SUrvey of Risk Factors in Coronary Heart Disease (SURF CHD)

A clinical audit program of cardiovascular risk factor management in daily practice

Min Zhao

SUrvey of Risk Factors in Coronary Heart Disease (SURF CHD):
A clinical audit program of cardiovascular risk factor management in daily practice
ISBN: 978-94-028-1333-3

Layout and design by Marilou Maes, persoonlijkproefschrift.nl.
Printed by Ipskamp Printing, proefschriften.net

Survey voor risico factoren van coronaire hartziekten (SURF CHD)

Een klinisch auditprogramma voor management van cardiovasculaire risico factoren in de dagelijkse praktijk

(met een samenvatting in het Nederlands)

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. H.R.B.M Kummeling,
ingevolge het besluit van het college voor promoties in het openbaar
te verdedigen op dinsdag 19 februari 2019 des ochtends te 10.30 uur

door

Min Zhao

geboren op 2 augustus 1986
te Shanxi, China

Promotiecommissie:

Promotoren: Prof.dr. D.E. Grobbee
Prof.dr. I.M. Graham

Copromotoren: Dr. I. Vaartjes
Dr. K. Klipstein-Grobusch

The research described in this thesis was supported by a grant of the Netherlands Organization for Scientific Research (NWO; grant number: 0.22.005.021).

Financial support by the Dutch Heart Foundation for the publication of this thesis is gratefully acknowledged.

TABLE OF CONTENT


SURF
SUrvey of Risk Factors

1

General Introduction

BACKGROUND AND OBJECTIVES

Cardiovascular disease (CVD), particularly coronary heart disease (CHD), is the world's leading cause of death, accounting for 17.9 million deaths (17.7% of all deaths) globally in 2015.[1] CVD death rates have risen significantly in low- and middle-income countries over the last two decades. Eighty percent of CVD deaths occur in low- and middle-income countries and CVD deaths in these areas are expected to increase to 23.6 million by 2030.[2] Their mass occurrence is attributed primarily to modifiable cardiovascular risk factors and overwhelming evidence shows that controlling cardiovascular risk factors can reduce CVD mortality and morbidity, especially for patients with established CVD.[3,4] Current evidence-based clinical guidelines suggest that the top priority of CVD prevention is to control and manage these risk factors in daily practice.[5,6] However, there is still a substantial gap between guideline recommendations and CVD risk factor management in daily practice. [7–11] Several studies have indicated unsatisfactory cardiovascular risk factor control for CVD patients in high-income countries, even though prevention guidelines have been well established and regularly updated in these areas.[10,12] In low- and middle-income countries lack of appropriate local clinical guidelines or reliance on European or US clinical guidelines without adaptation to meet local requirements may impede effect of cardiovascular risk factor management. [13–17]

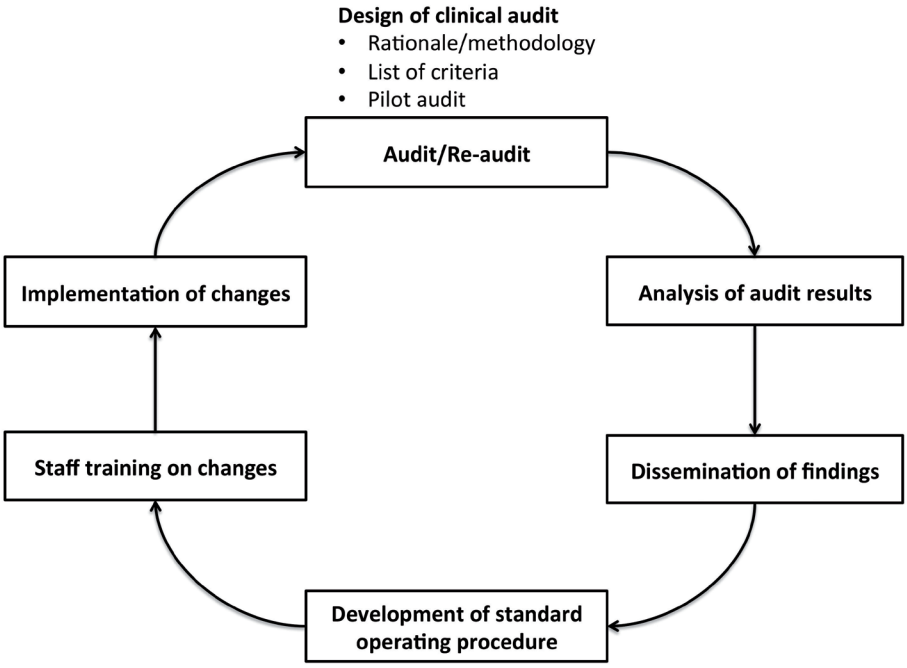
Clinical audit is considered to be an essential tool to facilitate regular monitoring and to emphasize the importance of guideline implementation in clinical practice.[18] It aims to monitor data recording and management, measure daily clinical performance against guideline standards, and inform both appropriate treatment and the modification of guideline recommendations accordingly to improve quality of care in routine practice (figure 1).[19–22] Robust data from audits can be used by all health professionals to improve their own practice in response to information about their daily performance, particularly when this falls below what are considered as desirable standards of care.[20]

A clinical audit is likely to be effective and efficient if it is:

- Adequately comprehensive;
- Straightforward to administer;
- Generalizable to meet different circumstances;
- Repeatable at different times;
- Able to provide accurate and immediate feedback;

- Designed to facilitate appropriate action to improve the standard of care;
- Supported by key stakeholders (policy makers, health professionals, and patients).

Figure 1. Defining a well-designed clinical audit



Clinical audits that are complex may not be practical in a busy clinic. The SUrvey of Risk Factors for Coronary Heart Disease (SURF CHD) was therefore designed as a clinical audit tool with a focus on practicality and easy of use to assess recording and monitoring of cardiovascular risk factors and to evaluate guideline implementation in daily practice for patients with established CHD during routine clinic visits. The feasibility of SURF CHD was tested in a pilot study between 2009 and 2010 in two regions (Europe and Asia).[23] The first phase of SURF CHD (also called SURF I in some chapters) was performed between 2012 and 2013 in three regions (Europe, Asia, and Middle East). This thesis first reviews the rationale for clinical audits with regards to cardiovascular risk factors, describes current audit programs and then presents original findings of SURF CHD.

Air pollution is suggested to be associated with increased cardiovascular risks.[24,25] A further component of this thesis is to assess the feasibility of data linkage by exploring the possibility of relating international data on air pollution to the risk factor data collected in SURF CHD. This work also aims to establish the technical and scientific possibility of developing future data linkage studies.

A preliminary analysis of the SURF CHD data and other studies suggested striking variations in use of cardiovascular medication between regions with lower usage in Asia, particularly in China.[26,27] We, therefore, review cardiovascular medication use in China over the last two decades in the last part of current thesis.

OUTLINE

The thesis first outlines the importance of clinical audit in daily practice and reviews current available audit programs in literature (chapter 2.1). Next, SURF CHD and its core results are introduced (chapter 2.2). Chapter 3 explores differences in cardiovascular risk factor recording and management in more details by SURF CHD data. It focuses on sex disparities (chapter 3.1) and other major determinants such as age and medical history of diabetes (chapter 3.2). Lastly, chapter 3.3 relates combined cardiovascular risk factor data from SURF CHD to air pollutant ($PM_{2.5}$) data from WHO to investigate the associations of long-term $PM_{2.5}$ with physical and laboratory measurements (blood pressure, lipids, and glucose). Chapter 4 systematically reviews current guideline-recommended cardiovascular medication use over the last two decades in China and also assesses potential factors potentially related to trends in cardiovascular medication use. In chapter 5, the implications of the findings from the studies in this thesis for future comprehensive cardiovascular risk factor management strategy in daily practice are discussed.

REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–1544.
2. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. *Nat Rev Cardiol* 2014; 11: 276–289.
3. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. *N Engl J Med* 2015; 372: 1333–1341.
4. Beaglehole R, Bonita R, Horton R, et al. Priority actions for the non-communicable disease crisis. *Lancet* 2011; 377: 1438–1447.
5. Authors/Task Force Members, Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207–274.
6. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
7. EUROASPIRE Study Group. EUROASPIRE A European Society of Cardiology survey of secondary prevention of coronary heart disease : Principal results. *Eur Heart J* 1997; 1569–1582.
8. Kotseva K, Wood DA, De Backer G, et al. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: Principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; 22: 554–572.
9. EUROASPIRE II Study Group. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009; 373: 929–940.
10. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23: 636–48.
11. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
12. Kotseva K, Wood D, Backer G De, et al. EUROASPIRE III : a survey on the lifestyle , risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Prev Cardiol* 2009; 16: 121–137.
13. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bull World Helath Organ* 2005; 83: 820–828.
14. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First

report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
15. Olayemi E, Asare EV, Benneh-Akwasi Kuma AA. Guidelines in lower-middle income countries. *Br J Haematol* 2017; 177: 846–854.
16. Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 743–800.
17. Owolabi M, Miranda JJ, Yaria J, et al. Controlling cardiovascular diseases in low and middle income countries by placing proof in pragmatism. *BMJ Glob Heal* 2016; 1: e000105.
18. Press RM. Principles for Best Practice in Clinical Audit. *Natl Inst Clin Excell* 2002; 206.
19. Burgess R. *NEW Principles of Best Practice in Clinical audit*. Radcliffe, 2011.
20. Gillam S, Frcp F. Frameworks for improvement : clinical audit , the plan–do–study–act cycle and significant event audit. *Qual Prim Care* 2013; 21: 123–130.
21. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback : effects on professional practice and healthcare outcomes (Review). *Cochrane database Syst Rev* 2012; 6: CD000259.
22. Paton JY, Ranmal R, Dudley J; RCPCH Clinical Standards Committee. Clinical audit: Still an important tool for improving healthcare. *Arch Dis Child Educ Pract Ed* 2015; 100: 83–88.
23. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
24. Cosselman KE, Navas-acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015; 12: 627–642.
25. Newby DE, Mannucci PM, Tell GS, et al. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015; 36: 83–93.
26. Cameron A, Roubos I, Ewen M, et al. Differences in the availability of medicines for chronic and acute conditions in the public and private sectors of developing countries. *Bull World Heal Organ* 2011; 89: 412–421.
27. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.


SURF
SUrvey of Risk Factors

2

Overview on clinical audit programs of cardiovascular risk factor management and introduction of SUrvey of Risk Factors (SURF CHD)


SURF
SUrvey of Risk Factors

2.1

Quality assurance and the need to evaluate interventions and audit program outcomes

Min Zhao, Ilonca Vaartjes, Kerstin Klipstein-Grobusch, Kornelia Kotseva, Catriona Jennings, Diederick E. Grobbee, Ian Graham

Eur J Prev Cardiol. 201; 24(3_suppl): 123-128

ABSTRACT

Evidence-based clinical guidelines provide standards for the provision of healthcare. However, these guidelines have been poorly implemented in daily practice. Clinical audit is a quality improvement tool to promote quality of care in daily practice and to improve outcomes through the systematic review of care delivery and implementation of changes.

A major priority in the management of subjects with cardiovascular disease (CVD) management is secondary prevention by controlling cardiovascular risk factors and providing appropriate medical treatment. Clinical audits can be applied to monitor modifiable risk factors and evaluate quality improvements of CVD management in daily practice. Existing clinical audits provided an overview of the burden of risk factors in subjects with CVD and reflect real-world risk factor recording and management.

However, consistent and representative data from clinic audits are still insufficient to fully monitor quality improvement of CVD management. Data are lacking in particular from low- and middle-income countries, limiting the evaluation of CVD management quality by clinical audit projects in many settings.

To support the development of clinical standards, monitor daily practice performance, and improve quality of care on CVD management at national and international levels, more widespread clinical audits are warranted.

Keywords: audit, quality assessment, cardiovascular disease, secondary prevention.

HEALTHCARE QUALITY

The provision of healthcare should be safe, effective, timely, efficient and equitable to maintain and improve the quality of healthcare services provided to patients. [1] This requires health professionals and providers to adhere to structured standards of care, monitor routine healthcare performance, and reduce inequalities in patient management.[1–3]

Evidence-based clinical guidelines provide standards for the provision of healthcare. They should reflect the conscientious, explicit, and judicious use of current best evidence in decision making and in delivering optimal care management strategies for individual patients.[4] Quality of care can then be quantified and measured against these established clinical guidelines to assess both health outcomes and performance of healthcare providers.

However, the availability of guidelines does not necessarily ensure a high standard of clinical care. Nor do they assure the monitoring of the quality of care on daily basis. Striking disparities and inequities in routine patient management have been recognized as a fundamental issue in healthcare performance regardless of strong recommendations from clinical guidelines.[5,6] A significant number of patients do not receive evidence-based care as suggested for their health conditions in terms of risk factor management and globally the quality of patient care is still poor.[7,8]

Thus, one of the key components in current healthcare settings should be implementation and evaluation of standardized care and assessment of health outcomes to ensure that high quality care is provided to patients in daily practice.[9,10]

INTRODUCTION OF CLINICAL AUDITS

A clinical audit is defined as a quality improvement cycle that involves measurement of the effectiveness of healthcare against agreed and proven standards for high quality care, and corrective action to bring practice in line with these standards so as to improve the quality of care and health outcomes (figure 1).[11]

Clinical audits allow valuable comparative information on local, national, or international levels to be obtained so that institutions and clinicians can compare and share this

information. It can also measure changes in health outcomes over times and to what extent these changes are sustained in the long term.[11,12]

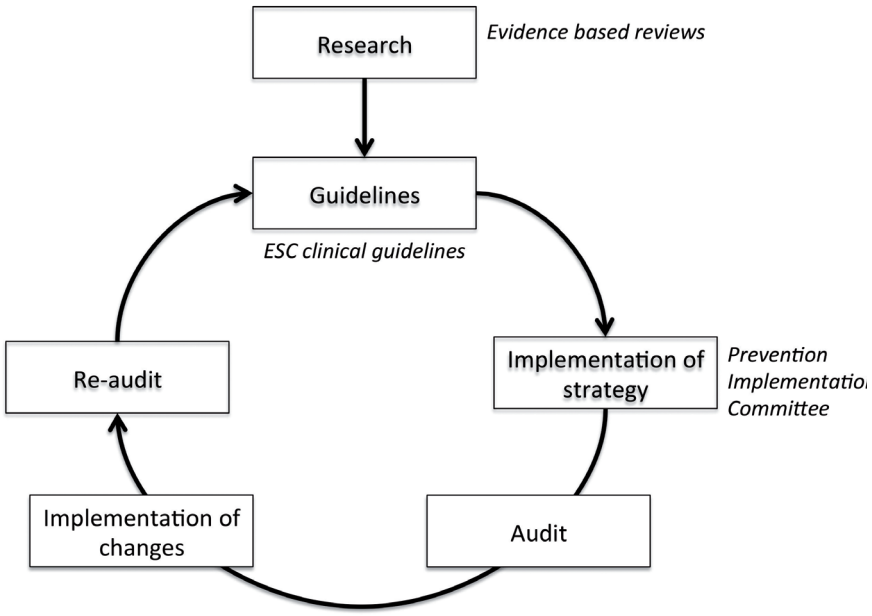


Figure 1. Clinical audit circle

Four essential stages are required for a good quality clinical audit:

- Audit preparation and planning
- Implementation to measure quality of care
- Implementation of changes in line with best practice guidelines
- Re-audit to sustain quality improvement

In each circle, clinical audits provide an objective assessment of defined outcomes and information on the process of care and the extent to which daily practice is being implemented according to defined standards. The re-audit activity facilitates the monitoring of healthcare performance regularly and the evaluation of improvements of quality of care in daily practice.

Given the diversity of clinical settings in daily practice, not all indicators can be applied for every clinical audit. Hence, before undertaking a clinical audit, it is essential to identify potentially suitable clinical conditions and indicators from current literature, define valid and reliable outcome measures and to develop and incorporate improved practices into clinical care. Apart from formally designed audits, both registries and observational studies can contribute useful audit information. A 'registry' can collect clinical outcomes and measure them against standards to assess healthcare performance. Repeated large-scale representative surveys can evaluate quality improvements and monitor changes in quality of care in daily practice. Similarly, prospective observational studies with a focus on quality assurance of healthcare could be also considered as audits.

INTERNATIONAL CLINICAL AUDITS OF CARDIOVASCULAR DISEASE MANAGEMENT

Clinical audit can be performed in a number of areas relevant to cardiovascular disease (CVD) management and the intentions of clinical audits can be interpreted in different ways to monitor whether quality of care has been improved. Thus, the study design can vary from study to study. In the current literature review, we selected five international studies as examples with different study designs to give a broad description of current audit program running for cardiovascular risk factor management (table 1). One study was performed as clinical audit during routine practice.[13,14] While others were applied as registries[15–17] or cross-sectional surveys.[18–22] A large-scale prospective cohort study[23,24] was also identified as an example that aimed to assess lifestyle risk factor management and cardiovascular medication use for CVD secondary prevention.

The findings of these five studies are broadly similar irrespective of their study design and time frame of data collection. They all demonstrated that the current management of modifiable cardiovascular risk factors and medical treatments are still insufficient with substantial variations at country and regional levels.[13–24] The presence of ongoing smoking, obesity, and diabetes remain major problems.[13–24]

EuroAspire

The European Society of Cardiology developed the EUROASPIRE (European Action on Secondary Primary Prevention by Intervention to Reduce Events) survey to measure modifiable risk factor and therapeutic management in coronary heart disease (CHD) patients and monitor the quality of secondary prevention care provided by individual

participating countries.[18]

EUROASPIRE is a European-based cross-sectional survey, conducted in four different time frames: 1995-96 in 9 European countries (EUROASPIRE I),[18] 1999-2000 in 15 European countries (EUROASPIRE II),[19] 2006-2007 in 22 European countries (EUROASPIRE III), [20] and 2012-2013 in 24 European countries (EUROASPIRE IV). [21]

EUROASPIRE data, collected by means of a face-to-face interview with standardized measurement of risk factors rather than from review of medical records, provide high quality comparative information on preventive care. In addition, four EUROPASIRE surveys with uniform collection method from the same participating centers allow multilevel comparison to evaluate any potential trends in CHD management over years.[25–27]

EUROASPIRE has major strengths in terms of highly standardized methods and centralized laboratory measurements. However, its detailed protocol requires considerable resources from participating centers in terms of cost and time. These factors and the low interview rate (<50%) arising may limit generalizability of the result to whole populations. Non-participants may be more likely to have poor CHD management.[21] The robust methodology should encourage efforts to apply EUROASPIRE to more centers in participating countries to increase representativeness but costs may be prohibitive.

SURF

The SURF (SUrvey of Risk Factor Management) was developed by The European Association of Preventive Cardiology, aiming to investigate daily data recording and assess cardiovascular risk factor management in routine clinics. SURF was first tested for feasibility as a pilot study in 7 countries[13] and the first Phase (SURF I) in 11 countries.[14]

SURF uses a one-page data sheet that can easily be collected during a routine clinic visit rather than requiring detailed examinations of patients or retrieving information from medical records. Its simplicity allows applicability to smaller centers with limited resources as well as major academic centers in Europe and beyond to monitor quality of care in daily practice with minimal workload and cost. It also allows regular re-audits to evaluate changes in cardiovascular risk factor management. Limitations to date include non-representativeness of participating centers in SURF countries. Following SURF I, SURF II is planned in mid-2017 with a wider and larger range of participating centers.

WHO-PREMISE

The WHO Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE) was carried out between 2002 and 2003 in 10 countries.[22]

WHO-PREMISE study was one of largest descriptive cross-sectional surveys in low- and middle-income countries to assess current secondary prevention strategy of CVD and record the use of cardiovascular medications. It also documented patients' attitude and knowledge towards CVD prevention management, demonstrating the necessity for cardiovascular education programs.

As data were collected by self-reported questionnaire, response bias may have occurred limiting generalizability, even though a face-to-face interview was applied to minimize missing or incorrect information. The second and third phases of the WHO-PREMISE study are planned to implement evidence-based, affordable, and sustainable interventions for secondary prevention of CVD both in the demonstration areas and nationally.

REACH registry

The Reduction of Atherothrombosis for Continued Health (REACH) Registry was developed in 44 countries across six regions between 2003 and 2004 to evaluate cardiovascular risk factor prevalence and medical treatment management of cerebrovascular, arterial, or peripheral arterial disease.[15–17]

The REACH registry extended its data collection beyond CHD to stroke and peripheral arterial disease with detailed follow-up information on reoccurrence of cardiac event to investigate possible contribution of cardiovascular risk factors on all types of vascular diseases. Furthermore, the REACH registry is more geographically diverse than the other audits considered here, which may improve representativeness. It is somewhat dated and it is hoped that the follow-up phase will incorporate more diverse geographic areas.

PURE

The Prospective Urban Rural Epidemiology (PURE) study is a large-scale community-based prospective cohort study conducted since 2003 in 17 countries.[23,24] One of the main purposes is to document the use of guideline-recommended cardiovascular medication and prevalence of modifiable risk factors in patients with established CVD. The PURE study can be considered partly as an audit, as it is used to assess quality of secondary prevention care in CVD management.

The unique sampling process enabled data collection from communities in both urban and rural areas to identify all traditional risk factors as well as societal and environmental determinants of CVD. These new and valuable data will provide policy makers with information to develop more efficient and comprehensive CVD prevention programs. The detailed examination and annual follow-up allows documentation of all potential disease events and monitoring the control of cardiovascular risk factors. However, as a prospective cohort study, PURE is facing challenges to maintain good quality data and a high response rate over time to guarantee its long-term monitoring of CVD management.

Table 1. Examples of current international audit programs on secondary prevention of cardiovascular disease (CVD)

Study	Performed area	Study design	Performed year(s)	Population	P% of women
EUROASPIRE Study group[18–21]	EUROASPIRE I: 9 EU countries EUROASPIRE II: 15 EU countries EUROASPIRE III: 22 EU countries EUROASPIRE IV: 24 EU countries	Cross-sectional survey	EUROASPIRE I: 1995-1996; EUROASPIRE II: 1999-2000; EUROASPIRE III: 2006-2007; EUROASPIRE IV: 2012-2013	EUROASPIRE I: 3569 EUROASPIRE II: 5556 EUROASPIRE III: 8966 EUROASPIRE IV: 7998	EUROASPIRE I: 25% EUROASPIRE II: 25% EUROASPIRE III: 27% EUROASPIRE IV: 27%
Cooney et al[13] Zhao M et al[14] SURF study group	7 countries in SURF pilot-3 in Europe and 4 in Asia. 11 countries in SURF I-8 in Europe, 2in Asia, and 1 in the Middle	Clinical audit	Pilot study: 2009-2010; SURF I: 2012-2013	SURF Pilot: 1070 SURF I: 10,186	SURF Pilot: 21% SURF I: 29%
Mendis S et al, 2005[22] WHO-PREMISE Study group	10 low- and middle-income countries	Cross-sectional survey	2002-2003	10,000	37%
REACH Registry Investigators*[15–17]	44 countries-2 in North America, 9 in Latin America, 18 in Europe, 4 in Middle East, 10 in Asia, and 1 in Australia	Registry	2003-2004	CHD: 40,258 CVD: 18843	CHD: 30% CVD: 40%
PURE Investigators*[23,24]	17 countries-5 in Asia, 1 in North America, 4 in Middle East, 2 in Europe, 4 in South America, 2 in Africa, and 3 in the Middle East	Prospective cohort	2003-2009	CHD: 5650	CHD: 54%

CVD: cardiovascular disease; CHD: coronary heart disease; %: percentage.

* Not only cardiovascular disease patients were recruited in these studies.

NATIONAL CLINICAL AUDITS IN CORONARY HEART DISEASE MANAGEMENT

Clinical audits have also been introduced at national-level in several countries. Evidence from the United Kingdom,[28,29] Australia,[30] Sweden,[31] Spain,[32] and Croatia[33] showed that clinical audit projects can be an effective tool to assist health professionals to monitor and improve the quality and outcomes of their local services. For instance, the ASPIRE-2-PREVENT survey in the UK was developed to determine whether CVD guidelines have been implemented properly and enable quality of care accessed in everyday practice.[28]

CHALLENGES ON CLINICAL AUDIT PROJECTS

The above quoted studies provide examples of the use of audits to monitor quality of care and give insight into daily practice of current CVD management. Prospective observational studies have indicated that the audit programs could improve quality of care and achieve better modifiable risk factor managements than usual care alone over times.[25–27,30]

However, there is a lack of randomized controlled trials to provide evidence of a reduction in hard CVD end points as a result of clinical audits. The quality of the audits reviewed varied and consistent and representative data at international or national level are still lacking, indicating that the potential for quality improvement of CVD management has not been fulfilled. Furthermore, there is also a striking dearth of data from low- and middle-income countries, which have not yet conducted any clinical audits to evaluate their CVD management quality. This is of concern, since resource constraints may make the delivery of high quality care even more challenging. It points to the need to promote simple audits with wider representativeness to facilitate healthcare improvements worldwide. Thus, a successful clinical audit program of CVD prevention in daily practice should contain these features:

- Simple but structured methodology
- Repeatability
- Adaptability
- Representativeness
- Multiple levels (local, national, or international)

CONCLUSION

Clinical audit enables both the recording and monitoring of cardiovascular risk factors to facilitate guideline-based standard operating procedures to improve clinical practice. Good quality clinical audit is still lacking. More highly standardized clinical audits are warranted to support the development of clinical standards, monitor daily practice performance, and improve quality of care on CVD management.

CONTRIBUTORS

MZ, IV, KKG, DG, and IG contributed to the conception and design of the work. MZ contributed to the acquisition and interpretation of data for the work and drafted the manuscript. IV, KKG, KK, CJ and IG critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

REFERENCES

1. Warrell DA., Cox TM., Firth JD. *Oxford textbook of medicine*. 5th ed. Oxford University Press, 2010.
2. Batalden PB, Davidoff F. What is 'quality improvement' and how can it transform healthcare? *Qual Saf Health Care* 2007; 16: 2–3.
3. Watkins SJ. Public health 2020. *Br Med J* 1994; 309: 1147–1149.
4. Sackett DL, Rosenberg WMC, Gray J a M, et al. Evidence based medicine: what it is and what it isn't. *Br Med J* 1996; 312: 71–72.
5. Forouzanfar MH, Alexander L, Anderson HR, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 386: 2287–2323.
6. World Health Organization. *Global Health Risks: mortality and burden of disease attributable to selected major risks*. 2009.
7. Grimshaw J, Freemantle N, Wallace S, et al. Developing and implementing clinical practice guidelines. *Qual Heal Care* 1995; 4: 55–64.
8. Grimshaw J, Eccles M, Tetroe J. Implementing clinical guidelines: current evidence and future implications. *J Contin Educ Health Prof* 2004; 24 Suppl 1: S31–S37.
9. Donabedian a. The quality of care. How can it be assessed? *JAMA* 1997; 260: 1743–1748.
10. Jennings C, Graham I, Gielen S. Ensuring quality of interventions. In: *The ESC Handbook of preventive cardiology: putting prevention into practice*. Oxford University Press, 2016.
11. Burgess R, Moorhead J. *New principles of best practice in clinical audit*. Radcliffe, 2011.
12. Hysong SJ, Best RG, Pugh JA. Audit and feedback and clinical practice guideline adherence: making feedback actionable. *Implement Sci* 2006; 1: 9.
13. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
14. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
15. Ohman EM, Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: An international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J* 2006; 151.
16. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295: 180–9.
17. Rodriguez F, Cannon CP, Steg PG, et al. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic disease: Findings from the REACH registry. *Clin Cardiol* 2013;

36: 721–727.
18. EUROASPIRE Study Group. EUROASPIRE A European Society of Cardiology survey of secondary prevention of coronary heart disease : Principal results. *Eur Heart J* 1997; 1569–1582.
19. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries Principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; 554–572.
20. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 121–137.
21. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2015; 59–61.
22. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE). *Bull World Helath Organ* 2005; 83: 820–828.
23. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.
24. Teo KK, Lear SA, Islam S, et al. Prevalence of a Healthy Lifestyle Among Individuals With Cardiovascular Disease in High-, Middle- and Low-Income Countries. *JAMA* 2013; 309: 1613–1621.
25. Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009; 373: 929–940.
26. Kotseva K, Wood D, De Backer G, et al. Clinical reality of coronary prevention guidelines: A comparison of EUROASPIRE I and II in nine countries. *Lancet* 2001; 357: 995–1001.
27. Kotseva K, De Bacquer D, Jennings C, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999–2013. *Glob Heart* 2017; 12: 315–322.e3.
28. Kotseva K, Jennings CS, Turner EL, et al. ASPIRE-2-PREVENT: a survey of lifestyle, risk factor management and cardioprotective medication in patients with coronary heart disease and people at high risk of developing cardiovascular disease in the UK. *Heart* 2012; 98: 865–71.
29. Herrett E, Smeeth L, Walker L, et al. The Myocardial Ischaemia National Audit Project (MINAP). *Heart* 2010; 1264–1267.
30. Jelinek M, Vale MJ, Liew D, et al. Improvements in Cardiovascular Risk Factors and Adherence to Recommended Medications —Two Years Follow-up. *Hear Lung Circ* 2009; 18: 388–392.

31. Kahan T, Wandell P. Risk factors in established coronary heart disease : evaluation of a secondary prevention programme. *J Cardiovasc Risk* 2001; 8: 73–80.
32. Munoz M, Rohlfs I, Masuet S, et al. Analysis of inequalities in secondary prevention of coronary heart disease in a universal coverage health care system. *Eur J Public Health* 2005; 16: 361–367.
33. Reiner Z, Mihatov S, Milicic D, et al. Treatment and secondary prevention of ischemic coronary events in Croatia (TASPIC-CRO study). *Eur J Prev Cardiol* 2016; 13: 646-54.


SURF
SUrvey of Risk Factors

2.2

Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries

Min Zhao, Marie Therese Cooney, Kerstin Klipstein-Grobusch, Ilonca Vaartjes, Dirk De Bacquer, Johan De Sutter, Željko Reiner, Eva Prescott, Pompilio Faggiano, Diego Vanuzzo, Hussam AlFaleh, Ian Menown, Dan Gaita , Nana Posogova, Wayne H-H Sheu, Dong Zhao, Huijuan Zuo, Diederick E. Grobbee, Ian M. Graham

Eur J Prev Cardiol. 2016 Jul;23(11):120

ABSTRACT

Background: To simplify the assessment of the recording and control of coronary heart disease (CHD) risk factors in different countries and regions.

Design: SURF is an international clinical audit.

Methods: Data on consecutive patients with established CHD from countries in Europe, Asia, and the Middle East were collected on a one-page collection sheet or electronically during routine clinic visits. Information on demographics, diagnostic category, risk factors, physical and laboratory measurements, and medications were included and key variables summarized in a cardiovascular health index score (CHIS).

Results: 10,186 CHD patients (29% women) were enrolled from 79 centres in 11 countries. Recording of risk factors varied considerably: smoking was recorded in over 98% of subjects, while about 20% lacked data on laboratory measurements relevant to cardiovascular disease risk. 16% of participants reported smoking, 29% were obese, and 46% had abdominal obesity. 60% of participants had blood pressure<140/90mmHg (140/80mmHg for diabetics), 48% had HbA1c<7%, 30% had LDL<1.8mmol/L, and 17% had a good CHIS.

There were substantial regional variations. Less than 3% of patients attended cardiac rehabilitation in Asia or the Middle East, compared with 45% in Europe. In Asia, 15% of patients had LDL cholesterol <1.8mmol/L compared with 33% in Europe and 36% in the Middle East. Variations in medications were noted, with lower use of statins in Asia.

Conclusions: SURF proved to be practical in daily practice. Results indicated poor control of risk factors with substantial variation between countries calling for development and implementation of clinical standards of secondary prevention of CHD.

Keywords: SURF, CHD, risk factors.

INTRODUCTION

Cardiovascular disease (CVD), particularly coronary heart disease (CHD), is the biggest cause of death worldwide.[1] Although cardiovascular death rates have declined in some high-income countries, rates of CHD have risen significantly in low- and middle-income countries.[2] The major risk factors for CHD are known, and there is good evidence that controlling them reduces morbidity and mortality.[3]

The main purpose of CHD prevention is the control and management of modifiable risk factors. Explicit, evidence-based guidelines exist to assist health care professionals with risk factor management.[4] Despite this, most studies report poor risk factor control even in high-risk patients with established CHD.[5–9]

EUROASPIRE is the best-known audit of risk factors in CHD patients in Europe. It obtains detailed information in a standardized manner.[6–8,10] It does, however, require considerable resources from participating centres including additional staff and a dedicated clinic, which may reduce the number of centres able to participate thus limiting the representativeness of the data. To complement EUROASPIRE, the SURF (SUrvey of Risk Factors) audit was developed in collaboration with the European Association for Cardiovascular Prevention and Rehabilitation. It is designed to be undertaken as part of routine clinic visits. The feasibility of SURF was tested in a pilot study conducted in 7 countries which demonstrated that the audit was indeed quick to perform.[9] This led to SURF I, which assesses risk factor recording and management of 11 countries from Europe, Asia, and the Middle East.

METHODS

Study setting and population

The SURF audit was carried out between 2012 and 2013 in 11 countries across three regions-Europe (Belgium, Croatia, Denmark, Ireland, Italy, Northern Ireland, Romania, Russia), the Middle East (Saudi Arabia), and Asia (Taiwan and China) (table 1). Consecutive CHD patients aged ≥18 years were recruited from cardiology outpatient clinics in participating centres (appendix part A).

Table 1. Participating countries and centres in SUrvey of Risk Factor (SURF) I

Country	Continent	Number of Centres	Number of patients
Belgium	Europe	*	604
Croatia	Europe	9	1514
Denmark	Europe	*	300
Ireland	Europe	11	1826
Italy	Europe	19	1223
Northern Ireland	Europe	2	166
Romania	Europe	8	625
Russia	Europe	8	464
Saudi Arabia	Middle East	5	1580
China	Asia	11	1150
Taiwan	Asia	4	734
Total		79	10186

*Centre information is not available; It will be counted as one single center

Data collection and management

Information on demographics, diagnostic category, risk factors, physical and laboratory measurements and medications was obtained by following a standardised procedure and recorded on a one-page data collection sheet (appendix part B). Details on collected data are given in table 2.

Data were entered online using Survey Monkey (www.surveymonkey.com). Alternatively, anonymous data could be submitted on a spread sheet with a unique security code. All data were downloaded and stored securely in restricted and password protected divisions.

Risk factor management

Risk factor management was assessed against targets specified by the 2012 version of European guidelines on CVD prevention. [4] As a summary measure to assess overall adherence to risk factor management, a simplified Cardiovascular Health Index Score (CHIS) was used adapted from the ideal Cardiovascular Health Score. [11] CHIS categories were defined by the summation of the number of six risk factors (smoking status, body mass index, physical activity, blood pressure, LDL cholesterol, and blood sugar) that were at target. Details are available in table 2.

Statistical analysis

Statistical analyses were undertaken using STATA (StataCorp. 2013. College Station, TX, USA). For continuous variables, mean and standard deviations were calculated if the distribution was normal. One-way ANOVA was used to assess for statistically significant differences between regions. For categorical variables, the Chi-square test was used to assess for differences between regions. Lipid (total cholesterol, LDL cholesterol, and HDL cholesterol) and glucose distributions were positively skewed, so comparison of results between regions was based on medians and the Kruskal-Wallis test.

RESULTS

Overall, data from 10,186 participants from 79 centres in 11 countries was included in SURF I (table1 and appendix part C). The mean age of all patients was 65.2±11.2 years and 29.3% were women.

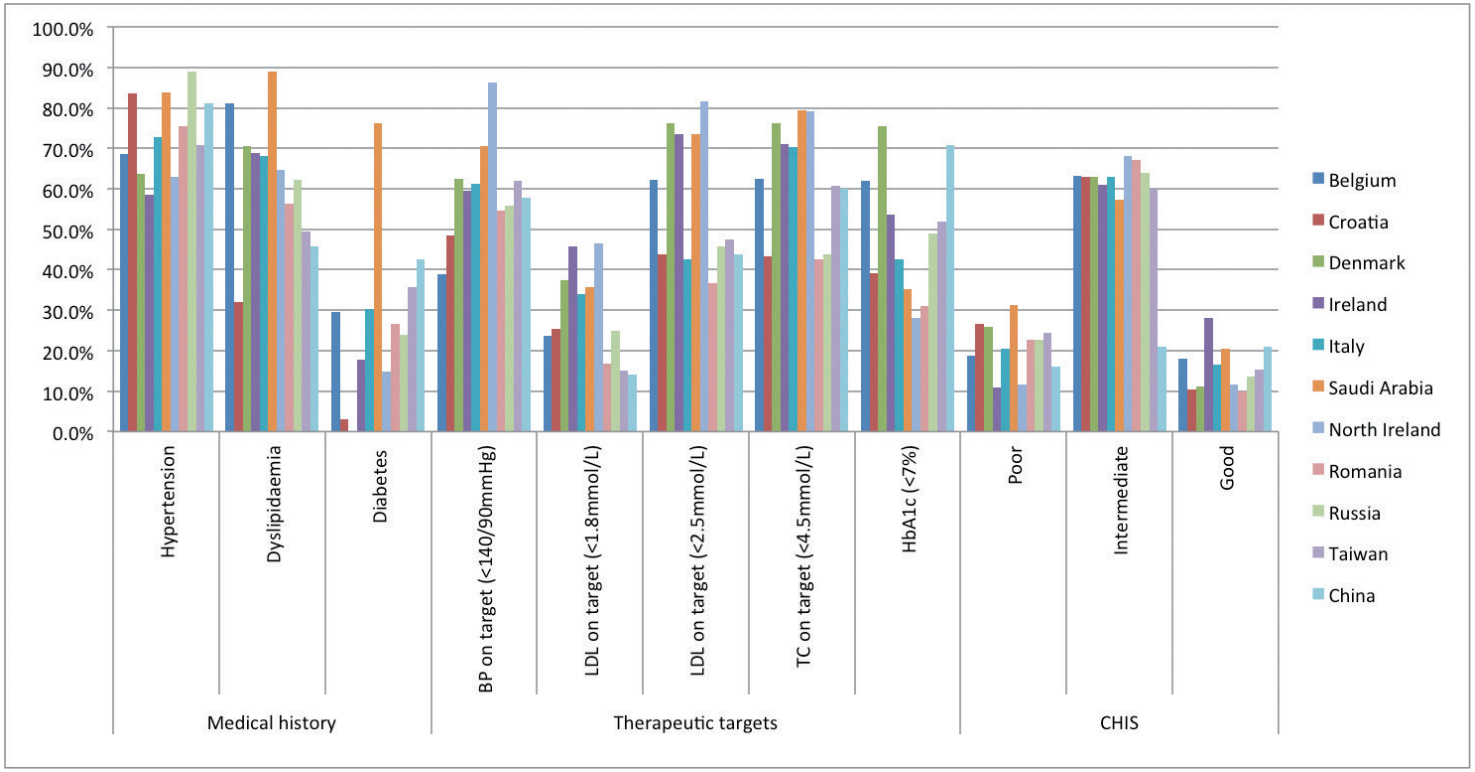
Recordings of fundamental demographic variables like age and gender were missing occasionally (0.7% and 1.3%, respectively). Completeness of data recording for other variables was variable. In general, modifiable risk factors and physical measurements had higher recording rates compared to laboratory measurements. Cigarette smoking and blood pressure were recorded in over 98% but data on lipids, blood glucose, waist circumference, and family history of premature CVD were missing in about 20%. Details on data recording are available in supplementary material part D.

A small proportion of Asian (2.6%) and Middle Eastern (2.8%) patients participated in a cardiac rehabilitation programme compared to 45% in Europe ($p<0.001$). The highest attendance of cardiac rehabilitation was in Ireland (65.9%), and the lowest was observed in China (1.4%) (figure 1). Smoking rates were 16.2% with higher levels of smoking in Europe (17.5%), compared to Asia (16.0%) and the Middle East (10.4%). All three regions reported low levels of patients reaching the recommended level of physical activity. Over 70% of patients were overweight or obese, varying from 47.4% in Asia to 83% in the Middle East ($P<0.001$). Overall medication usage on antiplatelets, statins, and beta-blockers were 90.1%, 81.2%, and 71.6%, respectively. A higher usage of statins was noted in Europe (86.8%) and the Middle East (93.2%) than in Asians (51%, $p<0.001$). Details are given in table 3.

Table 2. Information and definition of collected data, SUrvey of Risk Factors (SURF) I

Demographic information
Age: >18 years old; Gender: men and women
Risk factors
Smoking history: Current smoker; Ex-smoker: quit smoking more than months ago; Non-smoker. Physical activity: Less, more, and equal to recommended level (30 minutes of moderately vigorous activity three to five times a week) Family history: a first-degree relative with a history of atherosclerotic CVD before age 55 for a male or 65 for a female. History of hypertension, dyslipidemia, or diabetes and cardiac rehabilitation attendance: self-reported
Diagnostic category
Coronary Artery Bypass Grafting (CABG);Percutaneous Coronary Intervention (PCI); Acute Coronary Syndrome (ACS);Stable angina Pectoris (SAP); ACS: indicates cardiac chest pain at rest with objective evidence of acute ischemia or infarction; SAP: Clinical angina with objective confirmation from a clearly positive exercise ECG or ischemia on perfusion imaging, or a coronary angiogram showing a narrowing of 70% or more in at least one coronary artery
Physical measurements
Systolic/diastolic blood pressure, heart rate, height/ weight, and waist circumference measurements on the day. Body Mass Index (BMI)*: calculated by height and weight. The BMI categories were as follows: underweight<18.5 kg/m2, normal weight 18.5-24.9kg/m2, overweight 25-29.9 kg/m2, obese I 30-34.9 kg/m2, obese II 35-39.9kg/m2, obese III>=40kg/m2. [14] Abdominal obesity defined as waist circumference>=88cm in women and >=102cm in men. [14] * The same definitions of obesity and abdominal obesity have been used for Asian, Middle Eastern, and European populations.
Laboratory measurements and therapeutic targets
Most recent laboratory measurements: Systolic/diastolic blood pressure; Heart rate; Height; weight;waist circumference; most recent laboratory measurements Blood pressure target: <140/90 mmHg (for diabetic patients, blood pressure<140/80mmHg); Total cholesterol target<4.5 mmol/L;LDL cholesterol target <2.5 mmol/L; Stricter target of <1.8mmol/L; HbA1c target <7%. [4]
Medications
Antiplatelet agents; Statins; Other lipid-lowering agent; beta-blocker; Calcium-channel blocker; Diuretic; ACE inhibitor; Angiotensin-II receptor; Other antihypertensive agent; Nitrate; Insulin; Oral hypoglycaemic agents; Drug class only
Cardiovascular Health Index Score (CHIS) and categories
CHIS were defined by 6 risk factors. They are: non-/ex-smoker, body mass index (BMI)<25, moderate/vigorous physical activity, controlled blood pressure (blood pressure<140/90mmHg; 140/80mmHg for diabetics), controlled LDL cholesterol (<2.5mmol/L), and controlled blood sugar (HbA1c<7%; if HbA1c is not available, glucose<7mmol/L). The number of controlled risk factors was summed, ranging from 0 (poor) to 6 (good). CHIS categories were defined as follow: poor≤2, intermediate=3 or 4, and good=5 or 6.

Figure 1. Risk factors, therapeutic targets, and Cardiovascular Health Index Score (CHIS), SUrvey of Risk Factors (SURF) I by country



Cardiac rehab, cardiac rehabilitation; BP, blood pressure

* Blood pressure target: <140/90mmHg; <140/80mmHg for diabetics.

Table 3. Demographic characteristics, lifestyle risk factors and medication usage, SUrvey of Risk Factors (SURF) I by region

	Overall	Europe	Asia	Middle East	P value*
Patients	10186	6722	1884	1580	
Sex					<0.001
Men (%)	70.8	73.0	60.4	73.9	
Women (%)	29.3	27.0	39.6	36.1	
Age (year)	65.2±11.2	65.4±10.9	66.8±11.1	62.1±12.0	<0.001
CHD category (%)					
CABG	19.5	21.5	6.2	26.9	<0.001
PCI	47.0	47.4	35.0	59.4	<0.001
ACS	35.6	43.4	12.7	29.5	<0.001
SAP	30.8	26.7	58.4	15.5	<0.001
Hospital admission (%)	32.1	37.7	20.1	16.6	<0.001
Cardiac rehab (%)	30.2	45.0	2.6	2.8	<0.001
Family history (%)	31.7	37.7	20.1	16.6	<0.001
Risk factor history (%)					
Smoking history					<0.001
Current smoker	16.2	17.5	16.0	10.4	
Ex-smoker	39.2	45.7	27.4	25.8	
Never smoked	44.7	36.8	56.6	63.8	
Physical activity					<0.001
Less than	46.6	44.8	46.6	54.6	
Moderate	38.3	39.4	38.4	33.4	
More than	15.1	15.8	15.0	12.0	
Physical measurements					
BMI (kg/m^2) ¶	28.1±4.9	28.5±4.7	25.2±3.4	30.3±5.9	<0.001
Overweight or Obese (%)	72.5	77.9	47.4	83.0	<0.001
WC (cm) †	96.9±14.8	99.9±14.7	86.7±9.4	100.2±14.8	<0.001
Women	92.8±14.9	95.9±15.4	84.3±9.4	100.3±15.0	<0.001
Men	98.6±14.4	101.4±14.2	88.2±9.0	100.2±14.7	<0.001
Abdominal obesity (%)†	45.8	54.3	16.7	56.3	<0.001
Medications					
Anti-platelet	90.1	91.4	82.3	93.7	<0.001
Statin	81.2	86.8	51.0	93.2	<0.001
Other lipid lowering	8.0	10.0	2.6	5.9	<0.001

Table 3. (continued)

	Overall	Europe	Asia	Middle East	P value*
Patients	10186	6722	1884	1580	
Beta blocker	71.6	77.5	38.4	86.3	<0.001
Calcium antagonist	27.2	20.9	51.0	25.4	<0.001
Other anti-hypertensive	7.4	7.0	3.2	14.4	<0.001
ACE inhibitor	50.8	57.7	20.5	57.5	<0.001
Diuretic	23.3	24.9	14.9	26.7	<0.001
ARB	18.2	13.9	33.0	19.1	<0.001
Nitrate	32.3	26.6	57.3	26.6	<0.001
Insulin	9.8	6.6	6.6	26.8	<0.001
Oral hypoglycemic agent	22.4	14.9	28.0	47.8	<0.001

CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; SAP: stable angina pectoris; Cardiac rehab: cardiac rehabilitation; BMI: Body mass index; WC: waist circumference; ACE inhibitor: angiotensin-converting enzyme; ARB: angiotensin receptor blocker.

Numeric variables are mean± standard deviation (SD) and categorical variables are percentage. P values obtained from one-way ANOVA test for numeric variables and Chi-square test for categorical variables.

