular Medicine, University Medical Center Utrecht, Utrecht, the Netherlands; [14]Department of Vascular Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands; [15]Department of Experimental Cardiology, University Medical Center Groningen, Groningen, the Netherlands; [16]Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands; [17]Department of Nephrology, Amsterdam UMC, Amsterdam, the Netherlands; [18]Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands; [19]Department of Molecular and Clinical Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [20]Department of Clinical Physiology, Sahlgrenska University Hospital, Region Västra Götaland, Gothenburg, Sweden; [21]Division of Internal and Cardiovascular Medicine, Department of Medicine, University of Perugia, Perugia, Italy; [22]Division of Internal Medicine, Cortona Hospital, Cortona, Italy; [23]Wallenberg Laboratory for Cardiovascular Research, University of Gothenburg, Gothenburg, Sweden; [24]Department of Neurology, Tokyo Women's Medical University, Tokyo, Japan; [25]Boden Institute of Obesity, Nutrition, Exercise and Eating Disorders, University of Sydney, Sydney, NSW 2006, Australia; [26]Australian Research Centre for Population Oral Health, University of Adelaide, Adelaide, SA, Australia; [27]Department of Internal Medicine, University Clinic of Navarra, Navarra, Spain; [28]MRC Population Health Research Unit, Clinical Trial Service Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK; [29]Faculty of Medicine, University of Southampton - Southampton General Hospital, Southampton, UK; [30]Southampton NIHR Biomedical Research Centre, University Hospital Southampton -

Southampton General Hospital, Southampton, UK; [31]University Department of Nephrology, Hippokration General Hospital, Thessaloniki, Greece; [32]Department of Nephrology, University Medical Centre Maribor, Maribor, Slovenia; [33]Faculty of Medicine, University of Maribor, Maribor, Slovenia; [34]Department of Global Health, Amsterdam UMC- Location AMC, Amsterdam, the Netherlands; [35]Amsterdam Institute for Global Health and Development, University of Amsterdam, Amsterdam, the Netherlands; [36]Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands; [37]Department of Clinical Medicine, State University of Rio de Janeiro, Rio de Janeiro, Brazil; [38]Division of Nephrology, Shinmatsudo Central General Hospital, Chiba, Japan; [39]Ultrasound Vascular Laboratory, National Medical Research Center of Cardiology, Moscow, Russia; [40]Atherosclerosis Department, National Medical Research Center of Cardiology, Moscow, Russia; [41]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK; [42]Department of Cardiology, Oslo University Hospital, Oslo, Norway; [43]Faculty of Medicine, University of Prishtina, Prishtina\Kosovska Mitrovica, Serbia; [44]Faculty of Medicine, University of Kragujevac, Kragujevac, Serbia; [45]Department of Internal Medicine and Diabetology, Poznan University of Medical Sciences, Poznan, Poland; [46]Department of Internal Medicine, Kantonsspital Frauenfeld, Frauenfeld, Switzerland; [47]Department of Angiology, University Hospital Basel, Basel, Switzerland; [48]Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan; [49]Department of Internal Medicine, HMC+ (Bronovo), the Hague, the Netherlands; [50]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [51]Stroke Prevention & Atherosclerosis Research Centre, Western University, London, Canada; [52]Department of Internal Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [53]School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; [54]Radiology Department, Universidad Autónoma de Madrid, Madrid, Spain; [55]Internal Medicine Department, Universidad Autónoma de Madrid, Madrid, Spain; [56]Department of Epidemiology & Biostatistics, Amsterdam UMC-Location Vumc, Amsterdam, the Netherlands; [57]Department of General Practice, Amsterdam UMC- Location Vumc, Amsterdam, the Netherlands; [58]Department of Internal Medicine and Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Centre, Maastricht, the Netherlands; [59]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA; [60]METHODS Core, Centre de Recherche Epidémiologie et Statistique Paris Sorbonne Cité (CRESS), Institut National de la Santé et de la Recherche Médicale (INSERM) UMR 1153, Paris, France; [61]Faculty of Medicine, University Paris Descartes, Paris, France; [62]Paris Cardiovascular Research Centre (PARCC), University Paris Descartes, Paris, France; [63]Assistance Publique, Hôpitaux de Paris, Hôpital Broca, Paris, France; [64]Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio Campus, Kuopio, Finland; [65]SISA Center for the Study of Atherosclerosis, Bassini Hospital, Cinisello Balsamo, Italy; [66]Department of Pharmacological and Biomolecular Sciences, University of Milan, Milan, Italy; [67]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [68]Clinical Informatics & Medical Statistics Research Center, Chang Gung University, Taoyuan, Taiwan; [69]Department of Neurology, Technische Universität München, Munich, Germany; [70]Department of Psychiatry and Psychotherapy, Technische Universität München, Munich, Germany; [71]Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands

