

Cardiovascular Risk Scoring for the Prevention of Cardiovascular Disease in Low-Resource Settings

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Christ Church
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*A thesis submitted for the degree of
Doctor of Philosophy*

Trinity 2017

Abstract

The aim of this thesis was to examine the use of total cardiovascular risk scoring for the prevention of cardiovascular disease (CVD) in low-resource settings. While risk scoring is popular in high-income countries, the overarching hypothesis was that it was sub-optimal for the prevention of CVD in low-resource settings. To achieve its aim, this thesis first synthesised evidence through a systematic review of systematic reviews on the impact of total CVD risk scoring on important patient outcomes. Second, it developed an R package to calculate World Health Organisation/International Society of Hypertension (WHO/ISH) CVD risk scores for all epidemiological subregions of the world. Third, using mixed methods and intensive fieldwork, it evaluated the practical implementation of WHO/ISH CVD risk scores in Médecins Sans Frontières clinics for Syrian refugees in Jordan. Lastly, it explored the potential to simplify CVD risk scores by replacing cholesterol information with body mass index using a contemporary CVD risk cohort from New Zealand. Overall, the findings showed that CVD risk scoring is sub-optimal for low-resource settings due to a lack of evidence of effectiveness, its difficulty to implement and test, and its potential to be simplified. Focus should be shifted towards conducting high quality randomised trials in low-resource settings, using simplified risk scores that can be completed in a single consultation, and further implementation studies in primary health care. With this in mind, cardiovascular risk scoring as a pivotal intervention for the prevention of CVD in low-resource settings should be judiciously compared to other alternatives, and if implemented, closely monitored for its impact on health outcomes.

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An international delegation questions an Uzbek family physician about WHO/ISH cardiovascular risk scores (Qarshi, Uzbekistan)

Acknowledgements

Professor Carl Heneghan, Dr. Alison Ward, and Professor Rod Jackson provided academic supervision of this thesis. Their acumen in the fields of evidence-based medicine, clinical epidemiology, and cardiovascular epidemiology contributed greatly to my development as an academic and to the development of my research. I am particularly inspired by their dedication to impact and to teaching and I aspire to carry forth these values in my future.

As a Rhodes Scholar, this thesis would not have been possible without The Rhodes Trust. Beyond providing me with the financial means to pursue this work, the Trust provided me with a community of unwavering support to pursue my dreams.

To my parents, Kathleen James, Phred Collins, and sister, Emily-Sky Collins, I extend immeasurable gratitude for their support and encouragement.

I am thankful to my friends and colleagues for their support: Niklas Bobrovitz, Benjamin Fletcher, Constantinos Koshari, Igho Onakpoya, Alice Thompson, Ruth Davis, Parmjot Gill, and Michael Mackley. And to my mentors and role models, Dr. Darlene Hammell, Professor Jane Buxton, Franca Gucciardi, and Professor Charlotte Loppie.

Abstract

The aim of this thesis was to examine the use of total cardiovascular risk scoring for the prevention of cardiovascular disease (CVD) in low-resource settings. While risk scoring is popular in high-income countries, the overarching hypothesis was that it was sub-optimal for the prevention of CVD in low-resource settings. To achieve its aim, this thesis first synthesised evidence through a systematic review of systematic reviews on the impact of total CVD risk scoring on important patient outcomes. Second, it developed an R package to calculate World Health Organisation/International Society of Hypertension (WHO/ISH) CVD risk scores for all epidemiological subregions of the world. Third, using mixed methods and intensive fieldwork, it evaluated the practical implementation of WHO/ISH CVD risk scores in Médecins Sans Frontières clinics for Syrian refugees in Jordan. Lastly, it explored the potential to simplify CVD risk scores by replacing cholesterol information with body mass index using a contemporary CVD risk cohort from New Zealand. Overall, the findings showed that CVD risk scoring is sub-optimal for low-resource settings due to a lack of evidence of effectiveness, its difficulty to implement and test, and its potential to be simplified. Focus should be shifted towards conducting high quality randomised trials in low-resource settings, using simplified risk scores that can be completed in a single consultation, and further implementation studies in primary health care. With this in mind, cardiovascular risk scoring as a pivotal intervention for the prevention of CVD in low-resource settings should be judiciously compared to other alternatives, and if implemented, closely monitored for its impact on health outcomes.

Statement of Contributions

I certify that the work of this thesis is my own. Where others have contributed to the work, their initials are used. The contributions of others are summarised as follows:

- **Niklas Bobrovitz** (NB) conducted duplicate extraction of information from WHO/ISH CVD risk charts and reviewed R code for simplicity as described in Chapter 4.
- **Thomas Frost** (TF) conducted duplicate qualitative data coding and contributed to the development of the final codes and coding framework in collaboration with me, as described in Chapter 6.
- **Constantinos Koshlaris** (CK) reviewed R code for errors as described in Chapter 4.
- **Joseph Lee** (JL) conducted duplicate extraction of information from WHO/ISH CVD risk charts and reviewed R code for simplicity as described in Chapter 4. He also generated a list of risk factors and risk scores using Octave as described in Chapter 4.
- **Igho Onakpoya** (IO) conducted duplicate GRADE assessment of studies, as described in Chapter 3.
- **Nia Roberts** (NR) reviewed the search strategy as described in Chapter 3.
- **Alice Thompson** (AT) conducted duplicate screening of articles for inclusion and duplicate data extraction, as described in Chapter 3.

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List of Abbreviations

AMSTAR		Assessing the Methodological Quality of Systematic Reviews
BPLT		Blood Pressure Lowering Treatment.
CoRA		Consultation-Dependent Risk Assessment.
CVD		Cardiovascular Disease.
DM		Diabetes Mellitus.
EMR B		Eastern Mediterranean Subregion B.
GRADE		Grading of Recommendations Assessment, Development and Evaluation.
ICD-10-AM		International Classification of Disease 10 Australian Modification.
ICT		Information and Communications Technology.
IQR		Interquartile Range.
LaRA		Laboratory-Dependent Risk Assessment.
LD		Laboratory-Dependent.
LDL		Low Density Lipoprotein.
LI		Laboratory-Independent.
LLT		Lipid Lowering Treatment.
LMIC		Low- and Middle-Income Country.
MD		Mean Difference.
MSF		Médecins Sans Frontières.
mmol/L		Millimol per Litre.
mmHg		Millimetre of Mercury.
NHEFS		National Health and Nutrition Examination Survey Follow-up Study.
NCD		Non-Communicable Disease.
OxTREC		Oxford Tropical Research Ethics Committee.

RCT		Randomised Controlled Trial.
RR		Risk Ratio.
SBP		Systolic Blood Pressure.
SDI		Socio-demographic Index.
SEAR D	. . .	South-East Asia Subregion D.
TC:HDL	. . .	Total Cholesterol to High Density Lipoprotein.
UN		United Nations.
UNAIDS	. . .	United Nations Programme on HIV/AIDS.
UNHCR	. . .	United Nations High Commissioner for Refugees
WHO		World Health Organisation.
WHO PEN	. .	WHO Package of Essential Non-Communicable Disease Interventions for Primary Health Care in Low-Resource Settings.
YLL		Years of Life Lost.

1

Overview and Structure of Thesis

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1.1 Overview of Thesis

1.1.1 Aim of Thesis

The aim of this thesis was to examine the use of total cardiovascular risk scoring for the prevention of cardiovascular disease (CVD) in low-resource settings.