¶ BMI was calculated by weight and height. Its categories were defined as follows: underweight<18.5kg/m2, normal weight 18.5-24.9kg/m2, overweight 25-29.9 kg/m2, obese I 30-34.9 kg/m2, obese II 35-39.9kg/m2, obese III>=40kg/m2.

†Abdominal obesity defined as waist circumference>=88cm in women and >=102cm in men.

*Comparison between regions

Table 4 shows therapeutic control of lipids, blood pressure and glucose. About two thirds of patients reported previously diagnosed dyslipidaemia. For patients from the Middle East a considerably higher prevalence of dyslipidaemia, compared to those from Europe and Asia was reported (88.9%, 68.7%, and 47.2%, respectively). Asian patients seemed less likely to achieve the stricter LDL cholesterol target (14.6%) compared with European (32.9%) and Middle Eastern patients (35.6%). Among participating countries, the best LDL cholesterol control was observed in patients from Northern Ireland, whereas patients from China showed the lowest (figure 1).

The overall prevalence of hypertension was high (74.5%), ranging from 71.7% in Europe to 83.9% in the Middle East. Overall 60% of all patients participating in SURF I met the guideline target (<140/90mmHg; 140/80mmHg for diabetics). Despite the highest frequency of a known history of hypertension, 70.6% of Middle Eastern patients were

at blood pressure target.

Reported diabetes was prevalent in patients from all regions, especially the Middle East (76.1%), compared to 40% in Asia and 25.2% in Europe (p<0.001). An HbA1c of <7% was rarely achieved. Figures were 47.6%, 64.5%, and 35.2% for patients in Europe, Asia, and the Middle East, respectively.

Table 4. Therapeutic control of lipids, blood pressure, glucose and HbA1c, and Cardiovascular Health Index Score (CHIS), SUrvey of Risk Factors (SURF) I by region

	Overall	Europe	Asia	Middle East	P value*
Lipid					
Dyslipidemia (%)	67.6	68.7	47.2	88.9	<0.001
Total cholesterol (mmol/L)	4.1 (8320)	4.1 (5506)	4.2 (1598)	3.7 (1216)	0.001
LDL cholesterol (mmol/L)	2.3 (7672)	2.2 (4872)	2.6 (1532)	2.0 (1268)	0.001
HDL cholesterol (mmol/L)	1.1 (7780)	1.1 (5036)	1.1 (1533)	0.9 (1211)	0.001
Triglycerides (mmol/L)	1.4 (8130)	1.4 (5291)	1.4 (1610)	1.4 (1229)	0.083
At targets (%)¶					
Total cholesterol	62.3	59.2	60.3	79.4	<0.001
LDL cholesterol	59.4	60.2	45.2	73.4	<0.001
Stricter LDL cholesterol	29.7	32.9	14.6	35.6	<0.001
Blood pressure					
Hypertension (%)	74.5	71.7	77.2	83.9	<0.001
SBP (mmHg)	131.5±18.6	132.4±19.5	130.7±16.4	128.4±17.2	<0.001
DBP (mmHg)	76.1±11.0	77.0±10.8	77.0±10.9	71.5±10.4	0.111
Heart rate (bpm)	70.9±12.7	70.2±13.0	73.6±12.4	70.8±11.4	<0.001
At target (%)¶					
Blood pressure	60	57.6	59.4	70.6	<0.001
Diabetes					
Diabetes (%)	34.5	25.2	40	76.1	<0.001
Type I diabetes	2.1	1.6	0.1	15.3	<0.001
Type II diabetes	32.9	23.8	39.8	73.7	<0.001
Glucose (mmol/L)	5.7 (7891)	5.6 (5167)	5.8 (1524)	6.6 (1200)	0.001
Non-diabetics	5.5 (5688)	5.5 (4082)	5.3 (899)	6.0 (707)	0.001
Diabetics	7.4 (2203)	7.4 (1085)	6.9 (625)	8.3 (493)	0.001

Table 4. (continued)

	Overall	Europe	Asia	Middle East	P value*
HbA1c (%)	7.4±1.6	7.3±1.5	7.3±1.5	7.9±1.8	0.001
Non-diabetics	7.1±1.7	6.8±1.4	6.0±0.9	7.7±1.8	0.001
Diabetics	7.5±1.6	7.6±1.5	7.0±1.4	8.3±1.8	0.001
HbA1c at target (%)¶					
Overall	48.2	47.6	64.5	35.2	<0.001
Non-diabetics	57.8	63.7	90.6	42	<0.001
Diabetics	42.1	38.6	56.6	26.2	<0.001
Cardiovascular Health Index Score (CHIS) (%)†					
Poor	21.4	19.9	19.1	31.2	<0.001
Intermediate	61.9	63.0	62.0	57.3	
Good	16.7	17.1	18.9	11.6	

All cholesterol and glucose measurements in mmol/L; All blood pressure measurements in mmHg; All HbA1c measurements in %.

Numeric variables are mean± standard deviation (SD) or median (number of measurements) and categorical variables are percentage. P values obtained from one-way ANOVA test for numeric variables and Chi-square test for categorical variables.

¶Total cholesterol target is <4.5mmol/L; LDL cholesterol target is< 2.5mmol/L and stricter LDL cholesterol target is 1.8mmol/L; Blood pressure target is defined as: <140/90mmHg, and <140/80mmHg for diabetics.

†CHIS categories were defined by the summed number of controlled risk factors: poor≤2, intermediate=3 or 4, and good=5 or 6.

*Comparison between regions

Good, intermediate, and poor CHIS were noted in 16.7%, 61.9%, and 21.4%, respectively. CHD patients in the Middle East seemed less likely to reach good CHIS (11.6%) compared to those in Europe (17.1%) and Asia (18.9%) (p<0.001). Figures are shown in table 4.

The supplementary appendix part E documents the considerable variations between countries with regard to risk factor management, therapeutic targets, CHIS, and medication usage.

DISCUSSION

SURF proved easy to be quick and easy to undertake as part of a routine clinic attendance, making it attractive clinical audit tool applicable in a wide range of settings. SURF I shows inadequate control of cardiovascular risk factors, even in these high-risk patients with established CHD, particularly with regard to continued smoking, high rate of obesity, insufficient achievement of therapeutic targets, and underuse of cardiac medications. It documents substantial variations between regions and countries of participating centres with regard to both risk factor management and cardiac medications.

The high prevalence of modifiable risk factors like smoking, body weight, and physical activities are remained as a major problem in CVD prevention. Among these modifiable risk factors, the high rate of obesity is of particular concern as it is strongly associated with raised blood pressure, cholesterol, and glucose.[12] Current uniform BMI cut-off values for obesity may not be appropriate, especially for ethnic minorities, resulting in either over- or underestimation of obesity prevalence. Reflecting this, the WHO has recommended additional lower BMI cut-off for Asian countries but this issue remains controversial.[13] As a large prospective cohort study in China indicated the association between cardiovascular mortality and BMI to be similar to those observed in Western populations, suggesting the use of uniform BMI cut-off points in all populations.[14] In addition, for the Middle East, there was limited evidence for defining separated BMI cut-off points.[15] Irrespective of discussion on BMI cut-off points, the prevalence of obesity has risen substantially in the last few decades, particularly in developing countries.[1] This situation is creating concerns about a potential future worldwide increase in CHD rates.

Cardiac rehabilitation, involving advice and supervision on the management of modifiable risk factors, has been recommended as a cost-effective tool for CHD prevention. A Cochrane Review on 47 randomised control trials demonstrated that exercise-based cardiac rehabilitation is effective in reducing both total and cardiac mortality.[16] However, the availability and the quality of cardiac rehabilitation services differ, which contributes to poor participating rates in many countries.[17,18] SURF also noted large variations in cardiac rehabilitation participations, which was observed to be grossly underused, especially in Asia and Middle East. The inequalities in access to cardiac rehabilitation may relate to lack of an appropriate, defined health care policy at central, regional or hospital level, inadequate funding and/or lack of professional guidelines.

Lipid management remains a cause for concern. Correction of dyslipidemia, particularly LDL cholesterol, is recommended by all guidelines for CVD prevention.[4,19] The Treating to New Target (TNT) trial suggested aggressive lipid lowering therapy, especially statin therapy, improves clinical outcomes for CHD patients.[20] This audit showed that to achieve recommended LDL cholesterol target level (1.8mmol/L) and take such lipid-lowering therapy is problematic, especially for Asia. In Asia, only 15% of CHD patients achieved the 1.8mmol/L goal with only 51% taking statins. These results are in line with results from the PURE study observing that optimal LDL cholesterol targets are hard to achieve for CHD patients in daily clinical practice.[21] There are several possible explanations for the poor control of lipids in Asia including health economic issues, professional attitudes, patient preferences, and ineffective implementation of guidelines.

Apart from the high prevalence of dyslipidemia and large number of patients not at cholesterol targets, SURF I also demonstrated a high prevalence of hypertension and inadequate anti-hypertensive treatment not only in Europe but also in countries from Asia and the Middle East. The known history of hypertension was even higher than in Asia and the Middle East, which may be partly explained by excess salt intake. A global review found that populations in East Asia and the Middle East had much higher salt intakes compared those in Western regions.[22] Salt intake has continued to increase, regardless of the strong evidence on the benefits of salt reduction. Thus, the control of hypertension in day-to-day life continues to pose substantial challenges.

Diabetes at least doubles the risk for CVD, independently of other conventional risk factors.[23] It has been estimated that the prevalence of diabetes will increase progressively, particularly in developing countries.[1] This is likely to give rise to a rapid increase in CHD. Glycaemic control in CHD patients is normally assessed by HbA1c and an HbA1c<7% for CHD patients with diabetes is recommended in the current ESC guideline.[4] A large proportion of CHD patients have raised HbA1c values, which are frequently unrecognised.[24] It is necessary, especially for CHD patients with diabetes, to check HbA1c regularly and assess their diabetes risk. In this regard availability of HbA1c information in daily clinical practice in only 57% of our diabetic patients is of concern (appendix part D). Thus, there may be appreciable under-diagnosis of diabetes, which is related to a poor prognosis in CHD. Our results underline the importance of including diagnostic testing for diabetes for CHD patients with diabetes.

The overall risk factor management of SURF I participants was summarised by the use

of a simplified CHIS. Over 80% had poor or intermediate CHIS, indicating inadequate risk factor control. A large collaborative analysis, based on three randomized controlled trials, confirmed the difficulty in achieving a healthy lifestyle and attaining therapeutic targets for CHD patients.[25] The CHIS does not reflect the fact that the relative importance of each risk factor may not be equal, but underlines need for an integrated, multi-disciplinary approach to risk factor modification.

SURF, as a pragmatic audit, collects its data when patients attend routine clinics and thus helps to track data recording in daily practice with very little increase in workload. So, another important finding of our study is the high frequency of missing data in current data recording system, where in the current study we observed a rate of missing data above 20% and even variables like sex and age are occasionally not recorded (appendix part D). Effective risk factor control is clearly impossible if there is no record of the factors concerned no matter how good prevention guidelines may be. Routine clinical practice standards remain sub-optimal. SURF does provide a good opportunity to monitor routine clinic practice, improve data quality in future and hopefully to support the development of standard operating procedures (SOPs) appropriate to local conditions.

There are several limitations to this study. It should be stressed that SURF is a simple audit. Unlike EUROASPIRE, laboratory measurements are not standardised. The high frequency of missing data might reduce the reliability of prevalence estimates. Participating centres from each country were identified by personal contact and as a result of presentations at meetings and as thus may not be representative of health care facilities treating CHD patients in participating countries. So, we cannot judge their representativeness. It is possible that the standard of care is in fact higher than the local average, because of the interest of the centres in participating in SURF. Followed by SURF I, a new phase, SURF II, will use a more formal recruitment procedure to enhance representativeness of centres and patients.

The simplicity of SURF is its strength. It is easy to undertake at low cost and with minimal workload for health care providers. It is particularly suitable as an audit instrument for use in low-resource settings and allows multiple comparisons of risk factor management in different regions. In addition, SURF may serve to validate, support and complement other audits to describe the on-going burden of risk factor management in CVD prevention. This, and the potential to generate international and local publications, provides added value for participating centres. Many countries also require evidence for participation

in clinical audits for training and accreditation purposes. SURF underlines the need for structured data documentation and standard operating procedures to assist in guideline implementation with a view to improving both risk factor recording and control.

In conclusion, this international audit study of CHD patients has shown the applicability of SURF I in different settings. The results indicate patchy recording and poor control of risk factors in CHD patients with substantial regional variations. These observations call for judicious and validated approaches to the development and implementation of clinical standards, operating procedures and performance measures.

ACHKNOWLEDGEMENT

The SURF study group is grateful to all participating centres and their staffs for their enthusiastic participation and support. We also thank Isabella Higgins for helping with data management.

FUNDING

This project was funded in part by an unrestricted educational grant from MSD Ireland. MZ has been supported by a grant from the Netherlands Organisation for Scientific Research (NWO). MSD and NWO had no input into the design, execution, analysis, or writing up of the study.

REFERENCES

1. Bill F, Foundation MG. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015; 6736: 1990–2013.
2. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. *N Engl J Med* 2015; 372: 1333–1341.
3. Beaglehole R, Bonita R, Horton R, et al. Priority actions for the non-communicable disease crisis. *Lancet* 2011; 377: 1438–1447.
4. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
5. Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009; 373: 929–940.
6. Kotseva K, Wood DA, De Backer G, et al. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: Principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; 22: 554–572.
7. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009; 16: 121–137.
8. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23: 636-648.
9. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
10. Wood D, De Bacquer D, De Backer G, et al. A European Society of Cardiology survey of secondary prevention of coronary heart disease: Principal results. *Eur Heart J* 1997; 18: 1569–1582.
11. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. *Circulation* 2010; 121: 586–613.
12. Van Gaal LF, Mertens IL, De Block CE. Mechanisms linking obesity with cardiovascular disease. *Nature* 2006; 444: 875–880.
13. WHO. Public health Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. WHO 2004; 363: 157–163.
14. Gu D, He J, Duan X, et al. Body weight and mortality among men and women in China. *J Am Med Assoc* 2006; 295: 776–783.
15. Esteghamati A, Zandieh A, Zandieh B, et al. Leptin cut-off values for determination of metabolic syndrome: Third national surveillance of risk factors of non-communicable diseases in Iran (SuRFNCD-2007). *Endocrine* 2011; 40: 117–123.
16. Heran BS, Chen JM, Ebrahim S, et al. Exercise-based cardiac rehabilitation for

coronary heart disease. *Cochrane database Syst Rev* 2011; CD001800.
17. Turk-Adawi K, Sarrafzadegan N, Grace SL. Global availability of cardiac rehabilitation. *Nat Rev Cardiol* 2014; 11: 586–596.
18. Bjarnason-Wehrens B, McGee H, Zwisler A-D, et al. Cardiac rehabilitation in Europe: results from the European Cardiac Rehabilitation Inventory Survey. *Eur J Cardiovasc Prev Rehabil* 2010; 17: 410–418.
19. Reiner Ž, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias. *Eur Heart J* 2011; 32: 1769–1818.
20. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; 352: 1425–1435.
21. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.
22. Powles J, Fahimi S, Micha R, et al. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open* 2013; 3: e003733.
23. van der Leeuw J, van Dieren S, Beulens JWJ, et al. The validation of cardiovascular risk scores for patients with type 2 diabetes mellitus. *Heart* 2014; 101: 222–229.
24. Bartnik M, Rydén L, Ferrari R, et al. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe: The Euro Heart Survey on diabetes and the heart. *Eur Heart J* 2004; 25: 1880–1890.
25. Farkouh ME, Boden WE, Bittner V, et al. Risk factor control for coronary artery disease secondary prevention in large randomized trials. *J Am Coll Cardiol* 2013; 61: 1607–1615.

SUPPLEMENTS

A. Protocol of Survey of Risk Factor Management (SURF)
B. SURF data collection sheet and explanation sheet
C. Participating countries, centers, and investigators in SURF I
D. Missing information in SURF I
E. Demographic characteristics, risk factors, medical history, therapeutic targets, Cardiovascular Health Index Score (CHIS), and medication usage in SURF I by country

A. Protocol of Survey of Risk Factor Management (SURF): A simple audit of cardiovascular risk factor management

Ian Graham, Marie-Therese Cooney, on behalf of the SURF Steering Committee.
Principal Investigator: Ian Graham (ian@grahams.net)
International co-ordinator and data centre: Marie-Therese Cooney (therese.cooney@yahoo.com)
Irish National Co-ordinator: Patricia O'Donoghue (patriciaodonoghue2007@yahoo.com)

The Adelaide and Meath Hospital incorporating the National Children's Hospital, Tallaght, Dublin 24 and Trinity College, Dublin, Ireland and The Prevention, Epidemiology and Population Science Committee, the European Society of Cardiovascular Prevention and Rehabilitation

ATTACHMENTS:

1. Data collection sheet
2. Explanation sheet
3. Draft letters to individual centres inviting participation
   3.1 For new centres
   3.2 For centres that participated in the pilot phase
4. National co-ordinator information*
5. Details of each participating hospital*
6. Details of individual investigators*
7. Publication policy

*To be submitted by the national co-ordinators

INTRODUCTION

Atherosclerotic cardiovascular diseases (CVDs) are the biggest cause of death in most developed and developing countries. Their mass occurrence relates strongly to modifiable risk factors such as smoking, blood cholesterol, raised blood pressure, diabetes, inactivity and overweight. There is indisputable evidence that risk factor modification reduces mortality, especially in the highest risk subjects- those with established vascular disease. For this reason, the current European guidelines on the prevention of cardiovascular disease in clinical practice[1] give such people the highest priority for preventive advice as well as more stringent risk factor targets.

EuroAspire[2] is the major European audit of the efficacy of risk factor intervention in subjects with established coronary heart disease (CHD). It has consistently reported that risk factor control is sub-optimal, particularly with regard to raised blood pressure, smoking, body weight and diabetes. Many of these subjects, who are at high risk for further CHD, have not achieved the risk factor targets established by the European Society of Cardiology (ESC).

EuroAspire may be regarded as an exemplar audit in that many countries are surveyed, the surveys are very detailed and standardised methods are employed. It requires considerable resources in terms of staff, time and money which may limit participation to well resourced centres and therefore reduce representativeness, especially as it is limited to two centres per country.

SURF (SUrvey of Risk Factors) was conceived as a simple audit of risk factor management to allow wider and hopefully more representative usage to complement more detailed audits such as EuroAspire. It has the following characteristics:

1. It is designed to be conducted at the time of usual clinic attendances rather than requiring the subject to return for a detailed examination. This will minimise selection and participation bias.
2. This demands that SURF must be very quick and easy to administer and require minimal input in terms of time and no extra resource requirements.
3. It has been designed initially for use in patients with CHD, but can readily be adapted for use in subjects with other forms of CVD, or indeed in apparently healthy subjects.
4. It is designed to complement EuroAspire by using the same diagnostic categories

with the addition of stable angina pectoris with objective confirmation.

5. While piloted in paper format, data can now also be entered and submitted electronically using Survey Monkey. This may be preferred by centres who are on-line during their clinics.
6. It is designed to give added value to participating centres by their participation in an international project. In addition, many countries require evidence of participation in audits for quality control and for accreditation of trainees.

An initial protocol was developed in 2009 and piloted in three European and four Asian countries in 2010. Data on over 1000 subjects were collected. It proved as quick and easy to perform as had been hoped, and additional countries have asked to join the project. The pilot data suggest interesting differences between Asia and Europe.

THE PROPOSAL

It is now proposed to move on to the formal launch of SURF by developing a more representative sampling frame in the existing partner countries and by recruiting additional countries on a phased basis. Proposed partner countries for this phase are below It is appreciated that their entry will of necessity be phased:

- Belgium (Johan de Sutter and Dirk De Bacquer)
- Croatia (Zeljko Reiner)
- Denmark (Eva Prescott)
- Germany (Ulrich Keil- tbc)
- Ireland (Ian Graham, Marie-Therese Cooney, Patricia O'Donoghue,Alexandra Dudina,)
- Italy (Diego Vanuzzo)
- India (Ambrish Mithal)
- Korea (Namsik Chung)
- Malaysia (Oteh Maskon)
- Northern Ireland (Ian Menown)
- Romania (Dan Gaita)
- Russia (Rafael Oganov,Nana Posogova- tbc)
- Saudi Arabia (Hussam Al-Faleh)
- Singapore (Yean Teng Lim)
- Sweden (Lars Ryden)
- Taiwan (Wayne H-H Sheu- also co-ordinator for the Asian region)

- Thailand (Chaicharn Deerochanawong)
- The Philippines (Artemio Roxa)
- Turkey (Lale Tokozoglu)

The named leaders in these countries will be the **national co-ordinators** and members of the **Steering Committee**.

Centres are encouraged to collect data continuously to allow on-going audit of risk factor control. For centres that do not wish this, annual re-examinations over a three month period are suggested.

STRUCTURE

1. A one-page audit form that can be completed in 60 to 90 seconds (Attachment 1).
2. A similarly formatted sheet of instructions and definitions (Attachment 2).
3. For centres that wish to submit data electronically, this can be done through Survey Monkey. Having tested the paper version, this is now the preferred method of data collection for centres who are on-line in their clinics. A **personalised link** for each centre will be sent by M-T C (Director, data centre) to those who chose this method of data collection. The attachments 3-5 (centre and investigator information) should be sent to MTC after which the personalised link will be forwarded.

Centres are currently actively joining the project, so that the initial data collection will be staggered over the first half of 2012. Starting on a defined date each year, participating centres will be invited to collect risk factor information on consecutive subjects attending the outpatients department with established CHD. While there is no lower limit, it is hoped that each centre will contribute at least 50 cases. These will preferably be returned to the co-ordinating centre in Excel spread sheet format for collation and analysis, although raw data sheets can be returned if necessary. A **template excel spreadsheet** will be forwarded on request. Individual centre's results will be returned to them, together with comparative grouped mean results for their region.

The data collection sheets have been designed so that they may easily be adapted in future to audit subjects with cerebrovascular disease, peripheral vascular disease, diabetes, renal failure or other subjects at risk of CVD.

SAMPLING FRAME

The national co-ordinator is responsible for the invitation of individual centres within each country into SURF. While centres submit data directly to the co-ordinating centre, the national co-ordinator is asked to seek periodic up-dates and to actively encourage participation and recruitment.

The following are suggested targets. It is recognised that such targets will put a heavier burden on larger countries and regions, and it is acceptable if it is only possible to recruit a smaller number of centres. Subsequent grant applications may allow a grant for administrative costs, but this is not yet possible [participation in this international project has enabled some centres to obtain funds from their institutions].

- Small country (population 10 million or less):
    - 10 centres (3 tertiary, 7 regional)
- Medium country (population 10- 60 million):
    - 20 centres (6 tertiary, 14 regional)
- Large country (population more than 60 million):
    - 30 centres (9 tertiary, 21 regional)

Example: In Ireland (small country) for the pilot study centres were recruited as follows: All 40 hospitals which admit patients with acute coronary syndromes were identified. We contacted the consultants responsible for these patients at each of the centres by email and written letter. All centres which responded positively were included in the survey (10). Centres which did not respond were contacted by telephone also. In many centres the project was administered by the cardiology clinic nurse, which proved very effective. Experience has shown that, once a centre tries the project in a clinic, they find that it really is easy and not a burden.

SUBJECTS

Consecutive subjects of both genders and any age with objective evidence of CHD will be studied. They must have one or more of the following diagnoses.

Diagnostic groups are not mutually exclusive and are:

- **Coronary artery bypass surgery** (CABG)
- **Percutaneous coronary intervention** (PCI)
- **Acute coronary syndrome** (ACS) (cardiac chest pain at rest with serial ischaemic ECG changes and/or a rise in troponin or CKMB levels)
- **Stable angina pectoris** (clinical angina pectoris with at least one of (a) clearly positive exercise ECG, (b) Positive stress myocardial perfusion scan or (c) At least one stenosis of 70% or more on coronary arteriography.

The patient must have one or more of the above diagnoses to be eligible.

In contrast to EuroAspire *there is no timeframe*- patient may enter at any point from their first out-patient clinic attendance onwards. Patients are eligible *whether or not* they have ever been admitted to hospital (for example, in the case of stable angina)

DATA: WHAT IS COLLECTED AND HOW

The data to be collected are shown in fig 1, with definitions and instructions in fig 2. Demographic data include initials, hospital, year of birth, gender, date of examination, category of CHD and whether admitted in the previous one year.

Risk factor data include information on smoking, activity, educational level as a proxy for social class, history of known hypertension, dyslipidaemia or diabetes and most recent risk factor measurements (fig1). Attendance at cardiac rehabilitation is noted. Drug usage is recorded by category only. Data are collected at routine out-patient attendances. They can and should be updated with the usual measurements on the day of attendance, such as height, weight, waist circumference and blood pressure. Extra visits to update, for example lipid measures are not encouraged because one of the purposes of the audit is to see how often such data are not recently available. Data can be stored and forwarded to the data collection centre when convenient- in batches or all together at the end of the data collection period.

It is preferred that data be transferred on an excel spread sheet or electronically on-line by Survey Monkey, but raw data forms may be submitted if necessary.

As mentioned under Structure above, the data centre co-ordinator (Marie-Therese Cooney) will forward a **personalised link** to those who choose to use the on-line survey monkey, or a **template excel spreadsheet** to those who choose this method of data submission.

PATIENT INFORMATION AND CONSENT

While the data sheets may be completed after the patient has left the clinic, it is preferable to explain the project to the patient and to ask for their permission to complete the data collection sheet as part of the interview. We have used language like "We are trying to learn how to get better at helping our patients with risk factors such as blood pressure or cholesterol, so is it OK if we collect information on you? It will be kept completely confidential." We then complete the sheet with the patient. To date the response has been enthusiastic and interested.

Regulations regarding audits and data usage vary from country to country and from institution to institution. However, for SURF, only data that are already available in the patient record are being used and anonymity is preserved. There are no interventions. Therefore verbal consent as outlined above is usually all that is required.

ANALYSIS AND PRESENTATION OF RESULTS

Results will be presented overall and by age, gender and diagnostic category.
Continuous variables will be presented as arithmetic means +/- SD if normally distributed. If not, medians or geometric means will be used.
Categorical variables will be presented as percentages.
The proportion of subjects achieving ESC risk factor targets will be presented in tabular and graphic form and compared with EuroAspire data.
Possible determinants of successful risk factor control will be examined. These might include age, gender, educational level, and admission to hospital, diagnostic category and participation in cardiac rehabilitation.
Ways to improve risk factor control will be discussed.

Results for individual centres will be returned in tabular form together with grouped mean results from other centres for comparison purposes.
No individual centre's results shall be disclosed to any other party unless the centre

wishes this. Publication and authorship policies are outlined in a separate attachment.

TIMELINES

August-September 2011: Approval of documentation
Late August 2011: Funding review
September 2011- mid 2012: Recruitment of centres
Feb 2012: Progress review
Data collection: Centres already collecting data are encouraged to continue to do so. New centres to start during the first six months of 2012
May 2012: Review of data and future planning- continuous project or annual, for example.

NOTE: This project has been supported by an unrestricted grant from MSD Ireland, who have been informed of the design and progress of the project but have had no input into the project otherwise- apart from enthusiastic support which is gratefully acknowledged

REFERENCES

1. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. Fourth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007;14 Suppl 2:S1-113.
2. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE III: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009;16(2):121-37.

3.1 Draft letter to individual centers inviting participation

(For use in centers not involved in SURF pilot phase)

This letter can be modified by the national co-coordinator

Dear colleague,

I am writing to invite participation in a simple audit of risk factor management in secondary prevention of CHD, called SURF (Survey of Risk Factor management). The survey has already been successfully piloted in 3 European and 4 Asian countries in 2009/2010. The one page data collection sheet is attached here, along with a simple explanation sheet, which includes the very straight-forward inclusion criteria. The data required are all information which would be captured during a routine out-patient clinic appointment. The sheet has been shown to take only 60-90 seconds to complete and as such should not add appreciable extra time to the routine out-patient visit.

We believe that participation in SURF brings certain benefits-

1. Involvement in a collaborative international project that has been endorsed by the Epidemiology Section of the European Association of Cardiovascular Prevention and Rehabilitation.

2. SURF is a practical audit of the level of risk factor control. Our experience has been that using it encourages greater efforts to reach risk factor targets.

3. Increasingly, accreditation of Continuing Medical Education requires evidence of participation in audits, both foe senior physicians and trainees.

4. The opportunity to write papers for local journals and to participate in international publications.

Although there is no lower limit, we would ask that, if possible, at least 50 patients would be included from each center. These would be consecutive patients with a diagnosis of CHD attending a routine out-patient clinic. Patients should be aged over 18 years, but there is no upper age limit. In the country of the coordinating center we were advised that ethics committee approval was not required and only verbal consent needed. This is because only data that are available in the chart or during the consultation are entered and all cases are anonymized. However, you are advised to check local regulations with your ethics committee. A simple system for the online collection of data has also been developed using Survey Monkey for those who prefer this to filling out paper forms. Regarding authorship of publications, the full SURF publication policy is attached here.

Many thanks for considering this collaboration and I look forward to hearing from you,

Yours Sincerely,

3.2 Draft letter to individual centers inviting participation

(For use in centers who were involved in the SURF pilot phase)

This letter can be modified by the national co-coordinator

****

Dear colleague,

I write to thank you for your major contribution to the pilot phase of SURF, the international Survey of Risk Factor management in subjects with coronary heart disease (CHD). The pilot was very successful in that, with your help, we collected data on more than 1,000 patients from 3 European and 4 Asian centers- considerably more than originally planned. We attach an abstract of the main results for your interest. As promised, we also attach the results for your center with grouped results for comparison purposes. We now invite your participation in the first phase of the full SURF project.

The one page data collection sheet is attached here, along with a simple explanation sheet, which includes the very straight-forward inclusion criteria. The data required are all information which would be captured during a routine out-patient clinic appointment. The sheet has been shown to take only 60-90 seconds to complete and as such should not add appreciable extra time to the routine out-patient visit.

We believe that participation in SURF brings certain benefits-

1. Involvement in a collaborative international project that has been endorsed by the Epidemiology Section of the European Association of Cardiovascular Prevention and Rehabilitation.

2. SURF is a practical audit of the level of risk factor control. Our experience has been that using it encourages greater efforts to reach risk factor targets.

3. Increasingly, accreditation of Continuing Medical Education requires evidence of participation in audits, both foe senior physicians and trainees.

4. The opportunity to write papers for local journals and to participate in international publications.

Although there is no lower limit, we would ask that, if possible, at least 50 patients would be included from each center. These would be consecutive patients with a diagnosis of CHD attending a routine out-patient clinic. Patients should be aged over 18 years, but there is no upper age limit.

In the country of the coordinating center we were advised that ethics committee approval was not required and only verbal consent needed. This is because only data that are available in the chart or during the consultation are entered and all cases are anonymized. However, you are advised to check local regulations with your ethics committee. A simple system for the online collection of data has also been developed using Survey Monkey for those who prefer this to filling out paper forms. Regarding authorship of publications, the full SURF publication policy is attached here.

Many thanks for considering this collaboration and I look forward to hearing from you,

Yours Sincerely,

4. National coordinator information

Country: _____

National coordinator information:

- Name: _____
- Degrees: _____
- Affiliation: _____
- Position: _____
- Address: _____
- Email: _____
- Phone: _____

- Page 1 is only to be completed once for each country involved in SURF
- Page 2 is to be filled separately for each center in this country
- Page 3 is to be filled separately for each investigator

5. Details of each participating hospital

SURF - Centre information:

Hospital Name:	
Hospital Address:	
Type of hospital:	☐ University/ teaching/ tertiary hospital ☐ Regional or district hospital
Number of beds in hospital:	
Type of out-patient clinic:	☐ General medicine ☐ Cardiology ☐ Risk factor management ☐ Cardiac rehabilitation ☐ Cardiac Surgery ☐ Diabetic ☐ Other – specify
Lead investigator: (Enter name here – also fill separate detailed investigator information sheet & attach)	
Co-investigator 1: (Fill detailed investigator information sheet for each co-investigator also)	
Co-investigator 2:	
Co-investigator 3:	
Co-investigator 4:	

6. Details of individual investigators

Detailed investigator information sheet

- Name: _____
- Country: _____
- Centre: _____
- Degrees: _____
- Affiliation: _____
- Position: _____
- Address: _____
- Email: _____
- Phone: _____

☐ Lead investigator at this center
☐ Co-investigator at this center

7. Publication Policy

1. Each country is to have a national coordinator.
2. The national coordinator will all be part of the steering committee of SURF.
3. Each member of the steering committee will be included as a co-author in generic SURF publications (unless editorial policies of specific journal dictate a limited number of authors).
4. Before commencing the SURF audit each national coordinator will specify a lead investigator from each center involved. The lead investigators from each center will be included as co-authors on any publications concerning their data, if editorial policies of journals permit this number of co-authors. If not, authorship will be assigned on the basis of the number of cases submitted. Co-investigators from each center will also be specified.
5. All co-investigators will be included as collaborators on publications concerning their data.
6. Each national coordinator is responsible for giving permission for the analysis, write-up and publication of the individual country's national SURF data.
7. National coordinators are asked to ensure that these data are not published before the publication of the main SURF paper.
8. The principle investigator of SURF undertakes that the main paper will be published in a timely manner (in order to facilitate point 6 above

B. SURF Data Collection Sheet and explanatory sheet

Demographics							
Initials:		Year of birth:			Hospital Name:		
Gender:	☐ Male	☐ Female					
Only include if one of these diagnoses:							
CHD Category:	☐ CABG	☐ PCI	☐ Acute coronary syndrome	☐ Stable AP	Date of examination:		
Was the patient admitted to hospital in the last year with for a CHD related reason? ☐ Yes ☐ No					☐ Public patient	☐ Private patient	

Risk factor history			Most recent risk factor measurements	
Smoking history	☐ Current smoker ☐ Ex smoker ☐ Never smoked		Systolic BP	mmHg
			Diastolic BP	mmHg
			Heart rate	bpm
Physical activity	☐ Less than below ☐ Moderate (moderately vigorous activity) 30 mins 3 to 5 times per week ☐ More than this		Waist circumference	cm
			Height	m
			Weight	kg
Family history of premature CVD [1st degree relative <55 years in men or <65 in women]	☐ Yes	☐ No		
At what age did the patient complete full time education?	____ Years		Fasting bloods within 1 year?	☐ Yes ☐ No
			If yes, date of fasting bloods:	
Known history of (Patient was told of diagnosis previously)	Yes / No		Fasting total chol	mmol/l
	☐ ☐ Hypertension		Fasting LDL chol	mmol/l
	☐ ☐ Dyslipidaemia		Fasting HDL chol	mmol/l
	☐ ☐ Diabetes type 2		Fasting triglycerides	mmol/l
	☐ ☐ Diabetes type 1		Fasting glucose	mmol/l
Did the patient ever participate in cardiac rehab?	☐ Yes, fully or in part ☐ No		HbA1C (if diabetic)	%

Medications			
☐ Any anti-platelet	☐ Any beta-blocker	☐ Any ACE inhibitor	☐ Any nitrate
☐ Any statin	☐ Any Ca antagonist	☐ Any diuretic	☐ Any insulin
☐ Any other lipid lowering agent	☐ Any other anti-hypertensive	☐ Any ARB	☐ Any oral hypoglycaemic agent

Demographics			
Initials:		Hospital:	
Year of birth:			
Gender:	☐ Male ☐ Female	Date of examination:	
Study Eligibility & CHD Category:	• Patient is eligible for study if they have objectively confirmed CHD **with or without** admission to hospital. • The patient **must** have one of the listed diagnoses to be eligible for inclusion - Only the diagnosis is required for eligibility – there is no timeframe • PCI includes elective or emergency. • Acute coronary syndrome indicates cardiac chest pain at rest with objective evidence of acute ischaemia or infarction • Stable AP = Clinical angina with objective confirmation from a clearly positive exercise ECG or ischaemia on perfusion imaging, or a coronary angiogram showing a narrowing of 70% or more in at least one coronary artery • Mark all diagnoses that apply.		

Risk factor history		Most recent risk factor measurements	
Smoking history	*Considered ex smoker if quit smoking more than 6 months ago* *Considered a smoker if any smoking now or in the last six months*	Systolic BP	*Complete with information from day of out-patient visit – can be measured by nurse*
		Diastolic BP	
Physical activity	*Mark one answer only* *Moderately vigorous activity includes brisk walking, swimming etc.*	Heart rate	
		Waist circumference	
At what age did the patient complete full time education?	*Enter age in years*	Height	
		Weight	
		Fasting bloods within 1 year?	☐ Yes ☐ No
Family history of premature CVD	Family history of CVD (diagnosis of stroke, coronary heart disease or peripheral vascular disease) before age 55 in a male or 65 in a female first degree relative. First degree relative = parent, sibling or child	If yes, date of fasting bloods:	
Known history of (Patient was told of diagnosis previously)	Mark "Yes" if the patient was previously told that they had this risk factor Either Yes or No should be marked for each individual *Self reported information only is required*	Fasting total chol	*Complete with most recent fasting bloods if taken within 1 year – **otherwise leave blank***
		Fasting LDL chol	
		Fasting HDL chol	
		Fasting triglycerides	
Did the patient ever participate in cardiac rehab?	*Self report of attendance*	Fasting glucose	
		HbA1C (if diabetic)	

Medications
Mark the drug class if the patient is taking it currently. *Do not write in drug name or dose.* *Do not write in drugs which the patient is taking which are not listed.*

C. Participating countries, centers, and investigators in SURF I

Table C.1: Participating countries and centers in SURF I

Country	Continent	Number of Centers	Number of patients
Belgium	Europe	*	604
Croatia	Europe	9	1514
Denmark	Europe	*	300
Ireland	Europe	11	1826
Italy	Europe	19	1223
Northern Ireland	Europe	2	166
Romania	Europe	8	625
Russia	Europe	8	464
Saudi Arabia	Middle East	5	1580
China	Asia	11	1150
Taiwan	Asia	4	734
Total		**79**	**10186**

*Centre information is not available; It will be counted as one single centre

The SURF was carried out as a section flagship project of the European Association for Cardiovascular Disease Prevention and Rehabilitation.

The member of SURF study group are: Dirk De Bacquer (Department of Public Health, Ghent University, Gent, Belgium), Johan De Sutter (AZ Maria Middelares Hospital Gent and Gent University, Gent, Belgium), Željko Reiner (University Hospital Centre Zagreb, School of Medicine, Zagreb University, Croatia), Eva Prescott (Bispebjerg University Hospital, Copenhagen, Denmark), Pompilio Faggiano (Cardiology Department, Spedali Civili and University of Brescia, Brescia, Italy), Diego Vanuzzo (Cardiovascular Prevention Centre, Health Unit 4 “Friuli Centrale”, Udine, Italy), Hussam AlFaleh (King Saud University, Riyadh, Saudi Arabia), Ian Menown (Craigavon Cardiac Centre, Craigavon, N. Ireland, UK), Dan Gaita (University of Medicine and Pharmacy “Victor Babes”, Cardiology Department, Timisoara, Romania), Nana Posogova (National Research Centre for Preventive Medicine, Russia), Wayne H-H Sheu (Division of Endocrinology and Metabolism, Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan), Dong Zhao (Beijing Anzheng Hospital, China).

The structure of the administrative organization is described below followed by a list of participating study centres and organizations, and investigators and other research

personnel.

Belgium AZ Maria Middelares Hospital, Gent, Belgium: J. De Sutter; Gent Univerisity, Gent, Belgium: D. Debacquer, G. DeBacker.

Croatia University Hospital Centre, Zagreb, Croatia: Z. Peiner; University Hospital Centre Split, Croatia: J. Bagatin; University Hospital Centre Rijeka, Croatia: L. Zaputovic; University Hospital Centre Osijek, Croatia: R. Steiner;University Hospital Centre Sestre Milosrdnice, Croatia: D.D. Brkljacic;Karlovac General Country Hospital, Croatia: V.S. Jelic;Koprivnica General Country Hospital, Croatia: K. Sutalo;Pula General Country Hospital, Croatia: N. Jukic;Zadar General Country Hospital, Croatia: A. Jovic.

Denmark Bispebjerg University Hospital, Copenhagen, Denmark: E.Prescott.

Ireland Charlemont Cardiology, Ireland: I.Graham; Adelaide Meath Hospital, Dublin, Ireland: MT. Cooney; Cardiology Department, Tallaght Hospital, Tallaght, Dublin, Ireland: A. Reynolds; Cardiology Department, Tallaght Hospital, Tallaght, Dublin, Ireland: D. Moore; Cardiac rehabilitation Department, Tallaght Hospital, Tallaght, Dublin, Ireland: N.Fallon; Cardiology Department, Sligo General Hospital, The Mall, Sligo, Ireland: D. Murrary;Cardiology Department, Wexford General Hospital, Wexford, Ireland: A.Buckey; Cardiolog Department, Letterkenny General Hospital, Letterkenny, Co. Donegal: S.David; CREST Directorate, Hospital 7, St James' Hospital, Dublin, Ireland: R.T. Murphy; Cardiology Department, South Tipperary General Hospital, Western road, Clonmel, Ireland: D.Spelman; Cardiology Department, St Luke's General Hospital, Freshford road, Kilkenny, Ireland: M.Conway.

Italy Cardiology Department, Spedali Civili and University of Brescia, Brescia, Italy: P. Faggiano; Cardiovascular Prevention Centre, Health Unit 4 "Medio Friuli", Udine, Italy: D. Vanuzzo; Cardiology Department, University of Brescia, Brescia, Italy: P. Faggiano; Division of Cardiology, San Filippo Neri Hospital, Rome, Italy: F. Colivicchi; Department of Experimental and Clinical Medicine University of Florence, Cardiac Rehabilitation Unit, Crareggi Hospital Florence: F.Fattirolli; Istituti Ospitalier di Cremona, Cremona, Italy: S.Frattini; UOC CARDIOLOGIA RIABILITATIVA, Presidio di Passirana-Azienda Ospedaliera "G. Salvini", Italy: A.Frisinghelli; Franco: Cardiac Rehabilitation Divison, Fondazione Salvatore Maugeri-IRCCS, Presidio MajorTorino, Italy: F.Tarrogenta; Affiliations are not specified: M.Ambrosetti, L.Corsiglia, P.Coruzzi, S.Defeo, A.Dilenarda, G.Furgi, A.Galati,

G.Mazzucco, G.F.Mureddu,L.Tarantini, S.Urbinati.

Northern Ireland Craigavon Cardiac Centre, Craigavon, N. Ireland, UK: I. Menown, N. Cinnamond, S. Hussey; Belfast Trust Hospitals, N.Ireland, UK: P. Mainie, D. Bernie, M. Mooney, J. Cunningham, B. McClements, G. Dalzell, N. Herity.

Saudi Arabia King Saud University, Riyadh, Saudi Arabia: H. Al-Faleh; Prince Sultan Cardiac Center, Saudi Arabia Hospital & Health Care: F. Al-Nouri; King Saud bin Abdulaziz University for Health Science, Riyadh, Saudi Arabia: T. Conboy.

Romania University of Medicine and Pharmacy "Victor Babes", Timisoara, Romania: D. Gaita, R.R., Lulia, T.A. Maria; Spitalul Judetean de Urgenta "Sf. Ioan cel Nou ", Cardiology Department: C. Mihai; Spital Clinic Municipal de Urgenta Timisoara: T.M. Cleopatra, C.M. Ioana; Emergency County Hospital Baia Mar: P.Calin, F.Dan; "George I.M. GEORGESCU" CARDIOVASCULAR DISEASES INSTITUTE: C.A. Georgescu, C. Statescu, A.Gaitan, C.C. Boldea, L. Anghel; Country Hospital Arad: D.Darabantiu, A.P. Moldovan; ClujCountyEmergencyClinic Hospital: D.Olinic, M.Olinic, C. Homorodean, M.Ober, D.H. Comsa; Institute of Cardiovascular Disease "Prof.Dr.C.C.Iliescu", Fundeni: D.Gherasim; SC TITAN MEDICAL SRL (EUCARDIOS – Centru de preventive si tratament cardiovascular): N.A. Cristian, E.Vasilica, C.Florina, E.P. Daniel; Spitalul Clinic Judetean de Urgenta "Sf. Spiridon" Iasi: P.A. Octavian, I.Frasila; Cardiovascular Diseases Institute Timisoara: L.Petrescu, R.Dan, S.Crisan, D.Maximov, C. Mornos; EmergencyHospital of Bucharest: M.Dorobantu, G.Tatu-chitoiu, L.Calmac; Clinicco, Brasov: V.Lorga, N.C. Anghelache, C.Baba; Spitalul Judetean De Urgenta Zalau: B.Minodora, G.Aurelia, M.V. Gabriela, GP. Cristina.

Russia National Research Center for Preventive Medicine, Russia: N.Pogosova; Federal Bugetary Institusion, Russia: O.Oynotkinova, B.Shklovskiy, V.Baksheev, O.Baltuckaj; Non-state healthcare institution, Department clinical hospital at station Barnaul of Russian Railways: I.Osipova, V.Ustinov, D. Savina; National Research Center for Preventive Medicine: Y.Yufereva, A.Ausheva, O.Panichkina; State Institution Research Institute of Cardiology of Tomsk Research Center of Siberian, Department of Russian Academy of Medical Science: T.Nonka; Medical Budgetary Treatment and Prophylaxis Institution, Russia: N.Garganeeva; Yakutsk Republic Centre of Cardiology: K.I.Ivanov; FSBI "Federal Scientific Center for Medical and Preventive Health Risk Management Technologies": I.Ryamzina; FSBI "Research Institute for Cardiology": A.Repin.

Taiwan Taichung Veterans General Hospital, Taichung, Taiwan: W.Sheu, KW. Liang, CR. Tsau, IT. Lee, JS. Wang, CP. Fu; Chiyi branch, Taichung Veterans General Hospital, National Yang-Ming Hospital University School of Medicine, Taipei, Taiwan: J-C Lin.