Abstract

Atherosclerosis – the pathophysiological mechanism shared by most cardiovascular diseases – can be directly or indirectly assessed by a variety of clinical tests including measurement of carotid intima-media thickness, carotid plaque, ankle-brachial index, pulse wave velocity, and coronary artery calcium. The Prospective Studies of Atherosclerosis (Proof-ATHERO) Consortium (https://clinicalepi.i-med.ac.at/research/proof-athero/) collates de-identified individual-participant data of studies with information on atherosclerosis measures, risk factors for cardiovascular disease, and incidence of cardiovascular diseases. It currently comprises 73 studies that involve 106,202 participants from 24 countries and over 40 cities. 21 studies recruited participants from the general population (n=67,784), 16 from high-risk populations (n=22,677), and 36 as part of clinical trials (n=15,741). Baseline years of contributing studies range from April 1980 to July 2014; the lastest follow-up was until June 2019. Mean age at baseline was 59 (standard deviation: 10) years and 50% were female. Over a total of 828,929 person-years of follow-up, 17,210 incident cardiovascular events (including coronary heart disease and stroke) and 13,153 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum. The consortium is coordinated by the Clinical Epidemiology Team at the Medical University of Innsbruck, Austria. Contributing studies undergo a detailed data cleaning and harmonisation procedure before being incorporated in the Proof-ATHERO central database. Statistical analyses are being conducted according to pre-defined analysis plans and use established methods for individual-participant data meta-analysis. Capitalising on its large sample size, the multi-institutional collaborative Proof-ATHERO consortium aims to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

Introduction

Cardiovascular diseases (CVD) are the most common cause of death and disability worldwide. According to recent estimates from the Global Burden of Disease Study, about 18 million people die of CVD in a year, which account for over 30% of all global deaths [1]. The pathophysiological mechanism shared by many CVD is atherosclerosis, a gradual and progressive hardening and narrowing of the arteries over the course of life. Initial atherosclerotic alterationscan be found as early as in young adulthood [2, 3] and involve endothelial dysfunction, inflammation, and deposition of fat [4]. Advanced atherosclerotic lesions are characterised by formation of atherosclerotic plaque that can destabilise, rupture or fissure, and can ultimately lead to acute vessel occlusion or formation of a local thrombus with dislocation into distal arteries and thereby clinical sequelae [4].

Clinical and subclinical atherosclerosis can be directly or indirectly assessed using a range of different clinical tests which are simple, safe, and non-invasive, and therefore amenable for use in large-scale studies (**Fig. 1**). One of the imaging techniques for atherosclerosis most frequently used is the assessment of carotid intima-media thickness (cIMT). Using B-mode high-resolution ultrasound, the distance between the intimal and medial layer of the carotid arterial wall is quantified. Spatial resolution of this imaging technique is approximately 50 μm axially and 200 μm laterally. Ultrasound-based cIMT is considered as a marker of the early stage of atherosclerosis. It is related to unfavourable levels of traditional cardiovascular risk factors [5, 6] and has been shown to be in good accordance with "true" cIMT determined in histological studies [7]. Furthermore, increased cIMT has been associated with increased risk of cardiovascular events [8, 9].

Other scalable measures to ascertain vessel wall pathology and dysfunction include the carotid plaque [10, 11], ankle-brachial index [12], pulse wave velocity [13], and coronary artery calcium [14–16] (**Fig. 1**). According to the 2019 European Society of Cardiology Guidelines for the diagnosis and management of chronic coronary syndromes, atherosclerotic plaque detection by carotid artery ultrasound, assessment of coronary artery calcium score with computed tomography, and measurement of the ankle-brachial index may be considered as risk modifiers in cardiovascular risk assessment in asymptomatic subjects [17]. Because atherosclerosis typically develops over a long period of time and only causes symptoms at an advanced stage, these measures are important tools in clinical practice to quantify atherosclerosis burden and might help inform treatment decisions.

The Prospective Studies of Atherosclerosis (Proof-ATHERO) consortium is an international consortium coordinated by the Clinical Epidemiology Team at the Medical University of Innsbruck. It brings together individual-participant data from prospective cohorts with detailed information on atherosclerosis, covariates, and incidence of CVD outcomes. The present report provides a description of broad aims of Proof-ATHERO and the principal methodology involved in collating, harmonising, and analysing study data.

Design

Objectives

Capitalising on its large sample size and the comprehensive information available, the overarching aims of the Proof-ATHERO consortium are to: (i) better characterise the natural history, communalities, and differences of different atherosclerosis measures; (ii) to provide novel insight into the determinants of atherosclerosis development and progression; and (iii) to investigate clinical consequences of atherosclerosis. In contrast to prior reports in individual studies, the large-scale data of Proof-ATHERO enables the study team to conduct power-demanding analyses, including (i) characterisation of atherosclerosis trajectories over time; (ii) determination of the shapes of associations (e.g. linear vs. curvilinear vs. threshold effects); (iii) study of potential effect modifiers (e.g. age, sex, or medication); (iv) direct comparisons of the added predictive value of different atherosclerosis measures over and beyond assessment of conventional risk factors; and (v) reliable evaluation of atherosclerosis measures as surrogate markers for clinically manifest CVD endpoints. Overall, Proof-ATHERO aims to analyse world-wide available data to deliver results based on the highest scientific evidence.