1.1.2 Overall Hypothesis

The overarching hypothesis of this thesis was that cardiovascular risk scoring is sub-optimal for the prevention of CVD in low-resource settings.

1.1.3 Objectives

The objectives of this thesis were to:

1. Synthesise evidence from systematic reviews on the impact of total CVD risk scoring on important patient outcomes;

2. Develop the software tools required to study the use of World Health Organisation/International Society of Hypertension (WHO/ISH) CVD risk scores
3. Evaluate the practical implementation of total CVD risk scoring in a model low-resource setting; and
4. Develop and comparatively evaluate a simplified cardiovascular risk score which replaces the total cholesterol to high density lipoprotein ratio (TC:HDL) parameter with body mass index (BMI)

1.2 Structure of Thesis

Chapter 2: Background

Chapter 2 set the foundation of the thesis by discussing and summarising key concepts, existing work, and rationale for the thesis. It describes the global burden of CVD and the policy response of the United Nations and the WHO, including the use of total cardiovascular risk scoring in the WHO's Package of Essential Non-Communicable Disease (NCD) Interventions for Primary Health Care in Low-Resource Settings (WHO PEN). The chapter highlights the popularity but ambiguity of the term 'low-resource setting' and sets a working definition for the thesis. The chapter concludes with a rationale for the need to examine the use of CVD risk scoring for the prevention of CVD in low-resource settings.

Chapter 3: Cardiovascular Risk Scoring in Asymptomatic Adults: systematic review of systematic reviews

Chapter 3 examined the evidence from systematic reviews on the use of total CVD risk scoring in asymptomatic adults for the primary prevention of CVD. It illustrated that there was no evidence from systematic reviews that the prospective use of CVD risk scores translates to reductions in CVD-related morbidity or mortality, and low or very low quality evidence that it reduces levels of smoking, blood pressure and cholesterol. Furthermore, all evidence identified was from high-income countries, highlighting that trials in low-resource settings are likely needed before widespread adoption of CVD risk scoring in these jurisdictions.

Chapter 4: whoishRisk: an R Package to Calculate WHO/ISH CVD Risk Scores

Chapter 4 developed the methodological tools for Chapter 5, through the development of an R package to calculate WHO/ISH CVD risk scores for all epidemiological subregions of the world. This software was subsequently used to analyse routine clinical data collected in field clinics for Syrian refugees in Jordan (Chapter 5).

Chapter 5: Cardiovascular Disease Risk and Prevention Amongst Syrian Refugees in Jordan: quantitative strand of a mixed methods study

Chapter 5 reports the methods and findings of the quantitative strand of a mixed methods analysis of Médecins Sans Frontières (MSF's) NCD primary health care programme for Syrian refugees in Jordan. Its purpose was to evaluate MSF's precedent-setting implementation of WHO/ISH CVD risk scores in a model low-resource setting. Routine clinical data was used from 2,892 patients and the analysis showed that few eligible patients had documented risk scores, most risk scores were incorrectly calculated, and lipid-lowering treatment was discordant from total-risk based approaches despite the implementation of risk scoring.

Chapter 6: Cardiovascular Disease Risk and Prevention Amongst Syrian Refugees in Jordan: qualitative strand of a mixed methods study

Chapter 6 reports the methods and findings of the qualitative strand of a mixed methods analysis of MSF's NCD programme for Syrian refugees in Jordan, and integrates these findings with the quantitative strand (Chapter 5). It involved fieldwork in MSF clinics in Northern Jordan, near the Syrian border, to collect one-on-one interviews with MSF health workers who were using newly implemented CVD risk scores and total CVD-risk-based clinical guidance. These qualitative findings, when integrated with the quantitative findings of Chapter 5, showed that total CVD risk scoring and its guidance was sub-optimal for this setting and could be better adapted for low-resource settings. It highlighted the need for CVD risk scores that are laboratory-independent and require only one consultation with a clinician.

Chapter 7: Towards Simplified CVD Risk Scores: prognostic modelling study

Based on the findings of Chapter 3, 5, and 6 it become evident that if cardiovascular risk scores were to be trialled in low-resource settings, they would first need to be simplified to a score that could be used in a single consultation. Chapter 7 therefore aimed to determine the degree to which replacement of cholesterol information (TC:HDL ratio) with BMI in a prognostic CVD risk model would affect clinically meaningful performance. Using data from 326,827 adults, the analysis showed that the laboratory-independent model which used BMI performed as well as the laboratory-dependent model which used TC:HDL in terms of discrimination, calibration, net reclassification improvement, sensitivity, and specificity.

Chapter 8: Discussion and Conclusions

Chapter 8 summarises the main findings of chapters 3 to 7, and builds on these by discussing the implications for policy, practice, and patients. Overall strengths and limitations of the thesis are discussed, and finally the conclusions of the thesis.

1.3 Key Accomplishments

1.3.1 Research Collaborations

This thesis required several research collaborations. First, I developed a formal tripartite research collaboration between the University of Oxford, MSF, and the Ministry of Health of the Hashemite Kingdom of Jordan (Appendix D). This involved meeting directly with senior government officials in the Jordanian Ministry of Health and gaining written approval from the Minister of Health for my research to be conducted. MSF played a pivotal role through their on-going relationship with the Jordanian Ministry of Health, but formal in-person meetings were required of me to establish a research agreement for the work outlined in this thesis. This involved travelling to Jordan and meeting on several occasions with senior officials from the Ministry of Health. Second, a collaboration was developed with Professor Rod Jackson and his group in Auckland, New Zealand, which built on Professor

Jackson's immense contributions to the Centre for Evidence-Based Medicine and the field of cardiovascular risk scoring.

1.3.2 Fieldwork

Fieldwork is dynamic and unpredictable, not least in conflict and humanitarian settings. To accomplish the objectives of this thesis, three stints of fieldwork to The Hashemite Kingdom of Jordan were conducted (a map is shown in Chapter 5). The first (March 2015) was a scoping mission where I met with local academics at the Jordanian University of Science and Technology, the American University of Madaba, and the University of Jordan, as well as local non-governmental organisations including MSF and Médecins du Monde. The second trip (September 2015) involved meeting with local MSF staff and attending the Eastern Mediterranean Public Health Network Conference in Aqaba, Jordan, to deeply acquaint myself with the research and researchers of the region. The third trip (November 2015) was for the purpose of data collection and involved embedding myself in an MSF mission for Syrian refugees in Northern Jordan to collect qualitative and quantitative data (Chapters 4 and 5).

Fieldwork was also conducted in Auckland, New Zealand (August 2016) to establish research collaboration with Professor Rod Jackson, to gain skills in prognostic modelling, and to set-up the infrastructure required to complete thesis objective four (Chapter 7).

1.3.3 Funding

As a Rhodes Scholar I received no dedicated funding for research costs. Through the development of a research collaboration with MSF, MSF agreed to fund my research expenses including airfare, accommodation, and open access publishing fees related to thesis objective three (Chapters 5 and 6). I was further successful in obtaining the Murray Speight Award and Sir Peter Elworthy Research Grant to finance my fieldwork in New Zealand (thesis objective four; Chapter 7). This funding was supplemented by the Nuffield Department of Primary Care Health Sciences and the WHO Collaborating Centre for Self Care.