China Beijing Anzhen Hospital, China: D.Zhao, HJ. Zuo

D. Missing information in SURF I

	Belgium	Croatia	Denmark	Ireland	Italy	KSA	NI	Romania	Russia	Taiwan	China	Total
Demographic characteristics	604	1514	300	1826	1223	1580	166	625	464	734	1150	
Gender	8 (1.3%)	24 (1.6%)	0 (0.0%)	14 (0.8%)	20 (1.6%)	0 (0.0%)	2 (1.6%)	3 (0.5%)	1 (0.2%)	2 (0.3%)	0 (0.0%)	74 (0.7%)
Age	8 (1.3%)	10 (0.7%)	0 (0.0%)	89 (4.9%)	18 (1.5%)	2 (0.1%)	5 (3.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	134 (1.3%)
Clinics	525 (86.9%)	43 (2.8%)	300 (100.0%)	70 (3.8%)	1223 (100.0%)	447 (28.3%)	12 (7.2%)	7 (1.1%)	4 (0.9%)	15 (2.0%)	2 (0.2%)	2648 (26.0%)
Hospital admission	522 (86.4%)	13 (0.9%)	300 (100.0%)	61 (3.3%)	35 (2.9%)	124 (7.8%)	5 (3.0%)	9 (1.4%)	21 (4.5%)	0 (0.0%)	1052 (91.5%)	2142 (21.0%)
Risk factors												
Smoke status	13 (2.2%)	37 (2.4%)	2 (0.7%)	48 (2.6%)	13 (1.1%)	27 (1.7%)	5 (3.0%)	11 (1.8%)	5 (1.1%)	6 (0.8%)	0 (0.0%)	159 (1.6%)
Physical activities	16 (2.6%)	22 (1.5%)	35 (11.7%)	62 (3.4%)	21 (1.7%)	49 (3.1%)	8 (4.8%)	7 (1.1%)	4 (0.9%)	11 (1.5%)	2 (0.2%)	237 (2.3%)
Family history	594 (98.3%)	230 (15.2%)	29 (9.7%)	617 (33.8%)	354 (28.9%)	51 (3.2%)	106 (63.9%)	277 (44.3%)	7 (1.5%)	6 (0.8%)	0 (0.0%)	2271 (22.3%)
Education	524 (86.8%)	100 (6.6%)	1 (0.3%)	405 (22.2%)	376 (30.7%)	253 (16.0%)	64 (38.6%)	81 (13.0%)	26 (5.6%)	54 (7.4%)	321 (27.9%)	2205 (21.6%)
Cardiac rehabilitation	23 (3.8%)	58 (3.8%)	300 (100.0%)	119 (6.5%)	42 (3.4%)	151 (9.6%)	7 (4.2%)	16 (2.6%)	7 (1.5%)	7 (1.0%)	1 (0.1%)	731 (7.2%)

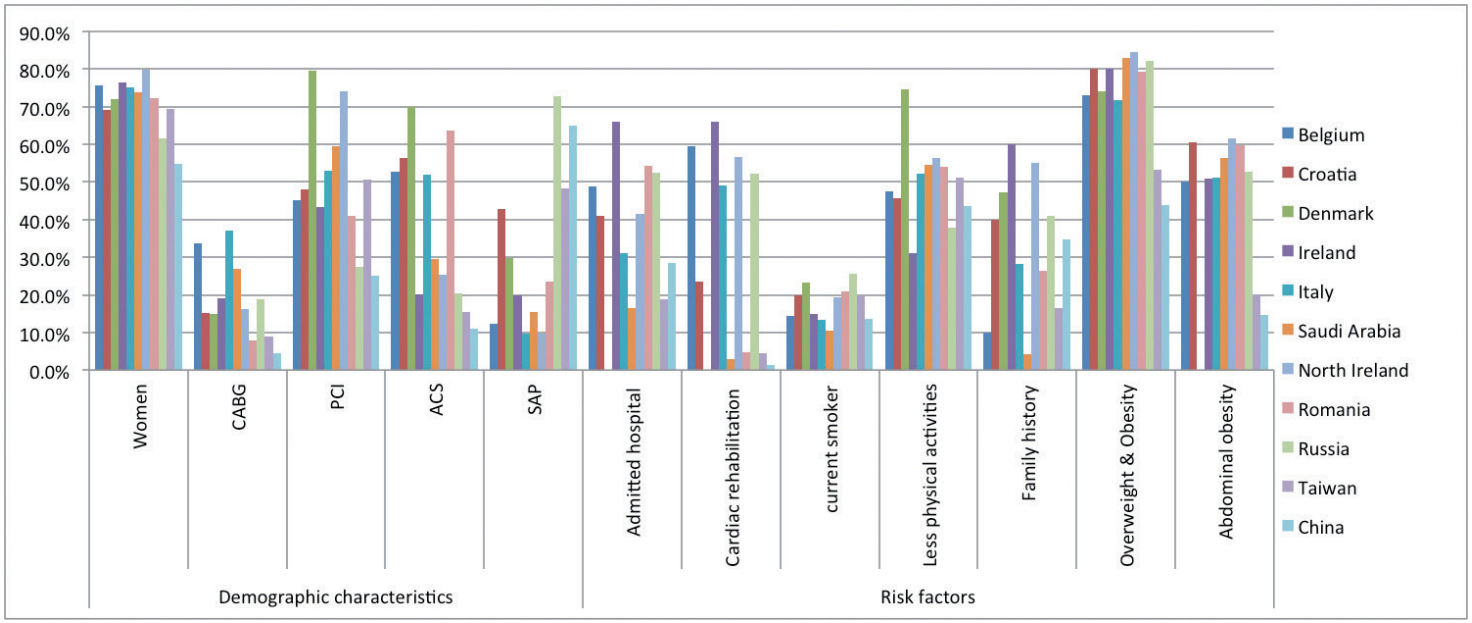
	Belgium	Croatia	Denmark	Ireland	Italy	KSA	NI	Romania	Russia	Taiwan	China	Total
Previous history												
Hypertension	25 (4.1%)	21 (1.4%)	1 (0.3%)	25 (1.4%)	16 (1.3%)	104 (6.6%)	4 (2.4%)	25 (4.0%)	5 (1.1%)	7 (1.0%)	1 (0.1%)	234 (2.3%)
Diabetes	526 (87.1%)	50 (3.3%)	300 (100.0%)	62 (3.4%)	417 (34.1%)	643 (40.7%)	4 (2.4%)	44 (7.0%)	5 (1.1%)	8 (1.1%)	5 (0.4%)	2064 (20.3%)
Dyslipidemia	23 (3.8%)	49 (3.2%)	4 (1.3%)	31 (1.7%)	18 (1.5%)	127 (8.0%)	5 (3.0%)	24 (3.8%)	6 (1.3%)	7 (1.0%)	7 (0.6%)	301 (3.0%)
Medical measurements												
Systolic blood pressure	12 (2.0%)	39 (2.6%)	3 (1.0%)	40 (2.2%)	16 (1.3%)	10 (0.6%)	7 (4.2%)	12 (1.9%)	6 (1.3%)	12 (1.6%)	1 (0.1%)	158 (1.6%)
Diastolic blood pressure	12 (2.0%)	43 (2.8%)	4 (1.3%)	38 (2.1%)	15 (1.2%)	10 (0.6%)	6 (3.6%)	13 (2.1%)	6 (1.3%)	12 (1.6%)	1 (0.1%)	160 (1.6%)
Heart rate	22 (3.6%)	50 (3.3%)	7 (2.3%)	53 (2.9%)	33 (2.7%)	23 (1.5%)	7 (4.2%)	17 (2.7%)	6 (1.3%)	16 (2.2%)	3 (0.3%)	237 (2.3%)
Waist circumference	340 (56.3%)	401 (26.5%)	300 (100.0%)	157 (8.6%)	207 (16.9%)	584 (37.0%)	61 (36.7%)	60 (9.6%)	38 (8.2%)	16 (2.2%)	5 (0.4%)	2169 (21.3%)
Height	20 (3.3%)	67 (4.4%)	0 (0.0%)	185 (10.1%)	86 (7.0%)	279 (17.7%)	10 (6.0%)	41 (6.6%)	34 (7.3%)	15 (2.0%)	4 (0.3%)	741 (7.3%)
Weight	19 (3.1%)	58 (3.8%)	0 (0.0%)	83 (4.5%)	64 (5.2%)	260 (16.5%)	8 (4.8%)	35 (5.6%)	32 (6.9%)	14 (1.9%)	4 (0.3%)	577 (5.7%)
BMI	24 (4.0%)	78 (5.2%)	0 (0.0%)	199 (10.9%)	92 (7.5%)	284 (18.0%)	10 (6.0%)	44 (7.0%)	34 (7.3%)	15 (2.0%)	4 (0.3%)	784 (7.7%)

	Belgium	Croatia	Denmark	Ireland	Italy	KSA	NI	Romania	Russia	Taiwan	China	Total
Total cholesterol	210 (34.8%)	167 (11.0%)	7 (2.3%)	421 (23.1%)	260 (21.3%)	364 (23.0%)	12 (7.2%)	110 (17.6%)	29 (6.3%)	70 (9.5%)	216 (18.8%)	1866 (18.3%)
LDL cholesterol	240 (39.7%)	212 (14.0%)	17 (5.7%)	444 (24.3%)	482 (39.4%)	312 (19.7%)	15 (9.0%)	264 (42.2%)	176 (37.9%)	132 (18.0%)	220 (19.1%)	2514 (24.7%)
HDL cholesterol	242 (40.1%)	225 (14.9%)	8 (2.7%)	429 (23.5%)	362 (29.6%)	369 (23.4%)	12 (7.2%)	234 (37.4%)	174 (37.5%)	130 (17.7%)	221 (19.2%)	2406 (23.6%)
TG	230 (38.1%)	156 (10.3%)	7 (2.3%)	430 (23.5%)	296 (24.2%)	351 (22.2%)	12 (7.2%)	205 (32.8%)	95 (20.5%)	53 (7.2%)	221 (19.2%)	2056 (20.2%)
Glucose	238 (39.4%)	106 (7.0%)	20 (6.7%)	716 (39.2%)	320 (26.2%)	380 (24.1%)	58 (34.9%)	72 (11.5%)	25 (5.4%)	138 (18.8%)	222 (19.3%)	2295 (22.5%)
Non-diabetics	234 (40.3%)	88 (8.4%)	/	572 (37.9%)	257 (26.2%)	160 (18.5%)	49 (34.5%)	59 (12.6%)	23 (6.5%)	111 (23.4%)	125 (18.9%)	1698 (23.0%)
Diabetics	4 (17.4%)	18 (3.9%)	/	144 (45.6%)	63 (25.9%)	220 (30.9%)	9 (37.5%)	13 (8.4%)	2 (10.4%)	27 (10.4%)	29 (5.9%)	597 (21.3%)
HbA1c	475 (78.6%)	1256 (83.0%)	243 (81.0%)	1636 (89.6%)	960 (78.5%)	707 (44.7%)	141 (84.9%)	583 (93.3%)	413 (89.0%)	487 (66.3%)	657 (57.1%)	7558 (74.2%)
Non-diabetics	466 (80.2%)	1025 (97.9%)	/	1482 (98.1%)	851 (86.8%)	372 (42.9%)	135 (95.1%)	468 (99.6%)	350 (98.9%)	445 (93.9%)	519 (78.5%)	6356 (86.1%)
Diabetics	9 (39.1%)	231 (49.5%)	/	154 (48.7%)	109 (44.9%)	335 (47.0%)	6 (25.0%)	115 (74.2%)	63 (57.3%)	42 (16.2%)	138 (28.2%)	1202 (42.9%)

*Medications and CHD category are not included in this table.

E. Demographic characteristics, risk factors, medical history, therapeutic targets, Cardiovascular Health Index Score (CHIS), and medication usage in SURF I by country

Figure E1. Demographic characteristic and risk factors in SURF I by country



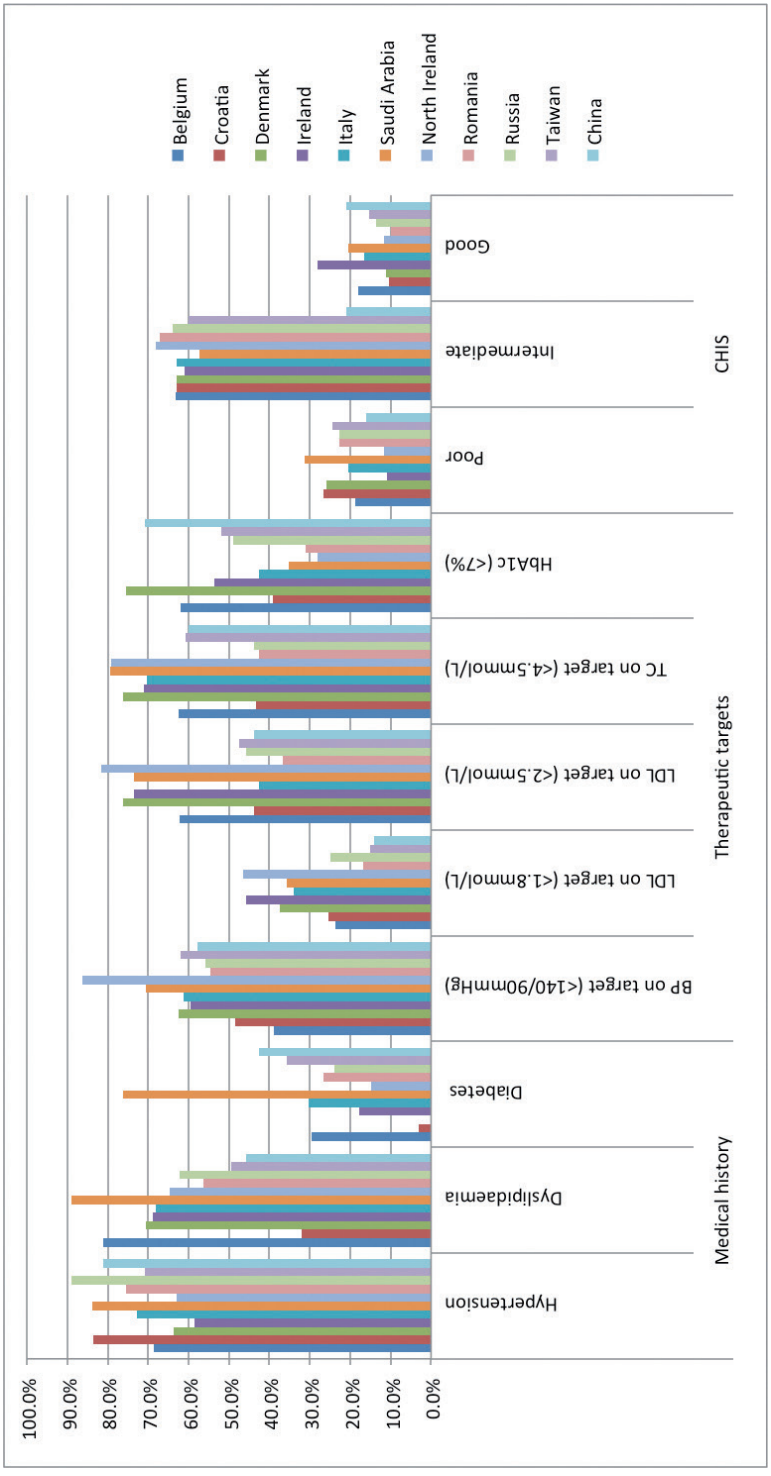


Figure E2. Medical history, therapeutic targets, and Cardiovascular Health Index Score (CHIS) in SURF I by country

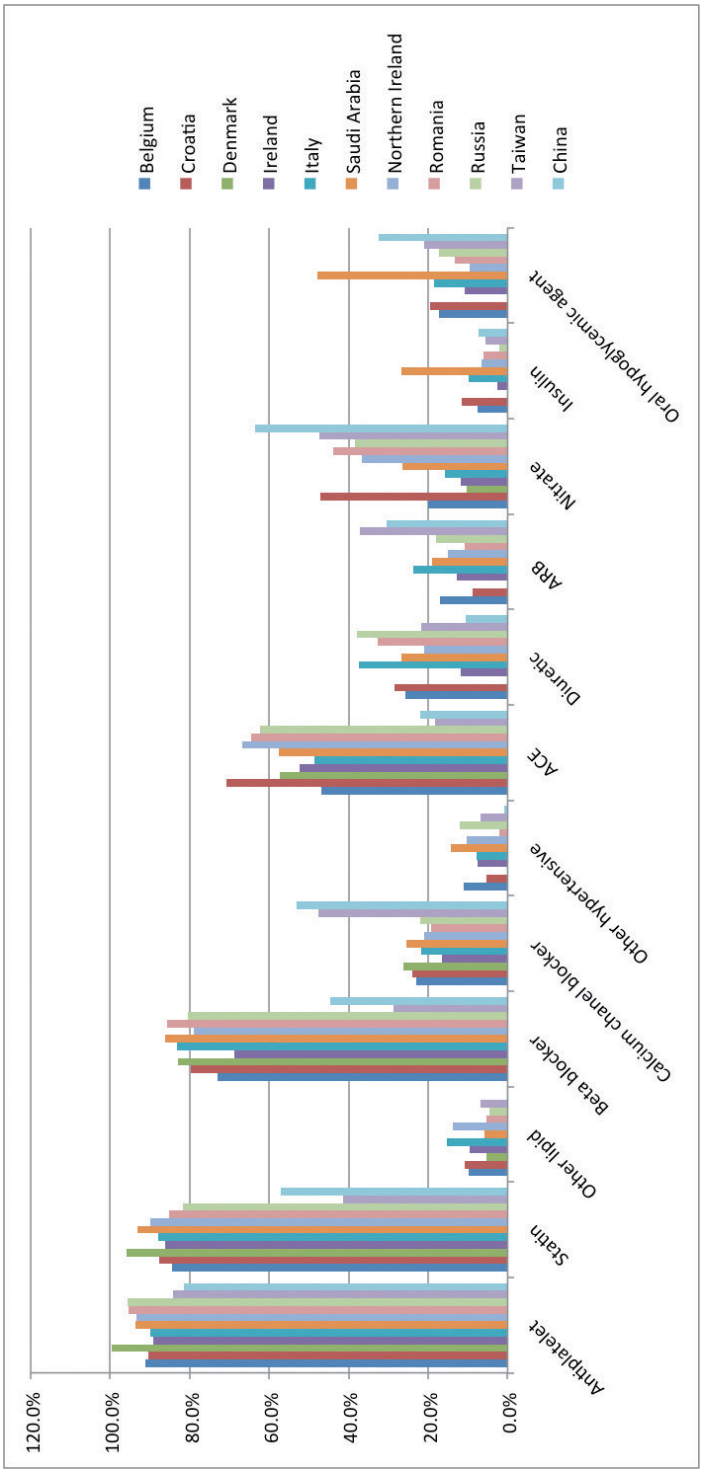


Figure E3. Medication usage in SURF I by country


SURF
SUrvey of Risk Factors

3

SURF CHD: Inequalities of cardiovascular risk factor management in daily practice and associated determinants


SURF
SUrvey of Risk Factors

3.1

Sex differences in risk factor management of coronary heart disease across three regions

Min Zhao, Ilonca Vaartjes, Ian Graham, Diederick E. Grobbee, Wilko Spiering, Kerstin Klipstein-Grobusch, Mark Woodward, Sanne A. E. Peters

Heart. 2017 Oct;103(20):1587-1594.

ABSTRACT

Objective: To investigate whether there are sex differences in risk factor management of patients with established coronary heart disease (CHD), and to assess demographic variations of any such sex differences.

Methods: Patients with CHD were recruited from Europe, Asia, and the Middle East between 2012-2013. Adherence to guideline-recommended treatment and lifestyle targets was assessed and summarized as a Cardiovascular Health Index Score (CHIS). Age-adjusted regression models were used to estimate odds ratio (OR) of women versus men (95% confidence intervals<CI>) in risk factor management.

Results: 10,112 patients (29% women) were included. Compared with men, women were less likely to achieve targets for total cholesterol (OR [95% CI]: 0.50[0.43-0.59]), LDL (0.57 [0.51-0.64]), and glucose (0.78 [0.70-0.87]), or to be physically active (0.74[0.68-0.81]), or non-obese (0.82 [0.74-0.90]). In contrast, women had better control of blood pressure (1.31 [1.20-1.44]) and were more likely to be a non-smoker (1.93 [1.67-2.22]) than men. Overall, women were less likely than men to achieve all treatment targets (0.75 [0.60-0.93]) or obtain an adequate CHIS (0.81 [0.73-0.91]), but no significant differences were found for all lifestyle targets (0.93 [0.84-1.02]). Sex disparities in reaching treatment targets were smaller in Europe than in Asia and the Middle East. Women in Asia were more likely than men to reach lifestyle targets, with opposing results in Europe and the Middle East.

Conclusions: Risk factor management for the secondary prevention of CHD was generally worse in women than in men. The magnitude and direction of the sex differences varied by region.

Keywords: Coronary heart disease, sex differences, secondary prevention, risk factors

INTRODUCTION

Coronary heart disease (CHD) remains one of the leading causes of death and disability worldwide. In 2015, 16% of all deaths in both men and women were caused by CHD.[1] Individuals with established CHD are at high risk of further events and require intensive risk factor management.[2] Despite convincing evidence on the major benefits of the management of modifiable risk factors in subjects with established CHD, an unacceptably large proportion of affected individuals do not reach guideline recommended risk factor targets.[3–5]

Previous studies in Western populations have suggested that the control of cardiovascular risk factors among patients with established CHD is generally even lower in women than in men.[6–8] For example, results from EUROASPIRE III indicated that, despite similar treatment rates, women were less likely than men to achieve medical target levels. EUROASPIRE IV largely confirmed these findings and also reported that sex differences were primarily seen among individuals with a lower education level or at older age, suggesting a double burden among women in these populations. Despite the growing burden of CHD in non-Western countries, such as those in Asia and the Middle East, it remains unknown whether sex differences in risk factor control for the secondary prevention of CHD also across geographically diverse regions.

We therefore used data from the SUrvey of Risk Factors (SURF) Phase I audit to investigate whether there are sex differences in management of CHD risk factors among patients with established CHD from three diverse regions.

METHODS

Study population

Details of the study protocol and methodology of SURF were reported previously.[4,5] Between 2012 and 2013, consecutive patients aged ≥18 years with established CHD (defined as a history of coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), acute coronary syndromes (ACS), or stable angina) were recruited from routine outpatient cardiology clinics in 11 countries across three regions: Europe (Belgium, Croatia, Denmark, Ireland, Italy, Northern Ireland, Romania, and Russia), Asia (Taiwan and China), and the Middle East (Saudi Arabia). Data on demographics, self-reported smoking status, physical activity, attendance of cardiac rehabilitation,

physical and laboratory measurements (i.e. body anthropometry, blood pressure<BP>, cholesterol, blood glucose, and HbA1c), and prescription of medications were obtained by trained research staff using standardized procedures.

Risk factor targets

The Joint European Societies guidelines were used to assess whether recommended targets for risk factor management were met.[2,9] The BP target was <140/90mmHg for patients without diabetes and <140/80mmHg for patients with diabetes. The targets for total cholesterol (TC), LDL-cholesterol, and blood glucose were <3 mmol/L, <1.8 mmol/L, and <7 mmol/L, respectively. HbA1c was only collected for patients with diabetes and its target was <7%. While the guideline does not define targets for HDL-cholesterol, values >1.0mmol/L for men and >1.2mmol/L for women were regarded as desirable. Obesity was defined as a body mass index (BMI) ≥30kg/m^2 and central obesity was defined as waist circumference ≥88cm for women and ≥102cm for men. 10 Adequate physical activity was defined as moderate or vigorous physical activity for at least 30 minutes three or more times a week.

A Cardiovascular Health Index Score (CHIS), adapted from the ideal Cardiovascular Health Score,[11] was used to summarize overall risk factor management. Since dietary information was not available, the CHIS included six risk factors: smoking status (current smoker vs. non-smoker <never/ex-smoker>), BMI (obese vs. not), physical activity (adequate vs. not), BP (on target vs. not), LDL-cholesterol (on target vs. not), and HbA1c/glucose (on target vs. not).[4] The number of risk factors on target could range from 0 to 6 and the risk factor profile was considered satisfactory if 5 or more risk factors were controlled. Additionally, risk factor control was assessed separately for therapeutic and lifestyle targets. 'All treatment targets' was defined as reaching targets for BP, LDL, and HbA1c/glucose. 'All lifestyle targets' was defined as reaching targets for smoking status, BMI, and physical activity.

Statistical analyses

Patient characteristics were presented as means (SD) for continuous variables and as percentages for categorical variables, separately for men and women. Age-adjusted logistic regression analyses were used to obtain odds ratios (OR) and 95% confidence intervals (CIs) for sex associated with individual and combined risk factor targets. Men served as the reference group. Complete case analyses were conducted. Subgroup analyses were performed by region (Europe, Asia, and the Middle East) and age group

(≤65 years and >65 years). In secondary analyses, we additionally adjusted for BP, smoking status, TC, HDL-cholesterol, and glucose.

To assess the impact of medication use on therapeutic target achievements, the analyses on the target achievements of BP, TC and LDL, glucose and HbA1c were stratified by the use of anti-hypertensive, lipid-lowering, and anti-diabetic medications, respectively. We also assessed whether the findings differed between defined CHD category (CABG, PCI, ACS, or stable angina). All analyses were performed with R version 3.2.2 and all tests were two tailed with statistical significance set at the 5% level.

RESULTS

A total of 10,112 patients, of whom 2958 (29%) were women, were included. On average, women were 4 years older than men; more women than men had stable angina but fewer had CABG. Women more frequently had a history of hypertension and diabetes (Table 1). Prescription of antiplatelet and lipid lowering therapy were less frequent in women than men. The percentage of not recorded data was broadly similar between the sexes (eTable 1).

Table 1. Patient characteristics and cardiovascular risk factors, stratified by sex and region

	Overall		**Europe**		**Asia**		**Middle East**	
	Men	Women	Men	Women	Men	Women	Men	Women
Total No.	**7154**	**2958**	**4851**	**1799**	**1136**	**746**	**1167**	**413**
Age (years)	64.2 (11.2)	67.5 (10.9)	64.4 (10.8)	68.3 (10.8)	*66.3 (11.7)*	*67.7 (10.1)*	*61.6 (11.9)*	*63.5 (12.2)*
Disease category								
CABG	22.3	12.8	24.0	14.8	7.7	3.8	29.2	20.3
PCI	49.8	40.1	49.4	41.9	41.6	24.7	*59.3*	*59.8*
SAP	26.9	40.2	24.5	32.2	51.5	69.8	13.5	21.3
ACS	36.9	32.7	*43.6*	*43.9*	*14.4*	*10.1*	*31.2*	*24.7*
Family history of CHD	31.1	33.3	*42.7*	*43.3*	24.6	32.5	*4.4*	*4.0*
Smoking status								
Current smoker	18.7	9.5	18.8	14.4	24.7	2.7	13.7	1.2

Table 1. (continued)

	Overall		**Europe**		**Asia**		**Middle East**	
	Men	Women	Men	Women	Men	Women	Men	Women
Total No.	**7154**	**2958**	**4851**	**1799**	**1136**	**746**	**1167**	**413**
Ex-smoker	47.5	17.6	52.8	26.6	42.0	5.2	34.1	2.0
Never smoker	32.8	72.1	28.5	59.0	33.3	92.1	52.2	9.7
Physical activity								
Adequate	83.4	88.9	82.3	89.8	84.4	85.7	87.0	91.0
Inadequate	16.6	11.1	17.7	10.2	15.6	14.3	13.0	9.0
Known history								
Hypertension	71.9	80.8	69.4	77.8	73.7	82.5	81.2	91.2
Dyslipidaemia	*67.8*	*67.1*	*68.6*	*68.8*	43.9	52.1	*89.0*	*88.8*
Diabetes	31.9	40.3	24.2	27.2	34.8	48.1	71.6	86.7
Type I	*1.9*	*2.5*	*1.3*	*2.1*	*0.3*	*0.4*	*13.4*	*20.5*
Type II	30.5	38.5	*23.0*	*25.3*	34.6	47.7	69.2	84.5
Physical and laboratory measurements								
BMI (kg/m^2)	*28.0 (4.5)*	*28.2 (5.8)*	*28.0 (4.3)*	*28.5 (5.6)*	*25.1 (3.3)*	*25.4 (3.5)*	29.4 (5.4)	32.8 (6.8)
Waist circumference (cm)	98.6 (14.4)	92.8 (14.9)	101.4 (14.2)	95.9 (15.4)	88.2 (9.0)	84.3 (9.5)	*100.2 (14.7)*	*100.3 (15.0)*
SBP (mmHg)	130.5 (18.2)	133.7 (19.3)	131.5 (18.9)	134.8 (20.4)	*130.0 (16.2)*	*131.8 (16.6)*	127.0 (16.7)	132.4 (18.1)
DBP (mmHg)	*76.2 (10.9)*	*76.0 (11.2)*	*77.0 (10.6)*	*77.0 (11.4)*	*77.2 (11.4)*	*76.7 (10.1)*	*71.8 (10.4)*	*70.5 (10.4)*
TC (mmol/L)	4.2 (1.5)	4.6 (1.5)	4.3 (1.7)	4.6 (1.8)	4.2 (1.0)	4.6 (1.0)	3.8 (1.0)	4.1 (0.9)
LDL (mmol/L)	2.4 (1.1)	2.7 (1.2)	2.4 (1.2)	2.7 (1.3)	2.6 (0.9)	2.8 (0.9)	2.1 (0.8)	2.3 (0.7)
HDL (mmol/L)	1.1 (0.4)	1.3 (0.5)	1.1 (0.4)	1.3 (0.5)	1.1 (0.3)	1.3 (0.4)	0.9 (0.3)	1.1 (0.3)
Glucose (mmol/L)	6.4 (2.5)	6.7 (2.8)	6.2 (2.2)	6.4 (2.6)	*6.2 (1.9)*	*6.5 (2.2)*	7.6 (3.6)	8.8 (4.0)
HbA1c (%)	*7.3 (1.6)*	*7.4 (1.6)*	*7.2 (1.5)*	*7.5 (1.4)*	*6.8 (1.4)*	*6.8 (1.3)*	*7.8 (1.7)*	*8.3 (2.0)*

Table 1. (continued)

	Overall		**Europe**		**Asia**		**Middle East**	
	Men	Women	Men	Women	Men	Women	Men	Women
Total No.	**7154**	**2958**	**4851**	**1799**	**1136**	**746**	**1167**	**413**
Medications								
Anti-platelet	91.7	86.3	92.2	89.5	86.1	76.5	95.1	89.8
Anti-hypertensive	*92.2*	*92.1*	*93.0*	*93.8*	*85.4*	*86.3*	*95.5*	*95.2*
Beta-blocker	73.0	68.4	*77.6*	*77.3*	*38.5*	*38.2*	*87.1*	*83.8*
CCB	25.5	31.5	*20.0*	*23.4*	*49.2*	*53.6*	*24.9*	*26.6*
ARB	16.5	22.2	12.8	16.6	*31.4*	*35.1*	*17.5*	*23.5*
ACE	53.0	45.5	*58.4*	*56.4*	*22.3*	*17.8*	60.7	48.4
Statin	83.5	75.7	88.4	83.2	*51.5*	*50.3*	*94.2*	*90.6*
Nitrate	30.5	37.0	24.6	32.2	60.7	52.0	*25.2*	*30.3*
Insulin	8.7	12.4	6.0	8.2	*5.7*	*8.0*	22.8	38.3
Oral hypoglycaemic agent	21.2	25.4	*14.5*	*15.8*	*24.7*	*33.1*	*45.8*	*53.3*

PCI: percutaneous coronary intervention; CABG: coronary artery bypass surgery; ACS: acute coronary syndrome; SAP: stable angina pectoris; BMI: body mass index; BP: blood pressure; ACE inhibitor: angiotensin-converting enzyme; ARB: angiotensin receptor blocker. Summary statistics are mean (standard deviation) for continuous variables and percentage for categorical variables. Comparisons with P<0.1% are printed Italics.

Achievement of risk factor targets

Control of cardiovascular risk factors was suboptimal in both men and women for all risk factors examined (Figure 1). BP levels were on target in 45% of women and 38% of men. The corresponding age-adjusted OR (95% CI) was 1.31 (1.20; 1.44), indicating that women had a 31% higher odds of meeting the BP target than men. Women were also more likely than men to be non-smokers; the OR for being a non-smoker, women versus men, was 1.93 (1.67; 2.22). Among these with diabetes, there was no significant difference between the sexes in achieving the HbA1c targets; 41% of women and 43% of men met the HbA1c target. In contrast, a smaller percentage of women than men reached the treatment targets for TC (8% vs 14%), LDL-cholesterol (22% vs 33%), and glucose (71% vs. 76%), respectively. After adjustment for age, women had 50%, 43%, 22% lower odds than men of achieving TC, LDL-cholesterol, and glucose targets (Figure 1). Similarly, women

had a 18% higher odds of being obese, a 26% lower odds of being physically active, and a 40% lower odds of attending cardiac rehabilitation than men. Overall, 6% of women and 8% of men reached all treatment targets and about one-third of men and women met all lifestyle targets; the ORs were 0.75 (0.60; 0.93) for all treatment targets and 0.93 (0.84; 1.02) for all lifestyle targets. Combined, 16% of women and 21% of men had an adequate CHIS, which corresponded 19% lower odds in women than in men (0.81 [0.73; 0.91]) (Figure 2).

Findings were similar in the analyses adjusted for major risk factors (eFigure 1). Stratification of our analyses by medication prescription or CHD disease category did not materially change the results (eTable 2).

Sex differences by region

There was some indication that sex differences in the target achievements differed between regions (Table 1 and Figure 3). In Europe, the odds of achieving treatment targets for TC, LDL-cholesterol, and glucose, respectively, were 34%, 31%, and 14% lower in women than men, compared to a 70%, 47%, and 30% lower odds for women in Asia, and a 76%, 53%, and 47% lower odds for achieving these targets for women in the Middle East. Sex differences in achieving all treatment targets were smallest in Europe and largest in the Middle East. Women in Asia and the Middle East were considerably more likely than men to be non-smokers, whereas no significant differences in smoking rates were observed between sexes in Europe (Asia: 11.5 [7.2; 8.4]; Middle East: 16.2 [5.9; 44.5]; Europe: 1.1 [0.9; 1.3]). In Asia, women were more likely to be physically active than men. In contrast, women in Europe and the Middle East were less physically active than their male counterparts (Figure 3). In Asia, women were more likely than men to meet all lifestyle targets, but a reverse pattern was seen in Europe and the Middle East.

In Asia, the odds of having an adequate CHIS was 33% higher in women than men, compared to a 29% and 49% lower odds in women than men Europe and the Middle East, respectively.

Sex differences by age

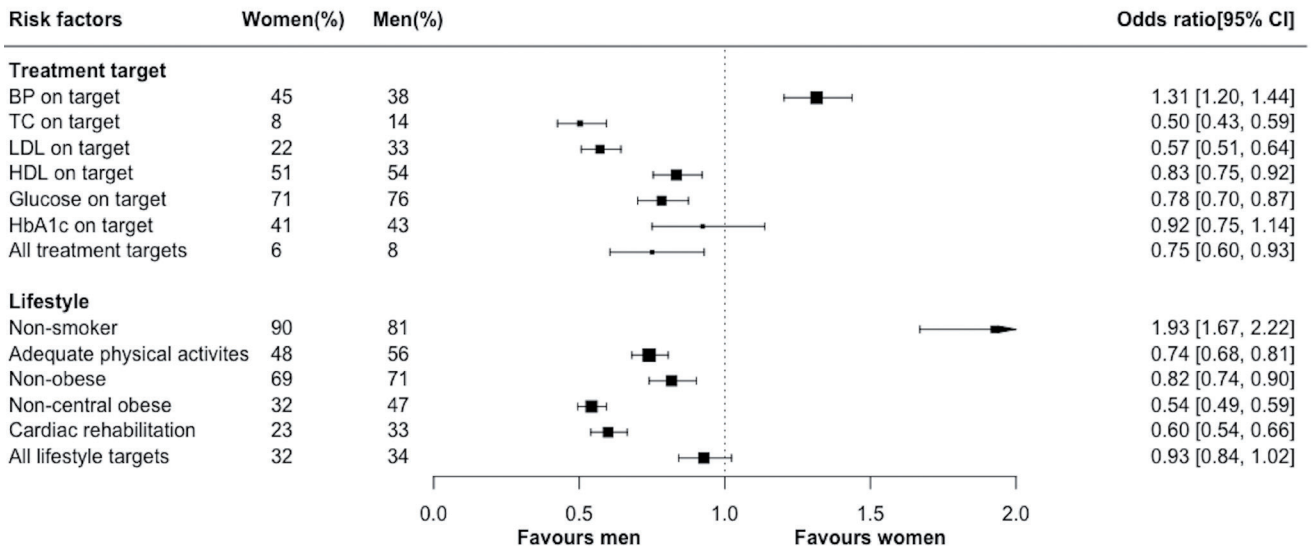
The sex differences in achieving treatment targets differed between those aged ≤65 years and those >65 years for TC, LDL-cholesterol, and glucose, but not for other risk factors (Figure 4). Compared with younger men, younger women were 59% less likely to meet the TC target, 53% less likely to meet the LDL-cholesterol target, and 28% less likely to

meet the glucose target. Corresponding results in those aged >65 years were 42%, 34%, and 18%, respectively. There was no evidence that women's lower odds of all treatment targets, all lifestyle targets, or an adequate CHIS, compared with men, differed between those aged ≤65 vs. > 65 years.

Sex differences by age and region

Regional differences in achieving treatment and lifestyle targets varied between younger and older individuals (eTable 3). Due to higher smoking prevalence in younger men, in Asia and the Middle East, sex differences in smoking rates tended to be larger in those aged≤65 years than in those aged>65 years in these regions. In Europe and the Middle East, sex differences in overall risk factor management, to women's disadvantage, were larger among younger than among older individuals. In Asia, the odds of adequate risk factor management was higher among younger women than younger men, which was largely driven by better control of lifestyle factors in women. In older women in Asia, the odds of adequate risk factor management was lower than in their male counterparts.

Figure 1. Age-adjusted sex differences in risk factor management

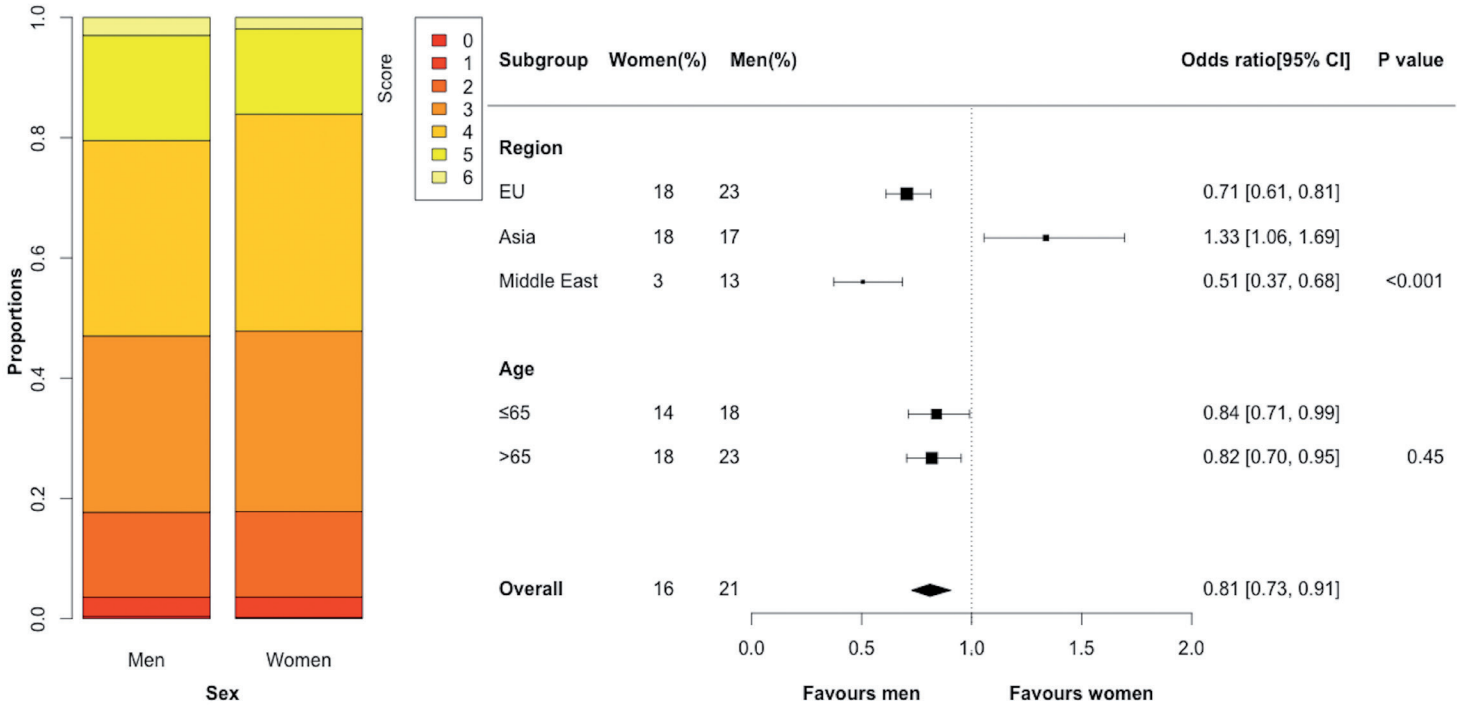


BP: blood pressure; TC: total cholesterol; LDL: LDL-cholesterol

Target blood pressure (BP) was defined as BP <140/90mmHg in those without diabetes or <140/80mmHg in those with diabetes. The target for TC, LDL-cholesterol and HDL-cholesterol levels were defined as <3 mmol/L, <1.8 mmol/L, and >1.0mmol/L for men and >1.2mmol/L for women, respectively. Target glucose was defined as <7 mmol/L. Information on HbA1c was only collected among patients with diabetes and its target was defined as <7%. *All three medical targets (BP on target, LDL on target, and glucose/HbA1c on target) are achieved was defined as all treatment targets.

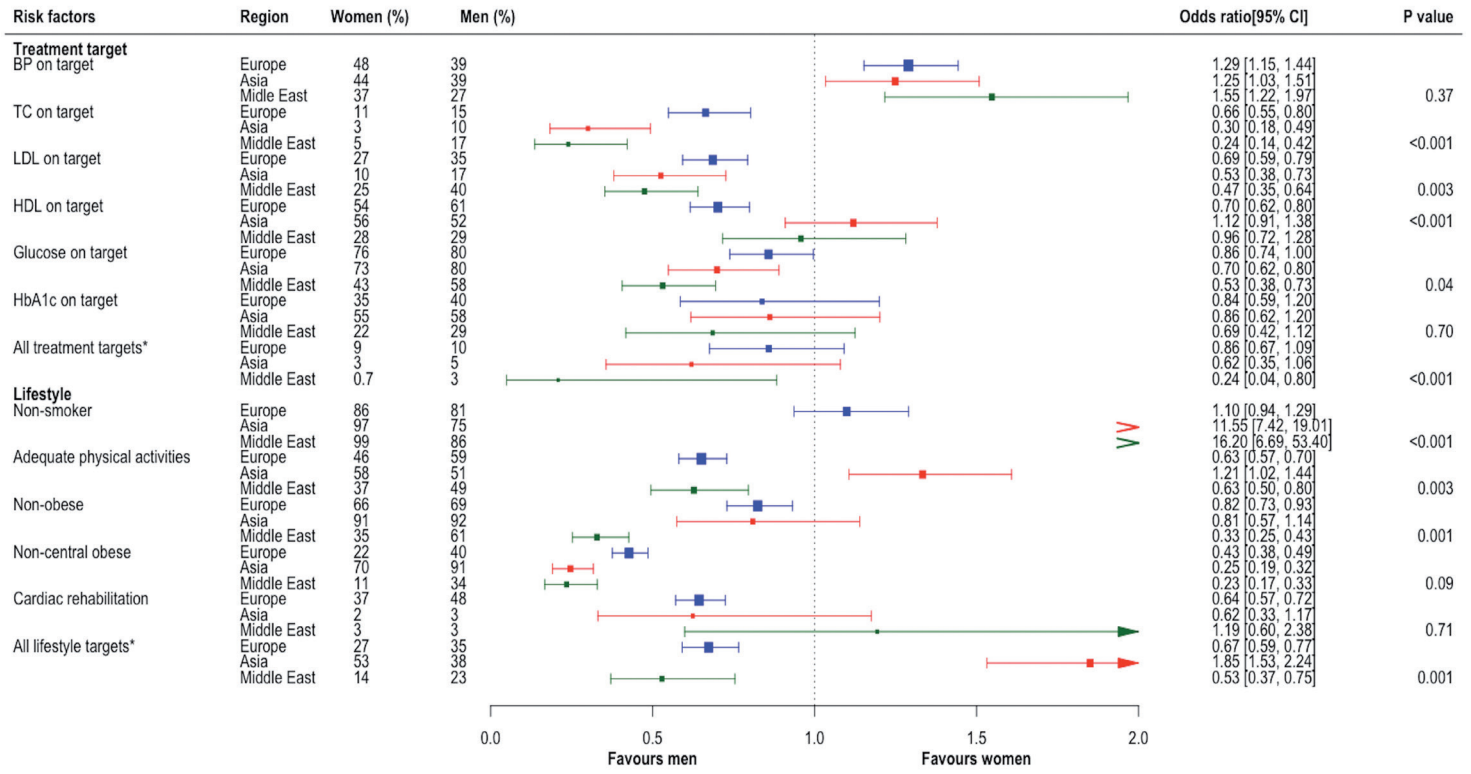
Obesity was defined as a body mass index (BMI) ≥30kg/m2 and central obesity was defined as waist circumference ≥88cm for women and ≥102cm for men. Smoking status was current smoker and non-smoker. Adequate physical activity level was defined as moderate or vigorous physical activity for at least 30 minutes three or more times a week. *All three lifestyle targets (non smoker, adequate physical activities, and non obesity) are reached was defined as all lifestyle targets.