Inclusion criteria

Prospective cohorts are eligible for inclusion in the Proof-ATHERO consortium if they were observational studies or clinical trials that: (i) have assessed one or more atherosclerosis measures (i.e. cIMT, carotid plaque, ankle-brachial index, pulse wave velocity, coronary artery calcium) repeatedly (i.e. at two or more time points); (ii) have ascertained comprehensive information on CVD risk factors (e.g. lifestyle, blood-based markers, history of disease, and medication intake); and (iii) have recorded incident CVD outcomes using well-defined criteria.

A crucial foundation for the Proof-ATHERO consortium was provided by the PROG-IMT project [18]. This initiative led by Professor Lorenz at the Goethe University at Frankfurt

am Main had collated and analysed individual-participant data on the progression of cIMT and, for instance, yielded milestone publications on the association of cIMT progression with future CVD risk in the general population [8], in people with type-2 diabetes [19], and in people at high cardiovascular risk [20]. When the PROG-IMT project was completed in 2017, a majority of contributing studies (81%) decided to continue the fruitful collaboration as part of the Proof-ATHERO consortium and to jointly investigate scientific questions which go beyond the initial aims of the PROG-IMT project. The commitment by these studies gave a unique head-start to the Proof-ATHERO consortium and enabled efficient data accrual at the beginning of the initiative.

Identification and incorporation of new eligible studies is ongoing and we invite researchers to contact the coordinating centre if they wish to contribute to the Proof-ATHERO consortium.

Atherosclerosis measures

Data have been sought from investigators on carotid ultrasound parameters, ankle-brachial index, pulse wave velocity, and coronary artery calcium at baseline and any subsequent re-examinations during follow-up. Atherosclerosis measures assessed by the individual studies are summarised in **Table 1**. Parameters based on carotid ultrasound are being collected systematically on up to twelve sites (common carotid artery, carotid bifurcation, and internal carotid artery; left and right side; near and far wall) and include cIMT, vessel diameter, presence of plaques (yes *vs.* no), number of plaques, plaque thickness (height in mm), plaque area in a longitudinal view (in mm^2), and plaque morphology according to the Gray-Weale classification [21]. The methodologies which studies used to cIMT and carotid plaque are summarised in **Table S2** and **Table S3**, respectively.

Participant characteristics at the baseline and follow-up surveys

Data on participant characteristics at baseline and follow-up surveys have been sought from investigators on age, sex, ethnicity, socio-economic status, smoking, systolic and diastolic blood pressure, body-mass index, lipid markers (e.g. total cholesterol, high- and low-density lipoprotein cholesterol, triglycerides), markers of inflammation (e.g. C-reactive protein, fibrinogen, leukocyte count), markers of dysglycaemia (e.g. fasting glucose, HbA_{1c}), use of medication (e.g. antihypertensive, antidiabetic, lipid-lowering medication), and pre-existing diseases (e.g. coronary heart disease, stroke, diabetes, or hypertension). Furthermore, in clinical

trials, information on the type of interventions (and dosages, if appropriate) and on adherence to allocated regimens have been collated.

Incident disease outcomes

Data on incident disease outcomes have been collated predominantly on fatal and non-fatal CVD events, including myocardial infarction, angina pectoris, and subtypes of stroke. In addition, information on cause-specific death has been sought. In 15 studies, cause of death was ascertained based on the death certificate; 43 studies supplemented the death certificate with information from additional sources (e.g. medical records, autopsy findings). Studies assessed prevalent CVD at study baseline using self-report only or supplemented by objective criteria. A detailed description of ascertainment and classification of prevalent and incident CVD provided in **Table S4**.

Coordination of the consortium

The Proof-ATHERO consortium is coordinated by the Clinical Epidemiology team at the Medical University of Innsbruck, Austria. An outline of the processes involved in Proof-ATHERO coordination is provided in **Fig. 2**. Standardised data request forms are sent to eligible studies, inviting them to participate in the initiative. Upon receipt of study data, data cleaning and harmonisation are performed by a dedicated data management team using a range of tools for detecting inconsistencies and ambiguities in the data. Any queries arising during this process are clarified through direct correspondence with study investigators. Upon completion of the data management process, study data are stored in a central database at the coordinating centre. The data management system of the coordinating centre has been implemented in *SAS 9.4*. Proposals for analyses can be submitted by all members of the Proof-ATHERO study group (i.e. all named investigators of studies contributing data to Proof-ATHERO) via the consortium's webpage. Upon receipt, proposals are reviewed by a dedicated Proof-ATHERO steering committee, which then allocates resources at the coordinating centre according to resource availability and scientific priority of the project. For contractual reasons, data are stored and analysed exclusively at the Proof-ATHERO Coordinating and Statistics Centres (Medical University of Innsbruck and University of Cambridge). At each step from development of a statistical analysis plan, to the conduct of statistical analyses, and the creation of a manuscript draft, investigators of contributing studies and expert panels are contacted for

feedback and comments, therefore making use of the broad and diverse community of experts in the field involved in the initiative.