1.3.4 Training and Skills Development

I completed the following courses offered by the Centre for Evidence-Based Medicine and Department of Continuing Education: Practice of Evidence-Based Health Care, Mixed Methods in Health Research, Teaching Evidence-Based Medicine, and Introduction to Study Designs and Research Methods. I completed the course entitled “Analysing Qualitative Interviews” offered by the Health Experiences Research Group in the Nuffield Department of Primary Care Health Sciences. Through the Data Science programme from Johns Hopkins University on Coursera, I have learned to programme in R and have completed the following courses: The Data Scientist’s Toolbox, R programming, and Getting and Cleaning Data (Appendix A). I have learned about prognostic modelling through reading textbooks, watching tutorials, and working closely with senior statisticians who specialise in CVD risk models in Auckland, New Zealand. I took an intensive Arabic course (June/July 2015) from the University of Oxford Language Centre to prepare for fieldwork in Jordan. I also completed the University of Oxford’s Overseas Field Work Safety and Security Course (February 2015).

1.3.5 Teaching and Knowledge Translation

My philosophy to scholarship is driven by impact on human health and therefore I have invested much energy into teaching and knowledge translation. With respect to teaching I have taught on the following courses: Practice of Evidence-Based Health Care, Introduction to Study Designs and Research Methods, and Teaching Evidence-Based Practice. I have also taught the undergraduate and postgraduate entry medical students and the MSc in International Health and Tropical Medicine students.

With respect to knowledge translation, I have shared the findings of this thesis through publications in the BMJ Open,[1] F1000 Research,[2], BMC Conflict and Health [3], in textbooks[4], and by presenting at Evidence Live (June 2016) and Preventing Overdiagnosis conferences (September 2016)(Appendix A). I have also supported the WHO by teaching at the Workshop on Implementation of a Package

of Essential NCD Interventions in Primary Health Care in Samarkand, Uzbekistan (May 2016) and in Helsinki, Finland (March 2017) to delegates from the Ministries of Health of Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, Turkey, and Uzbekistan.

2

Background

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2.1 The Epidemiology of Cardiovascular Disease

2.1.1 Global Burden

Cardiovascular disease (CVD) is a group of conditions that affect the heart and blood vessels and includes coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart diseases, congenital heart diseases, and venous thromboembolism.[5] Together, CVD is the leading cause of death worldwide, predominantly due to ischemic heart disease and cerebrovascular disease from atherosclerosis.[6]

Over the last 20 years ischemic heart disease and cerebrovascular disease have transitioned from the fourth and fifth leading cause of years of life lost (YLL)

globally, to the first and second, respectively, replacing lower respiratory infections and neonatal preterm birth complications.[7] In 2015, of the 56 million global deaths, 40 million were attributable to non-communicable diseases (NCDs) of which 18 million were due to CVD – more than any other NCD.[7] While the age-standardized death rate due to CVD is decreasing, the absolute number of deaths is increasing.[7] Globally, this is driven by decreases in deaths and age-standardised death rates of communicable diseases, a growing, aging population,[7, 8] and increasing CVD deaths in low- and middle-income countries (LMIC).[9] From 1990 to 2013, age-standardised death rates dropped from 381 (95% CI 363, 400) per 100,000 persons to 332 (95% CI 312, 347) in LMIC and from 283 (95% CI 268, 291) per 100,000 persons to 160 (95% CI 154, 176) in high-income countries.[9] Despite these decreases, in the same time period the number of CVD deaths increased by 66% in LMIC and did not significantly change in high-income countries.[9]

YLL – a measure of premature mortality – is also increasing for CVD in LMIC.[9] YLL is highest amongst countries in the mid-range of socio-demographic index (SDI), and decreases at the lowest and highest ends of SDI.[7] At the lowest range of SDI the leading contributors to YLL are communicable diseases, which may cause death earlier in life before the development of CVD. Conversely at the highest margins of SDI, health systems may function well enough to prevent and successfully treat CVD. This leaves populations in the mid-range of SDI in a position with resource-limited health systems, decreasing YLL due to communicable diseases, aging, growing populations, resulting in increasing YLL due to CVD.[7] Despite this documented burden, the different methods used to measure communicable diseases and, more recently, NCDs may impact the estimates of NCD burden in LMIC.

2.1.2 Risk Factors

Given its immense burden and contribution to premature mortality, the risk factors of CVD – particularly ischemic heart disease and cerebrovascular disease as a result of atherosclerosis – have been the focus of much research. The Framingham Heart Study was the first systematic attempt to determine the causes of CVD, initiating

Table 2.1: Risk factors for CVD adapted from the Global Atlas on Cardiovascular Disease Prevention and Control [17]

Risk Factor Category	Behavioural	Metabolic	Other
Modifiable	Tobacco Use	Hypertension	Psychosocial Factors
	Physical Inactivity	Diabetes	
	Unhealthy Diet	Cholesterol	
	Harmful Use of Alcohol	Overweight and Obesity	
Non-Modifiable			Age
			Sex
			Genetics/Family History
			Socioeconomic Status

a long history of research on CVD risk factors and prognosis.[10] It was from this study that convincing scientific evidence was first generated for the predictive power of cholesterol, smoking, and hypertension in the aetiology of CVD.[11, 12] Some estimates conclude that raised blood pressure, smoking, and cholesterol, in combination, account for up to 80% of cases of CVD, thereby focusing many clinical interventions to these risk factors.[13, 14] Risk factors for CVD are interrelated, but can be broadly categorised into modifiable and non-modifiable (Table 2.1). Globally, nine modifiable risk factors account for 90% of the population attributable risk for myocardial infarction: smoking, raised lipids, hypertension, diabetes, abdominal obesity, psychosocial factors, unhealthy diet, harmful use of alcohol, and physical inactivity.[15] What constitutes a healthy diet is the subject of much debate, however a recent cohort study across 18 countries and five continents showed no association between fat intake and cardiovascular morbidity or mortality.[16]

It is important to situate CVD and its clinical risk factors (e.g. blood pressure, cholesterol, blood sugar) in the broader context of exposure and cause (Figure 2.1). Social determinants of health, such as income, education, and occupation, together shape an individual's proximal determinants of health. These include physical inactivity, diet, and tobacco use which have a cascading effect on pathophysiological determinants, leading to disease and its sequelae.[18] Preventive interventions can therefore be classified by risk factors they target. The social determinants of

CVD, such as income, education, and occupation, are targeted by public policy and social development. Public health interventions tend to focus on proximal determinants like inactivity, smoking and diet, whereas clinical interventions target pathophysiological determinants and disease outcomes.

2.2 The Global Policy Response

Given the threat of NCDs, including CVD, to human and economic development, a UN High Level Meeting on NCDs was held in 2011. This was the second time in history a UN High Level Meeting was convened for a health topic, reflecting the magnitude of potential harm for human health. The only other occasion a High Level Meeting was called for a health topic was for Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), which resulted in the establishment of the United Nations Programme on HIV/AIDS (UNAIDS).[19] The results firmly situated NCDs on the global policy agenda and initiated an unprecedented response from the World Health Organisation (WHO), the UN, and their partners including national governments. It was unclear at this time, though, how LMIC could tackle the NCD burden.