Figure 2. Age-adjusted sex differences on cardiovascular health index score



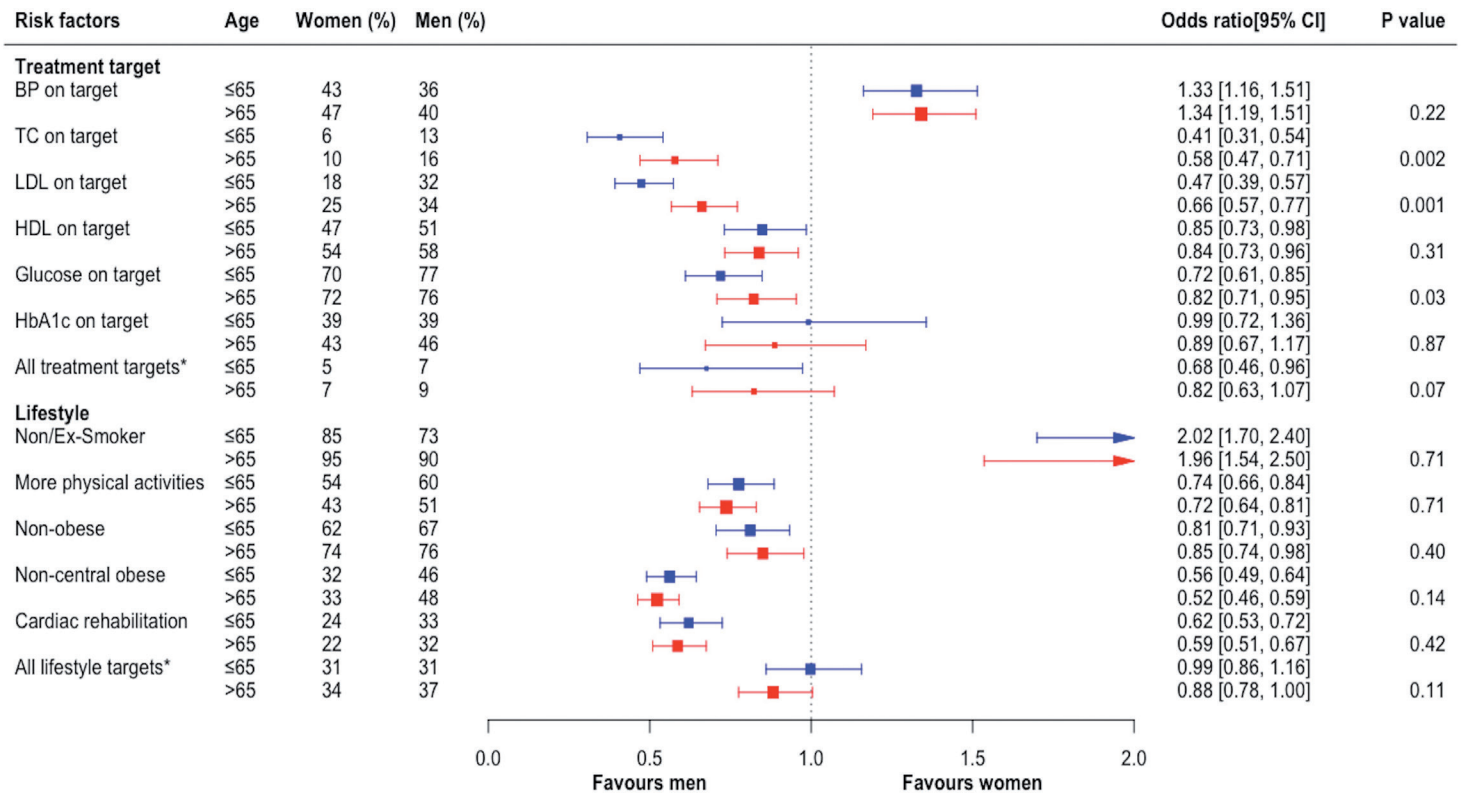
The cardiovascular health index score (CHIS) included six risk factors: smoking status (current smoker or non-smoker), body mass index (obese or not), physical activity (adequate or not), blood pressure (on target or not), LDL-cholesterol (on target or not), and HbA1c/glucose (on target or not). The number of controlled risk factors was summed, ranging from 0 to 6. A good CHIS was defined as 5 or more risk factors controlled (CHIS=5 or 6).

Figure 3. Age-adjusted sex differences on treatment targets and lifestyle factors management, stratified by region



Conventions as in Figure 1

Figure 4. Sex differences in treatment targets and lifestyle factors management, stratified by age



Conventions as in Figure 1

DISCUSSION

The present study among over 10,000 individuals with CHD indicated that, overall, risk factor management for the secondary prevention of CHD is worse among women than men. However, the magnitude and direction of the sex differences in the likelihood of meeting guideline-recommended targets varied across component treatment and lifestyle targets. Blood pressure control was better in women than in men whereas women were less likely to reach target lipid and glucose levels. Sex differences in risk factor management also varied across regions, with contrasting patterns for treatment and lifestyle targets.

Previous studies on sex differences in risk factor management for the secondary prevention of CHD have also shown that women, in general, have a worse risk factor profile and are less likely to meet therapeutic targets than men. The EUROASPIRE III and IV, two large surveys on the control of cardiovascular risk factors among coronary patients across Europe, reported that women were less likely than men to achieve target lipid and HbA1c levels.[6,7] Additionally, EUROASPIRE IV demonstrated that the largest sex differences were seen among elderly patients and among those with lower levels of education.6 EUROASPIRE III reported that blood pressure control was also worse among women than men, whereas EUROASPIRE IV found similar rates between sexes. [6,7] In the present study, we found that, although blood pressure levels were higher among women than men. Blood pressure control was considerably better in women than in men. Lipid and glucose targets, however, were less likely to be achieved by women than men.

Sex differences in the availability of evidence-based medications may be responsible for women's lower likelihood of achieving treatment targets. While, the EUROASPIRE surveys reported broadly similar treatment rates between sexes,[6,7] several other studies found lower rates in women than men.[12–16] For instance, the CRUSADE study, a large national study among in 36,000 coronary patients in the US, demonstrated that women were less likely than men to receive aspirin, ACE-inhibitors, or statins at hospital discharge after a cardiac event, even after adjustment for women's worse cardiovascular risk profile at admission.[17] Moreover, a study among 15,000 coronary patients in the Netherlands found persistent sex differences in the use of lipid-lowering and antithrombotic medications, particularly in younger patients.[13] Others also reported that women are less likely than men to receive intensive lipid-lowering therapy so to achieve their optimal lipid goals.[14,16] However, our analyses stratified by medication use did not alter our main findings on

sex differences of risk factor management, nevertheless the prevalence of medication use differs between sexes.

Despite this, as shown in our findings that women with CHD tended to be older, women's older age at diagnosis of CHD with more comorbidities might also explain their lower likelihood of receiving pharmacological therapy.[18,19] This is also problematic for younger women when their CHD conditions are often considered less serious, compared to men.[18] Consistent with previous evidence,[13] the sex difference in achieving lipid targets in this study were larger among younger than among older patients, indicating that younger women are particularly disadvantaged. Furthermore, our findings revealed differential distribution of CHD category between women and men and less CABG patients were recruited as women. As such, women may pay less attention to their CHD risk factor management, resulting less cardiovascular medication used and less targets achieved by women. This is unfortunate as clinical guidelines recommend, based on evidence from large randomized controlled trials, the use of preventative medications and strategy of CHD prevention for all adult CHD patients, irrespective of age, sex, or severity of disease.[2,19]

Most previous studies on sex differences in cardiovascular risk management are conducted in Western populations. Our study not only showed that substantial sex differences in cardiovascular risk management exist in Europe, Asia and the Middle East, but also indicated that regional variations in the size and direction of these sex disparities are present. Sex differences in smoking habits varied most notably across regions; while the prevalence of smoking was similar between the sexes in Europe, women in Asia and the Middle East were considerably less likely to smoke than their male counterparts. In contrast, sex disparities in the achievement of treatment targets were smaller in Europe than in Asia and the Middle East, especially for lipid and glucose levels. Lack of knowledge among female patients about their disease or the necessity of adequate guideline-recommended treatment could contribute to these sex differences in risk factor management.[20–24] A survey in the US found that only 55% of women were aware that CHD is the leading cause of death in women and less than half of women was familiar with optimal levels of CHD risk factors.[21] Additionally, a 12-year follow-up survey in the US showed the majority of women did not adhere to appropriate secondary prevention and often used non-evidence-based therapies to prevent CHD.[22] Comparative studies among men have not been conducted, neither is there robust data on the awareness of CHD risk among women, and men, from non-Western populations. However, it is

conceivable that women's awareness of CHD risk and the benefits of the management of major risk factors is particularly low in non-Western populations, where CHD rates are increasingly rising, risk factor profiles are different, and the uptake of preventive strategies remains lower than in the West. Greater knowledge and awareness of CHD in women, better understanding of regional differences, as well as more widespread use of women-specific clinical guidelines appropriate to local settings could help to decrease the sex disparities in CHD risk factor management and could improve CHD outcomes in both men and women.

SURF, a pragmatic clinical audit, is undertaken as part of routine clinics at low cost and minimal increase in workload, aiming to document and investigate CHD risk factor management for secondary prevention. It is particularly suitable as an audit instrument for use in low-resource settings and facilitates multiple comparisons of risk factor management across different regions and, in future iterations, over time. Some limitations of SURF deserve mention. Unlike EUROASPIRE, SURF data are collected during outpatient visits and laboratory measurements are not performed with a standardized scientific methodology. Although the high frequency of missing data might reduce the reliability of prevalence estimates, the percentage of missing data was broadly similar between sexes, and hence it is unlikely to alter our conclusions. Moreover, participating centers were identified through personal contact and may not be representative of health care facilities treating CHD patients in participating countries. Finally, more than 60% of patients were recruited from European centers. While these limitations may have affected the descriptive characteristics, the comparisons of sex differences in cardiovascular risk factor management are less likely to be affected. A new phase of SURF, SURF II, will increase representativeness both in terms of patients participation and by allowing the participation of a wide variety of centers, irrespective of size and resources.

CONCLUSION

In conclusion, we observed substantial differences between men and women in cardiovascular risk factor management for the secondary prevention of CHD, most often to the detriment of women. Sex disparities in risk factor management differed across regions, suggesting the need for tailored strategies to reduce these inequalities and to improve the uptake of guideline-recommended care for the secondary prevention of CHD in both men and women.

ACKNOWLEDGEMENT

The SURF study group is grateful to all participating centers and their staff for their participation and support.

CONTRIBUTORS

MZ, SP, MW, KK, IV, RG, and IG conceived and designed the study. MZ, SP, and MW analyzed and interpreted the data. MZ drafted the manuscript and all authors contributed to critical revision of the manuscript.

REFERENCES

1. GBD 2015 Mortality and Causes of death Collaborators. Global , regional , and national life expectancy , all-cause mortality , and cause-specifi c mortality for 249 causes of death , 1980 – 2015 : a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–544.
2. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207–274.
3. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 223: 636-48.
4. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
5. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
6. De Smedt D, De Bacquer D, De Sutter J, et al. The gender gap in risk factor control : Effects of age and education on the control of cardiovascular risk factors in male and female coronary patients . The EUROASPIRE IV study by the European Society of Cardiology. *Int J Cardiol* 2016; 209: 284–290.
7. Dallongevillle J, De Bacquer D, Heidrich J, et al. Gender differences in the implementation of cardiovascular prevention measures after an acute coronary event. *Heart* 2010; 96: 1744–1749.
8. Mosca L, Barrett-Connor E, Kass Wenger N. Sex/gender differences in cardiovascular disease prevention: What a difference a decade makes. *Circulation* 2011; 124: 2145–2154.
9. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
10. WHO. Public health Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157–163.
11. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. *Circulation* 2010; 121: 586–613.
12. Simpson CR, Hannaford PC, Williams D. Evidence for inequalities in the management of coronary heart disease in Scotland. *Heart* 2005; 91: 630–634.
13. Koopman C, Vaartjes I, Heintjes EM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment

of coronary heart disease, 1998-2010. *Eur Heart J* 2013; 34: 3198–3205.
14. Victor BM, Teal V, Ahedor L, et al. Gender differences in achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol* 2014; 113: 1611–1615.
15. DeWilde S, Carey IM, Richards N, et al. Trends in secondary prevention of ischaemic heart disease in the UK 1994 2005: use of individual and combination treatment. *Heart* 2008; 94: 83–88.
16. Virani SS, Woodard LD, Ramsey DJ, et al. Gender Disparities in Evidence-Based Statin Therapy in Patients With Cardiovascular Disease. *Am J Cardiol* 2015; 115: 21–26.
17. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Initiative. *J Am Coll Cardiol* 2005; 45: 832–7.
18. Zhang H, Plutzky J, Shubina M, et al. Drivers of the Sex Disparity in Statin Therapy in Patients with Coronary Artery Disease: A Cohort Study. *PLoS One* 2016; 11: e0155228.
19. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol* 2013; 61: 78–140.
20. Shah T, Palaskas N, Ahmed A. An Update on Gender Disparities in Coronary Heart Disease Care. *Curr Atheroscler Rep* 2016; 18: 28.
21. Ramachandran HJ, Wu VX, Kowitlawakul Y, et al. Awareness, knowledge and healthy lifestyle behaviors related to coronary heart disease among women: An integrative review. *Heart Lung J Acute Crit Care* 2016; 45: 173–185.
22. Mosca L, Mochari-Greenberger H, Dolor RJ, et al. Twelve-year follow-up of American women's awareness of cardiovascular disease risk and barriers to heart health. *Circ Cardiovasc Qual Outcomes* 2010; 3: 120–127.
23. Mosca L, Mochari H, Christian A, et al. National study of women's awareness, preventive action, and barriers to cardiovascular health. *Circulation* 2006; 113: 525–534.
24. Maas AHEM, Van Der Schouw YT, Regitz-Zagrosek V, et al. Red alert for womens heart: The urgent need for more research and knowledge on cardiovascular disease in women. *Eur Heart J* 2011; 32: 1362–1368.

APPENDIX

Figure Legends

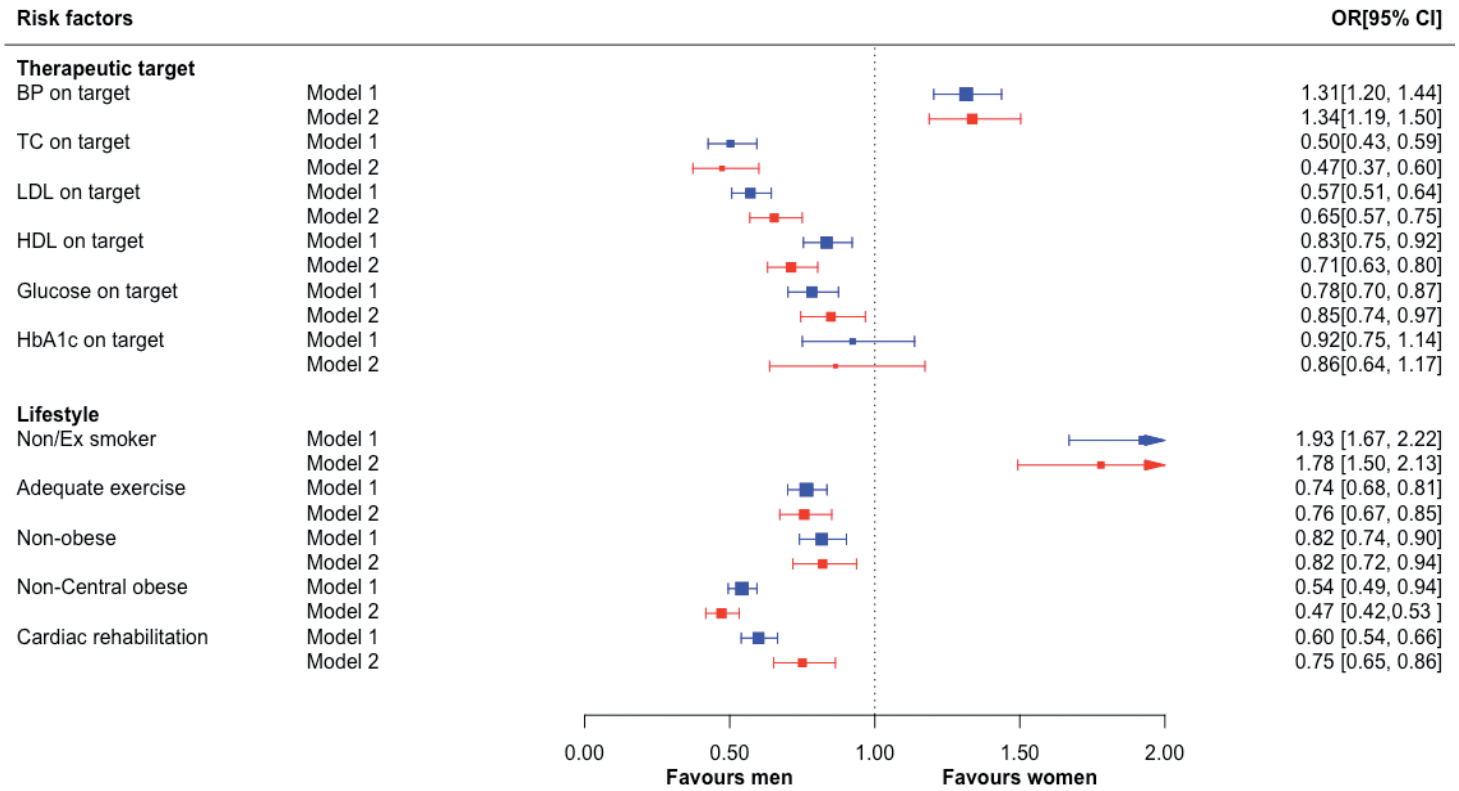
eFigure 1: Sex differences in risk factor management in age-adjusted and multiple-adjusted model

BP: blood pressure; TC: total cholesterol; LDL: LDL-cholesterol

Target blood pressure (BP) was defined as BP <140/90mmHg or <140/80mmHg for diabetic patients. The target for TC, LDL-cholesterol and HDL-cholesterol levels were defined as <3 mmol/L, <1.8 mmol/L, and >1.0mmol/L for men and >1.2mmol/L for women, respectively. Target glucose was defined as <7 mmol/L. Information on HbA1c was only collected among patients with diabetes and its target was defined as <7%. *All three medical targets (BP on target, LDL on target, and glucose/HbA1c on target) are achieved was defined as all treatment targets.

Obesity was defined as a body mass index (BMI) ≥30kg/m2 and central obesity was defined as waist circumference ≥88cm for women and ≥102cm for men. Smoking status was current smoker and non-smoker. Adequate physical activity level was defined as moderate or vigorous physical activity for at least 30 mins three or more times a week. *All three lifestyle targets (non smoker, adequate physical activities, and non obesity) are reached was defined as all lifestyle targets.

Model 1 was age adjusted logistic regression model; Model 2 was logistic regression model with multiple adjustment with BP, smoking status, TC, HDL-cholesterol, glucose, and therapeutic target achievements. Odds Ratios (ORs) and 95% confidence interval (95% CI) presented as women versus men.


Risk factors
OR[95% CI]
Therapeutic target
BP on target
Model 1
1.31[1.20, 1.44]
Model 2
1.34[1.19, 1.50]
TC on target
Model 1
0.50[0.43, 0.59]
Model 2
0.47[0.37, 0.60]
LDL on target
Model 1
0.57[0.51, 0.64]
Model 2
0.65[0.57, 0.75]
HDL on target
Model 1
0.83[0.75, 0.92]
Model 2
0.71[0.63, 0.80]
Glucose on target
Model 1
0.78[0.70, 0.87]
Model 2
0.85[0.74, 0.97]
HbA1c on target
Model 1
0.92[0.75, 1.14]
Model 2
0.86[0.64, 1.17]
Lifestyle
Non/Ex smoker
Model 1
1.93 [1.67, 2.22]
Model 2
1.78 [1.50, 2.13]
Adequate exercise
Model 1
0.74 [0.68, 0.81]
Model 2
0.76 [0.67, 0.85]
Non-obese
Model 1
0.82 [0.74, 0.90]
Model 2
0.82 [0.72, 0.94]
Non-Central obese
Model 1
0.54 [0.49, 0.94]
Model 2
0.47 [0.42,0.53]
Cardiac rehabilitation
Model 1
0.60 [0.54, 0.66]
Model 2
0.75 [0.65, 0.86]
0.00
0.50
1.00
1.50
2.00
Favours men
Favours women

eTable 1: Missingdata by region and sex, n (%)

	Overall		Europe		Asia		Middle East	
	Men	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**
Total No.	**7154**	**2958**	**4851**	**1799**	**1136**	**746**	**1167**	**413**
Basic demographics								
Age	87 (1%)	38 (1%)	86 (2%)	37 (2%)	0 (0%)	0 (0%)	1 (0.1%)	1 (0.1%)
Risk factors								
FH	1647 (23%)	591 (20%)	1605 (33%)	576 (32%)	4 (0.4%)	2 (0.3%)	38 (3%)	13 (3%)
Smoking	112 (2%)	38 (1%)	89 (2%)	28 (2%)	4 (0.4%)	2 (0.3%)	19 (2%)	8 (2%)
Exercise	172 (2%)	55 (2%)	126 (3%)	39 (2%)	10 (0.9%)	3 (0.4%)	36 (3%)	13 (3%)
BMI	564 (6%)	211 (2%)	341 (5%)	131 (2%)	13 (0.7%)	6 (0.3%)	210 (13%)	74 (5%)
WC	1575 (22%)	574 (19%)	1122 (23%)	422 (23%)	14 (1%)	7 (1%)	439 (38%)	145 (35%)
Known history								
HTN	183 (3%)	43 (2%)	91 (2%)	23 (1%)	5 (0.4%)	3 (0.4%)	87 (8%)	17 (4%)
Dyslipidaemia	199 (3%)	92 (3%)	101 (2%)	49 (3%)	9 (0.8%)	5 (0.7%)	89 (8%)	38 (9%)
Diabetes	1532 (21%)	507 (17%)	1016 (21%)	367 (20%)	7 (0.6%)	6 (0.8%)	509 (44%)	134 (32%)
Medical treatment target								
BP on target	125 (2%)	29 (1%)	108 (2%)	23 (1%)	9 (0.8%)	4 (0.5%)	8 (0.7%)	2 (0.5%)
TC on target	1279 (18%)	568 (19%)	859 (18%)	338 (19%)	171 (15%)	115 (15%)	249 (21%)	115 (28%)
LDL on target	1903 (27%)	827 (28%)	1377 (28%)	550 (31%)	264 (23%)	157 (21%)	262 (23%)	120 (29%)
HDL on target	1650 (23%)	737 (25%)	1184 (24%)	482 (27%)	213 (19%)	138 (19%)	253 (22%)	117 (28%)
Glucose on target	1629 (23%)	645 (22%)	1150 (24%)	384 (22%)	221 (20%)	139 (19%)	258 (22%)	122 (30%)
HbA1C on target	807 (45%)	388 (39%)	480 (52%)	200 (51%)	98 (25%)	82 (23%)	229 (49%)	106 (44%)

FH: family history; HTN: hypertension

eTable 2: Sex differences in risk factor control and management, stratified by medication use and CHD category.

	Medication*		CHD category¶			
	Yes	No	CABG	PCI	Angina	ACS
BP on target	1.34 (1.23-1.47)	0.98 (0.69-1.39)	1.21 (0.96-1.53)	1.37 (1.19-1.57)	1.29 (1.11-1.50)	1.31 (1.12-1.53)
TC on target	0.48 (0.37-0.62)	0.64 (0.43-0.93)	0.43 (0.27-0.66)	0.34 (0.25-0.45)	0.61 (0.45-0.82)	0.66 (0.52-0.84)
LDL on target	0.66 (0.51-0.65)	0.71 (0.50-1.00)	0.65 (0.48-0.86)	0.66 (0.55-0.78)	0.58 (0.46-0.72)	0.72 (0.59-0.87)
HDL on target	NA	NA	0.73 (0.56-0.95)	0.83 (0.72-0.97)	0.81 (0.69-0.96)	0.69 (0.58-0.82)
Glucose on target	0.92(0.77-1.10)	0.82 (0.69-0.99)	0.73 (0.56-0.96)	0.63 (0.53-0.74)	0.87 (0.72-1.06)	0.74 (0.62-0.89)
HbA1c on target	0.88 (0.70-1.11)	1.19 (0.74-1.94)	0.77 (0.42-1.39)	0.73 (0.53-1.00)	0.92 (0.67-1.27)	0.73 (0.46-1.16)
Non-smoker	NA	NA	2.64 (1.62-4.57)	1.56 (1.27-1.93)	3.16 (2.45-4.11)	1.31 (1.06-1.63)
Adequate exercise	NA	NA	0.72 (0.57-0.90)	0.66 (0.57-0.75)	0.88 (0.76-1.02)	0.71 (0.60-0.82)
Non-obese	NA	NA	0.69 (0.53-0.89)	0.68 (0.58-0.79)	0.96 (0.81-1.14)	0.74 (0.63-0.88)
Non-central obese	NA	NA	0.32 (0.24-0.42)	0.44 (0.38-0.51)	0.65 (0.56-0.75)	0.42 (0.35-0.49)
Cardiac rehab	NA	NA	0.80 (0.63-1.01)	0.75 (0.64-0.87)	0.99 (0.98-1.00)	0.73 (0.62-0.87)
CHIS	NA	NA	0.68 (0.51-0.92)	1.02 (1.00-1.03)	0.99 (0.82-1.19)	0.85 (0.60-1.58)

BP: blood pressure; TC: total cholesterol; EU: Europe; Cardiac rehab: cardiac rehabilitation; CHIS: cardiovascular health index score; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; SAP: stable angina; ACS: acute coronary syndroms; NA: not applicable.

Results are shown as odds ratios (95% confidence interval) of women versus men.

*BP on target was stratified by anti-hypertensive medication (yes or no); TC and LDL on target were stratified by lipid-lowering medication (yes or no); Glucose and HbA1c on target were stratified by anti-diabetic medication (yes or no); no stratified analysis was performed for HDL on target, lifestyle achievement, or CHIS.

¶ In SURF, recruited patients may have more than one recorded CHD category. For example, patient could be recorded as both 'CABG' and 'PCI'. The current stratified analyses were performed for CABG (yes or no), PCI (yes or no), SAP (yes or no), or ACS (yes or no), respectively.

eTable 3: Sex differences in risk factor management, stratified by age group and region.

			Age≤65			Age>65		
		Interaction P value	Women N(%)	Men N(%)	OR (95%CI)	Women N(%)	Men N(%)	OR (95%CI)
Therapeutic targets								
BP on target	Europe	Reference	292 (43.2%)	940 (37.8%)	1.25 (1.05-1.49)	542 (50.9%)	935 (43.1%)	1.37 (1.18-1.58)
	Asia	<0.001	133 (46.0%)	215 (40.7%)	1.24 (0.93-1.66)	192 (42.4%)	220 (36.7%)	1.27 (0.99-1.63)
	Middle East	0.07	86 (36.9%)	187 (26.1%)	1.65 (1.21-2.27)	63 (35.6%)	123 (27.9%)	1.43 (0.98-2.07)
TC on target	Europe	Reference	45 (7.9%)	295 (13.9%)	0.53 (0.38-0.73)	112 (12.9%)	293 (16.3%)	0.76 (0.60-0.96)
	Asia	0.2	7 (2.8%)	36 (7.7%)	0.35 (0.14-0.75)	13 (3.4%)	56 (11.2%)	0.28 (0.14-0.50)
	Middle East	0.7	6 (3.7%)	90 (16.3%)	0.20 (0.08,0.42)	8 (5.9%)	63 (17.2%)	0.30 (0.13-0.61)
LDL on target	Europe	Reference	102 (20.9%)	612 (33.2%)	0.53 (0.42-0.67)	237(32.0%)	570 (36.4%)	0.82 (0.68-0.99)
	Asia	0.3	18 (7.9%)	60 (14.2%)	0.51 (0.29, 0.88)	41 (11.4%)	88 (19.6%)	0.53 (0.35-0.78)
	Middle East	0.8	38 (23.2%)	216 (39.6%)	0.46 (0.30-0.68)	35 (27.1%)	150 (41.7%)	0.52 (0.33-0.80)
HDL on target	Europe	Reference	249 (48.9%)	1133 (58.2%)	0.69 (0.57-0.84)	442 (56.1%)	1054 (63.7%)	0.73 (0.61-0.86)
	Asia	0.01	130 (55.3%)	198 (44.4%)	1.55 (1.13-2.13)	212 (56.8%)	286 (60.0%)	0.88 (0.67-1.16)

eTable 3: (continued)

			Age≤65			Age>65		
		Interaction P value	Women N(%)	Men N(%)	OR (95%CI)	Women N(%)	Men N(%)	OR (95%CI)
Therapeutic targets								
	Middle East	0.02	45 (27.3%)	163 (29.6%)	0.89 (0.60-1.31)	39 (29.8%)	106 (29.2%)	1.03 (0.66-1.58)
Glucose on target	Europe	Reference	418 (77.4%)	1603 (81.5%)	0.78 (0.62-0.98)	649 (75.5%)	1302 (77.7%)	0.88 (0.73-1.07)
	Asia	0.8	182 (75.5%)	355 (80.3%)	0.76 (0.52-1.10)	262 (71.6%)	375 (79.3%)	0.66 (0.48-0.90)
	Middle East	0.02	60 (38.5%)	314 (57.2%)	0.47 (0.32-0.67)	65 (28.8%)	217 (32.9%)	0.61 (0.41-0.91)
HbA1c on target	Europe	Reference	23 (36.5%)	83 (40.9%)	0.83 (0.46-1.48)	43 (34.4%)	91 (38.1%)	0.85 (0.54-1.34)
	Asia	0.6	58 (59.2%)	70 (53.0%)	1.28 (0.76-2.19)	92 (52.3%)	102 (62.6%)	0.65 (0.42-1.01)
	Middle East	0.2	15 (17.9%)	42 (26.3%)	0.61 (0.31-1.16)	15 (28.8%)	27 (32.9%)	0.83 (0.38-1.75)
Lifestyle								
Non-smoker	Europe	Reference	505 (74.8%)	1821 (72.9%)	1.10 (0.91-1.34)	984 (92.7%)	1977 (90.6%)	1.30 (1.00-1.72)
	Asia	0.04	280 (96.6%)	349 (65.6%)	14.68 (8.02-30.2)	444 (97.8%)	503 (83.8%)	8.56 (4.63-17.7)
	Middle East	0.2	228 (98.7%)	569 (80.0%)	18.97 (7.09-77.4)	172 (99.4%)	421 (96.6%)	6.13 (1.23-11.1)

eTable 3: (continued)

			Age≤65			Age>65		
		Interaction P value	Women N(%)	Men N(%)	OR (95%CI)	Women N(%)	Men N(%)	OR (95%CI)
Therapeutic targets								
Adequate exercise	Europe	Reference	372 (55.7%)	1573 (63.2%)	0.73 (0.62-0.87)	417 (39.4%)	1148 (53.3%)	0.57 (0.49-0.66)
	Asia	<0.001	182 (62.8%)	247 (46.6%)	1.93 (1.44-2.59)	247 (54.5%)	323 (54.2%)	1.01 (0.79-1.30)
	Middle East	0.9	80 (35.2%)	400 (57.2%)	0.41 (0.30-0.55)	65 (37.8%)	149 (34.6%)	1.15 (0.79-1.66)
Non-obese	Europe	Reference	387 (61.3%)	1534 (64.8%)	0.86 (0.71-1.03)	688 (68.6%)	1498 (72.7%)	0.82 (0.70-0.97)
	Asia	0.04	256 (89.2%)	469 (89.3%)	0.99 (0.62-1.58)	420 (92.7%)	569 (95.2%)	0.65 (0.39-1.08)
	Middle East	0.7	57 (28.4%)	350 (57.6%)	0.29 (0.21-0.41)	60 (43.5%)	229 (65.6%)	0.40 (0.27-0.60)
Non-central obese	Europe	Reference	155 (22.6%)	1015 (40.0%)	0.44 (0.36-0.53)	227 (21.1%)	878 (46.8%)	0.41 (0.35-0.49)
	Asia	0.8	213 (73.2%)	479 (89.7%)	0.31 (0.21-0.46)	309 (67.9%)	549 (91.2%)	0.20 (0.14-0.29)
	Middle East	0.2	23 (9.8%)	247 (34.3%)	0.21 (0.13-0.32)	20 (11.3%)	144 (32.4%)	0.27 (0.16-0.43)
Cardiac rehab	Europe	Reference	258 (40.9%)	1135 (48.8%)	0.73 (0.61-0.87)	332 (33.9%)	958 (46.8%)	0.58 (0.50-0.68)
	Asia	0.04	3 (1.0%)	14 (2.6%)	0.38 (0.09-1.20)	11 (2.4%)	19 (3.2%)	0.76 (0.35-1.59)

eTable 3: (continued)

			Age≤65			Age>65		
		Interaction P value	Women N(%)	Men N(%)	OR (95%CI)	Women N(%)	Men N(%)	OR (95%CI)
Therapeutic targets								
	Middle East	0.09	5 (2.4%)	15 (2.3%)	1.04 (0.33-2.71)	7 (4.4%)	13 (3.2%)	1.38 (0.51-3.43)
All treatment target	Europe	Reference	30 (6.8%)	140 (8.4%)	0.79 (0.58-0.86)	72 (10.4%)	156 (11.0%)	0.94 (0.69-1.26)
	Asia	0.3	5 (2.3%)	14 (3.6%)	0.63 (0.20-1.67)	14 (4.1%)	28 (6.6%)	0.61 (0.31-1.15)
	Middle East	0.4	2 (1.3%)	15 (2.9%)	0.45 (0.07-1.63)	0 (0%)	11 (0.3%)	NA*
All lifestyle target	Europe	Reference	157 (25.7%)	760 (32.9%)	0.70 (0.58-0.86)	270 (27.6%)	736 (36.9%)	0.65 (0.55-0.77)

CHIS: Cardiovascular Health Index Score; OR (95% CI): Odds ratio (95% confidence interval)

Results are shown as number (percentage). Odds Ratios (ORs) and 95% confidence interval (CI) presented as women versus men.

*No result available for '0' cell


SURF
SUrvey of Risk Factors

3.2

Determinants in risk factor management of coronary heart disease across three regions

Min Zhao, Ian Graham, Marie-Therese Cooney, Diederick E. Grobbee,
Ilonca Vaartjes, Kerstin Klipstein-Grobusch

In press

ABSTRACT

Background: The SURF (SUrvey of Risk Factors) indicated poor control of risk factors in subjects with established coronary heart disease (CHD). The present study aimed to investigate determinants of risk factor management in CHD patients.

Methods and Results: SURF recruited 9987 consecutive CHD patients from Europe, Asia, and the Middle East between 2012-2013. Risk factor management was summarized as a Cardiovascular Health Index Score (CHIS) based on six risk factor targets (non/ex-smoker, body mass index<30, adequate exercise, controlled blood pressure, controlled low-density lipoprotein, and controlled glucose). Logistic regression models assessed associations between determinants (age, sex, family history, cardiac rehabilitation, previous hospital admission, and diabetes) and achievement of moderate CHIS (≥3 risk factors controlled). Results are presented as odds ratio (OR) with corresponding 95% confidence intervals (CI).

A moderate CHIS was less likely to be reached by women (OR 0.84. 95% CI 0.74-0.95), those aged<55 years old (OR 0.62, 95% CI 0.52-0.74), and with diabetes (OR 0.38, 95% CI 0.34-0.43). Attendance of cardiac rehabilitation was associated with better CHIS achievements (OR 1.63, 95% CI 1.41-1.89). Younger Asian and European patients tended to have poorer risk factor management; whereas for patients from the Middle East age was not significantly associated with risk factor management. The availability and applicability of cardiac rehabilitation varied by region.

Conclusions: Overall, risk factor management was poorer in women, those younger than 55 years old, those with diabetes and those who did not participate in a cardiac rehabilitation program. Determinants of cardiovascular risk factor management differed by region.

Keywords: coronary heart disease, risk factors, determinants, SURF, secondary prevention.

KEY QUESTIONS

What is already known about this subject?

- Cardiovascular risk factor management was generally poor across Europe, Asia, and the Middle East.
- Previous studies have suggested poor cardiovascular risk factor management was attributed to demographic characteristics, the level of care these patients received, and complications.

What does this study add?

- This study showed that patients who were women, younger than 55 years old, those with diabetes, and those who did not participate in a cardiac rehabilitation, were more likely to have uncontrolled cardiovascular risk factors.
- Benefits from cardiac rehabilitation for cardiovascular risk factor management were pronounced in Europe; cardiac rehabilitation facilities, however, were limited in the Middle East and Asia.

How might this impact on clinical practice?

- Insight in barriers to cardiac rehabilitation is needed and more comprehensive and structured cardiac rehabilitation programs are warranted for Asia and the Middle East.
- Given regional variations on cardiovascular risk factor management, tailored prevention guidelines and strategies are recommended.

INTRODUCTION

Cardiovascular disease (CVD), especially coronary heart disease (CHD), remains the leading cause of death worldwide, with 17.9 million deaths annually.[1] The CVD prevalence has rapidly increased in low- and middle-income countries, particularly in Asia and the Middle East.[1,2] Current CHD prevention guidelines for patients with established CHD pose a high priority to intensive control of CHD risk factors.[3] However, overall risk factor control has been evidently poor with substantial regional variations, indicating a huge gap between guideline implementation and daily practice in terms of CHD risk factor management.[4,5]

These striking challenges to CHD risk factor management may relate to other characteristics, such as age, sex, or even cardiovascular complications. [6] For instance, the previous SURF analysis confirmed that risk factor management was generally worse in women than in men.[7] EUROASPIRE III observed that a history of diabetes was associated with poorer risk factor management.[6] Understanding associated characteristics or determinants would be essential for all health providers to guide future secondary prevention strategies and adjust current guidelines to improve quality of care in daily practice. Furthermore, these studies were predominantly conducted in Europe. It remains unknown whether these associated determinants differ in Asia and the Middle East.

We therefore analyzed data from a large international audit, SUrvey of Risk Factors (SURF), to identify characteristics that had a significant impact on overall risk factor management in secondary prevention of CVD in Europe, Asia, and the Middle East.

METHODS

Study population

The study protocol and methodology of SURF have been published previously.[5,7] Briefly, SURF is an international clinical audit of the recording and management of cardiovascular risk factors from 11 countries among three regions (Europe, Asia, and the Middle East). Consecutive patients aged≥18 years with established CHD (defined as a history of coronary artery bypass graft surgery (CABG), percutaneous coronary intervention (PCI), acute coronary syndromes (ACS), or stable angina) were recruited from routine outpatient cardiology clinics. Detailed data on demographics, self-reported smoking status, physical activity, attending a cardiac rehabilitation program, physical

and laboratory measurements (i.e. body anthropometry, blood pressure (BP), blood cholesterol, blood glucose, and glycated hemoglobin <HbA1c>), and medication classes were recorded on a one-page collection sheet by trained research staff.

Overall risk factor management profile

An overall risk factor management profile was assessed by Cardiovascular Health Index Score (CHIS), and adapted from the ideal Cardiovascular Health Index Score (CHIS).[8] CHIS was defined by six risk factors: smoking status, body mass index (BMI), physical activity, blood pressure, LDL-cholesterol, and HbA1c (or, if HbA1c was not available, blood glucose). The summation of controlled risk factors could range from 0 to 6. If three or more risk factors were on target, this was considered a moderately satisfactory score (moderate CHIS).

The risk factor targets were those of the 2012 and 2016 Joint European guidelines:[9,10]

- Self-reported non-smoker (never/ex-smoker);
- Non-obese (BMI<30);
- Self-reported adequate physical activity (at least 30mins three or more times a week);
- Blood pressure <140/90mmHg without diabetes and <140/80 mmHg with diabetes;
- Lipoprotein (LDL) cholesterol<1.8 mmol/L;
- HbA1c <7% for diabetes (or glucose<7mmol/L, if HbA1c is not available)

Determinants

Several studies have suggested that basic demographics, hospital care, and geographical areas may relate to cardiovascular risk factor management.[6,7,11] Specific variables collected in SURF were analyzed for potential impact on cardiovascular risk factor management (appendix 1). Potential determinants included demographics (age group and gender), family history, hospital admission within a year due to a cardiac event before study entry, cardiac rehabilitation attendance, and known history of diabetes. Education was not included as a possible determinant due to high frequency of missing and incomplete data.

Statistical analyses

Logistic regression analyses were used to assess which determinants were associated with achievement of moderate CHIS. Results were presented using odds ratios (OR) with

a corresponding 95% confidence interval (CI) adjusted for age and gender. Stratified analyses were performed by regions (Europe, Asia, and the Middle East) and diagnostic groups (CABG, PCI, acute coronary syndromes, and stable angina).

SURF, as an audit, collected data from routine clinic visits. Given high frequency of missing data (missing data information is available in appendix 2), we used imputed data in our primary analysis.[5] Briefly, we applied 10 datasets to impute for missing data with multivariate imputation by chained equations (MICE package in R).[12] MICE predicts missing data by iteratively optimizing a series of regression models using other potentially predictive variables, such as basic demographics and geographic area. Continuous variables including height, weight, blood pressure, TC, LDL, HDL, and glucose are predictive mean matching and the categorical data including smoking status and physical activity were imputed with logistic regression. A sensitivity analysis was performed using complete case analysis without imputed data (appendix 3).

All analyses were undertaken using R version 3.2.2 and all tests were two tailed with statistical significance set at the 5% level.

RESULTS

Cardiovascular Health Index Score (CHIS) information was based on 9987 SURF patient records. The mean age of these patients was 65.2±11.2 years; 29.2% were women. The median of CHIS was 4, ranging from 0 to 6 and a moderate CHIS (three or more risk factors controlled) was achieved by 82.6% SURF patients.

Overall determinants of achieving moderate CHIS

Figure 1 shows the ORs associated with the achievement of moderate CHIS in unadjusted and age- and gender-adjusted models.

In the adjusted model, younger patients were less likely than those older than 75 years of age to reach moderate CHIS; the corresponding ORs were 0.62 [95% CI 0.52 to 0.74] for those aged<55 years old and 0.82 [95% CI 0.69 to 0.97] for those aged between 55 and 65 years old. A moderate CHIS was achieved by 81% of women and 83% of men; the corresponding OR for women vs men was 0.84 (95% CI 0.74 to 0.95). Attending cardiac rehabilitation was associated with better success in reaching moderate CHIS, compared to non-attendance (OR: 1.63; 95% CI: 1.41-1.89). Furthermore, patients with a previous

medical history of diabetes were 62% less likely to achieve moderate CHIS (95% CI 0.34 to 0.43). Admission to hospital in the previous year and family history of premature CHD were not determinants. Similar results were also found in unadjusted models.

Appendix 3 compares the results from imputed data with those from complete case data, showing that determinants of reaching moderate CHIS were similar in sensitivity analysis. In appendix 4 the associations with individual target achievement are presented. A lower smoking rate, more adequate physical activities, and more targets achievements on BP, LDL, and glucose were significantly associated with attending cardiac rehabilitation.

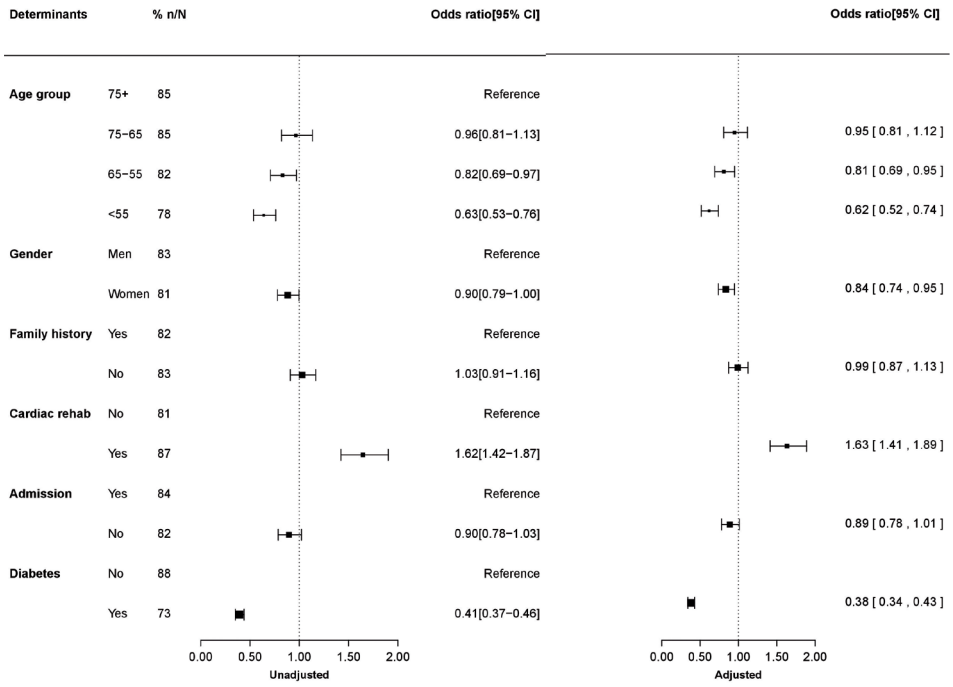
Determinants by region

Determinants varied across regions (figure 2). Younger patients (<55 years old) were less likely to reach a moderate CHIS than those above 75 years old in Europe and Asia; while there was no significant age difference on achieving a moderate CHIS among Middle Eastern patients (Europe: 0.71 [95%CI 0.56-0.88]; Asia: 0.42 [95%CI 0.26-0.66]; Middle East 0.67 [0.42-1.06]). After adjusting for age, women had 20% and 42% lower odds than men of achieving moderate CHIS in Europe and the Middle-East, respectively (Europe: 0.80 95% CI [0.69, 0.92]; Middle East: 0.58, 95% CI [0.43, 0.77]). In contrast, the odds of having moderate CHIS were 41% higher in Asian women than their counterparts. All diabetic patients were shown to have a lower rate of achieving moderate CHIS than those without, irrespective of regions (Europe: 0.27, 0.20-0.37; Asia: 0.27, 0.20-0.37; Middle East: 0.65, 0.46-0.90).

Nearly half of European patients participated in a cardiac rehabilitation program for secondary prevention. In Europe, attending cardiac rehabilitation was strongly associated with greater success in reaching a moderate CHIS (1.49; 95% CI [1.26, 1.77]). In contrast, a tiny number of patients in Asia (2.6%) and the Middle East (2.8%) have attended a cardiac rehabilitation program precluding a meaningful analysis.

Subgroup analysis by region showed no significant difference between age groups in Middle Eastern patients; for younger Asian and European patients (<55 years old), a less beneficial risk factor control was observed. Determinants for achieving moderate CHIS were similar in the different diagnostic groups (appendix 5).

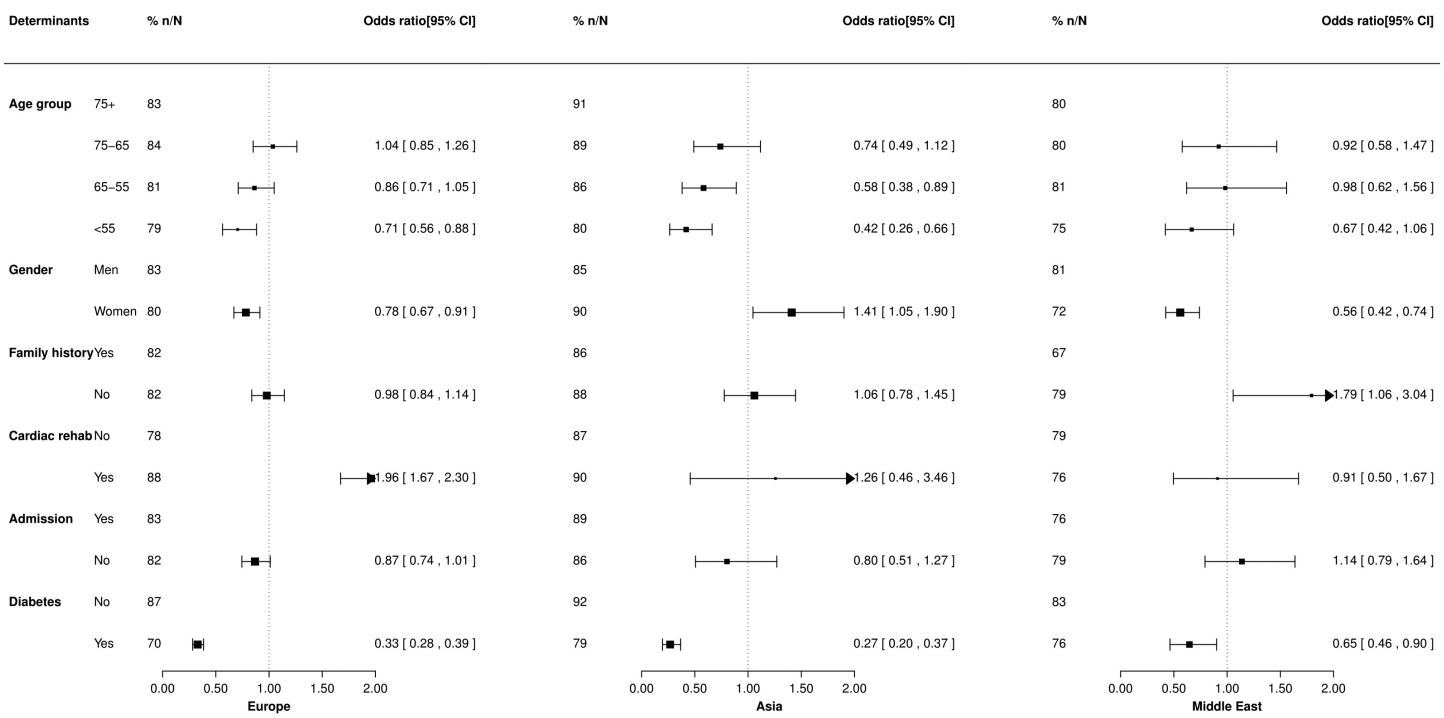
Figure 1. Determinants of moderate Cardiovascular Health Index Score (achieving three or more risk factor targets)



Cardiac rehab: cardiac rehabilitation; Admission: hospital admission

The CHIS included six risk factors: smoking status (current smoker or non-smoker), obesity (body mass index≥30 or not), physical activity (adequate or not), blood pressure (on target or not), low-density lipoprotein (LDL) cholesterol (on target or not), and HbA1c/glucose (on target or not). The number of controlled risk factors was summed, ranging from 0 to 6. If three or more risk factors were on target, moderate CHIS was assigned and considered as satisficed overall risk factor management. Age and gender were adjusted for in the adjusted model. Results were presented as odds ratios with corresponding 95% confidence interval.