General approach to statistical analyses

For each scientific project, statistical analyses will be performed according to a pre-specified analysis plan. Statistical analyses will follow established methods in the analysis of individual-participant data [22–27]. Generally, the multi-level structure of data (e.g. multiple cohorts) will be taken into account by combining study-specific estimates using meta-analytical methods or by using mixed regression models with appropriate specification of random effects. Analyses will also involve assessments of between-studies heterogeneity. More details on specific analytical methods will be provided in publications resulting from each scientific project.

Data protection and ethics considerations

All studies contributing data to Proof-ATHERO have previously reported results and have obtained relevant local ethics approval and participants' consent. The data provided by each study remain entirely the property of the principal investigators of that study and are held in confidence by the Proof-ATHERO coordinating centre. To safeguard the identity of individuals at all stages of the analysis and to ensure compliance with data protection legislation and confidentiality guidelines, study data are transferred to the coordinating centre using encrypted connections. De-identified data are being stored securely in a central database at the coordinating centre, protected by firewalls and accessible only to authorised staff. Participants and collaborating studies have the right to withdraw from the Proof-ATHERO consortium at any time and without giving reasons.

Characteristics of contributing studies

As of 21 January 2020, a total of 73 studies involving 106,202 participants are part of the Proof-ATHERO consortium. The designs of contributing studies and key study-level characteristics are shown in **Table 2**. In summary, 21 studies recruited participants from the general population, 16 studies were conducted in patient populations with specific pre-existing diseases (e.g. with diabetes), and 36 studies were randomised controlled trials covering a range of different patient populations. The numbers of people enrolled in these three types of studies were 67,784, 22,677, and 15,741, respectively. Baseline years ranged from April 1980 to July 2014; the last follow-up was in June 2019. Mean age at baseline was 59 years (standard

deviation: 10); 50% of participants were female. **Fig. 3** demonstrates the geographical location of contributing studies. Study locations were spread across four continents and are based in 24 countries and over 40 cities. The median duration of follow-up (i.e. the time from baseline to first event or end of follow-up) was 6.1 years (interquartile range: 2.7-10.4). Over a total of 828,929 person-years of follow-up, 17,210 incident CVD events and 13,153 deaths were recorded, corresponding to cumulative incidences of 2.1% and 1.6% per annum, respectively. As Proof-ATHERO evolves further, up-to-date information on contributing studies are being made available on the consortium's webpage at https://clinicalepi.i-med.ac.at/research/proof-athero/.

Conclusion

The Proof-ATHERO consortium is a multi-institutional collaborative project that is coordinated at the Medical University of Innsbruck. The consortium brings together large-scale data from prospective studies in the field of atherosclerosis. Proof-ATHERO combines data on CVD risk factors, repeat assessments of atherosclerosis, and clinical outcomes with cutting-edge data management and analytical tools. By inclusion of data from 24 countries and different clinical settings, the generalisability of findings will be of particular value. Building on these strengths, Proof-ATHERO will help to better characterise, understand, and predict the development of atherosclerosis and its clinical consequences.

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Author Contributions

L. Tschiderer, L. Seekircher, G. Klingenschmid, and P. Willeit are part of the coordinating centre and are responsible for data management and data analysis of the Proof-ATHERO consortium. L. Tschiderer and L. Seekircher drafted the manuscript, conducted the analyses, and interpreted the data. G. Klingenschmid interpreted the data. M. J. Sweeting provided supervision for statistical analyses. P. Willeit is responsible for the conception and design of

the work, drafted the manuscript, conducted the analyses, and interpreted the data. All other authors were responsible for data acquisition. All authors revised the manuscript critically for important intellectual content approved the final version of the manuscript.

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Figure Legends

Fig. 1. Measures for quantifying atherosclerosis.

Fig. 2. Data management and analysis workflow in the Proof-ATHERO consortium.

Fig. 3. Location of studies contributing data to the Proof-ATHERO consortium as of 21 January 2020. Full study names and references are provided in **Table S1**.