Two years later, the World Health Assembly endorsed the Global Action Plan for the Prevention and Control of NCDs 2013-2020 in May 2013, committing 194 countries to achieving nine voluntary targets by 2025 to curb the burden of NCDs (Table 2.2).[20] These targets largely tackle risk factors for NCDs including CVD, such as harmful use of alcohol, physical inactivity, salt intake, tobacco use, blood pressure, overweight, and diabetes, in addition to treatment targets. Of particular note for the prevention of CVD are the goals of a 25% reduction in risk of premature mortality from CVD, cancer, diabetes or COPD by 2025 and at least 50% of people with cardiovascular risk of $\geq 30\%$ on drug therapy (Table 2.2).[20] The Global Action Plan therefore put total cardiovascular risk scoring as a central component of its strategy to reduce CVD mortality through preventive drug therapy.

Action by the UN and WHO have firmly placed the control of NCDs on the agendas of many governments, and strengthening the role of primary health care for

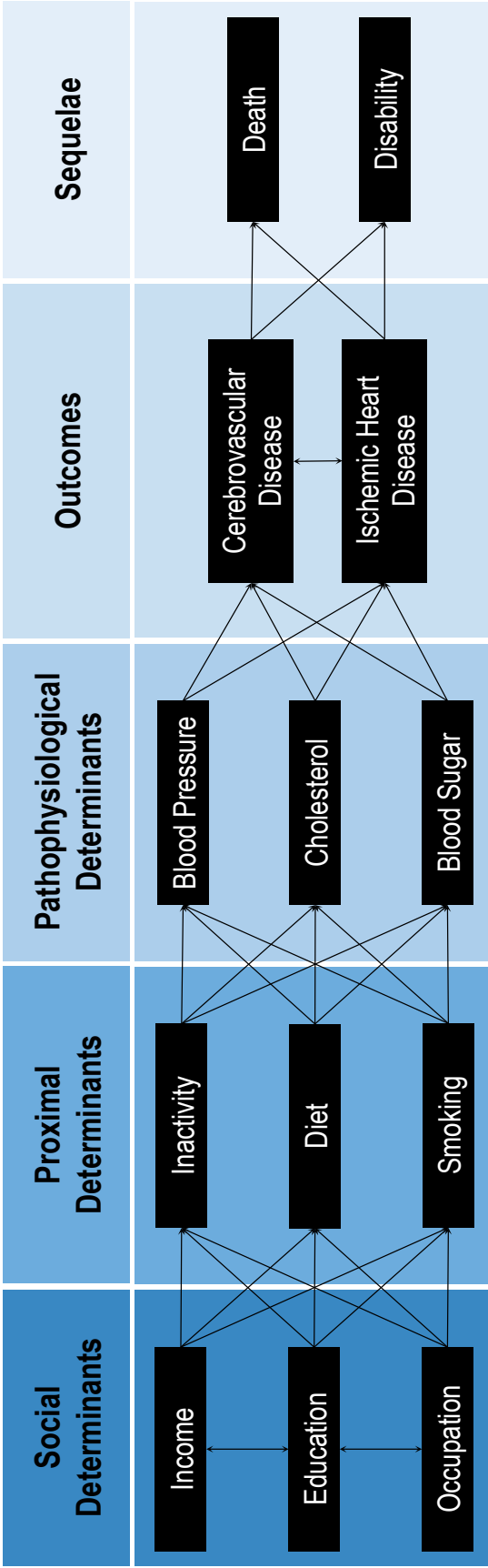


Figure 2.1: An example of some risk factors for cardiovascular disease to illustrate that they are inter-related network of distal social determinants of disease, proximal determinants, pathophysiological determinants, that together cause disease and their sequelae [18]

2.2. The Global Policy Response

Table 2.2: The nine global voluntary targets of the WHO's Global Action Plan for the Prevention and Control of Noncommunicable Diseases 2013-2020.[20]

Target	Goal	Indicator
Premature Mortality	A 25% relative reduction in risk of premature mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases	Unconditional probability of dying between ages of 30 and 70 from CVD, cancer, diabetes, or chronic respiratory diseases
Harmful Use of Alcohol	At least 10% relative reduction in the harmful use of alcohol, as appropriate, within the national context	Total (recorded and unrecorded) alcohol per capita (aged 15+ years old) consumption within a calendar year in litres of pure alcohol, as appropriate, within the national context Age-standardised prevalence of heavy episodic drinking among adolescents and adults, as appropriate, within the national context Alcohol-related morbidity and mortality among adolescents and adults, as appropriate within the national context
Physical Inactivity	A 10% relative reduction in prevalence of insufficient physical activity	Prevalence of insufficiently physically active adolescents, defined as less than 60 minutes of moderate to vigorous intensity activity daily Age-standardised prevalence of insufficiently physically active persons aged 18+ years (defined as less than 150 minutes of moderate-intensity activity per week, or equivalent)
Salt Intake	A 30% relative reduction in mean population intake of salt/sodium	Age-Standardised mean population intake of salt (sodium chloride) per day in grams in persons aged 18+ years
Tobacco Use	A 30% relative reduction in prevalence of current tobacco use in persons aged 15+ years	Prevalence of current tobacco use among adolescents Age-standardised prevalence of current tobacco use among persons aged 18+ years Age-Standardised prevalence of raised blood pressure among persons aged 18+ years (defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg) and mean systolic blood pressure
Blood Pressure	A 25% relative reduction in the prevalence of raised blood pressure or contain the prevalence of raised blood pressure, according to national circumstances	Age-Standardised prevalence of raised blood glucose/ diabetes among persons aged 18+ years (defined as fasting plasma glucose concentration ≥ 7.0 mmol/l (126 mg/dl) or on medication for raised blood glucose) Prevalence of overweight and obesity in adolescents (defined according to the WHO growth reference for school-aged children and adolescents, overweight – one standard deviation body mass index for age and sex, and obese – two standard deviations body mass index for age and sex)
Diabetes and Obesity	Halt the risk in diabetes and obesity	Age-standardised prevalence of overweight and obesity in persons aged 18+ years (defined as body mass index ≥ 25 kg/m ² for overweight and body mass index ≥ 30 kg/m ² for obesity) Proportion of eligible persons (defined as aged 40 years and older with a 10-year cardiovascular risk $\geq 30\%$, including those with existing cardiovascular disease) receiving drug therapy and counselling (including glycemic control) to prevent heart attacks and strokes
Preventive Drug Therapy	At least 50% of eligible people receive drug therapy and counselling (including glycemic control) to prevent heart attacks and strokes	Availability and affordability of quality, safe and efficacious essential NCD disease medicines, including generics, and basic technologies in both public and private facilities
Essential NCD Medicines and Technologies	An 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs both in public and private facilities	

the prevention and control of NCDs is central to the WHO's recommendations.[21] However, meeting these targets will be a challenge for many LMIC where primary health care systems are not strong enough to identify and manage people with NCDs, operate within limited health care expenditures,[22, 23] and where there is little precedent and readiness to provide NCD care.[21, 23] The solution to reducing the global burden of CVD will require high-level coordinated action from governments which address the root causes and social determinants of health, in combination with clinical approaches to prevention. While these targets were a necessary step in coordinating a global response to NCDs, they did little to help individual countries with the practicalities of implementing interventions to meet these goals.