Figure 2. Determinants of moderate Cardiovascular Health Index Score (achieving three or more risk factor targets), stratified by region



Conventions as in figure 1. Adjusted Odds ratios (95% CI) presented.

DISCUSSION

The present study dethat CHD patients younger than 55 years, women, those with diabetes, and those who did not attend cardiac rehabilitation were less likely to have their risk factors at target. Substantial regional variations were observed. Younger patients (<55 years old) were more likely to achieve three or more targets in Europe and Asia; while there was no age difference in the Middle East. Asian women had better control of risk factors than men in contrast to those from Europe and the Middle East. Benefits from cardiac rehabilitation were recognized for European patients; whereas lack of cardiac rehabilitation facilities in the Middle East and Asia hampers assessment of benefits from cardiac rehabilitation for these regions.

Participation in a cardiac rehabilitation program was associated with better overall cardiovascular risk factor management in SURF patients consistent with results from several other studies, indicating cardiovascular rehabilitation to be an effective tool for the management of modifiable risk factors to achieve a healthy lifestyle and therapeutic targets. [6,13–16] In the current study we observed that attending cardiac rehabilitation was related to reduced smoking, achievement of adequate physical activity, a more healthier body weight, and a higher likelihood of achievement of therapeutic targets (LDL and glucose targets)(appendix 4). Thus, similar to other studies, our study confirmed that cardiac rehabilitation, encompassing supervised exercise training, education, and nutritional guidance, is multi-disciplinary approach to secondary prevention of CVD, although the audit setting of SURF does not allow to assess direct effectiveness.[13,16]

Availability and applicability of cardiac rehabilitation in the current study are evidently limited for Asian and Middle-Eastern participating centers. Due to limited available information on cardiac rehabilitation, we could, thus, not perform any meaningful analysis in these two regions. Several previous studies showed cardiac rehabilitation programs remain grossly underused and of varying quality in Asia and the Middle East.[17–19] Insufficient financial and staff support and low awareness of the necessity of cardiac rehabilitation may impede its use for secondary prevention. [17,20–22] Furthermore, lack of a structured framework and limited capability may reduce its implementation.[19] Previously, we reported that less than 3% of Asian and Middle Eastern patients attended cardiac rehabilitation.[5] Our study calls for appropriate cardiac rehabilitation programs worldwide.

Data regarding the relationship between age and risk factor control in patients with

CHD are conflicting.[6,23–25] For instance, EUROASPIRE III reported increasing age to be associated with decreased likelihood of meeting combined targets of lipids, blood pressure, smoking, and HbA1c in diabetics; however, such relationships disappeared after controlling for confounders.[6] In contrast, our results indicated that older patients (>75 years) were more likely to meet the targets and achieve a better CHIS compared to younger patients, which is in line with a study performed in patients with peripheral arterial disease.[26] Although older patients may present with multiple disease states and require more complex medical management, their awareness of the importance of cardiovascular risk factor management is more likely to be high, leading to better compliance. [26-28] We observed that older patients were more likely to achieve a healthier lifestyle with regard to smoking, physical activity, body weight, and LDL-cholesterol, despite a higher prevalence of previous medical history on hypertension and diabetes and lower cardiovascular medication (appendix 6). Overall, better cardiovascular risk factor management was observed in older patients.

We have previously reported in detail on sex differences in risk factor control in SURF.[7] The current study confirms previous reports that women were disadvantaged in terms of risk factor management; except for Asia, where women were considerably less likely to smoke and far more likely to be physically active compared to their male counterparts.[29–31] Hence, overall risk factor management was expected to be better in Asian women. In general, low awareness of CHD risk, insufficient pharmaceutical therapy, and lack of a defined CHD prevention strategy for women may explain some of the inequalities in cardiovascular risk factor management among women.[32]

Diabetes is of major concern for cardiovascular risk factor management, given the detrimental impact of diabetes on cardiovascular disease and its coexistence with other traditional CVD risk factors including obesity, hypertension, and dyslipidemia.[33,34] Hence, as our results showed, CHD patients with diabetes could be more likely to have poor overall CVD risk factor management and may derive less benefit from standardized secondary prevention strategy. A large population-based study in Germany indicated poor blood pressure control in subjects with diabetes.[35] A study conducted in 47813 coronary patients in the US found poor lipid control in diabetes compared with their non-diabetic counterparts.[36] A Canadian survey reported that diabetes patients had difficulty with weight control and smoking cessation.[37] These studies indicate that patients with diabetes may need more intensive monitoring in terms of CVD prevention regardless of their region of residence.

There was no evidence that previous hospital admission was a determinant of risk factor management in the current study. Whereas, a Polish study reported admission to hospital was related to better lipid management in the post-discharge period with a higher lipid-lowering medication use, indicating that patients discharged from a specialized hospital may be offered a better secondary prevention strategy with appropriate discharge prescriptions.[11] This may imply that disease severity may affect cardiovascular risk factor management. Hence, we further analyzed stratified data on diagnostic group but did not observe any significant difference on risk factor management, indicating equal care offered to all CHD patients irrespective of their disease severity or previous admission history (appendix 5).

SURF is an international audit conducted in three different regions, aiming to provide a more effective tool to monitor daily practice and to improve quality of care. This allowed for comparative analyses to investigate associated determinants and whether they differ between geographical regions. We observed poor risk factor management across three regions with less than 20% of patients being able to have five or more risk factors controlled. For the current analysis, we used a more practical and realistic tool to assess overall risk factor management (moderate CHIS with three or more controlled risk factors) to provide for a better understanding of determinants for risk factor management.

We recognize several limitations of our study. The simplified SURF methodology only collects core cardiovascular risk factor data, so that information, such as on socio-economic status, duration of CHD, and incidence of event, is not included to perform more sophisticated research. Although SURF aimed to demonstrate quality of care in routine practice by recording missing data on cardiovascular risk factors, high frequency of missing data is also a potential source of bias in the current analysis. We, thus, imputed missing data to address current issue. Furthermore, our complete case analysis indicted that missing information is at random among SURF participants with minor effects on the observed associated determinants (appendix 3). Therefore, our conclusions are unlikely to be altered. Education information, unfortunately, could not be accounted for in the current analysis due to not only the high frequency of missing data but also differences in understanding of the SURF question on educational attainment. SURF II will attempt to collect information on educational attainment in an easily understandable and standardized way to minimize missing or incomplete data. Lastly, participation of centers in the SURF audit was facilitated by personal contact and may thus not be representative in participating countries. However, the simplicity of SURF permits participation by

centers with limited resources. As SURF expands, we expect to progressively include more data from different regions, enhancing representativeness and generalizability of SURF findings to better assist in both process improvement and examination of secondary prevention internationally.

CONCLUSION

Patients who were women, younger than 55 years old, those with diabetes, and those who did not attend cardiac rehabilitation, were more likely to have uncontrolled risk factors. The most notable regional variation was availability and applicability of a cardiac rehabilitation program. Benefits from cardiac rehabilitation for risk factor management was pronounced in European patients, whereas cardiac rehabilitation services in Asia and the Middle East were limited and of concern. Insight in barriers to cardiac rehabilitations and development of comprehensive and structured programs for Asia and the Middle East is warranted.

ACKNOWLEDGEMENTS

The SURF study group is grateful to all participating centers and their staff for their participation and support.

COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form (www.icmje.org/coi_disclosure.pdf) and declare no support from any organizations for submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; and no other relationships or activities that could appear to have influenced the submitted work.

FUNDING

MZ is supported by a grant from the Netherlands Organization for Scientific Research (NWO; grant number: 0.22.005.021). NWO had no input to the design, execution, analysis, or writing up of the study. IV is supported by a grant from the Dutch Heart Foundation (grant DHF project 'Facts and Figures').

CONTRIBUTORS

MZ, IG, KK, and IV conceived and designed the study. MZ analyzed and interpreted the data. MZ drafted the manuscript and all authors contributed to critical revision of the manuscript.

REFERENCES

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; 388: 1459–1544.
2. Roth GA, Forouzanfar MH, Moran AE, et al. Demographic and Epidemiologic Drivers of Global Cardiovascular Mortality. *N Engl J Med* 2015; 372: 1333–1341.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207–274.
4. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23(6): 636-48.
5. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
6. Cooney MT, Kotseva K, Dudina A, et al. Determinants of risk factor control in subjects with coronary heart disease : a report from the EUROASPIRE III investigators. *Eur J Prev Cardiol* 2012; 20: 686–691.
7. Zhao M, Vaartjes I, Graham I, et al. Sex differences in risk factor management of coronary heart disease across three regions. *Heart* 2017; 103: 1587–1594.
8. Lloyd-Jones DM, Hong Y, Labarthe D, et al. Defining and setting national goals for cardiovascular health promotion and disease reduction: The american heart association's strategic impact goal through 2020 and beyond. *Circulation* 2010; 121: 586–613.
9. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
10. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016; 37: 2315–2381.
11. Kawecka-jaszcz K, Jankowski P, Paja A. Determinants of appropriate lipid management in patients with ischaemic heart disease . Cracovian Program for Secondary Prevention of Ischaemic Heart Disease. *Int J Cardiol* 2003; 91: 15–23.
12. Groothuis-oudshoorn K. MICE: Multivariate Imputation by Chained. *J Stat Softw* 2011; 45(3):1-67.
13. Kachur S, Chongthammakun V, Lavie CJ, et al. Impact of cardiac rehabilitation and exercise training programs in coronary heart disease. *Prog Cardiovasc Dis* 2017; 60: 103–114.

14. Harber MP, Kaminsky LA, Arena R, et al. Impact of Cardiorespiratory Fitness on All-Cause and Disease-Specific Mortality: Advances Since 2009. *Prog Cardiovasc Dis* 2017; 60: 11–20.
15. Kotseva K, Wood D, De Backer G, et al. Use and effects of cardiac rehabilitation in patients with coronary heart disease: Results from the EUROASPIRE III survey. *Eur J Prev Cardiol* 2013; 20: 817–826.
16. Anderson L, Taylor RS. Cardiac rehabilitation for people with heart disease : an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2014: 12(12):CD011273.
17. Turk-Adawi K, Sarrafzadegan N, Grace SL. Global availability of cardiac rehabilitation. *Nat Rev Cardiol* 2014; 11: 586–596.
18. Grace SL, Turk-Adawi KI, Contractor A, et al. Cardiac Rehabilitation Delivery Model for Low-Resource Settings: An International Council of Cardiovascular Prevention and Rehabilitation Consensus Statement. *Prog Cardiovasc Dis* 2016; 59: 303–322.
19. Lima de Melo Ghisi G, Pesah E, Turk-Adawi K, et al. Cardiac Rehabilitation Models around the Globe. *J Clin Med* 2018; 7: 260.
20. Shanmugasegaram S, Perez-Terzic C, Jiang X, et al. Cardiac rehabilitation services in low- and middle-income countries: A scoping review. *J Cardiovasc Nurs* 2014; 29: 454–463.
21. Oldridge NB, Pakosh MT, Thomas RJ. Cardiac rehabilitation in low- and middle-income countries: A review on cost and cost-effectiveness. *Int Health* 2015; 8: 77–82.
22. Wang W, Ying S, Thompson DR, et al. Health care professionals 'perceptions of hospital-based cardiac rehabilitation in mainland China: an exploratory study. *J Clin Nurs.* 2009; 18(24): 3401–3408.
23. Asia Pacific Cohort Studies Collaboration. The impact of cardiovascular risk factors on the age-related excess risk of coronary heart disease. *Int J Epidemiol* 2017; 35:1025–1033.
24. Chew BH, Mastura I, Shariff-Ghazali S, et al. Determinants of uncontrolled hypertension in adult type 2 diabetes mellitus: an analysis of the Malaysian diabetes registry 2009. *Cardiovasc Diabetol* 2012; 11 (1): 54.
25. Tiffe T, Wagner M, Rücker V, et al. Control of cardiovascular risk factors and its determinants in the general population- findings from the STAAB cohort study. *BMC Cardiovasc Disord* 2017; 17: 1–12.
26. Banta MR, Ma F, Bravata DM, et al. Incidence of and factors associated with achieving target lipid levels in patients with peripheral arterial disease. *J Gen Intern Med* 2006; 21: 711–714.
27. Rich MW, Chyun DA, Skolnick AH, et al. Knowledge gaps in cardiovascular care of the older adult population. *Circulation* 2016; 133 (21): 2103–2122.
28. Yazdanyar A, Newman AB. The Burden of Cardiovascular Disease in the Elderly: Morbidity, Mortality, and Costs. *Clin Geriatr Med* 2009; 25: 563–577.
29. De Smedt D, De Bacquer D, De Sutter J, et al. The gender gap in risk factor control :

Effects of age and education on the control of cardiovascular risk factors in male and female coronary patients. The EUROASPIRE IV study by the European Society of Cardiology. *Int J Cardiol* 2016; 209: 284–290.

30. Dallongevillle J, De Bacquer D, Heidrich J, et al. Gender differences in the implementation of cardiovascular prevention measures after an acute coronary event. *Heart* 2010; 96: 1744–1749.
31. Blomkalns AL, Chen AY, Hochman JS, et al. Gender disparities in the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes: large-scale observations from the CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines) National Quality Improvement Intiative. *J Am Coll Cardiol* 2005; 45 (6): 832–7.
32. Maas AHEM, Van Der Schouw YT, Regitz-Zagrosek V, et al. Red alert for womens heart: The urgent need for more research and knowledge on cardiovascular disease in women. *Eur Heart J* 2011; 32 (11): 1362–1368.
33. van der Leeuw J, van Dieren S, Beulens JWJ, et al. The validation of cardiovascular risk scores for patients with type 2 diabetes mellitus. *Heart* 2014; 101: 222–229.
34. Leon BM, Maddox TM. Diabetes and cardiovascular disease : Epidemiology, biological mechanisms , treatment recommendations and future research. *World J Diabetes* 2015; 6: 1246–1258.
35. Rückert I, Baumert J, Schunk M, et al. Blood Pressure Control Has Improved in People with and without Type 2 Diabetes but Remains Suboptimal : A Longitudinal Study Based on the German DIAB-CORE Consortium. PLoS One. 2015; 10(7) e0133493.
36. Massing MW, Foley KA, Sueta CA, et al. Trends in lipid management among patients with coronary artery disease: Has diabetes received the attention it deserves? *Diabetes Care* 2003; 26: 991–997.
37. Agborsangaya CB, Gee ME, Johnson ST, et al. Determinants of lifestyle behavior in type 2 diabetes : results of the 2011 cross-sectional survey on living with chronic diseases in Canada. *BMC Public Health* 2013; 7: 451.

APPENDIX

Table 1. Cardiovascular Health Index Score (CHIS) stratified by potential determinants

	Percentage of achieved moderate CHIS	Percentage of below moderate CHIS
Region		
Europe	80%	20%
Asia	81%	19%
Middle East	69%	31%
Diagnostic category		
CABG	80%	20%
PCI	79%	21%
SAP	79%	21%
ACS	76%	24%
Age		
75+	80%	20%
65-75	80%	20%
55-65	78%	22.0%
<55	76%	25%
Sex		
Men	80%	20%
Women	74%	26%
Family history		
Yes	79%	21%
No	78%	23%
Cardiac rehabilitation		
Yes	85%	15%
No	76%	24%
Admitted to hospital		
Yes	80%	20%
No	77%	23%
History of diabetes		
Yes	66%	34%
No	87%	13%

Table 2. Missing data in SURF

Variables	No. of missing	Imputation status
Country	0	No imputation
Region	0	No imputation
Age	0	No imputation
Sex	0	No imputation
Diagnostic group	0	No imputation
Smoking status	146	Imputed
Blood pressure	146	Imputed
Physical activity	220	Imputed
Cardiac rehabilitation	702	No imputation
Height	722	Imputed
Weight	560	Imputed
Diabetes	2012	No imputation
Admission to hospital	2116	No imputation
Family history	2135	No imputation
LDL cholesterol	2448	Imputed
HbA1c	7388	Imputed

Table 3. Sensitivity analysis-complete case data: determinants of moderate Cardiovascular Health Index Score (achieving three or more risk factor targets)

	N (%) moderate CHIS	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age group			
75+	1966 (88.8%)	Reference	Reference
65-75	2757 (87.8%)	0.91 (0.76-1.07)	0.88 (0.74-1.04)
55-65	2567 (87.1%)	0.85 (0.72-1.01)	**0.81 (0.68-0.97)**
<55	1497 (85.6%)	**0.75 (0.62-0.90)**	**0.70 (0.63-0.82)**
Gender			
Men	6328 (88.5%)	Reference	Reference
Women	2518 (85.1%)	**0.75 (0.66-0.85)**	**0.72 (0.63-0.82)**
Family history			
Yes	2183 (86.9%)	Reference	Reference
No	4668 (86.4%)	0.96 (0.83-1.10)	0.94 (0.81-1.08)
Cardiac rehabilitation			
No	5664 (85.8%)	Reference	Reference
Yes	2596 (90.9%)	1.65 (1.43-1.91)	1.61 (1.39-1.86)
Admitted to hospital			
Yes	2286 (88.6%)	Reference	Reference
No	4748 (86.9%)	**0.86 (0.74-0.99)**	**0.86 (0.74-0.99)**
History of diabetes			
No	4918 (92.4%)	Reference	Reference
Yes	2246 (80.2%)	**0.33 (0.29-0.38)**	**0.33 (0.29-0.38)**

CHIS: cardiovascular health index score.OR (95% CI): odds ratio (95% confidence interval); significant results are highlighted as **BOLD.** Adjustments included age and gender.

Table 4. Association between cardiac rehabilitation attendance and individual component of Cardiovascular Health Index Score (CHIS)

	Attendance, N (%)	**Non-attendance, N (%)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)***
Non-smoker	85.9%	83.0%	1.25 (1.10-1.42)	1.33 (1.16-1.53)
Adequate exercise	61.6%	49.8%	1.62 (1.47-1.77)	1.58 (1.44-1.73)
Non-obese	29.2%	27.5%	1.12 (1.02-1.25)	1.14 (1.03-1.25)
BP on target	86.0%	83.6%	1.19(1.05-1.35)	1.17(1.03-1.33)
LDL on target	37.5%	25.6%	1.73(1.56-1.92)	1.68 (1.51-1.86)
Glucose/HbA1c on target	82.1%	72.6%	1.74(1.55-1.97)	1.71 (1.51-1.93)

OR: odds ratio; CI: confidence interval

OR (95% CI) presents as attended vs non-attended. Age and gender were adjusted in logistic regression model.

Table 5. Determinants of moderate Cardiovascular Health Index Score (achieving three or more risk factor targets), stratified by diagnostic group

		CABG	**PCI**	**ACS**	**SAP**
Age	75+	Reference	Reference	Reference	Reference
	75-65	0.89 (0.62-1.28)	0.87 (0.68-1.12)	0.88 (0.68-1.13)	1.06 (0.82-1.43)
	65-55	0.95 (0.63-1.42)	0.79 (0.62-1.01)	0.82 (0.64-1.06)	0.86 (0.65-1.14)
	<55	0.58 (0.36-0.93)	0.62 (0.48-0.81)	0.61 (0.47-0.80)	0.62 (0.45-0.86)
Gender	Men	Reference	Reference	Reference	Reference
	Women	0.81 (0.63-1.20)	0.68 (0.79-1.15)	0.72 (0.59-0.88)	1.03 (0.83-1.27)
Family history	Yes	Reference	Reference	Reference	Reference
	No	0.87 (0.63-1.20)	0.96 (0.79-1.15)	1.07 (0.87-1.30)	0.90 (0.71-1.14)
Cardiac rehab	No	Reference	Reference	Reference	Reference
	Yes	1.49 (1.10-2.02)	1.85 (1.51-2.26)	1.89 (1.53-2.32)	1.44 (1.09-1.90)
Admission	Yes	Reference	Reference	Reference	Reference
	No	1.01 (0.73-1.40)	0.81 (0.68-0.97)	0.77 (0.64-0.93)	1.02 (0.80-1.31)
Diabetes	No	Reference	Reference	Reference	Reference
	Yes	0.42 (0.31-0.55)	0.36 (0.30-0.43)	0.46 (0.38-0.55)	0.28 (0.23-0.36)

Odds ratios (95% CI) presented. Age and sex were adjusted in logistic regression models.

Table 6. Cardiovascular risk factor, medical history and medication use, stratified by age group

	Age<55	**Age: 55-65**	**Age: 65-75**	**Age: 75+**
Current smoker	32%	20%	11%	6%
Adequate exercise	44%	40%	46%	59%
Obesity	76%	75%	73%	65%
History of hypertension	62%	73%	79%	80%
History of dyslipidaemia	67%	69%	69%	64%
History of diabetes	28%	34%	39%	36%
Aspirin	89.9%	92.2%	90.7%	87.4%
Statin	81.4%	84.3%	82.7%	75.4%
Beta blocker	72.3%	73.6%	73.2%	66.7%
ACE inhibitor	54.1%	52.1%	50.2%	48.2%
Calcium channel block	17.2%	25.9%	30.5%	32.5%
Diuretics	12.3%	18.9%	26.0%	34.7%
Insulin	8.2%	10.5%	10.6%	9.1%


SURF
SUrvey of Risk Factors

3.3

A global analysis of associations between fine particle air pollution and blood pressure, lipids, and glucose in patients with coronary heart disease

Min Zhao, Gerard Hoek, Maciej Strak, Diederick E. Grobbee,
Ian Graham, Kerstin Klipstein-Grobusch, Ilonca Vaartjes

Submitted

ABSTRACT

Background: Studying the associations between particulate air pollution and cardiovascular risk factors on a global scale is challenging and rarely done. We aimed to determine the associations of long-term exposure to particles smaller than 2.5µm ($PM_{2.5}$) with systolic and diastolic blood pressure (SBP/DBP), lipids (total, low-density, and high-density cholesterol), and glucose using existing data from 10 countries in Europe, Asia, and the Middle-East.

Methods: Cardiovascular risk factor data were obtained from the SUrvey of Risk Factors (SURF) for coronary heart disease (CHD) patients. Annual average $PM_{2.5}$ concentrations were estimated using recent global WHO $PM_{2.5}$ maps combining satellite and surface monitoring data for the location of the 71 participating centers. Associations of $PM_{2.5}$ with risk factors were assessed by mixed-effect generalized estimation equation models adjusted by sex, age, exercise, and smoking. We assessed whether additional adjustment for country affected associations.

Results: 8392 patients (30% women) were included. Globally, an increase of 10 µg/m^3 in $PM_{2.5}$ was significantly associated with decreased BP and increased glucose. No associations were found in lipids. After controlling for country, an increase of 10 µg/m^3 in $PM_{2.5}$ was associated with decreased BP and increased LDL (SBP: -0.45mmHg, 95% CI: -0.85, -0.06; DBP: -0.47mmHg, 95% CI: -0.73, -0.20; LDL: 0.04mmol/L, 95%CI: 0.01, 0.08). The association with glucose attenuated (0.08mmol/L, 95% CI: -0.23, 0.16).

Conclusion: Global associations of $PM_{2.5}$ and cardiovascular risk factors can be determined linking risk factor and geospatial air pollution data but the sensitivity of effect estimates to adjustment for country stress the need for multiple centers per country. After country adjustment, $PM_{2.5}$ was associated with small increases in LDL and small decreases in BP.

Keywords: air pollution, environmental health, cardiovascular disease, risk factors

BACKGROUND

Cardiovascular disease (CVD) remains one of the leading causes of death worldwide, accounting for 18% of total deaths in 2016.[1] Traditionally, evidence based guidelines and daily practice on secondary prevention of CVD have focused on modifiable risk factor management, including both lifestyle and management of physical and laboratory parameters (blood pressure, lipids, and glucose).[2,3] Several recent epidemiological studies have suggested air pollution could also be associated with CVD risks. [4–7] The number of studies investigating the association between $PM_{2.5}$ and modifiable cardiovascular risk factors such as blood pressure (BP), lipids, and glucose is scarce.[8–13] These studies have predominantly been conducted in Western countries with rather low levels of $PM_{2.5}$ concentrations. [8–10] In contrast, low- and middle-income countries, for which have limited data on the association of $PM_{2.5}$ and risk factors, show much higher $PM_{2.5}$ concentrations.[14] Existing evidence on the role of environmental exposure on cardiovascular risk factors may however not be generalizable to these settings since the chemical composition and characteristics of $PM_{2.5}$ may differ significantly from those in Western countries.[14] This, together with a rapid increase of CVD prevalence in many low- and middle-income countries, stresses the importance of a better understanding of global associations of PM with cardiovascular risk factors.

Conducting targeted studies on the association between $PM_{2.5}$ and cardiovascular risk factors on a global scale is challenging, time consuming and costly. We therefore aim to study the potential association between $PM_{2.5}$ and cardiovascular risk factors (BP, total cholesterol<TC>, low-density lipoprotein cholesterol <LDL>, high-density lipoprotein cholesterol<HDL>, and glucose) among patients with established coronary heart disease (CHD) in Europe, Asia, and the Middle East by linking CVD risk factor data to geospatial information on air pollution and explore the potentials and pitfalls of this methodology.

METHODS

Study population and outcomes

We used cardiovascular risk factors from the SUrvey of Risk Factors (SURF). Details of SURF have been reported previously.[15,16] Briefly, the study population consisted of patients aged≥18 years with a clinical diagnosis of CHD (coronary artery bypass surgery<CABG>, percutaneous coronary intervention <PCI>, acute coronary syndromes <ACS> or stable angina) from ten countries in three regions, including Europe (Croatia, Denmark, Ireland,

Italy, Northern Ireland, Romania, Russia), Asia (China and Taiwan), and Middle East (Saudi Arabia). The European population included countries that were infrequently included in air pollution epidemiology studies (Croatia, Romania, and Russia). Patients were recruited from 71 routine cardiology clinics between 2012 and 2013. Data on patient demographics (age, sex, and center location), cardiovascular lifestyle risk factors (smoking status and physical activity), physical and laboratory measurements (body anthropometry, BP, TC, LDL, HDL, and glucose), and medications were collected by trained research staffs using one-page data collection. Physical and laboratory data on BP, lipids, and glucose were measured according to local national guidelines and retrieved directly from medical records for SURF.

Air pollution data

The postal address of each clinic was transformed into geographical coordinates -the latitude, longitude coordinate system (5 digits)-using Google Earth. Residential addresses of the patients were not available. Local collaborators confirmed that 80% to 90% of the patients included in the study had their residence near their hospitals. We assigned only $PM_{2.5}$ concentrations to each center as $PM_{2.5}$ is a regionally varying pollutant with limited small scale spatial variation.[17] We did not use data from other key pollutants such as NO_2 because this component shows large small scale (within 100s meters) spatial variation and the lack of residential addresses is therefore a serious limitation. Furthermore, $PM_{2.5}$ is the main pollutant used in the Global Burden of Disease assessments.[11]

We linked the address of the clinic to a global map of annual average $PM_{2.5}$ concentrations for the year 2014 developed to assess global air pollution health risks by the World Health Organization (http://www.who.int/phe/health_topics/outdoorair/databases/modelled-estimates/en/). The database provides estimates of annual average concentration of PM2.5 at a spatial resolution of 0.1° × 0.1°, which is approximately 11x11km at the equator globally for the year 2014. Data for other years and pollutants were not available. The estimates are based on the recently developed Data Integration Model for Air Quality. [18] The model estimates $PM_{2.5}$ using satellite retrievals of aerosol optical depth, chemical transport models, population estimates, topography and ground measurements from 6003 stations worldwide. A Bayesian hierarchical model is used to integrate these information sources.[18] The major advantage of the model is that estimates are available from a consistent method globally, as opposed to ground measurements which are concentrated in limited regions of the world.

We additionally collected data for European centers from countries that report measurements data to the European Environment Agency using the Airbase database (https://www.eea.europa.eu/data-and-maps/data/airbase-the-european-air-quality-database-7). We first linked $PM_{2.5}$ data from the background monitoring stations in the town itself. If no station was available, we estimated $PM_{2.5}$ from the more frequently measured pollutant PM_{10} if available or used the average of the nearest two background stations if PM_{10} was also not available. We used country-specific ratios from EEA database to convert PM_{10} into $PM_{2.5}$ fractions if available. If not available, we used PM2.5/PM10 = 0.60 from a large European project or a generic $PM_{2.5}/PM_{10}$ ratio of 0.60 from a large European project if no country-specific estimates were available.[17] For a small SURF town, we used regional stations and for a large city urban stations.

For the 17 districts in the city of Beijing we also obtained online $PM_{2.5}$ data from the Beijing Municipal Environmental Protection Bureau for the year 2013. The local European and Beijing data were used in sensitivity analyses. We used 2013 local data, because this coincides with the year of observation for the SURF study. The global map was available for the year 2014 only. Annual average concentrations may vary from year to year due to variations in weather, but the spatial contrasts in air pollution are typically stable from year to year.[19]

Statistical analyses

The associations (95% CI) of cardiovascular risk factors (BP, TC, LDL-cholesterol, HDL-cholesterol, and glucose) with an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ were assessed by mixed-effect generalized estimation equation models. In these analyses, outcomes were nested within center (the random effect). Associations were investigated in fully adjusted models. Adjustment included sex, age, and individual risk factors (exercise <less, moderate, vigorous>, smoking status <current smoker, ex-smoker, never>, and body mass index<BMI>). [20] Education was not included as an adjustment due to high frequency of missing and incomplete data. Additionally, data on other lifestyle risk factors were not available. We further assessed whether additional adjustment for country affected associations with $PM_{2.5}$. Adjustment for country was performed to allow for differences in the measurements of our outcomes and to adjust for differences in covariates for which we did not have individual information. We consider the model with additional adjustment for country as our main model, although adjustment for country may lead to conservative estimates as it leads to reducing the exploited exposure contrast.

Imputed data were analyzed in the primary analysis. There were less than 4% missing data for all variables, except the lipid and glucose measurements with 10-13% missings (appendix table 1). Ten datasets were imputed for missing data with multivariate imputation by chained equations (MICE package in R). [21] Briefly, MICE predicts missing data by iteratively optimizing a series of regression models using other potentially predictive variables such as basic demographics and geographic area. The continuous variables including height, weight, blood pressure, TC, LDL, HDL, and glucose were imputed by predictive mean matching and the categorical data including smoking status and physical activity were imputed with logistic regression.

Because of uncertainty of the shape of the concentration response function at high concentrations, we performed sensitivity analyses excluding the two countries with the highest $PM_{2.5}$ levels (China and Saudi Arabia). We further analyzed associations of $PM_{2.5}$ retrieved from the Airbase for European countries and the database from the Beijing Municipal Environmental Protection Bureau for China with the same statistical strategy.

Statistical analyses were performed by using 'mice' [21] and 'geepack' packages [22] in R. All tests were two tailed with statistical significance assumed at the 0.05 level.

RESULTS

Baseline characteristics

A total of 8392 SURF patients were included. The mean age of all patients was 64.9 years; 29.6% were women; 16% reported current smoking (Table 1). The average systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, LDL, HDL, and glucose were 131.1mmHg, 75.8mmHg, 4.2mmol/L, 2.4mmol/L, 1.1mmol/L, and 7.5mmol/L, respectively (table 1). The average $PM_{2.5}$ exposure level from WHO database was 38.1 **µg/m**^{3}, ranging from 10.1 **µg/m**^{3} in Ireland to 92.7 **µg/m**^{3} in Saudi Arabia. The $PM_{2.5}$ concentrations derived directly from routine surface monitoring by the Airbase among European countries were similar; whereas, the $PM_{2.5}$ level from routine monitoring by the Chinese government was higher than the estimates from WHO ($PM_{2.5}$ WHO 67.4 **µg/m**^{3} VS $PM_{2.5}$ local 86.3 µg/m^3). Appendix Figure 1A illustrates the large variation of individual outcome variables, especially within countries. Potential systematic differences between countries are evident as well. For examples, relatively high TC and LDL were noticed in China, Croatia, Romania, Russia, and Taiwan.

Table 1. Description of patient characteristics, cardiovascular risk factors, and air pollutants.

	Overall	Europe	Croatia	Denmark	Ireland	Italy	NI	Russia	Romania	KSA	Taiwan	Beijing
No.	8392	5001	1223	300	1716	771	159	463	369	1509	732	1150
No. of Centre	71	51	8	1	11	14	2	8	7	4	4	12
Age, years	64.9±11.2	64.9±10.7	65.2±10.8	65.5±11.6	63.6±10.4	68.2±10.1	63.9±11.0	65.1±10.0	62.6±11.8	62.2±12.1	67.0±13.0	66.7±9.5
Women,%	29.6	26.8	30.8	28.0	23.0	21.5	20.8	38.4	28.5	26.4	30.7	45.3
$PM_{2.5}$ WHO	38.1±34.5	15.8±5.7	20.7±2.6	11.2*	10.1±0.27	22.6±7.4	10.6±0.6	16.7±4.4	20.5±3.1	92.7±31.6	34.1±3.9	67.4±14.7
$PM_{2.5}$ Local	NA	15.0±5.9	19.6±4.1	10.6*	10.5±0.5	20.3±7.2	10.2±1.0	NA	16.4±3.4	NA	NA	86.3±12.6
Smoker, %	16.1	17.9	20.5	23.2	14.6	14.6	20.0	25.5	17.3	10.3	20.0	12.3
Exercise, %	54.2	57.2	55.0	25.3	69.2	46.0	44.1	62.4	53.4	45	48.8	56.4
BMI, kg/m^2	28.1±34.5	28.6±4.7	28.7±4.2	28.3±4.8	29.0±5.0	26.9±4.0	30.7±5.5	29.5±5.1	28.5±4.5	30.3±6.0	28.0±4.0	25.0±2.9
SBP, mmHg	131.1±18.4	132.1±19.3	133±20.2	131±19.4	134.2±18.5	128.1±18.9	121.8±15.5	140.0±14.5	136.5±23.4	128.1±17.0	131.5±19.4	129.9±13.2
DBP, mmHg	75.8±10.9	76.7±10.7	79.9±11.6	76.0±10.4	74.3±10.0	75.4±9.3	71.3±8.1	79.9±9.1	79.9±12.7	71.3±10.3	75.8±12.7	77.5±8.8
TC, mmol/L	4.2±1.5	4.3±1.7	4.7±1.7	4.1±0.9	4.0±1.0	4.1±2.2	3.9±0.8	3.9±1.8	4.9±2.7	3.8±1.0	4.3±1.0	4.4±1.0
LDL, mmol/L	2.4±1.1	2.4±1.2	2.8±1.3	2.1±0.8	2.1±0.8	2.0±1.0	1.9±0.6	2.7±1.3	3.5±2.0	2.1±0.8	2.7±0.9	2.8±0.9
HDL, mmol/L	1.1±0.4	1.2±0.4	1.1±0.5	1.2±0.4	1.2±0.4	1.1±0.4	1.2±0.4	1.1±0.4	1.1±0.6	0.9±0.3	1.2±0.4	1.2±0.4
Glucose,mmol/L	7.5±1.5	6.1±2.1	6.7±2.6	6.4±2.4	5.8±1.4	6.1±1.8	6.4±2.6	5.3±1.4	6.3±2.7	7.8±3.6	6.5±2.5	6.2±1.6

EU: Europe; NI: Northern Ireland; KSA: Saudi Arabia; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; NA: not applicable. 'Smoker' was recorded as current smoker; 'Exercise' was recorded as adequate physical activities.

Numeric variables are mean± standard deviation and categorical variables are percentage. Units are **$\mu g/m^3$** for $PM_{2.5.}$

*Only one centre from Denmark participated in SURF so standard deviation could not be provided.

Associations between $PM_{2.5}$ and cardiovascular risk factors

Appendix Figure 1B shows the crude association between $PM_{2.5}$ and outcomes (BP, lipids, and glucose), including weak associations if any.

Globally, a 0.26mmHg decrease in SBP per 10 **µg/m**^{3} increase in $PM_{2.5}$ was observed (figure 1). After controlling for country as an additional confounder, the observed negative association with SBP was slightly stronger but with wider confidence intervals (-0.45mmHg; 95% CI: -0.85, -0.06). There were no statistically significant associations with SBP when the analysis was restricted to the European centers (-1.32mmHg; 95%CI: -6.73, 4.08).

Similar results were found for DBP: an increase of 10 **µg/m**^{3} in $PM_{2.5}$ was associated with decreased DBP (-0.36mmHg; 95% CI: 0.61, -0.10) and the association tended to be stronger (-0.47mmHg; -0.73, -0.20) after country adjustment on a global scale. On European level, a similar association between $PM_{2.5}$ and DBP was observed which became non-significant after country adjustment.

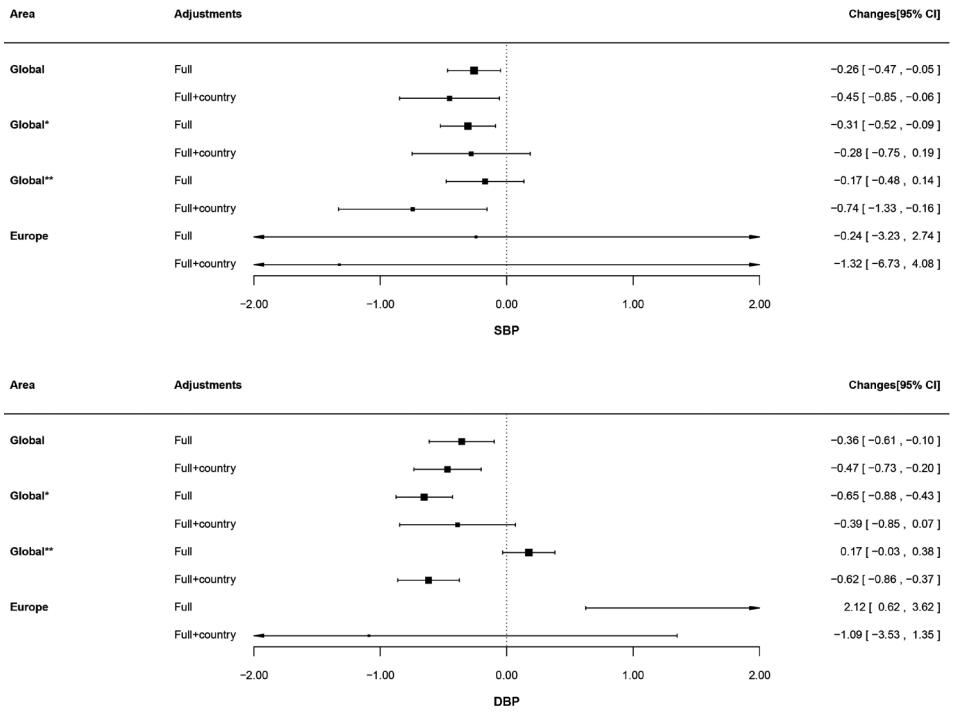
Figure 2 shows the association between $PM_{2.5}$ and lipid levels. Associations of $PM_{2.5}$ with all lipid levels (TC, LDL, and HDL) were not statistically significant on a global scale. After controlling for country non-significant associations remained for TC and HDL; while, an increase of 10 µg/m^3 in $PM_{2.5}$ was positively associated with an increased LDL level (0.04mmol/L, 95%CI: 0.01, 0.08). Weak positive associations of TC and LDL were observed among European participants (TC: 0.32mmol/L; 95% 0.01, 0.62; LDL: 0.30mmol/L, 95%CI: 0.03, 0.58), which disappeared after adjustment for country. There was no significant association for HDL among European patients with or without adjustment for country.

Globally, an increase of 10 µg/m^3 $PM_{2.5}$ was associated with elevated glucose level with 0.10mmol/L (95% CI: 0.03 to 0.16). For Europe the increase in glucose was 0.30mmol/L (95% CI: 0.06 to 0.53) (figure 3). These associations, however, disappeared when we additionally adjusted with country.

Sensitivity analyses

Separate analyses with exclusion of China and Saudi Arabia (called as 'global*' and 'global**' in figure 1-3) and with local $PM_{2.5}$ exposure data (appendix table 2) did not alter our main findings on association between $PM_{2.5}$ and risk factors (BP, TC, LDL, HDL, and glucose).

Figure 1. Changes (95% CI) in blood pressure increase in $PM_{2.5}$ derived from World Health Organization.



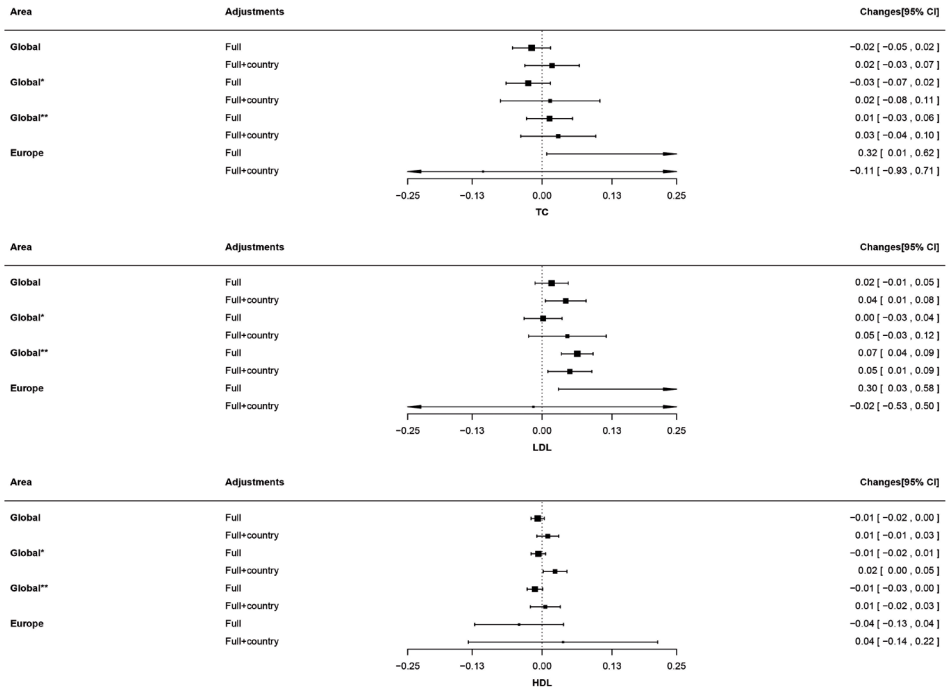
SBP: systolic blood pressure; DBP: diastolic blood pressure

All analyses were applied with generalized estimating equation model with centre clustered. 'Full' adjustment was sex, age, and risk factors (exercise, smoking status, and body mass index). 'Full+country' was sex, age, risk factors (exercise, smoking status, and body mass index), and country. Results are presented as changes in mmHg (95% CI).

'Global*' presented results are based on all participating countries except China;

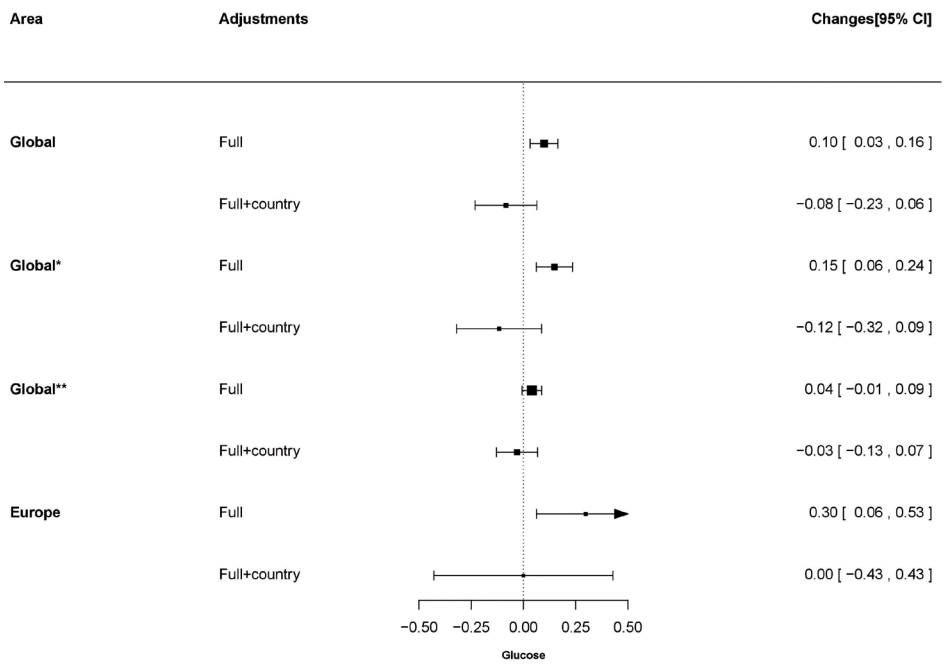
'Global**' presented results are based on all participating countries except Saudi Arabia.

Figure 2. Changes (95% CI) in lipids (Total cholesterol, LDL-cholesterol, and HDL-cholesterol) increase in $PM_{2.5}$ derived from World Health Organization.



TC: total cholesterol; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol
All analyses were applied with generalized estimating equation model with centre clustered. 'Full' adjustment was sex, age, and risk factors (exercise, smoking status, and body mass index). 'Full+country' was sex, age, risk factors (exercise, smoking status, and body mass index), and country. Results presented as changes in mmol/L (95% CI). 'Global*' presented results are based on all participating countries except China; 'Global**' presented results are based on all participating countries except Saudi Arabia.