504 **Fig. 1. Measures for quantifying atherosclerosis**
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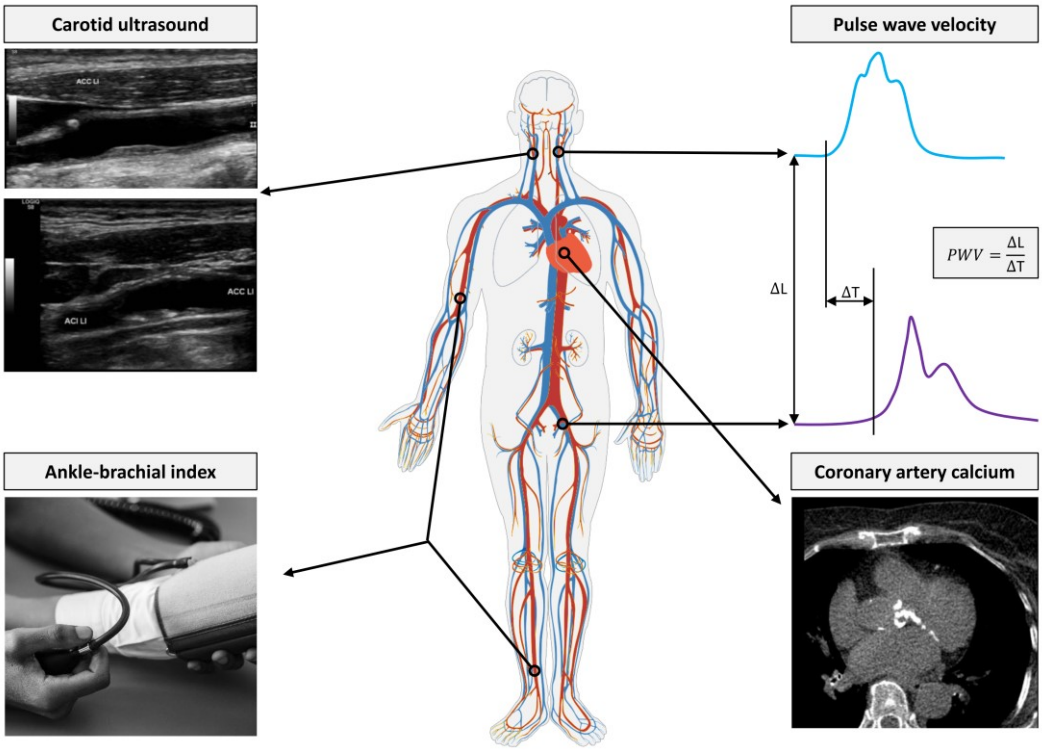

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Fig. 2. Data management and analysis workflow in the Proof-ATHERO consortium

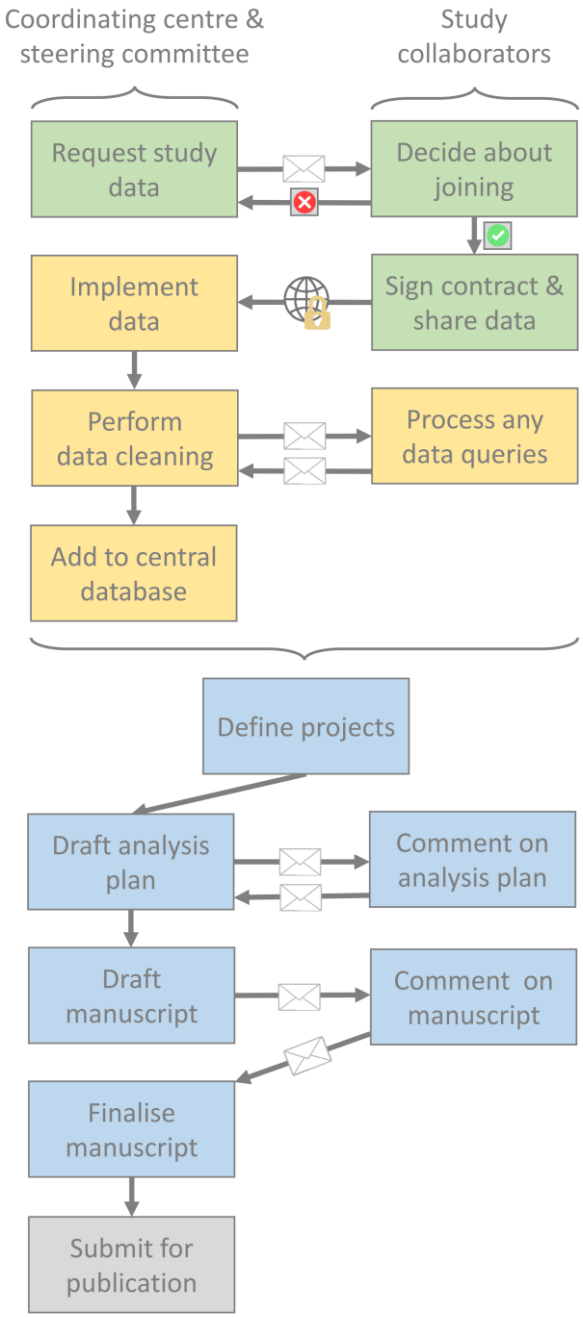
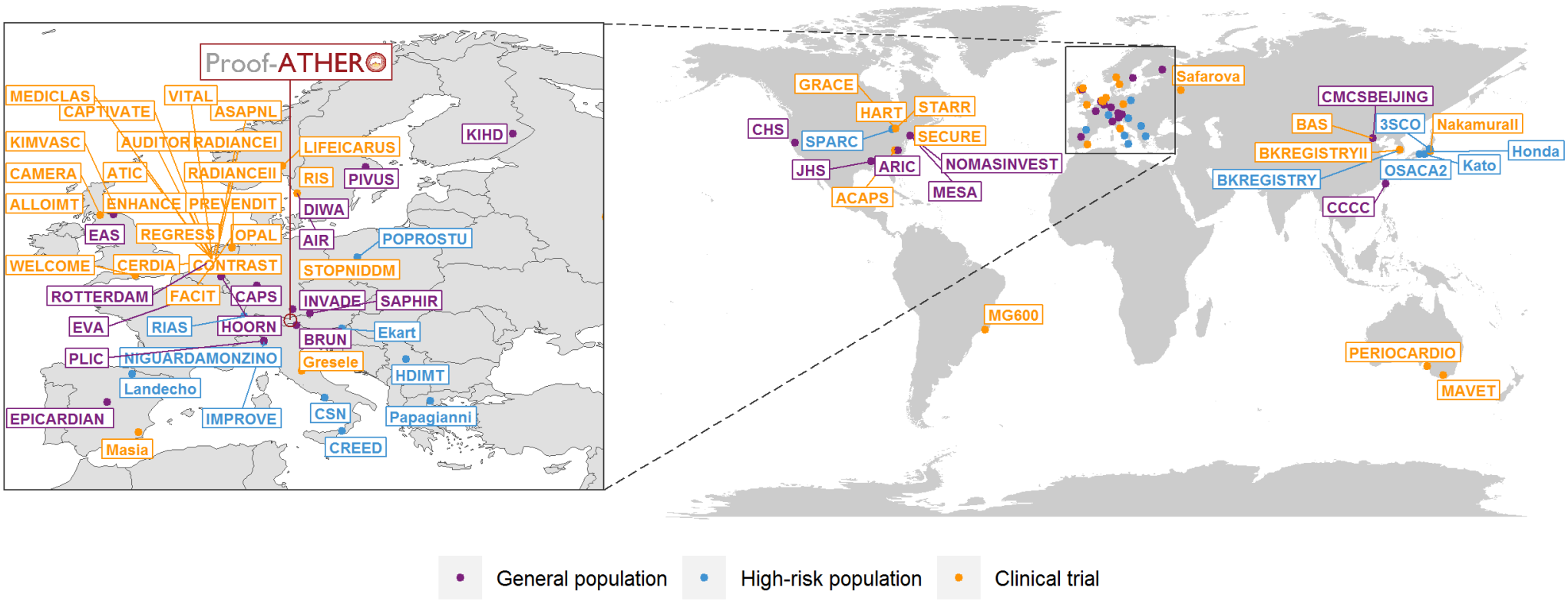