2.2.1 The Package of Essential NCD Interventions for Primary Health Care in Low-Resource Settings (WHO PEN)

Since countries with the highest burden of CVD had limited health care capacity, and experience managing NCDs, the WHO invested in the development of specific clinical protocols and tools for primary health care in low-resource settings. This came in the form of the Package of Essential NCD Interventions for Primary Health Care in Low-Resource Settings (WHO PEN).[24] WHO PEN provided a suite of tools and laid a framework for implementing essential interventions for NCDs in primary health care. This included clinical protocols; most notably Protocol One for the Prevention of Heart Attacks, Strokes, and Kidney Disease through the Integrated Management of Diabetes and Hypertension, which uses total CVD risk scoring to initiate preventive treatment. In combination with the International Society of Hypertension, the WHO developed and published the WHO/ISH CVD risk scores for use in low-resource settings as part of WHO PEN, since most low-resource settings did not have sufficient cohort data to model their own risk scores.[25] These charts had methodological limitations and the methods of their development were never fully published, but were considered a valuable stop-gap measure for clinical risk stratification.[26] It remained unclear, however, how current approaches to

risk-based prevention that have been developed and implemented in high-income countries applied to and function in low-resource settings.

2.3 Total Cardiovascular Risk

Since the largest burden of NCDs is attributed to CVD, health systems must provide due attention to the identification and management of people at high risk of CVD. This presents a challenge because half of CVD events happen in people who are clinically asymptomatic and single risk factors in and of themselves are generally poor predictors of CVD events.[27] Total cardiovascular risk shifts away from single-risk factor management toward an approach that assesses an individual's overall risk by considering a constellation of risk factors in the context of each other.

2.3.1 Cardiovascular Disease Risk Scores

CVD risk scoring (also referred to as absolute risk assessment, total risk assessment, or global CVD risk assessment) is an integrated approach that recognises the hazards of multiple risk factors to determine the absolute risk of experiencing a cardiovascular event in a given time period. CVD risk scores were an outgrowth from the findings of the Framingham Heart Study that showed risk factors for CVD tended to cluster together in individuals.[28] Since this, a mass proliferation of CVD risk scores has occurred. Some 363 different CVD risk models have been developed and half of these were developed in European populations.[29] Despite these numbers, the parameters used in these models are largely uniform and can include: age, gender, smoking status, diabetes status, total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol, systolic blood pressure, ethnicity, and family history of CVD, amongst others.[30] While the discrimination and calibration of CVD risk scores has improved with time, less attention has been given to their validation in external cohorts.[29] Still, the use of risk scores has been strengthened by epidemiological evidence that the absolute benefit of cholesterol-lowering treatment and blood-pressure lowering treatment are associated with baseline CVD risk.[31–33]

Given this, CVD risk scoring is seen as a systematic and cost effective way to allocate limited medical resources by stratifying asymptomatic populations by their probability of experiencing a fatal or non-fatal CVD event.[34] Risk scoring to target those at high CVD risk was therefore seen to be a pragmatic approach for the prevention of CVD and is an essential component of WHO PEN, despite a paucity of validated risk models for most LMIC.[21]

2.4 Clinical Interventions to Reduce CVD Risk

Clinical interventions to reduce CVD risk can be classified as primary prevention and secondary prevention. Primary prevention refers to prevention in individuals asymptomatic for CVD whereas secondary prevention refers to prevention in individuals with existing disease. Cardiovascular risk scores are predominantly used in primary prevention and their value lies in their ability to identify patients who are clinically asymptomatic but are at increased CVD risk. Individuals with existing CVD (i.e. secondary prevention) are considered high risk for subsequent CVD events and therefore do not require risk scoring.[27]

2.4.1 Primary Prevention in Asymptomatic Patients

A growing body of epidemiological evidence has driven clinical practice towards total CVD risk based blood pressure-lowering and cholesterol-lowering treatment, rather than target-based treatment for individual risk factors. The implications of using a total risk approach is that individuals with elevated individual risk factors may not be eligible for treatment, and vice versa.

Uncontroversial interventions include smoking cessation, limiting the use of alcohol, increasing physical activity, and improving diet.[21] Individuals with diabetes are at increased risk of CVD events, and this risk is higher in women than in men. However, aggressive glucose control in type two diabetics does not appear to be associated with improved patient outcomes.[35, 36] More highly debated interventions include blood-pressure lowering and cholesterol-lowering treatment, of which recent meta-analyses have provided some clarity.

With respect to CVD outcomes, there is no apparent blood pressure threshold below which benefit from treatment is lost.[37] Although clinical medicine has historically adopted a threshold-based approach for blood pressure-lowering (e.g. lowering systolic blood pressure to 140 mmHg or below), epidemiological evidence shows that the relationship between blood pressure and CVD is near continuous.[38] Aggressive blood pressure lowering to below 120 mmHg, compared to usual regimens targeting pressure to below 140 mmHg, has shown significant reductions in cardiovascular events.[39]

Similarly, there is no apparent threshold below which the benefits of LDL cholesterol reduction diminish. Absolute reduction in LDL cholesterol, not relative or target-based reduction, is associated with reduced incidents of major CVD events.[31] A relative risk reduction of 20% per mmol/L lowered can be expected for both primary and secondary prevention patients, which translates to an NNT of 40 and 21, respectively.[31] Even amongst low risk people, for each 1 mmol/L reduction in LDL cholesterol, a reduction of 11 events per 1000 people treated can be expected (NNT=91).[40] Earlier studies focused on total cholesterol, which can sometimes be used as a proxy for LDL cholesterol.[41] In these studies the range of relative reductions for each 1 mmol/L reduction in total cholesterol was from 50% to 15%, with the effects diminishing with age.[41]

The clinical algorithms that emerge from these findings are ones that initiate cholesterol-lowering and blood-pressure lowering treatment based on total CVD risk, rather than individual risk factor levels. What is less clear is the threshold at which BPLT and LLT should be initiated. This is largely a consideration of resource-level: as the threshold decreases the benefits increase, but so too do costs.[21] In the UK, for example, the CVD risk threshold for cholesterol-lowering treatment is set at 10% whereas it is set at 30% by the WHO for LMIC.[21, 42]

2.4.2 Secondary Prevention in Symptomatic Patients

Aside from secondary and tertiary care, secondary prevention in primary care is largely similar to primary prevention. Secondary prevention patients diverge from

primary prevention patients in two clinically relevant ways. First, they are considered amongst the highest risk category for experiencing a CVD event and therefore do not require risk scoring. In fact, nearly half of events happen in those with existing disease, and as case-fatality decreases this proportion may rise.[27] Second, since the absolute benefit of risk factor modification is correlated with baseline CVD risk, secondary prevention patients have very high baseline risk, relatively large absolute reductions in CVD risk can be observed in these patients.[43]

While outside the scope of this thesis, secondary prevention patients may benefit from additional drug treatment. Interventions include acetylsalicylic acid, atenolol and streptokinase for acute myocardial infarction, and in general aspirin, angiotensin-converting-enzyme inhibitor, beta-blocker, and statins post-myocardial infarction.[20, 21] Interventions post-stroke include aspirin, antihypertensives, and statins.[21] These medications are reflected in the essential medicines list of WHO PEN.[21]

2.5 Low-Resource Settings

Since this thesis explored cardiovascular risk assessment for the prevention of CVD in low-resource settings, it was important to describe the use of this term.