Figure 3. Changes (95% CI) in glucose increase in $PM_{2.5}$ derived from World Health Organization.



All analyses were applied with generalized estimating equation model with centre clustered. 'Full' adjustment was sex, age, and risk factors (exercise, smoking status, and body mass index). 'Full+country' was sex, age, risk factors (exercise, smoking status, and body mass index), and country. Results are presented as changes in mmol/L (95% CI).

'Global*' presented results are based on all participating countries except China;

'Global**' presented results are based on all participating countries except Saudi Arabia.

DISCUSSION

The long-term $PM_{2.5}$ exposure from a consistent global exposure model was linked to individual data on routinely measured CVD risk factors from a large international study of 8,392 CHD patients from 71 centers among 10 countries in Europe, Asia, and the Middle East to explore potential association between air pollution and cardiovascular risk factors. The analyses demonstrate the feasibility of linking these distributed data but also point at challenges in their interpretation. Notably, taking country into account in the analyses materially affected the observed associations. While the adjustment may account for unmeasured confounding the close association between air pollution and country could also lead to over adjustment.

Some additional comments need to be made on the methods and data used in this study. Unlike most epidemiological study, risk factor measurements were not standardized in SURF and might vary according to local methods. Also, although the key potential confounders like smoking status, physical activity and BMI were adjusted accordingly, several other potential confounding factors including socio-economic status, health care and access to appropriate medical services, could not fully adjusted for due to data availability. Additionally, cardiovascular medication use for CHD patients to control laboratory levels may vary from country to country due to differences in availability and affordability of these medications, although all CHD patients are recommended to be on cardiovascular medications irrespective of geographical areas. [23]

We observed an inverse association of $PM_{2.5}$ with BP globally and among European participants after adjustment for country, which is in contrast with several previous studies that found positive associations between long-term exposures to $PM_{2.5}$ and elevated blood pressure. [4,9,24,25] Other studies found no association between air pollution and BP. [10] For instance, findings from a national population-based study among 1024 elder Taiwanese participants suggested that an interquartile increase in $PM_{2.5}$ (48 μg/m^3) was associated with 32.1mmHg (95% CI 21.6-42.6) and 31.3mmHg (95%CI 25.4-37.1) increases in SBP and DBP, respectively, after controlling age, sex, BMI, smoking status, and drinking habitats.[26] However, our study was conducted in CHD patients who all received cardiovascular medications to control potential risk factors. Consequently, current study measured the potential impact of air pollution beyond medical treatment. A comprehensive meta-analysis among 113,926 patients from 15 European population-based cohort studies, ESCAPE, demonstrated inconsistent relationships between long-

term exposure to modeled air pollutants including $PM_{2.5}$ and BP in each cohort and the pooled results remained non-significance.[10] For short-term exposure to $PM_{2.5}$, diverse results with both positive and negative associations have been reported in the literatures. [9,25,27] Differences in the study design and methodology, characteristics of study populations, and exposure duration in different geographic research areas may contribute to the discrepancies in these findings. Studies on mechanisms have suggested that exposure to $PM_{2.5}$ could instigate acute autonomic imbalance and then lead BP increases. [4,5,25,28,29]

A large cross-sectional study with 39,863 health participants in Denmark demonstrated that the interquartile range (11.3 $\mu g/m^3$) of $PM_{2.5}$ was associated with a high level of TC (0.78mg/dl; 95% CI: 0.22-1.34).[30] An animal study also indicated that mice exposed to $PM_{2.5}$ had significantly higher levels of TC and LDL than those with filtered air.[31] But it should be noted that effect estimates are typically small and may have little clinical implications. Some previous evidence suggested that $PM_{2.5}$ may affect lipid levels but the quantity and quality of these studies is still limited and results are not fully consistent.[26,30,31] Some studies have suggested systemic inflammation and oxidative stress inducted by $PM_{2.5}$ could affect to lipoprotein function, leading to lipid metabolism dysfunction. [31,32]

We observed direct associations of $PM_{2.5}$ with glucose in both global and European analyses, although these associations attenuated after country adjustment. These findings are in line with several previous studies. [33,34] A cross-sectional study based on Chinese populations observed that both elevated glucose levels and increased type II diabetes prevalence was significantly associated with increased $PM_{2.5}$.[35] A review based of 21 published studies associating a high concentration of $PM_{2.5}$ was with insulin resistance and increased rates of type II diabetes.[33] Mechanisms suggested to link glucose metabolism to $PM_{2.5}$ with endothelial dysfunction, endoplasmic reticulum stress, insulin signaling abnormalities, and systematic inflammation. [5,12,34,35]

CONCLUSIONS

The current study has demonstrated the feasibility of linking global environmental data to individual patient data. The approach exemplifies the opportunity to assess the impact of the environment on cardiovascular risk factors across large geographic areas including low- and middle-income countries with limited resources. We noted that effect estimates were highly sensitive to adjustment for country. We found an increase of $PM_{2.5}$

was significantly associated with decreased BP and increased glucose in a global scale. After country adjustment, $PM_{2.5}$ levels are marginally associated with increases in LDL cholesterol and decreases in BP. This will likely be observed in future global analyses of routine data collected with non-standardized diagnostic methods and limited covariate data. The implication is that similar global studies should aim at multiple centers per country with sufficient within country exposure contrast to balance any effects of over adjustment.

LIST OF ABBREVIATIONS

SURF: SUrvey of Risk Factor; CVD: cardiovascular disease; CHD: coronary heart disease; $PM_{2.5}$: fine particulate matter; CABG: coronary artery bypass graft; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; BMI: body mass index; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; LDL: low density lipoprotein; HDL: high density lipoprotein.

ACKNOWLEDGEMENT

We gratefully acknowledge the support from Jie Chen from Utrecht University for her support with regard to air pollutant data collection from the Chinese government.

FUNDING

MZ is supported by a grant from the Netherlands Organization for Scientific Research (NWO; grant number: 0.22.005.021). NWO was not involved in the design, execution, analysis, or writing up of the study. IV is supported by a grant from the Dutch Heart Foundation (grant DHF project 'Facts and Figures').

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the SURF project, which have been published previously. The references have been included in the current study.

AUTHORS' CONTRIBUTIONS

MZ, GH, IG, DEG, KK, and IV conceived and designed the study. MZ, GH, and IV analysed

and interpreted the data. MZ drafted the manuscript and all authors contributed to critical revision of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

No applicable

CONSENT OF PUBLICATION

Not applicable

COMPETING INTERESTS

None

REFERENCES

1. Vos T, Abajobir AA, Abbafati C, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1211–1259.
2. Perk J, De Backer G, Gohlke H, et al. European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012). *Int J Behav Med* 201; 19: 403–488.
3. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016; 252: 207–274.
4. Cosselman KE, Navas-acien A, Kaufman JD. Environmental factors in cardiovascular disease. *Nat Rev Cardiol* 2015; 12: 627–642.
5. Newby DE, Mannucci PM, Tell GS, et al. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J* 2015; 36: 83–93.
6. Arden Pope C, Burnett RT, Turner MC, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: Shape of the exposure-response relationships. *Environ Health Perspect* 2011; 119: 1616–1621.
7. Cesaroni G, Forastiere F, Stafoggia M, et al. Long term exposure to ambient air pollution and incidence of acute coronary events: prospective cohort study and meta-analysis in 11 European cohorts from the ESCAPE project. *BMJ* 2014; 348: 7412.
8. Shanley RP, Hayes RB, Cromar KR, et al. Particulate Air Pollution and Clinical Cardiovascular Disease Risk Factors. *Epidemiology* 2015; 2: 1.
9. Brook RD, Rajagopalan S, Pope A, et al. Particulate matter air pollution and cardiovascular disease. *Circulation* 2010; 121: 2331–2378.
10. Fuks K, Weinmayr G, Foraster M, et al. Arterial Blood Pressure and Long-Term Exposure to Traffic-Related Air Pollution: An Analysis in the European Study of Cohorts for Air Pollution Effects (ESCAPE). *Environ Health Perspect* 2014; 896: 896–906.
11. Gakidou E, Afshin A, Abajobir AA, et al. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; 390: 1345–1422.
12. Strak M, Janssen N, Beelen R, et al. Long-term exposure to particulate matter, NO2and the oxidative potential of particulates and diabetes prevalence in a large national health survey. *Environ Int* 2017; 108: 228–236.
13. Eze IC, Hemkens LG, Bucher HC, et al. Association between ambient air pollution and diabetes mellitus in Europe and North America: systematic review and meta-

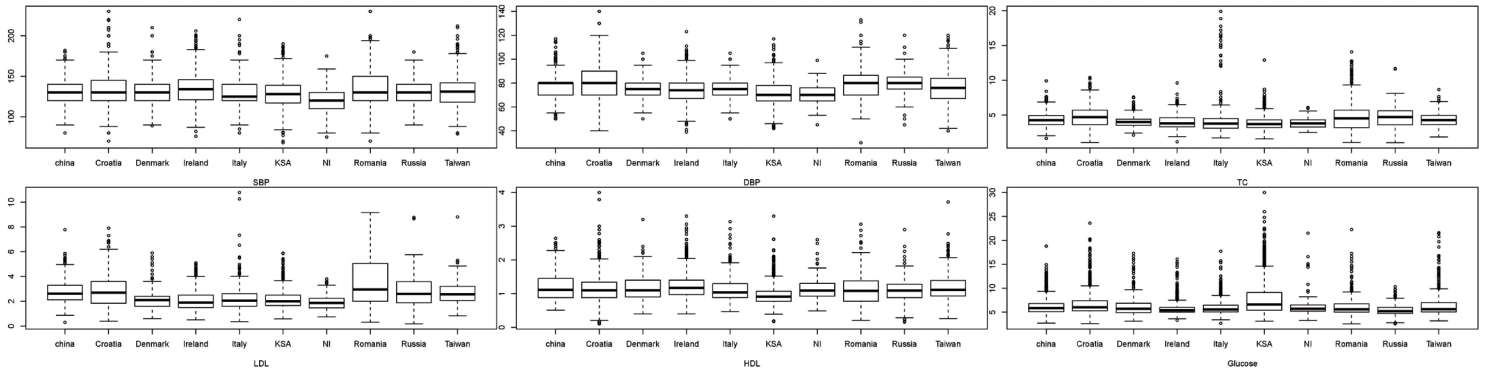
analysis. *Env Heal Perspect* 2015; 123: 381–389.
14. Indicators WD. Http://data.worldbank.org/data-catalog/world-development-indicators. *The World Bank*, http://data.worldbank.org/data-catalog/world-development-indicators.
15. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
16. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
17. Eefrens M, Tsai M, Ampe C, et al. Sptial variation of PM2.5, PM10, PM2.5 absorbance and PM coarse concentrations between and within 20 European study areas and the relationship with NO2: Results from the ESCAPE project. *Atmos Env* 2012; 62: 303–317.
18. Shaddick G, Thomas M, Green A, et al. Data integration model for air quality: A hierarchical approach to the global estimation of exposures to ambient air pollution. *J R Stat Soc Ser C Appl Stat* 2018; 67:231-253.
19. Beelen R, Stafoggia M, Raaschou-nielsen O, et al. Long-term Exposure to Air Pollution and Cardiovascular Mortality An Analysis of 22 European Cohorts. *Epidemiology* 2014; 25: 368–378.
20. Danaei G. Metabolic mediators of the effects of body-mass index, overweight, and obesity on coronary heart disease and stroke: A pooled analysis of 97 prospective cohorts with 1·8 million participants. *Lancet* 2014; 383: 970–983.
21. Groothuis-oudshoorn K. MICE : Multivariate Imputation by Chained. *J Stat Softw* 2011; 45(3):1-67.
22. Halekoh U, Hojsgaard S. The R package geepack for generalized estimating equations. *Jounral Stat Softw* 2006; 15.
23. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet* 2015; 6736: 1–9.
24. Chen H, Burnett R, Kwong J, et al. Spatial associations between ambient fine particulate matter and incident hypertension. *Circulation* 2014; 129: 562–569.
25. Brook RD, Urch B, Dvonch JT, et al. Insights into the mechanisms and mediators of the effects of air pollution exposure on blood pressure and vascular function in healthy humans. *Hypertension* 2009; 54: 659–667.
26. Chuang K, Yan Y, Chiu S, et al. Long-term air pollution exposure and risk factors for cardiovascular diseases among the elderly in Taiwan. *Occup Env Med* 2011; 68: 64–68.
27. Brook R, Rajagopalan S. Particulate matter, air pollution, and blood pressure. *J Am Soc Hypertens* 2009; 3: 332–350.
28. Chahine T, Baccarelli A, Litonjua A, et al. Particulate air pollution, oxidative stress genes, and heart rate variability in an elderly cohorts. *Env Heal Perspect* 2007; 115: 1617–1622.

29. Widdicombe J, Lee L-Y. Airway reflexes, autonomic function, and cardiovascular responses. *Env Heal Perspect* 2001; 109(suppl): 579–584.
30. Sørensen M, Hjortebjerg D, Eriksen KT, et al. Exposure to long-term air pollution and road traffic noise in relation to cholesterol: A cross-sectional study. *Environ Int* 2015; 85: 238–243.
31. Chen T, Jia G, Wei Y, et al. Beijing ambient particle exposure accelerates atherosclerosis in ApoE knockout mice. *Toxicol Lett* 2013; 223: 146–153.
32. Bai Y, Sun Q. Fine particulate matter air pollution and atherosclerosis: Mechanistic insights. *Biochim Biophys Acta* 2016; 1860:2863–2868.
33. Meo SA, Memon AN, Sheikh SA, et al. Effect of environmental air pollution on type 2 diabetes mellitus. *Eur Rev Med parmacology Sci* 2015; 19: 123–128.
34. Rajagopalan S, Brook RD. Air Pollution and Type 2 Diabetes Mechanistic Insights. *Diabetes* 2012; 61: 3037–3045.
35. Liu C, Yang C, Zhao Y, et al. Associations between long-term exposure to ambient particulate air pollution and type 2 diabetes prevalence, blood glucose and glycosylated hemoglobin levels in China. *Environ Int* 2016; 93: 416–421.

APPENDIX

Figure 1 Descriptive analysis

1A. Boxplot for individual cardiovascular risk factor by country;



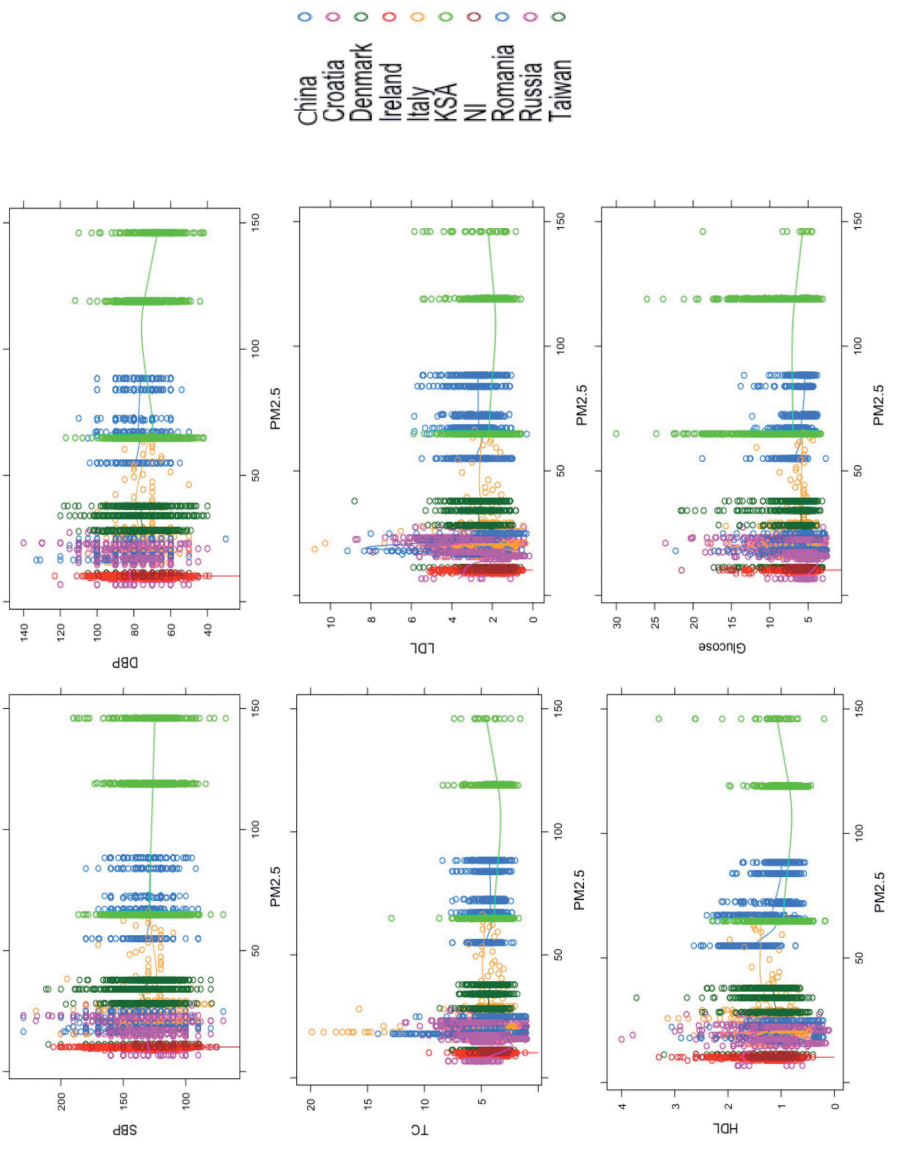


Figure 1B. Panel-plot for individual cardiovascular risk factor by country.

Table 1.Missing data in SURF

Variables	No. of Missing	Imputed in analysis
Country	0	No
Centre	0	No
Age	0	No
Sex	0	No
PM2.5	0	No
Smoking	84	Yes
Systolic blood pressure (SBP)	93	Yes
Diastolic blood pressure (DBP)	95	Yes
Exercise	127	Yes
Weight	227	Yes
Height	357	Yes
Total cholesterol (TC)	760	Yes
Low-density lipoprotein (LDL)	1254	Yes
High-density lipoprotein (HDL)	1139	Yes
Glucose	1093	Yes

Table 2. Associations between CVD risk factors and PM2.5 retrieved from WHO, airbase for European countries and local government database for China

		SBP (mmHg)	DBP (mmHg)	TC (mmol/L)	LDL (mmol/L)	HDL (mmol/L)	Glucose(mmol/L)
Croatia	WHO	5.4 (-2.0, 12.8)	-0.14 (-1.0, 0.7)	0.5 (-0.1, 1.0)	0.6 (0.3, 0.9)	0.08 (-0.2, 0.3)	-0.1 (-1.0, 0.7)
	Airbase	3.6 (-0.5, 7.7)	1.5 (-1.0, 4.0)	-0.02 (-0.1, 0.07)	0.1 (-0.4, 0.7)	-0.2 (-0.5, 0.04)	0.1 (-0.6, 0.8)
Ireland	WHO	59.5 (14.2, 104.8)	-3.1 (-10.5, 4.4)	-2.2 (-5.6, 1.2)	-2.0 (-4.3, 0.3)	0.3 (-0.1, 0.8)	-3.1 (-10.5, 4.4)
	Airbase	24.8 (6.6, 43.0)	3.3 (-6.0, 12.6)	-0.03 (-1.3, 0.7)	-0.07 (-1.4, 0.05)	0.07 (-0.1, 0.3)	-3.7 (-5.6, -1.9)
Italy	WHO	-4.9 (-14.4, 4.6)	0.15 (-0.3, 0.6)	-0.5 (-1.9, 0.9)	-0.1 (-0.5, 0.2)	0.1 (-0.4, 0.3)	0.2 (-0.3, 0.6)
	Airbase	-2.7 (-8.1, 2.7)	-0.7 (-3.5, 2.1)	-0.3 (-0.9, 0.3)	-0.05 (-0.3, 0.2)	0.05 (-0.07, 0.2)	0.3 (0.02, 0.5)
Romania	WHO	-6.1 (-30.9, 18.7)	-0.6 (-2.5, 1.2)	-2.0 (-5.8, 1.8)	-1.4 (-4.0, 1.2)	-0.3 (-1.1, 0.6)	-0.6 (-2.5, 1.2)
	Airbase	5.6 (-6.0, 17.1)	-0.2 (-7.5, 4.2)	-3.2 (-8.3, 1.8)	-1.9 (-5.3, 1.5)	-0.7 (-1.7, 0.2)	-1.7 (-3.8, 0.4)
Europe	WHO	-0.2 (-3.2, 2.7)	2.1 (0.6, 3.6)	0.3 (0.009, 0.6)	0.3 (0.03, 0.6)	-0.04 (-0.1, 0.04)	0.3 (0.06, 0.5)
	Airbase	-1.0 (-4.2, 2.2)	1.4 (-0.2, 3.0)	-0.07 (-0.4, 0.3)	0.05 (-0.2, 0.3)	-0.08 (-0.2, 0.02)	0.2 (-0.09, 0.5)
China	WHO	-0.3 (-1.0, 0.4)	-0.7 (-1.2, -0.3)	-0.2 (-0.1, 0.7)	0.01 (-0.04, 0.06)	-0.1 (-0.2, -0.06)	-0.3 (-0.4, -0.2)
	Local	-0.04 (-1.4,0.5)	-0.7(-1.3, -0.09)	-0.05(-0.2,0.05)	-0.03(-0.1,0.05)	-0.1(-0.2, -0.002)	-0.3 (-0.5, -0.09)

SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol.

Associations were presented as changes (95% confidence interval) with 10 **μg/m**^{3} increased in PM2.5 from model with gender, age, smoking status (current smoker, ex-smoker, and never smoke), physical activity (Less than recommended exercise, moderate exercise, and more than recommended exercise), and body mass index (under weight, normal weight, overweight, and obese) adjusted.


SURF
SUrvey of Risk Factors

4

Guideline-recommended cardiovascular medication use for secondary prevention on coronary heart disease


SURF
SUrvey of Risk Factors

4.1

Cardioprotective medication use in secondary prevention after myocardial infarction in China: a systematic review and meta-analysis

Min Zhao, Kerstin Klipstein-Grobusch, Xin Wang, Johannes B. Reitsma, Dong Zhao, Diederick E. Grobbee, Ian Graham, Ilonca Vaartjes

PLoS One. 2017; 12(4): e0175947.

ABSTRACT

Background: Myocardial Infarction (MI) has become a major cause of morbidity and mortality in China, but little is known about the use of guideline-recommended cardioprotective medications after MI events. This systematic review and meta-analysis aims to summarize cardioprotective medication use and to assess factors in associated with the trends in cardioprotective medications.

Method: A systematic search was conducted in four databases (Pubmed, Embase, CENTRAL, and CNKI) to obtain studies published between 1995 and 2015, reporting on the use of cardioprotective medications in China. Risk of bias of individual studies was appraised and selected studies were pooled for estimation of cardioprotective medication use. Prevalence of cardioprotective medication use for 1995 and 2015 was estimated by random effects meta-regression model.

Results: From 13,940 identified publications, 35 studies, comprising 28,000 patients, were included. The pooled prevalence for aspirin, beta-blockers, statins, ACE-Inhibitors, ACE-Inhibitor/ARBs and nitrates was 92% [95% confidence interval (CI): 0.89-0.95], 63% (95% CI: 0.57-0.69), 72% (95% CI: 0.60-0.82), 49% (95% CI: 0.41-0.57), 59% (95% CI: 0.48-0.69) and 79% (95% CI: 0.74-0.91), respectively. A significant increase in beta-blocker and statin use and a decrease of nitrate use was observed over time. The estimated prevalence of beta-blockers, statins, and nitrates was 78%, 91.1%, and 59.3% in 2015, compared to 32%, 17% and 96% in 1995, respectively.

Conclusion: Cardioprotective medication use after MI is far from optimal in Chinese patients, even though the prevalence of use increased over the period 1995-2015. With a rapidly increasing number of MI patients in China, a comprehensive strategy on secondary prevention is warranted.

Systematic review registration: PROSPERO (CRD42015025246)

Key words: China, myocardial infarction, prevalence, trend, medications, meta-analysis

INTRODUCTION

Rapidly increasing per capita income and an aging population have led to profound demographic and epidemiologic changes in China.[1–3] Cardiovascular disease (CVD) has become the leading non-communicable disease over the past two decades.[1] The number of ischaemic heart disease (IHD) events in China significantly increased from 0.75 million in 1990 to 1.4 million in 2013[2]; Currently, one million deaths are caused by myocardial infarction (MI) annually.[1,3]

Reflecting this, healthcare system reforms, improved medical insurance coverage and evidence-based guideline recommendations have been recently introduced by the Chinese government. This has led to some remarkable strides in MI management with better quality of care and more effective medical therapy.[1,3–5] Widespread and long-term medical therapy by using cardioprotective medications for secondary prevention after MI events have been highly recommended in the Chinese prevention guideline to reduce mortality rates from MI and recurrent acute cardiac events.[6] However, the use of guideline-recommended cardioprotective medication has been rarely assessed. There is little solid evidence about the current use and changes of cardioprotective medications after a MI event, especially for patients after hospital admission.[3]

Therefore, we aimed to perform a comprehensive review and meta-analysis of cardioprotective medication use in Chinese MI patients after their hospital admissions in China. The specific aims of our study were: i) to summarize the use of five specific classes of cardioprotective medication use in patients with previous MI in China from 1995 to 2015; and ii) to identify whether specific factors, such as study characteristics are associated with the use of cardioprotective medications.

METHODS

Search strategy and eligibility criteria

This review was written in accordance with the guidelines issued by PRISMA for reporting systematic reviews and meta-analysis (S1 Checklist)[7,8] and registered in the registry for systematic reviews PROSPERO (registration number: CRD42015025246).[9] A systematic literature search was conducted in the following databases: Pubmed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and China National Knowledge Infrastructure (CNKI). CNKI is an electronic platform created to integrate significant

Chinese knowledge-based information resources.

A combined text and subject heading terms (Mesh and EMTree) related to cardioprotective medication use (aspirin, beta-blockers, ACE-inhibitors <ACE-I>, statins, and nitrates) among adults in China, published between January 1, 1995 and August 10, 2015 was used (S1 Table). Articles were excluded from the review if: i) published in a language other than English or Chinese; ii) focused on primary care of MI only; iii) reported medication use for CVD but not specified for MI; iv) focused on cardioprotective medication use before or during hospital admission; v) performed outside of China or conducted in non-Chinese populations; vi) animal studies, study protocols, bimolecular studies, case reports, non-peer reviewed published reports of proceedings, and reviews.

In the current review, studies reporting broadly on Acute Coronary Syndromes (ACS) were included. Apart from explicit clinical diagnosis, current guidelines and evidence indicate no difference for medical treatment and prevention level for both ACS and MI.[10–12] Furthermore, angiotensin receptor blockers (ARB) are clinical recommended when patients do not tolerate ACE-Is.[6,11,12] Therefore, studies reporting ACE-I/ARB were also included. ACE-I/ARB was considered as an independent medication category and hence analyzed separately.

Selection process

Search results were downloaded into Refwork for Pubmed, EMBASE, and CENTRAL hits and EndnoteX7 for CNKI. Two independent reviewers (MZ and XW) screened all articles by title and abstract for inclusion and exclusion criteria. Duplicate records were automatically removed by reference management software. Any disagreements between the two reviewers on paper selection were discussed by explicit selection rules, and the full-text reviewed if necessary. For eligible articles, the full text of eligible articles were retrieved and assessed by two reviewers (MZ and XW) following processes.

Data extraction

A standardized data extraction form was designed to capture study characteristics, participants' characteristics, and outcome measures. Extracted items included were: sample size, performed geographic area, year of survey, participation rate, mean age, proportion of women, known history (CHD, MI, hypertension, dyslipidaemia, and diabetes), and prevalence of use of cardioprotective medication (aspirin, beta-blockers, statins, ACE-Is, ACE-I/ARB, and nitrates) in each study. If multiple publications were

derived from one study, all unique data were extracted and combined directly into a single data extraction form. If the reported study characteristics differed from publication to publication in the same study, the publication with most explicit participants' characteristics and outcome measures was extracted and others were excluded. When results were published multiple times, the data was used only once. Extraction was done by a single reviewer. Lack of clarity during the extraction process was resolved by consulting the second reviewer (XW).

Quality Assessment

To appraise the risk of bias of individual studies we used a tool developed by Li et al (S2A Table).[13] The tool consists of five items that assess the quality of the study design, study population, participation rate, participants' characteristics, and outcome. Presence of bias was assessed by scoring (low risk=2, moderate risk=1, high risk=0) each of the five items. Studies with a summative score below 6 were excluded from this review (S2A Table).

Data analysis

The prevalence of cardioprotective medication use was defined as the number of MI patients using the medication of interest divided by the total number of MI patients and displayed as proportions. A random-effects model to meta-analyse the logit-transformed proportions to obtain a pooled estimate together with a 95% confidence interval (CI) was used. The model took into account the precision by which this proportion has been estimated in each study using the binomial distribution and incorporating any additional variability beyond chance that exists between studies. Heterogeneity was quantified with the I^2 statistics and the Q test. $P<0.05$ was considered significant.

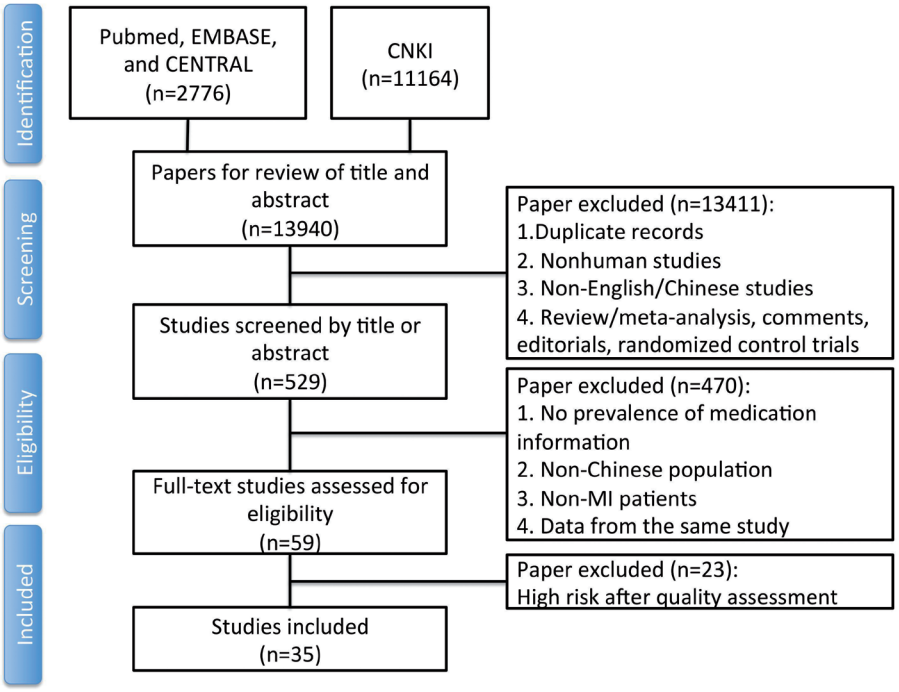
To identifly factors associated with the use of cardioprotective medication, we added several study characteristics as covariates to our random effect meta-regression models. The following characteristics extracted from individual studies were examined independently: year of survey, mean age, proportion of women and geographic area. The meta-regression models, showing statistically significant association between specific study characteristics and cardioprotective medication use, were then used to estimate the prevalence of cardioprotective medication use for 1995 and 2015. All tests were two tailed with statistical significance at 0.05 level. Statistical analyses were performed by using R 'metafor' package.[14]

RESULTS

Study Selection

The initial search resulted in 13,940 potentially relevant articles, of which 13,411 were excluded by screening title/abstract and 490 by full-text review (Fig 1). The main reasons for exclusion included: non-observational studies; non-English/Chinese studies; non-Chinese participants; non-MI participants; no data on the use of cardioprotective medication. Details are provided in the flow chart (Fig 1). After risk of bias assessment, 35 articles were selected, of which three were written in English. Detailed information on the basis assessment for the individual studies is provided in S2B Table.

Fig 1. Flowchart of records screened and included in the systematic review.



Graphical representation of the systematic search. Abbreviations in the flowchart: CENTRAL: Cochrane Register of Controlled Trials; CNKI: China National Knowledge Infrastructure.

Study characteristics

Table 1 summarizes the key characteristics of the included articles and outcomes of interest. Of the 35 studies, 25 included prevalence information on aspirin use,[15–38] 30 on beta-blocker use,[15–21,24–35,37–46] 24 on statin use,[16–21,24–33,37,38,40,42,44,45,47,48] 11 on ACE-I use,[15–17,21,26,39,41–43,49] 18 on ACE-I/ARB use,[17-19,24,27,29,32,35,37,38,40,43,46,48] and 12 on nitrate use.[15,17,19,24,27,32,38–41,43,48]

Table 1. Key characteristics of the 35 selected studies.

Study (year)	Language	Survey Year	Area	Sample size	Mean age	Women	Prevalence					
							Aspirin	BB	Statin	ACE-I	ACE-I /ARB	Nitrate
Liu (1999)[39]	CHN	1997	Nationwide	400	60.9	34.3	NR	44.4	NR	38.5	NR	85.5
Fang (2003)[49]	CHN	2002	North	122	68.0	42.6	NR	NR	NR	47.1	NR	NR
Zhao (2004)[40]	CHN	2002	South	226	66.7	27.9	NR	37.5	49.6	NR	NR	95.6
Wu (2005)[47]	CHN	1999	North	227	61.2	22.0	NR	N/A	40.4	NR	NR	NR
Wang (2005)[15]	CHN	2002	Central	178	63.2	11.8	90.7	27.0	NR	31.5	NR	87.6
OASIS (2005)[41]	CHN	2001	Nationwide	2294	62.8	37.8	NR	67.5	NR	59.1	NR	96.6
Xiang (2006)[16]	CHN	2004	South west	119	68.0	29.4	84.9	35.3	15.1	43.7	NR	NR
Fang (2006)[42]	CHN	2004	North	247	69.0	31.2	NR	40.9	14.6	47.7	NR	NR
Yang (2006)[43]	CHN	2005	Central	174	61.2	24.1	NR	27.6	NR	51.7	NR	86.8
Peng (2008)[17]	CHN	2007	East	143	68.9	22.2	96.9	74.8	76.3	55	NR	NR
Chai (2008)[18]	CHN	2006	North	344	60.1	22.7	99.4	77.3	98.0	NR	76.7	NR
Gui (2008)[19]	CHN	2007	East	209	72.2	19.6	93.6	59.2	49.2	NR	60.3	96.8
Ni (2009)[20]	CHN	2007	East	432	66.5	19.4	94.4	87.7	87.9	NR	NR	NR
Bi (2009)[21]	ENG	2006	Nationwide	2901	64.5	32.7	92.7	70.0	80.4	67.8	NR	NR
Zhou (2010)[22]	CHN	2008	South	220	58.4	36.8	88.5	NR	NR	NR	NR	NR
Wang (2010)[23]	CHN	2009	East	192	57.5	32.8	90.6	NR	NR	NR	NR	NR
Zhao (2010)[24]	CHN	2005	South	522	65.7	27.2	81.9	59.6	57.8	NR	69.3	77.6
Yan (2010)[25]	ENG	2008	North	422	59.2	21.8	79.3	54.3	55.8	NR	35.3	NR
Yao (2011)[26]	CHN	2009	North	200	66.5	38.0	96.5	72.5	84.5	NR	NR	NR
Liu (2011)[27]	CHN	2010	East	206	66.0	30.6	86.6	56.3	69.7	NR	42.3	72.5

Table 1. (continued)

Study (year)	Language	Survey Year	Area	Sample size	Mean age	Women	Prevalence					
							Aspirin	BB	Statin	ACE-I	ACE-I /ARB	Nitrate
Zhou (2011)[44]	CHN	2009	North	723	NA	NA	87.8	68.6	67.3	45.3	NR	NR
Zhang (2011)[28]	CHN	2010	North east	156	64.3	24.7	92.9	67.3	82.1	NR	52.6	NR
Han (2011)[29]	CHN	2009	East	249	66.4	30.9	99.1	93.6	99.1	NR	95.0	NR
Zhang (2012)[45]	CHN	2009	Nationwide	10753	NA	NA	89.2	61.9	59.3	NR	47.2	NR
Xu (2012)[30]	CHN	2010	North	180	69.0	37.2	91.7	66.7	81.1	NR	58.9	NR
Han (2012)[31]	CHN	2011	North	563	NA	42.6	81.6	49.1	56.0	NR	NR	NR
Li (2013)[32]	CHN	2014	East	1319	67.0	24.2	98.2	61.2	92.5	NR	62.2	47.3
Wang (2013)[46]	CHN	2009	Nationwide	221	NA	28.5	NR	53.4	NR	NR	66.5	NR
Yang (2013)[33]	ENG	2010	North	808	60.2	22.2	79.5	65.0	60.5	NR	49.4	NR
Zhang (2014)[34]	CHN	2012	North east	218	NA	26.1	98.6	67.4	NR	NR	65.6	NR
Li (2014)[35]	CHN	2013	North	180	63.7	38.9	92	72.0	93.0	NR	74.0	NR
Yang (2014)[36]	CHN	2013	Central	134	53.7	32.1	65.7	NR	NR	NR	NR	NR
Tian (2014)[37]	CHN	2013	North	490	64.3	34.3	89.8	78.8	72.2	NR	48.2	NR
Xiao (2014)[48]	CHN	2011	North east	110	66.5	40.9	NR	49.1	NR	NR	54.5	66.4
Zhang (2015)[38]	ENG	2008	North	2514	60.4	14.0	77	69.0	28.0	NR	11.0	NR

Women and medication prevalence are presented as percentage (%). Mean age is recorded as years.

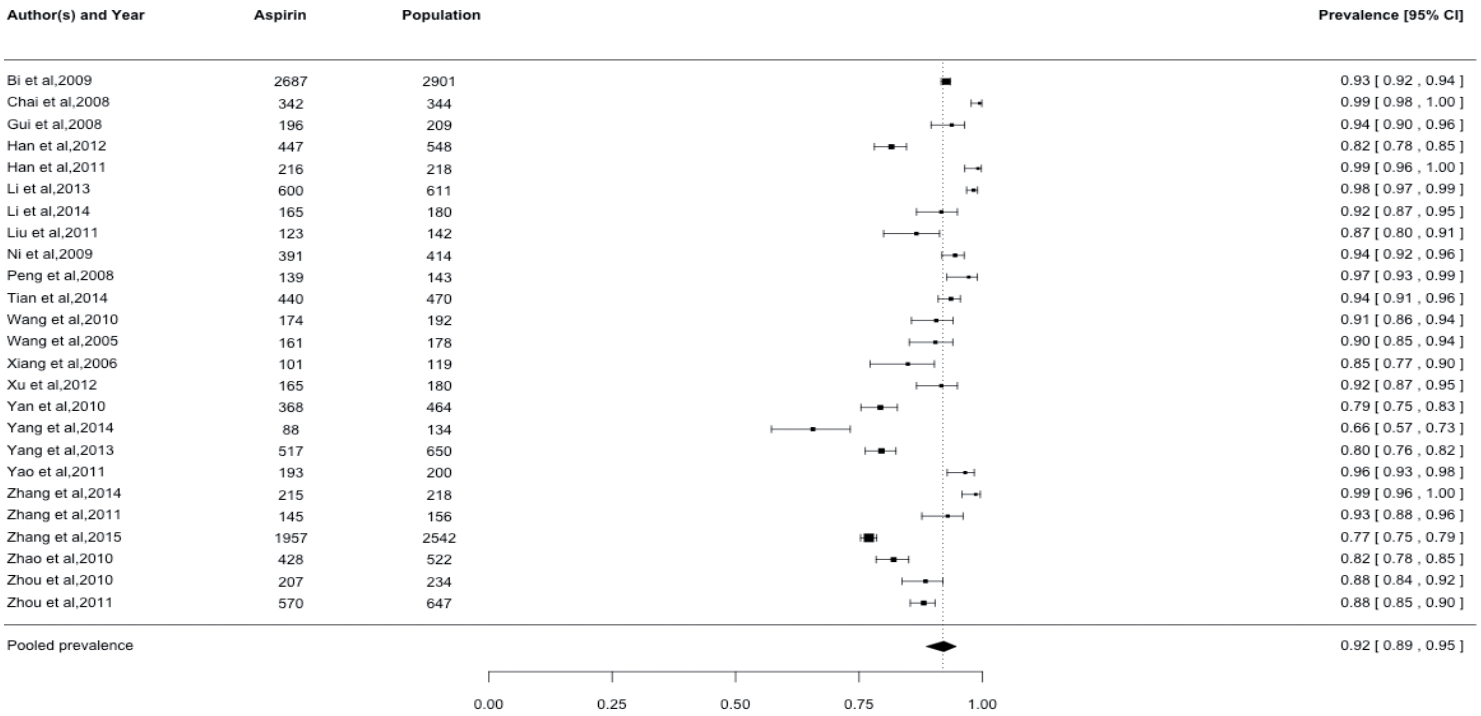
CHN: Chinese; ENG: English; BB: Beta blocker; ACE-I: ACE Inhibitor; ARB: angiotensin receptor blocker; NA: not applicable; NR: not recorded in study.

The overall sample size was 28,000 MI or ACS patients, with patient numbers ranging from 110[35] to 10753[45] per study. The characteristics of participants also varied considerably. Sixteen out of 35 studies reported discharge medications after hospital admission[18,19,21–23,35,41,49] or had specified the time period after discharge[17,26,27,29,34,36,37,44], whereas others set no time limits.

Prevalence of cardioprotective medication use

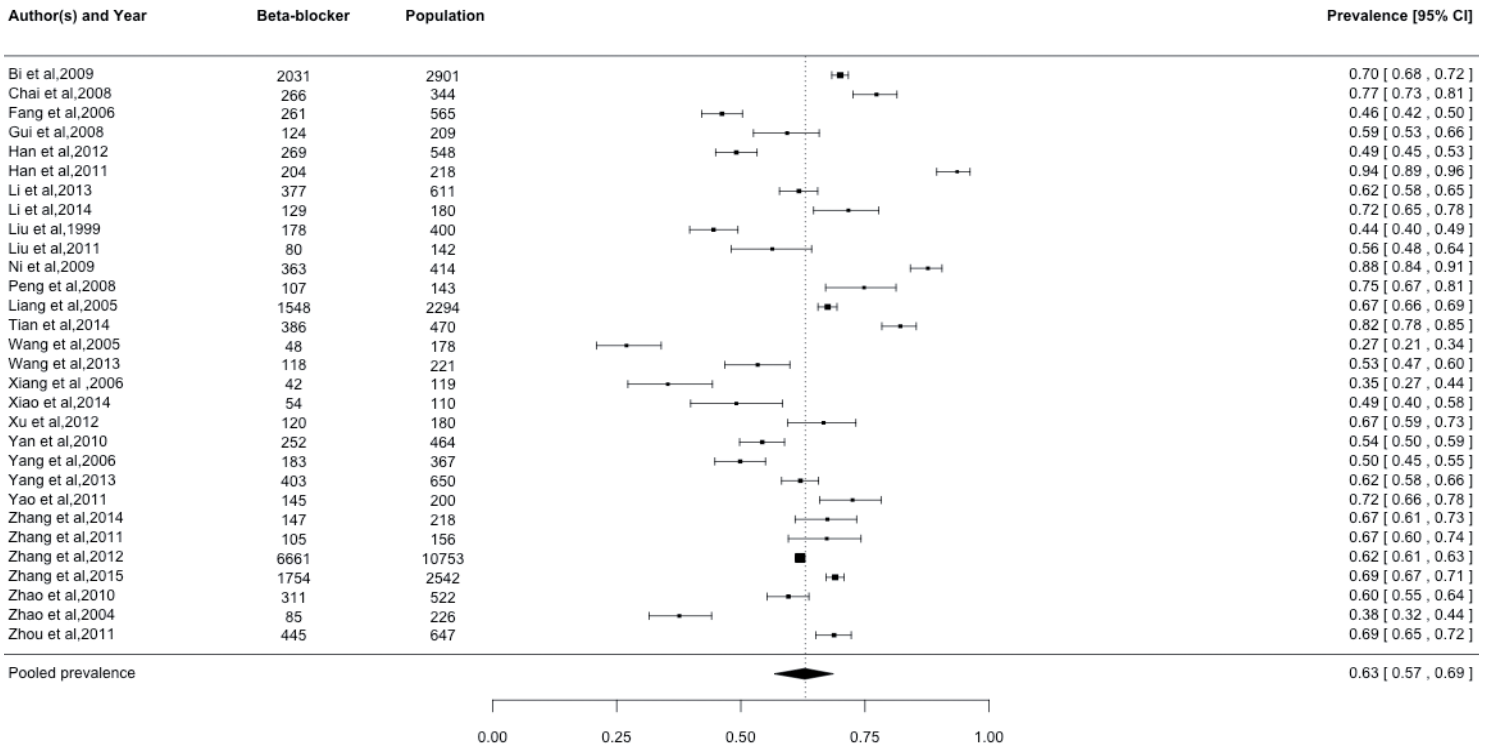
Pooled prevalence estimates for cardioprotective medication use are presented in Fig 2-6, respectively. Among these six cardioprotective medication categories, the pooled prevalence rate was 92% for aspirin (95% CI: 0.89-0.95), 63% for beta-blockers (95% CI: 0.57-0.69), 72% for statins (95% CI: 0.60-0.82), 49% for ACE-Is (95% CI: 0.41-0.57), 59% for ACE-I/ARBs (95% CI: 0.48-0.69), and 84% for nitrates (95% CI: 0.74-0.91).

Fig 2. Prevalence of aspirin by Chinese myocardial infarction patients after hospital admission.