Fig. 3. Location of studies contributing data to the Proof-ATHERO consortium as of 21 January 2020



Full study names and references are provided in **Table S1**.

Table 1. Availability of atherosclerosis measures in the Proof-ATHERO consortium as of 21 January 2020

Study acronym or first author [Reference]	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS
General population						
AIR	●	●	●	○	○	○
ARIC	●	●	●	●	●	○
BRUN	●	●	●	●	○	○
CAPS	●	●	●	○	○	○
CCCC	●	○	●	○	○	○
CHS	●	●	●	●	○	○
CMCS-BEIJING	●	●	●	○	○	○
DIWA	●	●	⁕	○	○	○
EAS	●	○	●	⁕	○	○
EPICARDIAN	●	●	○	○	○	○
EVA	●	●	●	○	○	○
HOORN	●	⁕	○	⁕	⁕	○
INVADE	●	○	●	●	○	○
JHS	●	○	●	●	●	●
KIHD	●	○	●	○	○	○
MESA	●	⁕	●	●	○	●
NOMAS-INVEST	●	●	●	○	○	○
PIVUS	●	●	●	⁕	○	○
PLIC	●	○	●	○	○	○
ROTTERDAM	●	●	●	⁕	⁕	⁕
SAPHIR	●	●	●	○	○	○
High-risk populations						
BK REGISTRY	●	○	●	○	○	○
CREED	●	○	○	○	○	○
CSN	●	●	●	○	○	○
Ekart	●	○	⁕	○	○	○
HD-IMT	●	●	○	○	○	○
Honda	●	○	○	○	○	○
IMPROVE	●	●	●	○	○	○
Kato	●	○	●	⁕	⁕	○
Landecho	●	○	●	○	○	⁕
NIGUARDA-MONZINO	●	●	●	○	○	○
OSACA2	●	●	○	○	○	○
Papagianni	●	○	●	○	○	○
POPROSTU	●	●	○	○	○	○
RIAS	●	○	⁕	○	○	○
SPARC	●	○	●	○	○	○
3SCO	●	●	○	○	○	○