2.5.1 Definition

The term low-resource setting is increasing in popularity in the literature, often appearing synonymous with “low- and middle-income country,” but is poorly defined (Figure 2.2). The Oxford English dictionary defines “resource” as “stocks or reserves of money, materials, people, or some other asset which can be drawn on when necessary” or “a means of supplying a deficiency or need; something that is a source of help, information, strength, etc.”[44] To this end and for the basis of this thesis, I define low-resource as “a context in which health care cannot function effectively because of a lack of financial, human, technological, or other forms of assets.”

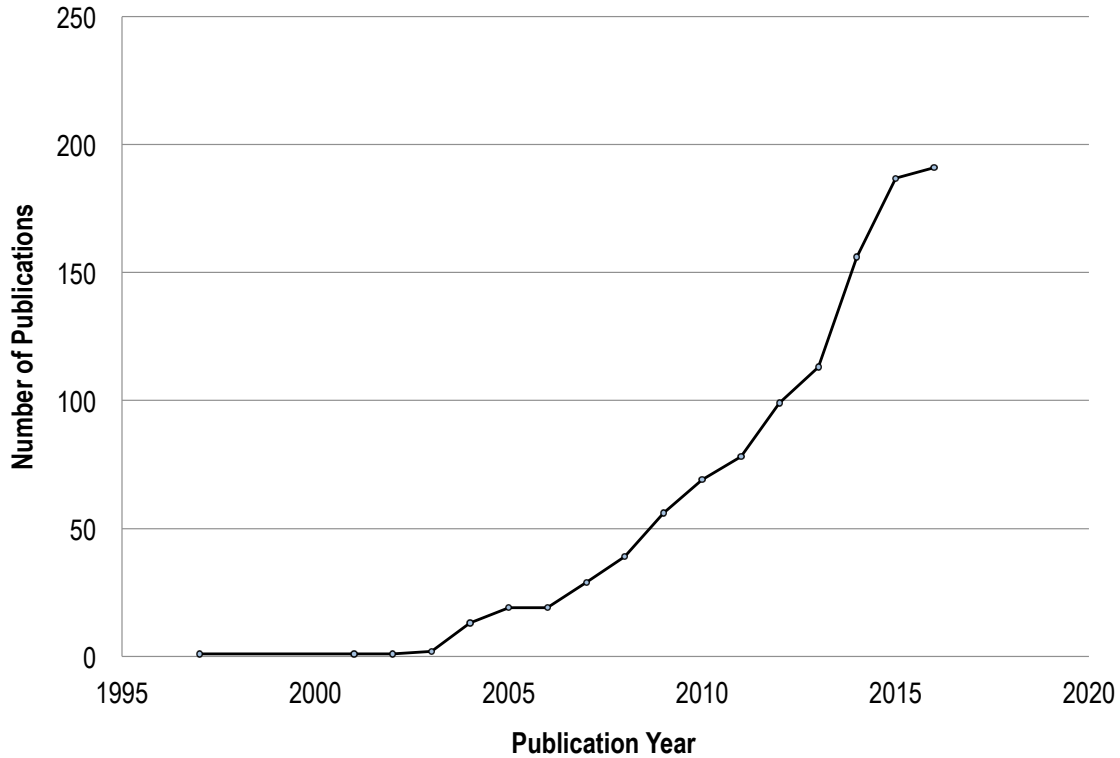


Figure 2.2: Number of publications indexed in PubMed which include “low resource setting*” or “low-resource setting*” or “resource-limited setting*” or “resource limited setting*”

While “low-resource setting” is often used and interpreted synonymously with World Bank classifications low-and-middle income country or the pejorative “developing country” it is not strictly synonymous because low-resource settings, by definition, can exist in any country of any income level. While it could be argued that most low-and middle-income countries (LMIC) are low-resource settings, taking these terms as synonymous is reductive because it fails to account for the many ways in which health systems function effectively in LMIC and the ways in which health systems are ineffective in high-income countries.

2.5.2 Low-Resource Settings in Low- and Middle-Income Countries

Given that 80% of CVD deaths occur in LMIC,[17] this thesis focused more specifically on low-resource settings in LMIC while also at times considering the implications for other low-resource settings. Given that low-resource settings

are diverse and widespread in health care, I focused on a setting which allowed an in-depth study of cardiovascular risk scoring in a real-life context. In this sense an intrinsic and instrumental case-study approach was used to examine the unique application of total cardiovascular risk scoring in a natural setting to gain a broader insight into the issue.[45]

2.6 Conclusion

CVD has become an immense global burden of disease, and this burden is highest in LMIC. As such, the global response moved quickly by endorsing strategies, such as total CVD risk scoring, that had been developed for years in high-income countries but had little precedent for their use in low-resource settings. I therefore hypothesised that while total CVD risk scoring is an entrenched practice in many high-income countries, the scores and their use were sub-optimal for the prevention of CVD in low-resource settings. Early evidence suggested that this may be the case, as when WHO PEN was developed, no CVD risk scores existed for most LMIC leading to the development of WHO/ISH CVD risk scores.

Specifically, I aimed to examine the following gaps in knowledge:

- First, the impact of risk scoring on patient outcomes even in high resource settings, where scores have long been developed and implemented, was unclear, especially on hard patient outcomes such as morbidity and mortality (Chapter 3)
- Second, since the underlying equation of WHO/ISH risk scores was not published, software was required to evaluate the implementation of these risk scores using routine clinical data (Chapter 4)
- Third, since WHO/ISH risk scores were newly developed for low-resource settings, the challenges of implementing these scores at the primary health care level in low-resource settings were not known (Chapter 5 and 6)

- Fourth, as a direct outgrowth of the findings of Chapters 5 and 6, it became clear that risk scores required simplification to be laboratory-independent, but it was uncertain the degree to which replacement of TC:HDL ratio with BMI may attenuate performance (Chapter 7)

2.7 Chapter Summary

- Ischemic heart disease and cerebrovascular disease, are the leading cause of death worldwide and YLL due to CVD are rising in LMIC
- Total cardiovascular risk scoring allows for the identification of asymptomatic individuals at high CVD risk and the targeting of risk factor modifying interventions
- The global response for the control of CVD emphasises the use of total cardiovascular risk scoring in primary health care in low-resource settings, most notably in the WHO PEN and the use of WHO/ISH risk scores
- Low-resource settings, for the purpose of this thesis, are defined as “contexts in which health care cannot function effectively because of a lack of financial, human, technological, or other forms of assets”
- It is hypothesised that CVD risk scores and their use are sub-optimal for the prevention of CVD in low-resource settings

3

Cardiovascular Risk Scoring in Asymptomatic Adults: systematic review of systematic reviews

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3.1 Publication Statement

Features of this chapter are published in BMJ Open.[1]

3.2 Introduction

Cardiovascular risk scoring is a widely accepted practice and is endorsed by many guidelines. Almost all cardiovascular disease (CVD) guidelines recommend some

form of risk scoring as a way to prioritise and plan primary prevention interventions.[21, 46, 47] This practice is entrenched in most high-income countries,[42, 46, 47] and endorsed by the World Health Organisation (WHO) for low- and middle-income countries (LMIC).[21] To this end it appeared to be an uncontroversial approach to prevention, but questions remained about its utility in clinical practice and impact on long-term patient outcomes such as CVD-related morbidity and mortality. Therefore, before examining the implementation of risk scoring in a model low-resource setting (Chapters 5 and 6), I first wanted to examine the evidence underpinning their use.