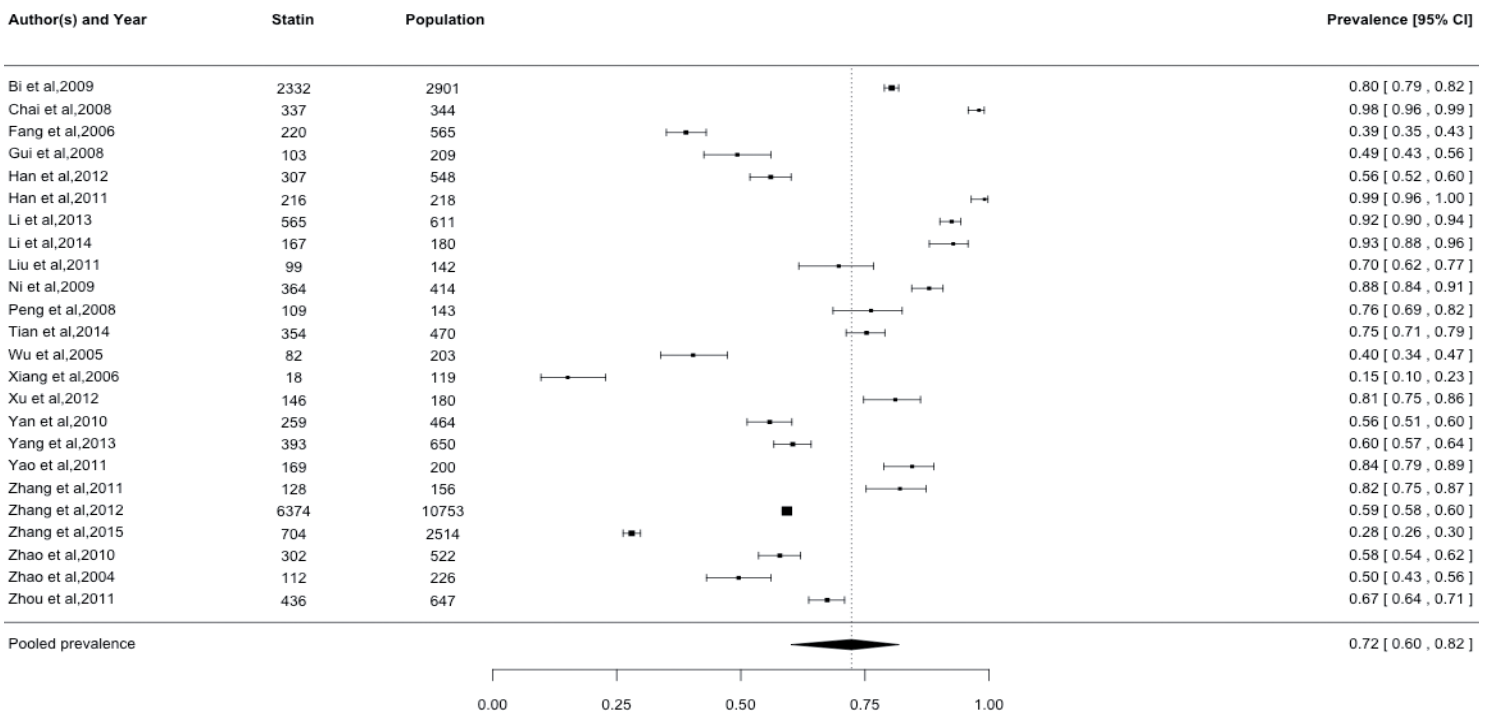
Studies followed alphabetical order. Squares and the horizontal lines represent the measures of effect (odds ratio) and associated confidence intervals for each of the studies and the diamond indicates the summary measure.

Fig 3. Prevalence of beta blockers by Chinese myocardial infarction patients after hospital admission.



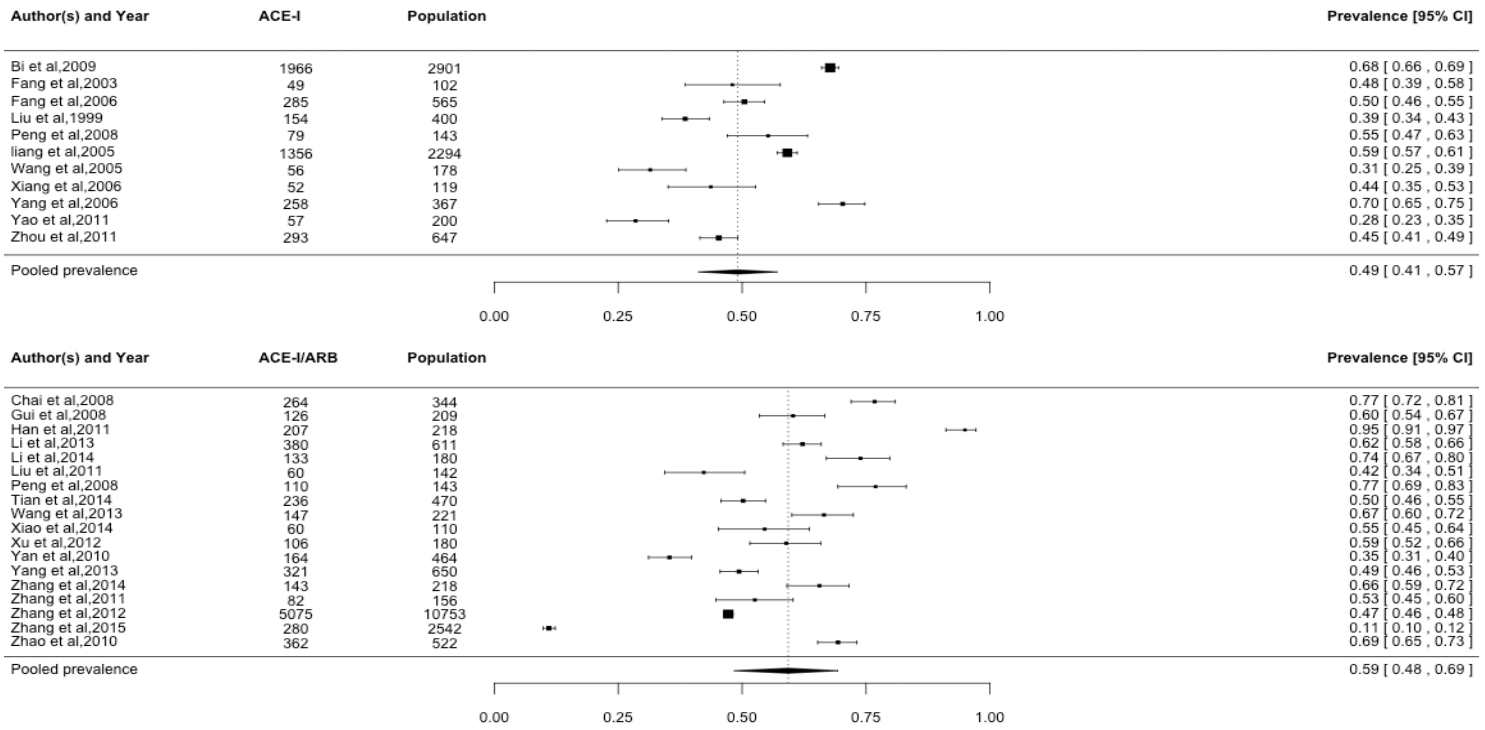
Studies followed alphabetical order. Squares and the horizontal lines represent the measures of effect (odds ratio) and associated confidence intervals for each of the studies and the diamond indicates the summary measure.

Fig 4. Prevalence of statins by Chinese myocardial infarction patients after hospital admission.



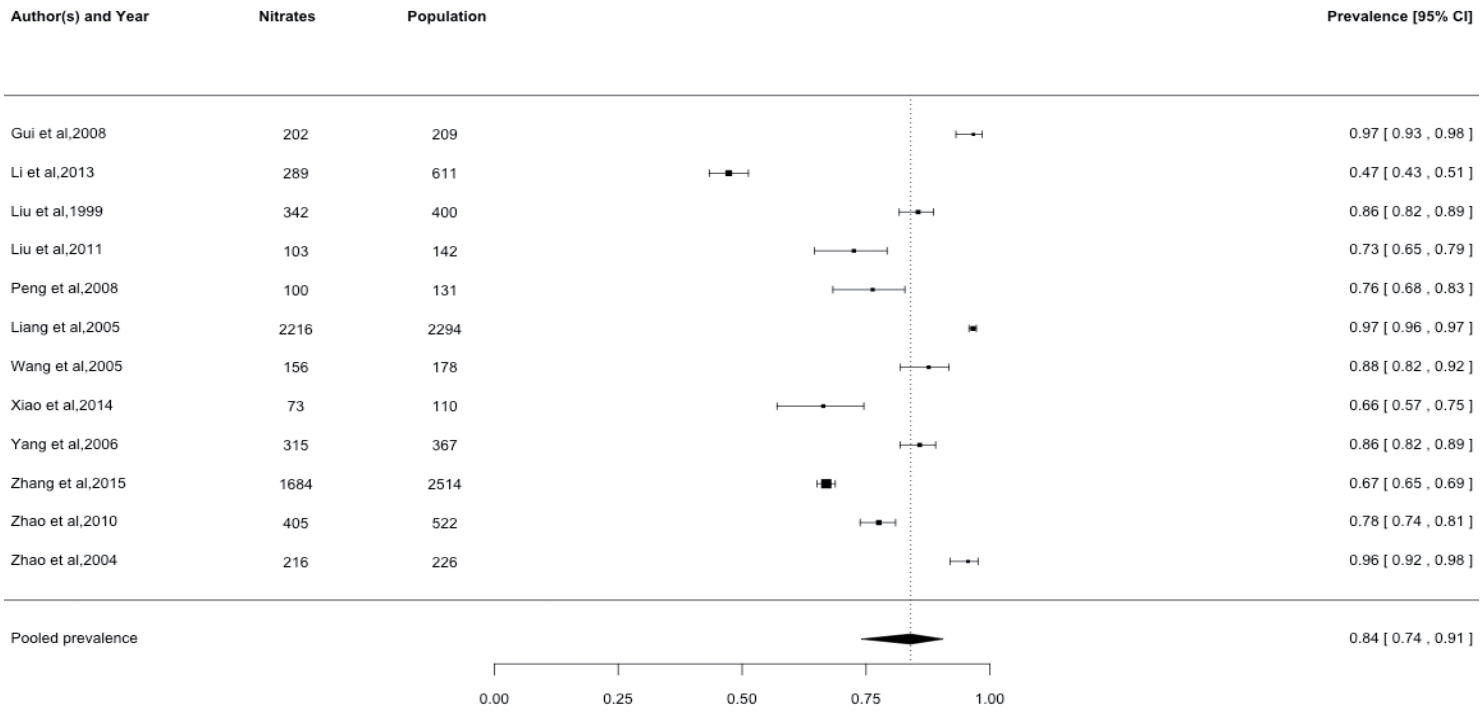
Studies followed alphabetical order. Squares and the horizontal lines represent the measures of effect (odds ratio) and associated confidence intervals for each of the studies and the diamond indicates the summary measure.

Fig 5. Prevalence of ACE-I/ARBs by Chinese myocardial infarction patients after hospital admission.



Studies followed alphabetical order. Squares and the horizontal lines represent the measures of effect (odds ratio) and associated confidence intervals for each of the studies and the diamond indicates the summary measure. ACE-I: ACE-inhibitor; ARB: angiotensin receptor blocker.

Fig 6. Prevalence of nitrates by Chinese myocardial infarction patients after hospital admission. Studies followed alphabetical order.



Squares and the horizontal lines represent the measures of effect (odds ratio) and associated confidence intervals for each of the studies and the diamond indicates the summary measure.

Temporal trends in prevalence of cardioprotective medication use

Fig 7 illustrates year-specific prevalences of individual cardioprotective medication use from 1995 to 2015. The meta-regression of the year over logit-transformed prevalence showed a trend towards an increasing prevalence of beta-blocker use from 1995 to 2015 with a slope of 0.1 ($p<0.0001$). This gives an estimate of 78% for beta-blockers use in 2015, compared to 32% in 1995. A similar increasing trend was demonstrated for statins use, even when the first available study was from 1999 (slope=0.26; P=0.0004). Accordingly, the estimated statin use was 17% in 1995 and 91% in 2015. In contrast, the estimated prevalence of nitrate use dropped from 95.5% in 1995 to 59.3% in 2015. There was no significant association between the year of survey and prevalence of aspirin, ACE-I, and ACE-I/ARB use.

Other demographic and geographic factors

Among studies that reported either demographic (the mean age and proportions of women) or geographic characteristics, there was little evidence for an association between these study characteristics and the logit-transformed prevalence of cardioprotective medications, except for aspirin (S3A and S3B Table). Aspirin use showed significant association with mean age (slope: 0.26, P=0.02), indicating that elderly patients with previous MI are more likely to take aspirin for their medical conditions.

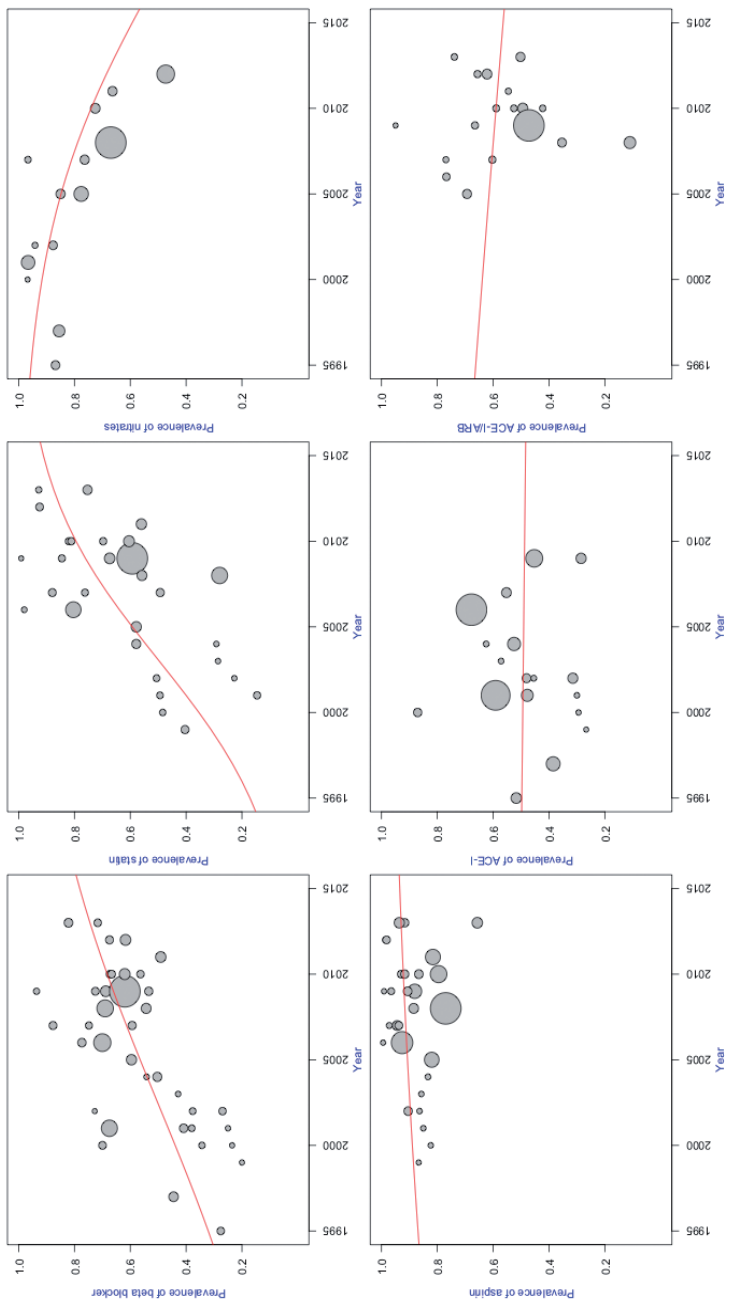


Fig 7. Temporal trends in the prevalence of cardioprotective medication use.

Bubbles are individual studies; diameters of the bubbles are proportional to studies weight for analysis. ACE-I: ACE-inhibitor; ARB: angiotensin receptor blocker.

DISCUSSION

Cardioprotective medications are considerably underused in China, even though a pronounced increase in beta-blocker and statin use has been noticed over the period from 1995 to 2015.

In the current review, the reported prevalence of cardioprotective medications in China varied widely across studies. The largest variation on prevalence of these six cardioprotective medications was reported for statin use, ranging from low (14.6%)[16] to high (99.1%)[29], among included studies. The prevalence variations of other cardioprotective medication use are also notable in this review. The lowest prevalence for beta-blockers, ACE-Is, ACE-I/ARB, and nitrates was 27%,[15] 31.5%,[15] 35.3%,[25] and 47.3%[32] in comparison to the highest prevalence with 93.6%,[29] 67.8%,[21] 95%,[29] and 96.8%[19] reported, respectively. Aspirin use showed the least variation for reported prevalence, varying from 65.7%[36] to 99.4%[18].

To investigate the determinants of these variations in cardioprotective medication use, meta-regression models were performed with specific study characteristics as covariates in current review. In line with previous findings,[50,51] elderly patients with previous MI were observed to be more likely to take aspirin. Aspirin is not only used to prevent cardiovascular events but also applied for other medical conditions[52] and thus, older patients may be more likely to report use of aspirin. Although several studies have demonstrated differences in use of cardioprotective medications by age, sex, or geographic area,[51,53–55] no other significant associations between demographic and geographic characteristics and cardioprotective medication use were observed in the current study. However, it should be noted that Chinese national guidelines recommend cardioprotective medications as part of secondary prevention strategy for all MI patients irrespective of age, sex, or geographic area.[6]

The observed trends of cardioprotective medications use are likely to be related to recent changes of the healthcare system, insurance coverage, and published national guidelines in China.[1,6,56] After the Chinese government implemented its healthcare system reform policies in 2009[1] and increased its insurance coverage up to 95.7% by 2011[57], the availability of health-care access and affordability of medication prescription have improved considerably in China[5,58]. Introduction and regular updates of the Chinese national guidelines of MI were additionally used to complement this renewed

healthcare system to standardize physician's daily practice and improve quality of care.[6,10] Furthermore, the Chinese National Essential Medicine List (EML) was developed and implemented to support rational drug use and improve the access to safe and effective essential drug.[5] The EML is composed of 307 types of medications, including all guideline-recommended cardioprotective medications, to be fully available by 2020.[5,21] Although the EML has only been introduced a notable reduction of inappropriate drug prescriptions was observed in a recent national survey.[59] Reflecting these achievements, the use of guideline-recommended cardioprotective medications is expected to gradually increase in China.

Despite material healthcare improvements in China, it is also important to realize that the current review shows that cardioprotective medication not to be on par with guideline recommendations indicating insufficient guideline implementation in day-to-day life. Studies have shown Chinese physicians to have a low awareness of up-to-date guidelines,[60,61] affecting clinical decisions in spite of guideline recommendations.[61–63] Moreover, lack of knowledge among patients about their disease or the necessity of adequate treatment could also have contributed to low use of cardioprotective medications.[60] Notwithstanding improvements of healthcare system and wider insurance coverage in China, CVD patients still face high personal expenditures on CVD care.[64] The Chinese national Bureau of Statistics showed private (out-of-pocket) expenditures to increase approximately by 10% per year, despite 20% annual increase on healthcare budget from government.[65] Thus given high out-of-pocket expenditures, Chinese patients may face considerable financial hardship after a MI event, which may hamper their ability to manage their medical conditions, seek proper medical advice, or adhere to prescribed medications, calling an increasing focus on the provision of accessible and to affordable healthcare service population for the Chinese population.[56,66,67]

Inadequate guideline-recommended cardioprotective medication use has been previousely reported for other low- and middle- countries.[68,69] The PURE study, a large international observational study in 30 countries, indicated a low use of the antiplatelet, beta-blockers, ACE-I/ARB and statins in South Asia (11.6%, 11.9%, 6.4%, and 4.8%), Malaysia (14.9%, 12.5%, 12.8%, and 15.9%), and Africa (3.4%, 1.9%, 6.8%, and 1.4%) and demonstrated the challenges of affordability and availability on these medications.[67,68,70] Generally, these medications were observed to be more commonly available and affordable in high-income countries with more advanced healthcare systems and better quality of care in daily practice,[67] resulting in higher reported cardioprotective medication

use in these countries is considerably higher.[71,72] Unless both healthcare system and insurance coverage are improved with wider availability and affordability of these medications, the use of guideline-recommended medication is likely to remain low in many low- and middle-income countries.

There are several limitations to this review. First, most published studies in China are more likely to come from centers with more advanced healthcare service and better facilities and prevalence of these drugs are rarely reported and published in centers with limited resources, especially in rural area. Due to limited published data, we could not perform stratified analysis of cardioprotective medication use by urban and rural area and results from these studies included in current review may not be representative for the whole country. This is a source of bias, which has overestimated the prevalence of cardioprotective medication use in China, and thus, the use of these drugs in daily practice are more likely to be lower. Secondly, the available information extracted from the included paper does not allow for individual patient data analysis. As a result, the potential to disclose associations between patient characteristics and cardioprotective medication use in this review is limited.

The strength of this review is its systematic identification from four databases including a large Chinese database. In current review, CNKI was used as a supplementary searching platform to incorporate both English and Chinese literature and to minimize limited access to Chinese publications from English language databases. Comprehensive Chinese searching terms were also used as part of our search strategy to cover more local published literature in China. Secondly, after validating all selected studies by a comprehensive quality assessment tool, meta-analysis and meta-regression models were performed to summarize the pooled estimate of cardioprotective medication use in China and detect its determinants. We observed significant year trends in prevalence of cardioprotective medication use over last two decades for secondary prevention of MI reflecting the rapid epidemiological changes in China. To our knowledge, this is the first review to investigate the trends of cardioprotective medication prevalence in China.

In summary, the current cardioprotective medication use in China is inadequate in comparison to guideline recommendations, although the reported use of these medications has increased over last two decades. It should act as a wake-up call to stimulate policymakers and healthcare bodies to forcefully restructure and implement secondary prevention strategies, educate health professionals to update clinical

knowledge and follow current guidelines recommendations for treatment, and create awareness among patients about health status and the benefits of appropriate medication.

ACKNOWLEDGEMENT

The research team would like to thank Dr Paulien Wiersma from Utrecht University for the support of search strategy.

REFERENCES

1. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; 381: 1987–2015.
2. Zhou M, Wang H, Zhu J, et al. Cause-specific mortality for 240 causes in China during 1990 – 2013 : a systematic subnational analysis for the Global Burden of Disease Study 2013.*Lancet* 2016; 251–272.
3. Li J, Li X, Wang Q, et al. ST-segment elevation myocardial infarction in China from 2001 to 2011 (the China PEACE-Retrospective Acute Myocardial Infarction Study): a retrospective analysis of hospital data. *Lancet* 2015; 385: 441–451.
4. Liu Y, Rao K, Wu J, et al. Health System Reform in China 7 China's health system performance. *Lancet* 2008; 372: 1914–1923.
5. Yip WC, Hsiao WC, Chen W, et al. Early appraisal of China's huge and complex health-care reforms. *Lancet* 2012; 379: 833–842.
6. China Society of Cardiology of Chinese Medical Association EB of CJ of C. Guideline on the diagnosis and therapy of ST-segment elevation myocardial infarction. *Zhonghua Xin Xue Guan Bing Za Zhi* 2015; 43: 380–393.
7. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases* 2010; 10(4):226.
8. Moher D, Liberati A, Tetzlaff J, et al. Reprint--preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Phys Ther* 2009; 89: 873–880.
9. Zhao M, Wang X, Klipstein-Grobusch K, et al. Prevalence of cardioprotective medication usage in secondary prevention of myocardial infarction (MI) in China. *PROSPERO* 2015; CRD4201502546.
10. China Society of Cardiology of Chinese Medical Association; Editorial Board of Chinese Journal of Cardiology. Editorial Board of Chinese Journal of Cardiology Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. *Chin J Cardiol* 2010; 38: 675–690.
11. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; 33: 1635–1701.
12. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of st-elevation myocardial infarction: A report of the American college of cardiology foundation/american heart association task force on practice guidelines. *J Am Coll Cardiol* 2013; 61: 78–140.
13. Li H, Oldenburg B, Chamberlain C, et al. Diabetes prevalence and determinants in adults in China mainland from 2000 to 2010: A systematic review. *Diabetes Research and Clinical Practice* 2012; 98: 226–235.
14. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. *J Stat Softw* 2010; 36: 1–48.
15. Wang S, Jia Y. Secondary prevention of acute myocardial infarction in 178 cases. *Zhongguo Xiang Cun Yi Yao* 2005; 12: 63–64.
16. Xiang Z, Li M, Zhang F, et al. Analysis of drug use in 119 cases of acute myocardial

infarction. *China Pharm* 2006; 17: 2–3.
17. Peng Y. Acute myocardial infarction in China: current status and medical treatment. *Fudan University*, 2008.
18. Chai R, Li W, Cong H. The medical treatment and relative outcomes after percutaneous coronary intervention in acute myocardial infarction patients. *J Tianjin Med Univ* 2008; 14: 495–497.
19. Gui X, Chen J, Tang H, et al. Acute coronary syndrome during hospital admission in Hefei. *Zhongguo Lao niang xue Za zhi* 2008; 10: 2024–2026.
20. Ni J. long-term therapeutics effects of varying treatment choices in patients with ST elevation acute myocardial infarction. *Fudan University*, 2009.
21. Bi Y, Gao R, Patel A, et al. Evidence-based medication use among Chinese patients with acute coronary syndromes at the time of hospital discharge and 1 year after hospitalization: Results from the Clinical Pathways for Acute Coronary Syndromes in China (CPACS) study. *Am Heart J* 2009; 157: 509–516.e1.
22. Zhou A, Wang X, Liao W, et al. Clinical survey of anti-platelet drugs use in bleeding patient with acute myocardial infarction out of hospital. *J clin Cardiol* 2010; 26: 36–38.
23. Wang D. Clinical survey on antiplatelet drug use in discharged patients with acute myocardial infarction. *China Mod Dr* 2010; 48: 29–30.
24. Zhao R. Analysis of forward prognosis and relevant factor of 522 Acute Myocardial Infarction patients in Chongqing. *Chongqing Medical University*, 2010.
25. Yan H, Zhao Y, Wang J, et al. Long-term follow-up after drug-eluting stents for patients with ST-segment elevation myocardial infarction: a single center study. *Zhonghua Yi Xue Za Zhi* 2010; 90: 2103–2106.
26. Yao D, Zhou L, Zhao H, et al. Effect of educational program on medication adherence and major adverse cardiac events in patients after percutaneous coronary angioplasty. *J Clin Exp Med* 2011; 10: 6–7.
27. Liu G. *Long-tim follow-up study of non-ST-segment elevation myocardial infarction*. Nanjing University, 2011.
28. Zhang B, Huang R, Yin D, et al. Management and prognosis in patients with ST-elevation myocardial infarction: from single-center study. *J Dalian Med Univ* 2011; 33: 462–465.
29. Han W, Zhang M, Wang J, et al. Effects of standardized secondary prevention on lifestyle of patients with acute coronary syndrome. *J Shanghai Jiaotong Univ Medical Sci* 2011; 31: 302–304.
30. Xu M, Guo J, Hua Q. Situation of secondary prevention medications application in elderly patients with acute myocardial infarction. *Chinese J Cardiovasc Med* 2012; 17: 18–22.
31. Han L, Cao S, Yu X, et al. Chinese characteristics of elderly patients with acute myocardial infarction in aged greater than 75 years Chinese. *J Cardiovasc Pulm Dis* 2012; 31: 579–583.
32. Li W. Retrospective study of acute myocardial infarction during hospitalization and

follow-up. *Second Military Medical University*, 2013.
33. Yang J, Pi L, Song L, et al. Impact of therapy options on in-hospital and three-year outcome of patients with ST-elevation myocardial infarction in Beijing. *Chin J Cardiol* 2013; 41: 474–479.
34. Zhang W, Liu Z, Sun H, et al. Follow-up analysis of Acute Coronary Syndromes after percutaneous coronary angioplasty. *Zhongguo Lao niang xue Za zhi* 2014; 34: 4424–4425.
35. Li X. Acute myocardial infarction treatment and quality control in Z hospital. *Beijing university of Chinese Medicine*, 2014.
36. Yang Q. Survey on antiplatelet treatment on acute myocardial infarction. *China J Pharm Econ* 2014; 5: 83–84.
37. Tian Q. The research about the use of drugs and the relevance of risk factors and prognosis in patients with acute coronary syndrome. *Shanxi Medical University*, 2014.
38. Zhang H, Yuan X, Zhang H, et al. Efficacy of long-term beta-blocker therapy for secondary prevention of long-term outcomes after coronary artery bypass grafting surgery. *Circulation* 2015; 131: 2194–2201.
39. Liu L, Wang W, Xie H, et al. Clinical Symptom and Prognosis in 400 Cases of Acute Coronary Ischemia Syndrome. *Chinese J Hypertens* 1999; 7: 301–302.
40. Zhao Y, Wei L. Survey of beta blockers and statins therapy in patients after acute myocardial infarction. *Acta Acad Med cpapf* 2004; 13: 296–298.
41. Liang Y, Tan H, Zhu J, et al. Risk factors of sudden death and death from arrhythmia in patients with non-ST acute coronary syndromes in China. *Chin Crit Care Med* 2005; 17: 142–145.
42. Fang C, Ju Y, Wang J, et al. The investigation and analyses about the situation of secondary prevention after myocardial infarction in Rong-cheng city. *Chinese J Med Guid* 2006; 8: 30–33.
43. Yang H, Su W, Zhang J, et al. Comparison analysis of acute myocardial infarction in secondary prevention over 10 years. *Chinese J Cardiovasc Rev* 2006; 4: 446–447.
44. Zhou L. Long-term adherence of secondary prevention medication in ST-elevation Myocardial infarction (STEMI) patients. *Hebei Medical University*, 2011.
45. Zhang H. The use of medications in secondary prevention of Coronary Heart Disease in China. *Perking Union Medical College*, 2012.
46. Wang W, Zhao D, Liu J, et al. The prevalence of comorbidities and pharmacologic management of hypertensive outpatients. *Chinese J Hypertens* 2013; 21: 738–742.
47. Wu J, Wu X, Han Z, et al. The usefulness of early statin treatment after acute myocardial infarction. *Chin J Geriatr Hear Brain Vessel Dis* 2005; 7: 324–326.
48. Xiao G, Gao L. Discharge medication compliance in patients with acute coronary syndrome: an analysis of 110 cases. *Chinese Med J Met Ind* 2014; 31: 348–349.
49. Fang Y. Integrative medicine for acute nyocardial infarction in Dongzhimen Hospital: a cross-sectional study. *Beijing University of Chinese Medicine*, 2003.
50. Ajani UA, Ford ES, Greenland KJ, et al. Aspirin use among U.S. adults: Behavioral

risk factor surveillance system. *Am J Prev Med* 2006; 30: 74–77.
51. Koopman C, Vaartjes I, Heintjes EM, et al. Persisting gender differences and attenuating age differences in cardiovascular drug use for prevention and treatment of coronary heart disease 1998 – 2010. *Eur Heart J* 2013; 3198–3205.
52. Mah I, Leizorovicz A, Caulin C. Aspirin for the Prevention of Cardiovascular Events in the Elderly. *Drugs aging* 2003; 20: 999–1010.
53. Zhang H, Plutzky J, Shubina M, et al. Drivers of the Sex Disparity in Statin Therapy in Patients with Coronary Artery Disease : A Cohort Study. *PLos One* 2016; 11 (5): e0155228.
54. Krämer HU, Raum E, Rüter G, et al. Gender disparities in diabetes and coronary heart disease medication among patients with type 2 diabetes : results from the DIANA study. *Journal of the American College of Cardiology* 2012; 1–9.
55. Chen Y, Li L, Zhang Q, et al. Use of drug treatment for secondary prevention of cardiovascular disease in urban and rural communities of China: China Kadoorie Biobank Study of 0.5million people. *Int J Cardiol* 2014; 172: 88–95.
56. Barber L YL. Health insurance systems in China: a briefing note. *World Heal Rep* 2010.
57. Meng Q, Xu L, Zhang Y, et al. Trends in access to health services and fi nancial protection in China between 2003 and 2011 : a cross-sectional study. *Lancet* 2011; 379: 805–814.
58. Tang S, Tao J, Bekedam H. Controlling cost escalation of healthcare : making universal health coverage sustainable in China. *BMC Public Health* 2012; 12: 1–13.
59. Ministry of Health of the People's Republic of China. Report on the implementation of national essential medicines policies. *Beijing, China*, 2011.
60. Zhao D, Hu D. Barriers to translating EU and US CVD guidelines into practice in China. *Nat Rev Cardio* 2012; 9: 425–429.
61. Jiang J, Hong T, Yu R, et al. Knowledge of secondary prevention guidelines for coronary heart disease : results from a physicians' survey in China. *European Journal of Preventive Cardiology* 2012; 19(5): 991-998.
62. Gong Y, Hong T, Jiang J, et al. Influence of education and working background on physicians ' knowledge of secondary prevention guidelines for coronary heart disease : results from a survey in China. *Journal of Zhejiang University Science* 2012; 13: 231–238.
63. Wang W, Tang J, Hu Y, et al. Gap between evidence and physicians' knowledge and practice regarding hypertension and its drug treatment: a survey in a Chinese city. *Chinese Medical Journal* 2011; 124: 1235–1241.
64. Wu Y, Benjamin EJ, Macmahon S. Prevention and control of cardiovascular disease in the rapidly changing economy of China. *Circulation* 2016; 133: 2545–2561.
65. National Bureau of Statistics of People's republic of China. Private expenditure on health care, http://data.stats.gov.cn/adv.htm?m=advquery&cn=C01 (accessed 20 July 2015).
66. Li X, Zhang H, Wang J, et al. Assessing patient satisfaction with medication-related

services in hospital settings: a cross-sectional questionnaire survey in China. *Int J Clin Pharmacol Ther* 2014; 52: 587–597.

67. Khatib R, McKee M, Shannon H, et al. Availability and affordability of cardiovascular disease medicines and their effect on use in high-income, middle-income, and low-income countries: an analysis of the PURE study data. *Lancet* 2015; 6736: 1–9.
68. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.
69. Krishnan MN, Nambiar AC. Optimal In-Hospital and Discharge Medical Therapy in Acute Coronary Syndromes in Kerala Results From the Kerala Acute Coronary Syndrome Registry. *Circ Cardiovasc Qual Outcomes* 2016; 6(4):436-43.
70. Corsi DJ, Subramanian S V., Chow CK, et al. Prospective Urban Rural Epidemiology (PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J* 2013; 166.
71. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2015; 59–61.
72. Simon DN, Thomas LE, Wang TY, et al. Modest associations between electronic health record use and acute myocardial infarction quality of care and outcomes. *Circ Cardiovasc Qual Outcomes* 2016; 576–586.

APPENDIX

S1 Checklist. PRISMA checklist. PRISMA checklist for 'Cardioprotective medication use in secondary prevention after myocardial infarction (MI) in China: a systematic review and meta-analysis'.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4

S1 Checklist (continued)

Section/topic	#	Checklist item	Reported on page #
METHODS			
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	4

S1 Table. Search strategy.

		Synonyms English	Pubmed/Medline MESH	EMBASE/OVID MTree	CENTRAL Cochrane	CNKI
Domain	Myocardial infarction	MI; Heart attack; STMI/NSTMI; Stroke; Myocardial infarct(s)	Myocardial infarction	Heart infarction	Myocardial infarction	心肌梗死 心梗 心肌梗塞
	China	Chinese; People's republic of China; Mainland China; Manchuria; Sinkiang; Inner Mongolia; Tibet; Asia; Asian; developing countries; International; Middle income; [all field] China	China	China; Chinese	China	NA
Determinants	Cardiovascular medication(s)	Cardiovascular drug(s); cardiovascular medication(s); cardioprotective drug(s)	Cardiovascular agent	Cardiovascular agent	Cardiovascular agents	心脏保护 保护心脏
	Aspirin	Acetylsalicylic acid; aspirin; brand name (Ecotrin, Acetylsalicylic acid; Bayer aspirin, Acylpyrin; Easpirin; Colfarit; Micristin)	Aspirin	Acetylsalicylic acid	Aspirin	阿司匹林 乙酰水杨酸 抗血小板
	Statin(s)	Statin(s); HMG-coenzyme A reductase inhibitor; HMG CoA reductase inhibitor; simvastatin; pravastatin; lovastatin	Hydroxymethylgutaryl-CoA Reductase inhibitors; hydroxymethylgutaryl-CoA reductase inhibitors [pharmacological action]	Hydroxymethylgutaryl coenzyme A reductase inhibitors	Hydroxymethylgutaryl-CoA Reductase inhibitors	他汀 降血脂药

S1 Table. (continued)

		Synonyms English	Pubmed/Medline MESH	EMBASE/OVID MTree	CENTRAL Cochrane	CNKI
	Beta blocker(s)	Beta-adrenoceptor blocking agents; atenolol; bisoprolol; carvedilol; timolol; acebutolol; bupranolol; butoxamine; carteolol; bunolol; ievobunolol; nadolol; pindolol; sotalol;	Adrenergic beta antagonists; adrenergic beta antagonists [pharmacological action]	Beta adrenergic receptor blocking agent	Adrenergic beta antagonists	β受体阻滞剂 受体阻断剂 高血压药物 地洛 洛尔
	ACEI	Antihypertensive agent (drug/medication); angiotensin-converting-enzyme; ramipril; lisinopril; cilazapril; quindopril; enalapril; captopril; enalaprilat; fosinopril; teprotide; brand name (lotension, capoten, aceon, mavik)	Angiotension-converting enzyme inhibitor; angiotensin-converting enzyme inhibitors [pharmacological action]	Dipeptidyl carboxypeptidase inhibitor	Angiotensin-conversing enzyme inhibitor	血管紧张素转换酶抑制剂 高血压药物 普利
	Nitrates	Nicorandil; isosorbide; brand name (Dilatrate, isordil, ISMO, Nitro-dur, Nitrolingual, Nitrostat)	Nitroglycerin; nitrates; isosorbide	Nitric acid derivative; Glyceryl trinitrate	Nitrates; nitroglycerin; isosorbide	速效救心丸 硝酸甘油 硝酸酯
Extra term	Secondary prevention	Secondary prevention(s) Early therapy Early therapies Drug therapy Drug therapies	Prevention and control Secondary prevention Drug therapy	Secondary prevention Drug therapy Medication therapy management	Prevention and control Secondary prevention Drug therapy	二级预防 药物治疗 药物应用现状 应用现状＋药物

S2A Table. Adjusted tool of risk of bias assessment

Bias type	Low risk	Moderate risk	High risk
Study design	Prospective data collection (clinical assessment)	Retrospective data collection (medical records or self-reported questionnaire/survey)	Unclear data collection and statistical analysis
Study population	• Specific and detailed sample selection criteria • Sample from general population but not selected group with multiple centres • Specific and detailed sample selection criteria	• Sample selected from large population but selection criteria not defined; • Sample selection ambiguous but may be representative; • Analysis to adjust for sampling strategy bias	• Unclear sample selection criteria; • Sample is selected from single centre and not representative
Participant rate	High participant rate (>85%)	Moderate participant rate (70-85%)	Low participant rate (<70%)
Participants' characteristics	• Myocardial infarction (MI) diagnosis using consistent criteria and direct examination; • Specific and detailed recruitment time period; • Consecutive MI participants>18 years old; • Specific and detailed determinants (e.g. age)	• MI diagnosis assessment from medical records, questionnaire, survey, administrative database or register; • Wide and undetailed recruitment time period; • Specific and detailed determinants	• Diagnosis assessment from non-validated data or generic estimate from overall population; • Unknown performed time or location; • No determinants information available.
Outcomes	• Detailed information on prevalence of cardioprotective medications usage with specific MI diagnosis; • Detailed information on absolute level of blood pressure, lipids, and glucose with specific MI diagnosis	Detailed information on prevalence of cardioprotective medications usage with specific MI diagnosis;	No outcome information available

S2B Table. Quality of risk bias assessment. Data collection and statistical analysis method were assessed in study design. Studies with summed score of 6 or below was considered as bad quality and excluded from this systematic review and meta-analysis.

Study	Study design	Sample population	Participation rate	Participants character-istics	Out-comes	Summed score
Ni et al2009	1	1	2	1.5	1	6.5
Liu et al 1999	1	2	0.5	2	1	6.5
Liu et al 2011	1	0.5	2	0.5	0.5	4.5
Liu et al 2001	1	1	0.5	2	2	6.5
Liu et al 2005	1	0.5	2	0.5	0.5	4.5
Liu et al 2010	1	1	2	1	1	6
Bao et al 2013	1	1	2	1	0.5	5.5
Xiang et al 2006	1	1	2	1	1	6
Wu et al 2005	1	1	2	1	1	6
Zhou et al 2010	2	1	2	2	2	9
Yao et al 2011	2	1	2	1	1	7
Sun et al 2014	1	0.5	2	1	1	5.5
Ji et al 2004	1	0.5	2	0.5	1	5
Zhang et al 2014	2	1	2	1.5	1	7.5
Zhang et al 2009	1	0.5	2	1	0.5	5
Zhang et al 2010	1	0.5	2	0.5	0.5	4.5
Zhang et al 2011	2	1	2	2	2	9
Zhang et al 2012	2	2	2	0.5	1	7.5
Zhang et al 2005	1	1	2	2	1	7
Peng et al 2008	1	1	2	2	2	8
Fang et al 2003	1	1	1	2	1	6
Fang et al 2001	1	1	2	1	1	6
Fang et al 2006	1	1	2	0.5	1	5.5
Fang et al 2006	1	1	2	1	2	7
Li et al 2013	1	1.5	1	2	2	7.5
Li et al 2014	1	1	2	2	2	8
Yang et al 2014	1	1	2	1	2	7
Yang et al 2006	1	1	2	2	1	7
Chai et al 2008	1	1	2	1	2	7
Gui et al 2008	1	1	2	1	1	6
Wang et al 2010	1	1	2	2	1	7
Wang et al 2005	1	1	2	1	1	6
Wang et al 2013	2	2	2	1	1	8

S2B Table. (continued)

Study	Study design	Sample population	Participation rate	Participants character-istics	Out-comes	Summed score
Tian et al 2014	1	1	2	1.5	2	7.5
Niu et al 2003	1	1	2	0.5	1	5.5
Luo et al 2014	1	1.5	2	0	1	5.5
Xiao et al 2014	1	1	2	1	2	7
Xiao et al 2012	1	0.5	0.5	0.5	0.5	3
Xu et al 2012	1	1	1	1.5	2	6.5
Xie et al 2012	1	0.5	2	1	1	5.5
Tan et al 2013	1	0.5	2	1	1	5.5
Zhao et al 2010	1	1	2	2	2	8
Zhao et al 2004	1	1	2	1	2	7
Lang et al 2006	1	1	2	1	2	7
Guo et al 2012	1	0.5	2	1	1	5.5
Tao et al 2014	1	0.5	2	1	1	5.5
Han et al 2012	1	1	2	1	2	7
Han et al 2011	1	1	2	1	2	7
Gao et al 2007	1	0.5	2	1	1	5.5
Bi et al 2009	2	2	2	2	1	9
Liang et al 2005	2	2	2	1	1	8
Ma et al 2010	2	1	1	0.5	0.5	5
Wang et al 2012	2	0.5	0	1	1	4.5
Yan et al 2010	2	0.5	2	1	1	6.5
Zhang et al 2015	2	1	2	1	1	7

* Data collection and statistical analysis method were assessed in study design. Studies with summed score 6 or below was considered as bad quality and excluded.

S3A Table. Correlation of year, mean age and proportion of women on prevalence of cardioprotective medications in China.

Prevalence of cardiovascular medications with covariates (year, mean age, and gender<women percentage>)									
	Year			**Mean age**			**Gender**		
	Intercept	coefficient	P value	Intercept	Coefficient	P value	Intercept	Coefficient	P value
Aspirin	-74.45	0.0383	0.445	-4.2264	0.1045	0.0169*	2.9	-0.0129	0.6403
Beta blocker	-202.39	0.1001	<0.0001*	0.6692	-0.0018	0.9685	0.44355	0.0034	0.856
Statin	-391.01	0.1952	0.0003*	3.2005	-0.0331	0.7147	0.0586	0.0347	0.4217
ACE inhibitor	5.2822	-0.0027	0.9515	0.691	-0.0108	0.8582	-0.085	0.0019	0.877
ACEI/ARB	42.0959	-0.0208	0.8361	-6.5926	0.1073	0.1155	-0.7479	0.0439	0.1733
Nitrates	271.0817	-0.1343	0.0024*	-1.1758	0.0434	0.6494	1.4185	0.009	0.803

Two decimals were applied. Significant P value was marked with asterisk (*).

S3B Table. Correlation of geographic area on prevalence of cardioprotective medications in China.

	Broad		**Central**		**East**		**North**		**North East**		**South**		**South West**	
	coef	P value	coef	P value	coef	P value	coef	P value	coef	P value	coef	P value	coef	P value
Aspirin	2.53	0.016*	-1.1	0.27	0.55	0.53	-0.29	0.73	0.86	0.4	-0.75	0.45	-0.79	0.5
Beta blocker	-0.44	0.36	-1.1	0.03*	0.53	0.17	0.09	0.8	-0.1	0.82	-0.63	0.2	-1.19	0.06
Statin	-1	0.51	NA	NA	0.37	0.76	-0.56	0.63	0.12	0.94	-1.26	0.36	-3.2	0.05
ACE inhibitor	-1.03	0.04*	-0.49	0.24	-0.34	0.5	-0.84	0.02*	NA	NA	NA	NA	-0.81	0.12
ACEI/ARB	-0.8	0.51	NA	NA	0.23	0.8	-0.71	0.44	-0.38	0.71	0.13	0.92	NA	NA
Nitrates	-1.57	0.15	-1.46	0.12	-2.07	0.016*	-2.65	0.014*	-2.67	0.015*	-1.24	0.19	NA	NA

Coef: coefficientTwo decimals were applied. Significant P value was marked with asterisk (*).


SURF
SUrvey of Risk Factors

5

Gereral Discussion

The highest priority in secondary prevention of patients with coronary heart disease (CHD) is to manage cardiovascular risk factors and provide appropriate medical treatment in order to reduce the likelihood of further clinical events.[1] This thesis explores cardiovascular risk factor recording and management and the use of guideline-recommended medication in routine practice; investigates differences in secondary prevention of CHD in three different regions (Europe, Asia and the Middle East); examines whether risk factor recording and management differs in certain population subgroups and relates international data on air pollution to cardiovascular risk factors.

KEY FINDINGS

The key findings of this thesis are the following:

1. Clinical audit is an effective tool with which to examine the recording and management of cardiovascular risk factors in routine clinical care. However, the lack of standardization and limited availability of clinical audits may impede improvements in the quality of care in CHD management (Chapter 2.1).

2. SURF CHD, an international clinical audit program of cardiovascular risk factor recording and management, has been shown to be feasible and applicable in different clinical settings across three regions (Chapter 2.2).

3. The SURF CHD findings indicate that there is patchy recording and poor management of cardiovascular risk factors in routine care of CHD patients with substantial regional variations among Europe, Asia and the Middle East. Obesity, poor achievement of therapeutic medical targets, and underuse of guideline-recommended cardiovascular medications are major problems (Chapter 2.2).

4. CHD patients who were women, younger than 55 years old, diabetic, and who did not have access to cardiac rehabilitation were more likely to have uncontrolled cardiovascular risk factors and underuse of guideline-recommended medications. The magnitude and direction of cardiovascular risk factor management and its associated determinants varied substantially across regions. In general, European participants had better control of cardiovascular risk factors and higher rates of cardiovascular medication use compared to Asian and Middle Eastern participants. Cardiac rehabilitation programs for secondary prevention were more commonly

available in Europe; the availability of such programs was limited in Asia and the Middle East (Chapter 3.1 & chapter 3.2).

5. It is feasible to use data from SURF CHD for global linkage studies. Through linkage with satellite data $PM_{2.5}$ was added to existing risk factor data from SURF CHD and the impact of air pollution on cardiovascular risk factor levels was explored (Chapter 3.3).