Study acronym or first author [Reference]	cIMT	Carotid diameter	Carotid plaque	ABI	PWV	CACS
Clinical trials						
ACAPS	●	○	○	○	○	○
ALLO-IMT	●	○	○	○	●	○
ASAP-NL	●	●	⁕	○	○	○
ATIC	●	○	○	○	○	○
AUDITOR	●	○	○	○	○	○
BAS	●	○	○	○	●	○
BK REGISTRY II	●	○	●	○	○	○
CAMERA	●	○	●	○	○	○
CAPTIVATE	●	●	○	○	○	○
CERDIA	●	○	○	○	○	○
CONTRAST	●	○	●	○	○	○
ENHANCE	●	○	●	○	○	○
FACIT	●	●	○	○	○	○
GRACE	●	○	⁕	⁕	○	○
Gresele	●	○	○	⁕	○	○
HART	●	○	⁕	⁕	○	○
KIMVASC	●	○	○	○	⁕	○
LIFE-ICARUS	●	●	●	○	○	○
Masia	●	○	●	●	○	○
MAVET	●	○	○	○	○	○
MEDICLAS	●	●	○	○	⁕	○
MG600	●	●	●	○	●	○
Nakamura II	●	●	⁕	○	⁕	○
OPAL	●	⁕	○	○	○	○
PERIOCARDIO	●	●	○	○	⁕	○
PREVEND IT	●	○	○	○	○	○
RADIANCE I	●	●	○	○	○	○
RADIANCE II	●	●	○	○	○	○
REGRESS	●	○	○	○	○	○
RIS	●	●	⁕	○	○	○
Safarova	●	○	⁕	⁕	⁕	○
SECURE	●	○	⁕	⁕	○	○
STARR	●	○	⁕	⁕	○	○
STOP-NIDDM	●	○	○	○	○	○
VITAL	●	○	○	○	○	○
WELCOME	●	○	●	○	○	○

● =available and provided, ⁕ =available but not provided, ○ =not available. ABI, ankle-brachial index; CACS, coronary artery calcium score; cIMT, carotid intima-media thickness; PWV, pulse wave velocity. Full study names and references are provided in **Table S1**.

517 **Table 2. Design and descriptive summary of studies in the Proof-ATHERO consortium**

Study acronym or first author	Country	Population source	Population type	Years of baseline	No.	♀, %	Mean age, years (SD)
General population							
AIR	Sweden	Population register	General population	1995-97	391	0	58 (0.1)
ARIC	USA	Household listings	General population	1986-90	15,121	55	54 (6)
BRUN	Italy	Population register	General population	1990	933	49	59 (11)
CAPS	Germany	Electoral rolls	General population	1995-00	6,970	51	51 (13)
CCCC	Taiwan	Community screening	General population	1990-91	3,602	53	55 (12)
CHS	USA	Medicare lists	General population	1989-93	5,888	57	73 (6)
CMCS-BEIJING	China	Population register	General population	2002	1,324	53	60 (8)
DIWA	Sweden	Population register	General population	2001-04	644	100	64 (0.3)
EAS	Scotland	GP lists	General population	1987-88	1,115	50	64 (6)
EPICARDIAN	Spain	Population register	General population	1993-04	446	59	68 (12)
EVA	France	Electoral rolls	General population	1992-93	1,135	59	65 (3)
HOORN	Netherlands	Population register	General population	1999-01	780	50	69 (7)
INVADE	Germany	Insurance company	General population	2001-03	3,908	59	68 (8)
JHS	USA	Household listings	General population	2000-04	3,883	63	55 (13)
KIHD	Finland	Population register	General population	1987-89	1,399	0	52 (6)
MESA	USA	Household listings	General population	2000-02	6,814	53	62 (10)
NOMAS-INVEST	USA	Random digit dialing	General population	1993-01	856	62	66 (8)
PIVUS	Sweden	Population register	General population	2001-04	1,016	50	70 (0.0)
PLIC	Italy	Hospital	General population	1998-03	1,782	59	55 (11)
ROTTERDAM	Netherlands	Population register	General population	1990-93	7,983	61	71 (10)
SAPHIR	Austria	GP lists/advert	General population	1999-02	1,794	37	52 (6)
High-risk populations							
BK REGISTRY	Korea	Hospital	CHD	2000-07	1,000	44	60 (10)
CREED	Italy	Hospital	On haemodialysis/CAPD	1997-98	138	41	60 (16)
CSN	Italy	GP lists	Hypertension	1980-14	14,158	44	53 (13)
Ekart	Slovenia	Hospital	On haemodialysis	1996-05	54	50	55 (15)
HD-IMT	Serbia	Hospital	On haemodialysis	2004-05	85	39	59 (12)
Honda	Japan	Hospital	On haemodialysis	2005-07	313	39	61 (13)
IMPROVE	Multinational	Hospital/community screening	≥3 CVD RFs	2004-05	3,703	52	64 (5)
Kato	Japan	Hospital	On haemodialysis	2008-09	284	30	64 (12)
Landecho	Spain	Hospital	Early kidney disease	1999-11	250	12	55 (10)
NIGUARDA-MONZINO	Italy	Hospital	Lipid clinic patients/ CVD RFs	1984-10	1,564	41	56 (12)
OSACA2	Japan	Hospital	≥1 atherosclerotic RF	2000-03	291	40	65 (9)
Papagianni	Greece	Hospital	On haemodialysis	2001	83	46	58 (15)
POPROSTU	Poland	Hospital	T1DM	1999	96	33	24 (6)
RIAS	Switzerland	Hospital	≥1 CVD RF/CVD	1999-00	145	43	64 (13)
SPARC	Canada	Hospital	Carotid plaque	2006-08	349	43	71 (9)
3SCO	Japan	Hospital	≥1 CVD RF	2007	164	74	80 (6)
Clinical trials							
ACAPS	USA	Mailing lists/ community screening	LDL-C 130-189 mg/dL	1989-90	919	48	62 (8)
ALLO-IMT	Scotland	Hospital	Ischaemic stroke/TIA	2009-10	80	43	68 (10)
ASAP-NL	Netherlands	Hospital	Heterozygous FH	1997-98	325	61	49 (11)
ATIC	Netherlands	Hospital	Chronic renal failure	2001-02	93	43	53 (12)
AUDITOR	Multinational	Hospital	Obesity+metabolic syndrome	2005-06	661	49	63 (6)
BAS	China	Community screening	cIMT↑	2010	125	63	57 (5)
BK REGISTRY II	Korea	Hospital	Coronary stent	2000-03	205	32	60 (10)
CAMERA	Scotland	Hospital/GP lists	CHD	2009-11	173	23	63 (8)
CAPTIVATE	Multinational	Hospital	Heterozygous FH	2004-05	719	NP	NP
CERDIA	Netherlands	Hospital	T2DM	1999-01	250	53	58 (11)
CONTRAST	Multinational	Hospital	On haemodialysis	2004-09	714	38	64 (14)