The prevention of CVD is challenging; even with an abundance of clinical guidance and effective interventions targeting modifiable risk factors, the majority of patients at risk do not achieve sufficient risk factor control.[48–53] In jurisdictions where risk scoring is part of routine clinical practice, this may be due to ineffective use or risk scoring because of physician attitudes to and understanding of CVD risk assessment,[53–55] challenges communicating risk to patients, and patients’ understanding of risk,[55, 56] or because of a lack of a true effect. While the development and validation (e.g. calibration and discrimination) of risk scores has been the focus of much research,[57–60] studies of these type do not provide information about effectiveness when risk scores are used prospectively for prevention in clinical practice.

The fact that many patients in jurisdictions where CVD risk scores are a part of routine clinical practice do not achieve sufficient risk factor control made me curious about the effectiveness of CVD risk scores for the primary prevention of CVD. For questions of intervention effectiveness, such as this, the highest quality evidence would be from a high quality systematic review of high quality randomised controlled trials.[61] And, given the prominence and history of CVD risk scoring, I hypothesised there would be a multitude of systematic review evidence to rationalise the widespread use of cardiovascular risk scoring. The benefit of conducting a systematic review of systematic reviews (also known as overviews) is that they can be used to synthesise evidence for a given intervention on a diversity of outcomes and

map the existing systematic review literature, in addition to identifying limitations in the methodology and quality of existing systematic reviews which may be used in evidence-based decision making.[62]

3.3 Aim and Objectives

3.3.1 Aim

The aim of this chapter was to determine the impact of cardiovascular risk scores on meaningful patient outcomes when used for primary prevention in adults, as reported by existing systematic reviews.

3.3.2 Objectives

To achieve the aim, the objectives of this chapter were to:

- Identify systematic reviews reporting the impact of cardiovascular risk scoring on CVD-related morbidity and mortality, total cholesterol, LDL cholesterol, systolic blood pressure, and smoking
- Critically appraise identified systematic reviews using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) checklist
- Synthesise the findings of identified systematic reviews narratively
- Meta-analyse reported randomised controlled trials (RCTs) and assess the quality of effect estimates using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method
- Determine the spatial and epidemiological origins from which the evidence is based

3.4 Methods

I prospectively registered the protocol on PROSPERO (Registration CRD42015019821).[63]

3.4.1 Search Strategy

The Cochrane Library, EMBASE, MEDLINE, and CINAHL databases were searched from January 2005 to October 2016 (see Appendix B for detailed search strategies). Searches were from 2005 because I felt that more recent systematic reviews were likely to capture the same primary studies as older systematic reviews. No language restrictions were applied. Search strategies used a mix of Medical Subject Heading (MeSH) terms and keywords and were reviewed by an information specialist (NR). This strategy was supplemented by hand searching the bibliographies of included reviews, forward citation searching on Google Scholar and Web of Science, and by contacting experts.

3.4.2 Inclusion Criteria

Systematic reviews of studies of any design that included adults (18 years of age or older) with no history of cardiovascular disease (including atrial fibrillation) were included. Reviews were eligible for inclusion if they considered interventions involving global CVD risk scoring relative to no risk assessment, irrespective of who performed the risk assessment, how it was performed, and to whom the information was directed. Studies were excluded if they were of peri-operative CVD risk scores, analogue patients, patients with existing CVD, validation studies, or accuracy studies of CVD risk scores.

The primary outcomes of interest were CVD-related morbidity or mortality. Secondary outcomes considered were systolic blood pressure (SBP), cholesterol, and smoking, because together these risk factors cause the majority of premature CVD and there are effective interventions to modify them.[13, 14]

3.4.3 Study Selection, Data Extraction, Quality Assessment

Study selection, data extraction, and quality assessment was done in two phases. First, systematic reviews were screened for inclusion, and then primary studies reported in the systematic reviews were screened as required.

Title and abstract screening was done independently and in duplicate by two people (DC, AT) for full text review and disagreement was resolved by consensus. Full text articles were screened for inclusion using the same method by the same two people (DC, AT). Salient characteristics about the included reviews and their description of included studies, including the classification of interventions as either directed toward the patient, provider, or both the patient and provider, were extracted independently in duplicate (DC, AT). The same two people independently assessed methodological quality using AMSTAR.[64] The method of quality assessment and the quality of primary studies were extracted as reported by the review authors. If a primary study was reported by more than one review, the quality score from the review with the highest AMSTAR rating was used.

It was not initially planned to extract data from primary studies; however, to address poor or insufficient reporting, or to verify intervention classifications, the second phase involved the same two reviewers extracting additional data from the primary studies as needed, independently and in duplicate. Data were extracted from primary studies as reported in systematic reviews and tabulated using Microsoft Excel 2010 and Microsoft Word 2010. In the event of a discrepancy between a primary study and an included systematic review, the data reported in the primary study rather than the systematic review was used. When outcomes were reported at multiple time points in a single study, the data from the longest follow-up time with complete data was chosen.

3.4.4 Data Synthesis

Included systematic reviews were narratively reported, and their salient characteristics tabulated, including review author conclusions and AMSTAR ratings. For the analysis of primary studies reported by systematic reviews, RevMan 5.3 was used to construct forest plots and inverse variance-weighted random effects meta-analyses.[65] A random effects model was chosen based on the assumption that there would be an underlying distribution of effect sizes, of which the mean of the distribution would be estimated.[66] I entered all data into RevMan and these

were independently verified by a second person (IO). I only included randomised controlled trials (RCTs) in meta-analyses; other study designs or randomised studies with insufficient data to meta-analyse were reported narratively. For continuous outcomes mean differences were calculated and for dichotomous outcomes, risk ratios. Subgroup analyses were conducted by the intended target of the intervention (patient, provider, or both). Standard error was imputed when reasonable, using the average standard error of studies reporting the same outcome and in the same subgroup, and in such cases a sensitivity analysis was performed. For each outcome meta-analysed, the GRADE methodology was used to rate the quality of evidence using GRADEpro GDT software.[67] This was done independently and checked by a second person experienced in GRADE methodology (IO); disagreements were resolved by consensus. I^2 values were used to estimate statistical heterogeneity.

To determine the geographical origin of the data included, primary studies reported by included reviews were grouped together based on the country the study was done in, and by WHO epidemiological subregion. The proportion of evidence arising from each epidemiological subregion was then compared to the population of each subregion, based on the latest available population estimates from WHO (2005).[68]

3.5 Results

After removing duplicate studies, 6,877 studies were screened for inclusion, 6,727 of which were excluded as irrelevant based on title and abstract (Figure 3.1). Following full text review of 150 studies, six systematic reviews met the inclusion criteria. The other 144 articles were excluded, the majority ($n=110$) due to the study design. The six included systematic reviews together reported 122 unique primary studies, 16 of which were relevant based on the inclusion criteria, including adults with no history of cardiovascular disease and global CVD risk scoring as an intervention relative to no risk assessment. Of these, none reported CVD-related morbidity or mortality, 12 reported SBP, ten reported cholesterol, and nine reported smoking cessation (Figure 3.1).