6. Current guideline-recommended cardiovascular medication use remains suboptimal in China; even though their prevalence of use has rapidly increased over the last two decades (Chapter 4).

METHODOLOGICAL CONSIDERATIONS

Most studies in the current thesis used data from the first phase of SURF CHD. SURF CHD collected data on 10,186 CHD patients from 79 centers in 11 countries among three regions (Europe, Asia and the Middle East) between 2012 and 2013. All patients were recruited during routine cardiology clinic visits and information on demographics, diagnostic category, risk factors, physical and laboratory measurements and medications was obtained from a one-page data collection sheet by trained research staff.

SURF CHD is a targeted, achievable and relevant audit with a straightforward methodology. SURF CHD focuses on essential cardiovascular risk factor questions arising out of local or national prevention priorities. All information can be collected within 90 seconds per patient and little resources in terms of finance, time, or staff are needed to undertake SURF CHD; allowing it to be easily performed and embedded in routine practice.[2] Although information on economic and mental health risk factors is currently unavailable, findings from SURF CHD are sufficient to reflect daily performance on cardiovascular risk factor management.

Unlike classical epidemiological studies, missing data recorded in a clinical audit are considered an outcome of interest. The frequency of missing data reported in SURF CHD can be used as a quality indicator to prompt improvements in quality of care.[3] However, missing data is also a potential source of bias in SURF CHD analyses, which may reduce the reliability of prevalence estimates. In general, the proportion of missing data was small, with less than 4% recorded for SURF CHD variables. The high frequency of missing data

(around 20%) was mostly recorded in laboratory measurements. Missing information is more likely to be recorded in patients with poorer cardiovascular risk factor management. [4,5] Therefore, we might have overestimated the true status of overall cardiovascular risk factor management in SURF CHD. It should be noted that the percentage of missing data seems to be random, irrespective of region, sex, or other demographic characteristics. Thus, our conclusions regarding regional variations, sex disparities and risk factor determinants are unlikely to be altered. Furthermore, we imputed missing data in some analyses to reduce bias and increase statistical power.

SURF CHD can be readily undertaken in all types of clinical settings, including centers with limited resources from low- and middle-income countries; with the potential for greatly enhanced representativeness. In our view of the literature, we observed that most existing clinical audits have been conducted in high-income countries or centers with sufficient resources to perform academic research.[6,7] SURF CHD data, collected from different geographical areas (national, regional, or international levels), not only permits comparative analyses to assess geographical difference in terms of cardiovascular risk factor recording and management but also helps local health organizations to develop appropriate prevention strategies to meet local requirements, especially in low- and middle-income countries where these have rarely been established. However, the generalizability of SURF CHD is still limited and representativeness needs to be improved as most of SURF CHD participating centers were identified by personal contact. Participation bias may result in higher standard of risk factor recording and management than the local average in participating centers. Thus, the findings might have overestimated the quality of risk factor management and the reality of cardiovascular risk factor management may be even worse than is suggested by current findings.

To date, SURF CHD has been performed as a pilot and subsequently as the first phase, with the potential to repeat it regularly to monitor changes and observe trends in terms of cardiovascular risk factor recording and management over time. This is clearly necessary if improvements in clinical practice are to occur and be recorded.

THE NATURE OF CURRENT CLINCIAL AUDITS

Several international audit programs like SURF CHD have been reported in the current literature to investigate recoding and management on cardiovascular risk factors for secondary prevention of CVD. [6–10] Current international clinical audits include EuroAspire,

REACH registry, WHO-PREMISE, PURE, and SURF CHD.

Study design and methodology

Given the diversity of clinical settings in different geographic areas, the study design and methodology may vary and the objectives may be interpreted in different ways. Apart from formally designed clinical audits, registries and observational studies may also have audit intention to describe cardiovascular risk factor management.

EuroAspire used highly standardized examinations and detailed face-to-face interviews and managed to explore cardiovascular risk factor management both cross-sectionally and over time.[6,11–13] It may be regarded as an exemplar audit in that many European countries are surveyed. However, it requires considerable resources in terms of staff capacities, time, and financial support. Thus the generalizability of such an audit is limited as participating countries or centers were, of necessity, well-resourced and mainly from high-income countries.

The REACH registry provided an international contemporary data set with inclusion of a large number of Asian populations and patients with several cardiovascular risk factors, CHD, or cerebrovascular disease were recruited.[8] Its large sample size and international scope may improve representativeness of current audit settings. However, the large number of centers that withdrew from the study may have limited both the results and the generalizability of the study. Nevertheless the detailed follow-up information may provide valuable information regarding cardiovascular risk.

WHO-PREMISE not only explored the current situation of CHD and cerebrovascular disease prevention but also identified barriers to risk factor management in low- and middle-income countries, which has rarely been assessed.[10] However, only self-reported risk factor information is collected, which may be less accurate than actual medical records.

PURE used a unique sampling process that enabled data to be collected from communities in both urban and rural areas.[14] It is primarily a prospective cohort study of social influences on risk factors and chronic non-communicable disease. A follow-up of 10 years is conducted to assess associated factors on mortality or cardiovascular events.[15] Similar to WHO-PREMISE, self-reported risk factor data may not reflect the most accurate risk factor information in daily practice.

Outcome comparison between SURF CHD and other current international clinical audits

Overall, the findings of SURF CHD are broadly the same as other current studies regarding clinical guideline adherence and implications irrespective of study design, performed geographical area, and time frame (Table 1).

Results of EuroAspire on cardiovascular risk factor management tended to be slightly more favorable compared to studies such as SURF and WHO-PREMISE, probably partly because the latter studies included low- and middle-income countries.[6,7,10,16–18] Lower use of cardiovascular medication for patients with CHD was reported in the PURE study, as compared to EuroAspire and SURF CHD, for aspirin (25% vs 98% vs 90%), beta blocker (17% vs 85% vs 72%), statins (15% vs 90% vs 81%), and ACEI/ARB (20% vs 77% vs 58%) respectively. All reported relatively high rates of smoking and inadequate physical activity, despite the fact that smoking cessation and cardiac rehabilitation with exercise training have been widely promoted in current clinical guidelines worldwide. The prevalence of uncontrolled hypertension, dyslipidemia, and diabetes remain high.

SURF CHD observed substantial regional differences in risk factor control and also examined determinants of control. The findings were broadly in line with findings from PURE, REACH, and WHO-PREMISE.[9,10,18–20] High-income countries were more likely to achieve risk factor control and showed higher guideline-recommended medication use.[9,21] SURF CHD noticed extremely low rates of attendance of cardiac rehabilitation programs in China and Saudi Arabia; whereas European patients appeared to materially benefit from such program.

Changes in risk factor management over time have rarely been reported in these studies with the exception of EuroAspire. The comparisons across the EuroAspire surveys showed paradoxically that lifestyle factors have deteriorated over time with increases in obesity and diabetes and little change in smoking noted.[13,22] However, the therapeutic target achievements for blood pressure and lipid management improved over time, demonstrating efforts by institutionalized care, although they are still far from optimal in Europe.[13,22]

Table 1. Comparison of lifestyle factors and medication intake in international clinical audits

	EuroAspire III	EuroAspire IV	SURF CHD	SURF pilot	WHO-PREMISE	PURE	REACH*
Total No.	8966	7998	6722	497	10000	424921	5650
No. Country	22	24	8	3	10	17	44
Women	25	24	27	21	37	53	32
Age	60	63	65	65	59	50	68
Current smoker	17	16	18	15	13	19	17
Insufficient exercise‡	70	60	41	47	53	65	NA
DM	35	31	22	25	32	24	25
HTN	67	78	71	72	68	76	76
Dyslipidaemia	51	73	77	68	40	NA	NA
Medication							
Antiplatelet	91	98	91	88	81	25	26
Beta blocker	80	86	78	76	48	17	20
Statin	78	90	87	85	30	15	17
ACEI/ARB	71	77	72	67	40	20	20

EuroAspire: European survey of Cardiovascular Disease prevention; SURF CHD: SUrvey of Risk Factor Coronary Heart Disease; WHO-PREMISE: WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE; PURE: Prospective Urban Rural Epidemiology; REACH: REduction of Atherothrombosis for Continued Health; NA: not application.

All numerical variables are mean±standard deviation and categorical variables are percentage.

* This column only presents results from coronary heart disease in REACH.

‡ Insufficient exercise: less than recommended physical activity (30 minutes of moderately vigorous activity three to five times weekly)

INTRODUCTION OF SURF CHD phase II

The second phase of SURF CHD (SURF CHD II) is designed to learn from these studies to develop a feasible, achievable, and relevant audit tool for use in daily practice. It remains a targeted tool but with a more comprehensive recruitment strategy and a dedicated online data collection system to provide regular and rapid information on cardiovascular risk factor recoding and management worldwide. SURF CHD will allow benchmarking against guideline recommendations in order to improve quality of care in day-to-day life.

Recruitment: generalizability

A more formal recruitment strategy is planned to enhance representativeness and generalizability in the second phase, aiming to recruit 300 centers worldwide over six regions with at least 50 cases to be recruited per site. Recruitment will be carried out through the extensive international network of the European Association of Preventive Cardiology (EAPC). The SURF CHD website will be re-designed to attract more global health professionals. Improved recruitment strategies will encourage more low- and middle-income countries with limited resources to participate to provide more accurate and up-to-date cardiovascular risk factor management information in these areas.

Data collection: comprehensive methodology

Data collection will remain easy to collect and will be focused on core cardiovascular risk factor questions. Some modifications have been made to ease understanding and to reduce entering invalid values. For instance, education will be categorized to reduce incomplete data due to the misunderstanding of audit question on educational attainment. Similarly, questions on laboratory variables have been reformatted to improve clarity.

A new electronic data collection system will be developed within REDCap, a secure web application for building and managing online surveys and databases; helping SURF CHD to be easily administered in a busy clinical setting. Before being uploaded to the central system, data can be collected both online and offline, which will facilitate the application of SURF CHD in all types of hospital facilities. The compulsory fill-in boxes and pre-defined boundaries for each audit question offer a double checking system for all clinicians to prevent medical recording errors and reduce missing and incomplete data to provide a basis for practice during routine clinics.

Re-audit: repeatability

Completion of the audit cycle involves implementing improvements in clinical practice such as establishment of standard operating procedures and repeating the audit to see if improvements have occurred.[23,24] The improved collection methodology and easy online data collection system will allow SURF CHD to be performed regularly. The same strategies for data analysis with minimized extra effect will be undertaken to ensure comparability with original SURF CHD audit.[25] It is hoped that SURF CHD also has the potential to inform future guidelines on the prevention of CVD by identifying areas that need the most attention.

Feedback: structured feedback system

Identifying the problems and bringing in changes is the most critical and difficult part of audits.[2,23,25] It is essential to demonstrate that changes have been implemented, are sustainable and result in improvement so a plan for future monitoring will be needed.[2] Findings of SURF CHD will be presented overall and by characteristics such as age, sex, diagnostic category and region. Annual audit reports for individual participating countries with detailed center information will be returned to national coordinators together with grouped mean results from other centers for comparison purposes. Individual center's results will also be returned to the participating center, together with comparative grouped mean results for their region. All results will be carefully reviewed and compared with previous SURF CHD reports.

Implementation: action plan

Feedback from audits would be more effective and efficient when accompanied by explicit targets and an appropriate action plan, and when associated with low baseline adherence to develop an agreed standard operating procedure for the next audit cycle.[26,27] SURF CHD can be used as a hospital accreditation tool to improve the quality and safety of healthcare by applying standards and promoting uptake of evidence-based clinical and organizational practice.[28–30]

All implementation activities usually require support from a number of key stakeholders-policy makers, clinicians, and patients. Policy makers could set specific clinical targets related to the SURF CHD results for all health professionals that they are expected to reach and agree an action plan with suggestions or advice about how to improve cardiovascular risk factor management.[26] Clinicians could use SURF CHD results to check whether their prevention strategy is effective and whether their performance meets

national or international standard expectations. [26,31,32] The electronic data collection system will ensure rapid feedback to facilitate process improvement. Communication of the SURF CHD results to patients may also help them to identify area such as lifestyle that are particularly challenging and need a partnership approach between the patient and the healthcare professional.

Data linkage and project extension

Data linkage is a logical, efficient, and cost-effective method for maximizing use of existing data and increasing amounts of other data that are being produced in order to improve healthcare delivery, patient care, and service infrastructure.[33,34] Such an innovative technique can be applied to SURF CHD. The possibility of data linkage between global health and other types of data for different objectives has been demonstrated in Chapter 3.3. It was an attempt to use audit data to investigate more health related research questions beyond cardiovascular risk factor management. However, it is still challenging to incorporate linkages with integrated audit research and conduct high-quality data linkage processes due to lack of standardized data definitions and inconsistent coding practices.[35] The new phase will exploit new opportunities for large-scale audits collecting data from routine clinics to link with different recourses and facilitate more sophisticated research that are likely only to be addressed with such data linkage technique.

SURF CHD is also practical to be expanded to other research areas associated with increased cardiovascular risk such as primary care, stroke, chronic lung disease and inflammatory arthritis. A pilot study has already been undertaken in these areas.[36]

CONCLUSION

In conclusion, poor cardiovascular risk factor recording and striking disparities in guideline implementations in daily practice are the major challenges for CVD secondary prevention worldwide, despite the wide availability of evidence-based guidelines on CVD prevention. There are substantial regional variations in cardiovascular risk factor management. The observations call for a more efficient and effective monitoring program for risk factor management to improve guideline adherence in daily practice.

A clinical audit is considered the best quality assessment tool. However, the availability and applicability of a well-designed clinical audit program is limited in current literature and its efficiency and effectiveness remains unrecognized. The main challenge is to undertake a high quality clinical audit, which is performed with a comprehensive methodology, has generalizability and feasibility for all types of clinical settings in different geographical areas, is repeatable in an agreed period of time, provides up-to-date feedback, and develops a clear and explicit action plan.

SURF CHD has demonstrated the feasibility of a practical audit tool for CVD risk factor recording and management during routine clinic visits. However, representativeness of the included sites is limited. The next phase with an upgraded data collection system and a better defined recruitment strategy will permit more audit data from daily practice, aiming to provide a better view of cardiovascular risk factor management and reduce the guideline implementation gap in the future.

REFERENCES

1. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation. *Atherosclerosis* 2016; 252: 207–274.
2. Paton JY, Ranmal R, Dudley J, et al. Clinical audit: Still an important tool for improving healthcare. *Arch Dis Child Educ Pract Ed* 2015; 100: 83–88.
3. National Institute for Clinical Excellence. Principles for Best Practice in Clinical Audit. *Radcliffe Medical Press* 2002; 206.
4. Committee for proprietary medicinal products (CPCM). Points to consider on missing data. *Eur Med Agency* 2001; 0–5.
5. Graham JW. Missing Data Analysis: Making It Work in the Real World. *Annu Rev Psychol* 2009; 60: 549–576.
6. Kotseva K, Wood D, Backer G De, et al. EUROASPIRE III : a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Prev Cardiol* 2009; 16: 121–137.
7. Kotseva K, Wood D, De Bacquer D, et al. EUROASPIRE IV: A European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. *Eur J Prev Cardiol* 2016; 23: 636–648.
8. Ohman EM, Bhatt DL, Steg PG, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: An international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. *Am Heart J* 2006; 151: 786.e1-10.
9. Teo K, Chow CK, Vaz M, et al. The Prospective Urban Rural Epidemiology (PURE) study: Examining the impact of societal influences on chronic noncommunicable diseases in low-, middle-, and high-income countries. *Am Heart J* 2009; 158.
10. Mendis S, Abegunde D, Yusuf S, et al. WHO study on Prevention of REcurrences of Myocardial Infarction And StrokE (WHO-PREMISE). *Bull World Health Organ* 2005; 83: 820–828.
11. EUROASPIRE Study Group. EUROASPIRE A European Society of Cardiology survey of secondary prevention of coronary heart disease : Principal results. *Eur Heart J* 1997; 1569–1582.
12. EUROASPIRE II Study Group. Lifestyle and risk factor management and use of drug therapies in coronary patients from 15 countries: Principal results from EUROASPIRE II Euro Heart Survey Programme. *Eur Heart J* 2001; 22: 554–572.
13. Kotseva K, De Bacquer D, Jennings C, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999–2013. *Glob Heart* 2017; 12: 315–322.e3.
14. Corsi DJ, Subramanian SV, Chow CK, et al. Prospective Urban Rural Epidemiology

(PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. *Am Heart J* 2013; 166: 636–646.e4.
15. Dehghan M, Mente A, Rangarajan S, et al. Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* 2018; 0: 1–10.
16. Cooney MT, Reiner Z, Sheu W, et al. SURF - SUrvey of Risk Factor management: First report of an international audit. *Eur J Prev Cardiol* 2014; 21: 813–822.
17. Zhao M, Cooney MT, Klipstein-Grobusch K, et al. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.
18. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): A prospective epidemiological survey. *Lancet* 2011; 378: 1231–1243.
19. Rodriguez F, Cannon CP, Steg PG, et al. Predictors of long-term adherence to evidence-based cardiovascular disease medications in outpatients with stable atherothrombotic disease: Findings from the REACH registry. *Clin Cardiol* 2013; 36: 721–727.
20. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA* 2006; 295: 180–9.
21. Teo KK, Lear SA, Islam S, et al. Prevalence of a Healthy Lifestyle Among Individuals With Cardiovascular Disease in High-, Middle- and Low-Income Countries. *JAMA* 2013; 309: 1613–1621.
22. Kotseva K, Wood D, De Backer G, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009; 373: 929–940.
23. Gillam S, Frcp F. Frameworks for improvement : clinical audit , the plan–do–study–act cycle and significant event audit. *Qual Prim Care* 2013; 21: 123–130.
24. Burgess R. *NEW Principles of Best Practice in Clinical audit*. Radcliffe, 2011.
25. Benjamin A. The competent novice. Audit: How to do it in practice. *BMJ* 2008; 336: 1241–1245.
26. Ivers N, Jamtvedt G, Flottorp S, et al. Audit and feedback : effects on professional practice and healthcare outcomes (Review). *Cochrane database Syst Rev* 2012; 6: CD000259.
27. Scott I. What are the most effective strategies for improving quality and safety of health care? *Intern Med J* 2009; 39: 389–400.
28. Devkaran S, O'Farrell PN. The impact of hospital accreditation on clinical documentation compliance: A life cycle explanation using interrupted time series analysis. *BMJ Open* 2014; 4: 1–9.
29. Brubakk K, Vist GE, Bukholm G, et al. A systematic review of hospital accreditation: The challenges of measuring complex intervention effects. *BMC Health Serv Res*

2005; 15.
30. Hinchcliff R, Greenfield D, Westbrook JI, et al. Stakeholder perspectives on implementing accreditation programs: A qualitative study of enabling factors. *BMC Health Serv Res* 2013; 13: 1.
31. Dallongeville J, Banegas JR, Tubach F, et al. Survey of physicians' practices in the control of cardiovascular risk factors: The EURIKA study. *Eur J Prev Cardiol* 2012; 19: 541–550.
32. Mosca L, Linfante AH, Benjamin EJ, et al. National study of physician awareness and adherence to cardiovascular disease prevention guidelines. *Circulation* 2005; 111: 499–510.
33. Andrew NE, Sundararajan V, Thrift AG, et al. Addressing the challenges of cross-jurisdictional data linkage between a national clinical quality registry and government-held health data. *Aust N Z J Public Health* 2016; 40: 436–442.
34. Martin-Sanchez F, Verspoor K. Big data in medicine is driving big changes. *Yearb Med Inform* 2014; 9: 14–20.
35. Cooke CR, Iwashyna TJ. Using existing data to address important clinical questions in critical care. *Crit Care Med* 2013; 41: 886–896.
36. Dudina A, Lane S, Butler M, et al. SURF-COPD: The recording of cardiovascular risk in patients with chronic lung disease. *QJM An Int J Med* 2018; 303–306.


SURF
SUrvey of Risk Factors

6

Appendix

Summary

Samenvatting

List of publications

Acknowledgement

About the author

SUMMARY

Cardiovascular disease (CVD) remains one of the leading causes of death worldwide. There has been a significant increase of CVD deaths in low- and middle-income countries over the last two decades. Current evidence-based guidelines offer explicit advice on CVD risk factor management, guideline implementation and the evaluation of risk factor management. Despite this, CVD risk factor management remains inadequate and there are few clinical audits to monitor cardiovascular risk factor recording and management.

SURF CHD (SUrvey of Risk Factors Coronary Heart Disease) was designed as a straightforward and targeted clinical audit tool that aimed to simplify the recording and monitoring of routine CVD risk factors in patients with established CHD.

The primary objectives of this thesis were to summarize the importance of clinical audits in daily practice, describe CVD risk factor recording and management in routine practice and assess inequalities in risk factor management and their determinants within and between different geographic regions. Routine CVD risk factor data were then related to air pollution data to explore the technical feasibility of data linkage. Finally, the use of preventive cardiovascular medication in China as a large country in which medical practice is developing was assessed.

Overview on clinical audit program of cardiovascular risk factor management and introduction to SUrvey of Risk Factors (SURF CHD)

In chapter 2 (chapters 2.1 and 2.2) the rationale for clinical audits regarding CVD risk factors were reviewed with a description of current audit programs and presentation of the findings of SURF CHD. Chapter 2.1 demonstrated the necessity of clinical audits to ensure that high quality of cardiovascular care is provided to CHD patients in daily practice. Existing clinical audits have been reviewed to provide an overall picture of the quality of CVD risk factor management. The consistency and representativeness of current audits were found to be limited. This chapter highlighted challenges of performing a good quality and representative clinical audit with an easily operated and structured methodology and repeatable data collection system.

In chapter 2.2, results from SURF CHD were presented. 10,186 patients with established CHD were recruited from 79 centers in 11 countries among three different regions (Europe, Asia, and the Middle East). Recording of routine CVD risk factor information

varied considerably. The highest frequency of missing data was noted in laboratory measurements such as lipids. CVD risk factor control was generally poor. Over 80% of participants had inadequate risk factor management with less than five risk factors being controlled. Sixteen percent of participants reported as smoker, 29% were obese, and 46% had abdominal obesity. There were substantial regional variations. For instance, in Asia or in the Middle East, less than 3% of patients attended cardiac rehabilitation, compared with 45% in Europe. The use of cardiovascular medications was generally lower in Asia.

SURF CHD: Inequalities in cardiovascular risk factor management in daily practice and associated determinants

In chapter 3 we explored differences in cardiovascular risk factor recording and management by SURF CHD data. In chapter 3.1, we investigated whether there were sex differences in risk factor management and assessed demographic variations in sex differences. 10,186 patients (29% women) were analyzed from SURF CHD. Risk factor management for secondary prevention was generally worse in women than in men. Women were less likely to achieve targets for total cholesterol (odds ratio <OR> 0.50, 95% confidence interval <CI> 0.43 to 0.59), low-density lipoprotein cholesterol (LDL) (OR 0.57, 95% CI 0.51 to 0.64), and glucose (OR 0.78, 95% CI 0.70 to 0.87), or to be physically active (OR 0.74, 95% CI 0.68 to 0.81) or non-obese (OR 0.82, 95% CI 0.74 to 0.90). The magnitude and direction of sex differences varied by region. The most notable regional difference was related to smoking habit. While the prevalence of smoking was similar between the sexes in Europe, women in Asia and the Middle East were considerably less likely to smoke than men. Sex disparities in reaching treatment targets were smaller in Europe than in Asia and the Middle East. Women in Asia were more likely than men to reach lifestyle targets, with opposing results in Europe and the Middle East.

In chapter 3.2 we investigated characteristics (age, family history, cardiac rehabilitation, previous hospital admission, and history of diabetes) that had a significant impact on overall CVD risk factor management. We identified 9,987 consecutive CHD patients from SURF CHD between 2012 and 2013. The overall risk factor management was summarized as Cardiovascular Health Index Score (CHIS) based on six CVD risk factor targets (non/ex-smoker, body mass index<30, adequate physical activity, controlled blood pressure, controlled LDL, and controlled glucose). A moderate CHIS (with three or more risk factor controlled) was less likely to be reached by women (OR 0.84. 95% CI 0.74-0.95), and those aged<55 years old (OR 0.62, 95% CI 0.52-0.74), and those with diabetes (OR 0.38, 95% CI 0.34-0.43). There were regional variations in determinants of risk factor management.

Younger Asian and European patients tended to have poorer risk factor management; whereas, there was no significant age difference in the Middle East. Participation in cardiac rehabilitation was demonstrated to be associated with better cardiovascular risk factor management in European patients. In contrast, availability and feasibility of cardiac rehabilitation is limited in Asia and the Middle East and thus its effectiveness cannot be analyzed appropriately.

In chapter 3.3 the long-term $PM_{2.5}$ exposure from a consistent global exposure model was linked to individual data on routinely measured CVD risk factors from SURF CHD to determine the feasibility of the methodology and to investigate associations between long-term $PM_{2.5}$ and cardiovascular risk factors (blood pressure, lipids, and glucose). A total of 8,392 CHD patients among 10 countries in Europe, Asia, and the Middle East were analyzed. The analyses demonstrated the feasibility of linking these distributed data but also pointed at challenges in their interpretation given that this was a secondary prevention population and therefore already exposed to active risk factor management. We found an increase of $PM_{2.5}$ was significantly associated with decreased BP and increased glucose in a global scale. After country adjustment, $PM_{2.5}$ was associated with small increases in LDL and small decreases in blood pressure.

Guideline-recommended cardiovascular medication use for secondary prevention of coronary heart disease

In chapter 4 we systematically reviewed and summarized cardiovascular medication use in China between 1995 and 2015 and assessed factors in associated with cardiovascular medication trends. Thirty-five studies from 13,490 identified publications were included. The pooled prevalence for aspirin, beta-blockers, statins, ACE-Inhibitors, ACE-Inhibitor/ARBs and nitrates was 92% (95% CI: 0.89±0.95), 63% (95% CI: 0.57±0.69), 72% (95% CI: 0.60±0.82), 49% (95% CI: 0.41±0.57), 59% (95% CI: 0.48±0.69) and 79% (95% CI: 0.74±0.91), respectively. We observed a significant increase in beta-blocker and statin use over the last two decades. Yet, in general, current cardiovascular medication use is still inadequate in China.

In the general discussion (chapter 5) we summarized the key findings, addressed methodological considerations of SURF CHD, and described the nature of clinical audit programs for secondary prevention of CHD. It is still challenging to perform an effective clinical audit embedded within routine practice. Using clinical audit data to assess guideline applications and make appropriate prevention changes requires commitment

at all levels, from international to local organizations, and support by all stakeholders, from policy makers to patients. Lastly, this thesis introduced the new phase of SURF CHD with improved methodology, an upgraded online data recruitment system, and better-structured recruitment strategy. This new phase is designed to be feasible, achievable, and a targeted audit tool for routine use to provide regular and rapid cardiovascular risk factor information in more geographic areas.

To conclude, it is recommended that healthcare professionals take the findings into account to have a better understanding of cardiovascular risk factor recording and management in daily practice. Improved recognition of clinical audit is urgently needed for all stakeholders. A targeted, achievable, and relevant clinical audit, like SURF CHD, should be considered worldwide, especially for low- and middle-income countries. Secondary prevention strategies should be developed accordingly to meet local requirements in different geographic areas.

SAMENVATTING

Hart- en vaatziekten (HVZ) blijven wereldwijd een van de belangrijkste doodsoorzaken. De afgelopen twee decennia is er een significante toename van HVZ geweest in lage- en middeninkomenslanden. De huidige richtlijnen bieden expliciet advies over HVZ risico factor management, richtlijn implementatie en de evaluatie van risico factor management. Desondanks blijft HVZ risicofactor management ontoereikend en zijn er weinig klinische audits om de registratie en het HVZ risicofactor management te controleren.

SURF CHD (Survey van risico factoren coronaire hartziekten) is ontworpen als een eenvoudige en doelgerichte klinische controletool, gericht op het vereenvoudigen van de registratie en de bewaking HVZ risico factoren in patiënten met gevestigde coronaire hartziekten (CHZ).

De primaire doelstellingen van dit proefschrift omvatten het belang van klinische audits in de dagelijkse praktijk samenvatten, de registratie en het beheer van HVZ risicofactoren in de dagelijkse praktijk te beschrijven en ongelijkheden in het risicofactoren management en de bijbehorende determinanten binnen en tussen verschillende geografische regio's te beoordelen. HVZ risicofactordata zijn vervolgens gerelateerd aan luchtvervuilingsdata om de technische haalbaarheid van gegevenskoppeling te verkennen. Ten slotte werd het preventieve gebruik van HVZ medicatie in China, een groot land waarin de medische praktijk zich nog ontwikkeld, beoordeeld.

Overzicht van het klinisch auditprogramma voor het HVZ risicofactoren management en de introductie van Survey van risicofactoren coronaire hartziekten (SURF CHD)

In hoofdstuk 2 (hoofdstukken 2.1 en 2.2) werden de redenen voor klinische audits met betrekking tot HVZ risicofactoren beoordeeld, met een beschrijving van de huidige auditprogramma's en de presentatie van de bevindingen van SURF CHD. Hoofdstuk 2.1 toonde de noodzaak van klinische audits aan om ervoor te zorgen dat hoogstaande cardiovasculaire zorg aan CHZ patiënten wordt geboden in de dagelijkse praktijk. Bestaande klinische audits zijn beoordeeld om een algemeen beeld te geven van de kwaliteit van het HVZ risicofactoren management. De samenhang en representativiteit van de huidige audits bleken beperkt te zijn. Dit hoofdstuk belichtte de uitdagingen voor het uitvoeren van een representatieve klinische audit van goede kwaliteit met een

eenvoudig te bedienen en gestructureerde methode en een systeem voor herhaalde gegevensverzameling.

In hoofdstuk 2.2 werden de resultaten van SURF CHD gepresenteerd. In 79 centra in 11 landen uit drie verschillende regio's (Europa, Azië en het Midden-Oosten) werden 10.186 patiënten met gevestigde CHZ gerekruteerd. De registratie van routinematig HVZ risicofactorinformatie varieerde aanzienlijk. De hoogste frequentie van ontbrekende gegevens werd gezien in laboratoriummetingen zoals lipiden. HVZ risicofactor controle was over het algemeen slecht. Meer dan 80% van de deelnemers had een ontoereikend risico factor management waarbij minder dan vijf risicofactoren onder controle waren. Zestien procent van de deelnemers was roker, 29% had obesitas en 46% had abdominale obesitas. Er waren aanzienlijke regionale variaties. Bijvoorbeeld, in Azië f het Midden-Oosten, woonde minder dan 3% van de patiënten een hartrevalidatie programma bij, vergeleken met 45% in Europa. Het gebruik van cardiovasculaire medicatie was over het algemeen lager in Azië.

SURF CHD: Ongelijkheden in HVZ risicofactor management in de dagelijkse praktijk en daarmee samenhangende determinanten

In hoofdstuk 3 hebben we de verschillen onderzocht in de registratie en het HVZ risicomanagement door middel van SURF CHD gegevens. In hoofdstuk 3.1 onderzochten we of er sprake was van sekseverschillen in het risicofactor management en beoordeelden we de demografische variaties in sekseverschillen. We analyseerden 10.186 patiënten (29% vrouwen) van SURF CHD. Risicofactor management voor secundaire preventie was over het algemeen slechter bij vrouwen dan bij mannen. Vrouwen bereikten minder vaak de doelen voor totaal cholesterol (Odds Ratio <OR> 0,50; 95% betrouwbaarheidsinterval <BHI> 0,43 tot 0,59; lagedichtheidlipoproteïne cholesterol (LDL) (OR 0,57; 95% BHI 0,51 tot 0,64); en glucose (OR 0,78; 95% BHI 0,70 tot 0,87), of om fysiek actief te zijn (OR 0,74; 95% BHI 0,68 tot 0,81) of niet-obesitas (OR 0,82; 95% BHI 0,74 tot 0,90). De omvang en richting van de sekseverschillen varieerden per regio. Het meest opvallende regionale verschil was gerelateerd aan rookgewoonten. Terwijl de prevalentie van roken vergelijkbaar was tussen de geslachten in Europa, hadden vrouwen in Azië en het Midden-Oosten aanzienlijk minder kans om te roken dan mannen. Sekse ongelijkheden bij het bereiken van behandeldoelen waren in Europa kleiner dan in Azië en het Midden-Oosten. Vrouwen in Azië hadden meer kans dan mannen om lifestyle-doelen te bereiken, met tegengestelde resultaten in Europa en het Midden-Oosten.

In hoofdstuk 3.2 onderzochten we kenmerken (leeftijd, familiegeschiedenis, hartrevalidatie, eerdere ziekenhuisopname en diabetesgeschiedenis) die een significante impact hadden op het algehele HVZ risicofactor management. We identificeerden 9.987 opeenvolgende CHZ-patiënten van SURF CHD tussen 2012 en 2013. Het algemene risicofactor management werd samengevat als Cardiovascular Health Index Score (CHIS) op basis van zes cardiovasculaire risicofactordoelen (niet/ex roker, body mass index <30, adequate fysieke activiteit, gecontroleerde bloeddruk, gecontroleerd LDL en gecontroleerde glucose). Een matige CHIS (met drie of meer gecontroleerde risicofactoren) werd minder door vrouwen bereikt (OR 0,84; 95% BHI 0,74-0,95) en personen van <55 jaar oud (OR 0,62; 95% BHI 0,52-0,74) en diegenen met diabetes (OR 0,38; 95% BHI 0,34-0,43). Er waren regionale variaties in determinanten van risicofactor management. Jongere Aziatische en Europese patiënten neigden naar een slechter risicofactor management; terwijl er geen significant leeftijdsverschil was in het Midden-Oosten. Deelname aan hartrevalidatie bleek geassocieerd te zijn met beter HVZ risicofactor management bij Europese patiënten. Echter is de beschikbaarheid en haalbaarheid van hartrevalidatie beperkt in Azië en het Midden-Oosten en dus kan de effectiviteit niet op de juiste manier worden geanalyseerd.

In hoofdstuk 3.3 werd langdurige $PM_{2.5}$-blootstelling van een consistent globaal blootstellingsmodel gekoppeld aan individuele gegevens over routinematig gemeten HVZ risicofactoren van SURF CHD om de haalbaarheid van de methodologie te bepalen en verbanden tussen langdurige $PM_{2.5}$ en cardiovasculaire risicofactoren (bloeddruk, lipiden en glucose) te onderzoeken. Een totaal van 8.392 CHZ-patiënten uit 10 landen in Europa, Azië en het Midden-Oosten werden geanalyseerd. De analyses toonden de haalbaarheid aan van het koppelen van deze verspreide gegevens, maar wezen ook op uitdagingen in hun interpretatie, aangezien dit een secundaire preventiepopulatie was en deze daarom al werd blootgesteld aan actief risicofactor management. We vonden dat een toename van $PM_{2.5}$ significant was geassocieerd met verlaagde bloeddruk en verhoogde glucose op wereldwijde schaal. Na correctie voor het land was $PM_{2,5}$ geassocieerd met kleine verhogingen van LDL en kleine verlagingen van de bloeddruk.

Cardiovasculair medicatie gebruik voor secundaire preventie van coronaire hartziekten aanbevolen door de richtlijnen

In hoofdstuk 4 hebben we het gebruik van cardiovasculaire medicatie in China tussen 1995 en 2015 systematisch beoordeeld en samengevat en onderzocht welke factoren verband hadden met cardiovasculaire medicatietrends. Vijfendertig studies van 13,490

geïdentificeerde publicaties werden geïncludeerd. De gepoolde prevalentie voor aspirine, bètablokkers, statines, ACE-remmers, ACE-remmers/ARB's en nitraten was 92% (95% BHI: 0,89 tot 0,95), 63% (95% BHI: 0,57 tot 0,69), 72% (95% BHI: 0,60 tot 0,82), 49% (95% BHI: 0,41 tot 0,57), 59% (95% BHI: 0,48 tot 0,69) en 79% (95% BHI: 0,74 tot 0,91), respectievelijk. We zagen de afgelopen twee decennia een significante toename van het gebruik van bètablokkers en statines. Maar over het algemeen is het huidige gebruik van cardiovasculaire medicatie nog steeds ontoereikend in China.

In de algemene discussie (hoofdstuk 5) hebben we de belangrijkste bevindingen samengevat, de methodologische overwegingen van SURF CHD behandeld en de aard van klinische auditprogramma's voor secundaire preventie van CHD beschreven. Het is nog steeds een uitdaging om een effectieve klinische audit uit te voeren ingebed in de dagelijkse praktijk. Het gebruik van klinische auditgegevens om richtlijntoepassingen te beoordelen en gepaste preventiewijzigingen aan te brengen vereist betrokkenheid op alle niveaus, van internationale tot lokale organisaties, en ondersteuning door alle belanghebbenden, van beleidsmakers tot patiënten. Ten slotte introduceerde dit proefschrift de nieuwe fase van SURF CHD met verbeterde methodologie, een verbeterd online rekruteringssysteem en een beter gestructureerde wervingsstrategie. Deze nieuwe fase is ontworpen om uitvoerbaar en haalbaar te zijn en een gerichte audittool voor routinegebruik om regelmatige en snelle informatie over cardiovasculaire risicofactoren te bieden in meer geografische gebieden.

Tot slot wordt aanbevolen dat beroepsbeoefenaren in de gezondheidszorg de bevindingen in overweging nemen om een beter inzicht te krijgen in de registratie en het management van cardiovasculaire risicofactoren in de dagelijkse praktijk. Verbeterde erkenning van klinische audits is dringend nodig voor alle belanghebbenden. Een gerichte, haalbare en relevante klinische audit, zoals SURF CHD, moet wereldwijd worden overwogen, vooral voor landen met lage en middelhoge inkomens. Secundaire preventiestrategieën moeten dienovereenkomstig worden ontwikkeld om te voldoen aan lokale vereisten in verschillende geografische gebieden.

LIST OF PUBLICATIONS

Chapter 2.1

Min Zhao, Ilonca Vaartjes, Kerstin Klipstein-Grobusch, Kornelia Kotseva, Catriona Jennings, Diederick E. Grobbee, Ian Graham. Quality assurance and the need to evaluate interventions and audit programme outcomes. *Eur J Prev Cardiol* 2017; 24: 123–128.

Chapter 2.2

Min Zhao, Marie Therese Cooney, Kerstin Klipstein-Grobusch, Ilonca Vaartjes, Dirk De Bacquer, Johan De Sutter, Zeljko Reiner, Eva Prescott, Pompilio Fraggiano, Diego Vanuzzo, Hussam AlFaleh, Ian Menown, Dan Gaita, Nana Pogosova, Wayne H-H Sheu, Dong Zhao, Huijuan Zuo, Diederick E. Grobbee, Ian Graham. Simplifying the audit of risk factor recording and control: A report from an international study in 11 countries. *Eur J Prev Cardiol* 2016; 23: 1202–1210.

Chapter 3.1

Min Zhao, Ilonca Vaartjes, Ian Graham, Diederick E Grobbee, Wilko Spiering, Kerstin Klipstein-Grobusch, Mark Woodward, Sanne AE Peters. Sex differences in risk factor management of coronary heart disease across three regions. *Heart* 2017; 103: 1587–1594.

Chapter 3.2

Min Zhao, Ian Graham, Marie Therese Cooney, Diederick E. Grobbee, Ilonca Vaartjes, Kerstin Klipstein-Grobusch. Determinants in risk factor management of coronary heart disease across three regions. *In press.*

Chapter 3.3

Min Zhao, Hoek Gerard, Maciej Strak M, Diederick E. Grobbee, Ian Graham, Kerstin Klipstein-Grobusch, Ilonca Vaartjes. A global analysis of associations between fine particle air pollution and blood pressure, lipids, and glucose in patients with coronary heart disease of the SUrvey of Risk Factors (SURF) study. *Submitted.*

Chapter 4

Min Zhao, Xin Wang, Kerstin Klipstein-Grobusch, Johannes B. Reitsma, Dong Zhao, Diederick E. Grobbee, Ian Graham, Ilonca Vaartjes. Prevalence of cardioprotective medication usage in secondary prevention of myocardial infarction (MI) in China. *PLoS One*. 2017; 12(4): e0175947.

ACKNOWLEDGEMENT

Studies described in this thesis were supported by Netherlands Organization for Scientific Research (NWO; grant number: 0.22.005.021).

Dear Prof. Ian Graham, thank you for being a wonderful supervisor! You have given me great opportunities to become an academic researcher. I still remember the first time I saw you in my master defense at Imperial College London. After 5 years, you are yet again my supervisor in my PhD defense. I am really grateful that you offered me a position in SURF, which has changed my life for the better. Thank you also for providing me with a great reference on 45th International 10-day seminar of Cardiovascular Disease Epidemiology and Prevention program. I've made lots of great academic friends in that seminar. Lastly but not least, thank you for introducing Julius Center to me. I am really glad that I am a PhD in UMCU.

Dear Prof. Rick Grobbee, thank you for offering me this fantastic PhD position and also being my ultimate promoter! I would like to thank you specifically for providing great ideas on my PhD topics. I feel so lucky to have you to guide me all the way along the journey.

Dear Dr. Kerstin Klipstein-Grobusch, I am really grateful to you for the interview and all administration work before my PhD officially started. I am also glad you are my daily supervisor to provide endless support in day-to-day PhD life, which required greater patience due to that I was remotely working in London.

Dear Dr Ilonca Vaartjes, thank you for understanding, compromising, and encouraging me to be a great academic researcher. I truly enjoyed working with you and always feel secure to have you as my colleague and co-promoter. It is also interesting to know that I am your second Chinese student and thank you so much for understanding our culture.

Dear Dr Sanne Peters, I am really glad to work with you! You are a role model to me and your work attitude has given me great inspiration! Thank you for supporting my work! I hope we could work together again in future!

Dear Prof. Mark Woodward, thank you for your support on my PhD work. I really learnt a lot from you on statistics and also on how to become an independent researcher!

Dear Dr. Marie-Therese Cooney, thank you for sharing the SURF data to complete my PhD. I could not appreciate more with your great contribution on SURF for designing study, data collection, and many other tasks!

Dear all SURF coordinators, thank you for your coordination effort in collecting the SURF data. Your positive responses help SURF faster and more efficiently!

Dear Prof. David Wood, Dr. Kornelia Kotseva, and Dr. Catriona Jennings, thank you for giving me another opportunity to work with you after my master. I always enjoy my work in Imperial College London.

Dear Dr. Gerard Hoek, I would like to specially thank you for your great contribution on air pollution paper!! I really learnt a lot! I could not imagine how to finish this work without your help!

Dear Dr. Dong Zhao, Dr. Huijuan Zuo, Dr Johannes Reitsma, Dr. Wilko Spiering, and Dr. Maciej Strak, it is great to work with you and thank you for your contribution on my thesis!

Dear Xin Wang, thank you for your help and let me have a great start in Julius Center! It is always great to have Chinese around and we could chat with our own language!

Dear Dr. Joyce Browne, thank you for showing me around UMCU and helping me have a smooth start in UMCU. It is a pity I never get chance to work with you but I hope we will have the opportunity to work together in the future.

Dear Prof. F.L.J Visseren, Prof. T.J.M Verheij, Prof. M.L Bots, Prof. W.M.M Verschuren, and Prof L. Hofstra, thank you for reading my thesis and being my opponents.

Dear Veerle and Yujie, thank you for being my paranimfen! It can be difficult to be someone's paranimfen who is not based in London! You have been nothing but amazing!

Dear Kim, Veerle, Anne Meike, Eline, and Josefien, you are the best colleagues and friends ever!! Thank you for visiting me in London while I was pregnant! And also thank you for giving so many helps while I was in Utrecht! I always feel very warm to have you around! I hope you are not annoyed by my silly questions (I may ask more)!

Dear Clare (haha! Chang Xiao), Yujie, Yuxi, Nana, Huiying, Gao Shan, and Long Xin, I am super glad to have you all in Netherlands! Thanks for your dinner, drink, and parties!!

To my colleagues from Julius Center (Amy, Ary, Joyce, Putri, Jaike, Sarah, Karlijn, Roel, and Roxanne), thank you for your advice and your helps in Utrecht.

Dear Giene and Melanie, thank you so much for your administration work!! It has been pleasure to work with you!

Dear Coby and the ICT team, thank you for your support.

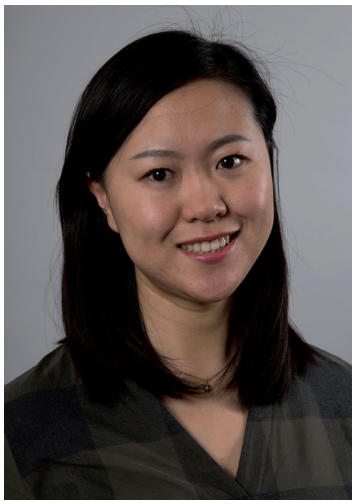
Dear Vroon and Marijke, thank you for your hospitality in the Biltstraat house.

Dear Alan, my love, thank you for supporting me to fulfill my dream-to became a PhD. You are also a mentor to me! Thank you for your great advice on both life and work! It can be hard for both of us as I work remotely. You never complain! 2018 was very tough for us to do everything together-have a newborn baby, sell our old flat, buy a new house, and finish my PhD thesis! But we managed and did a fantastic job! Just calm down and carry on! 一路有你，真好！

Dear Charlotte, you will be one year old when mummy finishes PhD. I feel very grateful you became my child. Mummy finalized this PhD work while taking care of you. It was tired but I really enjoyed it. 亲爱的宝贝，嘻嘻，妈妈真的很开心你的到来。我很荣幸当了你的妈妈。这一年，你带给了我们很多欢声笑语。希望你健健康康，茁壮成长！

亲爱的爸爸妈妈，感谢你们一路上的支持和无私的爱！我已经出国十年，谢谢你们让我出国这个决定改变了我的人生。也谢谢你们支持我走学术的道路， 让我能完成自己的梦想。做自己喜欢的职业！我爱你们！

ABOUT THE AUTHOR/CURRICULUM VITAE



Min Zhao was born on August 2, 1986 in Shanxi, China. She achieved her Bachelor's degree on pharmacy with first class from Sichuan University, Chengdu, China. In 2011, she completed a postgraduate course (MSc) in Preventive Cardiology at Imperial College London, UK. During her MSc, she has received various trainings on statistics, data management and academic writing and her research project was scored as distinction in that year. After graduated, she worked as a research assistant for Clinical Epidemiology Group at University College London between 2012 and 2015. At the time, she was involved in the Clinical Cohorts in Coronary disease Collaboration (4C) study. In July 2013, she was offered a place in 45th International 10-day seminar of Cardiovascular Disease Epidemiology and Prevention programme. In March 2015, she started to work on PhD research described in this thesis under supervision of Prof.Dr. Diederick E. Grobbee, Prof. Ian. Graham, Associate Prof. Ilonca Vaartjes, and Associate Prof. Kerstin Klipstein-Grobusch. In April 2017, she won young investigator prize in EuroPrevent 2017 on topic of 'sex differences in risk factor management of coronary heart disease across three regions'.