ENHANCE	Multinational	Hospital	Heterozygous FH	2002-06	720	49	47 (9)
FACIT	Netherlands	Municipal/blood bank registries	General population	2000-01	819	28	60 (6)
GRACE	Multinational	Hospital	Dysglycaemia+CVD RFs/CVD	2003-05	1,189	36	63 (8)
Gresele	Multinational	Hospital	Peripheral arterial disease	2003-05	442	21	67 (9)
HART	Canada	Hospital/GP lists	CVD/DM+≥1 CVD RF	1999-00	925	24	69 (7)
KIMVASC	Scotland	GP lists	CVD/hypertension/DM	2011-12	80	45	77 (5)
LIFE-ICARUS	Multinational	Hospital	Hypertension+LVH	1996-97	83	27	67 (6)
Masia	Spain	Hospital	HIV+≥2 CVD RFs	2006-07	68	10	52 (11)
MAVET	Australia	Newspaper advert	Smokers	1994-95	408	54	64 (6)
MEDICLAS	Multinational	Hospital	HIV	2003-05	48	0	42 (10)
MG600	Brazil	Hospital	Hypertension	2010-11	35	100	55 (7)
Nakamura II	Japan	Hospital	Chronic renal failure	2001	50	40	53 (7)
OPAL	Multinational	Hospital/GP lists/other[a]	General population	1997-99	866	100	59 (7)
PERIOCARDIO	Australia	Health facilities	Aboriginal Australians	2010-12	273	42	41 (10)
PREVEND IT	Netherlands	Population register	Microalbuminuria	1998-99	864	35	51 (12)
RADIANCE I	Multinational	Hospital	Heterozygous FH	2003-04	904	51	46 (13)
RADIANCE II	Multinational	Hospital	Mixed dyslipidaemia	2003-06	752	36	57 (8)
REGRESS	Netherlands	Hospital	CHD+TC 155-310 mg/dL	1989-91	255	0	56 (8)
RIS	Sweden	Hospital	Hypertension+≥1 CVD RF	1987-89	164	0	66 (5)
Safarova	Russia	Hospital	CHD	2007-09	60	0	55 (6)
SECURE	Canada	Hospital	CVD/DM+≥1 CVD RF	1994-95	731	24	66 (7)
STARR	Multinational	Hospital/GP lists/other[b]	Dysglycaemia	2001-03	1,320	55	53 (11)
STOP-NIDDM	Germany	High-risk population screening	Dysglycaemia	1996-98	119	42	54 (7)
VITAL	Netherlands	Hospital	Indication for statin use	2002-04	199	41	49 (12)
WELCOME	UK	Hospital	NAFLD	2010-11	103	42	51 (11)
Total				**1980-14**	**106,202**	**50**	**59 (10)**

CAPD, continuous ambulatory peritoneal dialysis; CHD, coronary heart disease; cIMT, carotid intima-media thickness; CVD, cardiovascular disease; DM, diabetes mellitus; FH, familial hypercholesterolaemia; GP, general practitioner; HIV, human immunodeficiency virus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; NAFLD, non-alcoholic fatty liver disease; NP, not provided; RF, risk factor; SD, standard deviation; TC, total cholesterol; TIA, transient ischaemic attack; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus. Full study names and references are provided in **Table S1**. [a]Existing ongoing population-based cohorts and advertisements in local print and broadcast media. [b]Public advertising and news reports in the media, internet items, referral from relatives, poster displays, diabetes screening fairs and direct mailing campaigns.