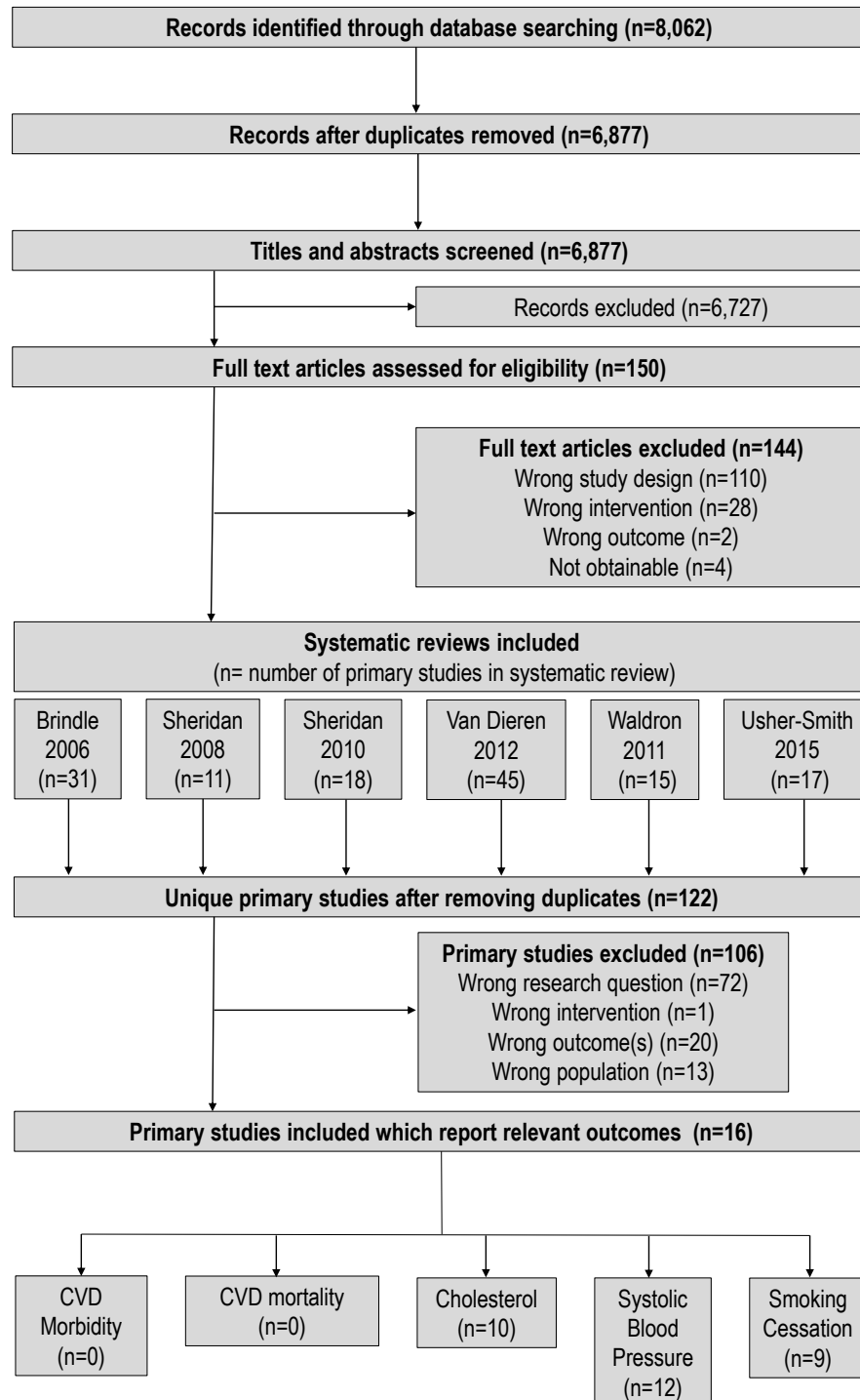


Figure 3.1: Flowchart showing the included systematic reviews, primary studies, and outcomes reported

3.5.1 Summary and Quality of Included Systematic Reviews

Characteristics of included systematic reviews are summarised in Table 3.1. Reviews were generally broad in scope, published from 2006 to 2015, considered all study designs, and collectively searched 11 databases. AMSTAR ratings ranged from 0/11 to 7/11 (mean 4.2/11); no reviews were excluded based on quality (Table 3.2). The conclusions of reviews were consistently of general uncertainty about the impact of cardiovascular risk scoring on hard patient outcomes.

Brindle 2006 (AMSTAR 4/11) sought to determine both the accuracy and impact of CVD risk scoring.[69] To assess impact, they considered RCTs of health care professionals using a CVD risk score to aid in primary prevention, relative to usual care, in populations predominantly free from symptomatic CVD (Table 3.1). Although the authors identified 31 primary studies, the majority of the studies assessed the accuracy of CVD risk assessment and therefore were beyond the scope of this review. The authors concluded that there was little evidence to support the use of risk scores for primary prevention.

Sheridan 2008 (AMSTAR 4/11) conducted a much more focused review, specifically aimed to assess the benefits and harms of physician knowledge of a global CVD risk score, relative to no formal risk assessment, in adults with no history of CVD.[70] Although the authors only searched MEDLINE, they identified 11 primary studies, most of which were relevant to the study (Table 3.1), and reached similar conclusions as Brindle 2006: “surprisingly little evidence that physician knowledge of global CHD risk translates into improved clinical outcomes.”[70]

Sheridan 2010 (AMSTAR 7/11) was distinct from Sheridan 2008 in that eligible interventions were targeted at patients rather than physicians.[71] To be eligible, studies (of any design) had to be interventions of global CVD risk information, solely or as part of a complex intervention, directed at adults with no history of CVD to determine the impact of patient-targeted risk information on patient outcomes (Table 3.1). In this review, the authors searched multiple databases and identified 18 primary studies; most were relevant for inclusion. They concluded

Table 3.1: Characteristics of included systematic reviews

Review ID						
Review Objective(s)	Brindle 2006[69]	Sheridan 2008[70]	Sheridan 2010[71]	Waldron 2011[72]	van Dieren 2012[73]	Usher-Smith 2015[74]
	"To determine the accuracy of assessing CVD risk in the primary prevention of CVD and its impact on clinical outcomes"	"To assess whether global CHD risk scores result in clinical benefits or harms"	"To assess the effect of providing global CHD risk information to adults"	"To compare different interventions used to communicate cardiovascular risk and assess their impact on patient related outcomes"	"To review the primary prevention studies that focused on the development, validation and impact assessment of a cardiovascular risk model, scores or rules"	"To systematically review whether the provision of information on cardiovascular disease (CVD) risk to healthcare professionals and patients impacts their decision-making, behaviour and ultimately patient health."
Population	People "predominantly free from symptomatic CVD"	"Adults (>18) with no prior history of CVD"	"Adults with no history of CVD"	Adults (>18)	"People with type 2 diabetes"	People "with no history of CVD"
Intervention(s)	"Healthcare professional using a CVD risk score to aid primary prevention"	"Physician knowledge of a global CHD risk score"	"Global CHD risk presentation as the primary intervention or part of a multipart intervention"	"Communication interventions (of any format) for individualised CVD assessment"	"CVD predictions models that have been developed... or validated in a diabetes population"	"Provision of a CVD risk model estimate to either physicians or patients"
Comparison(s)	Usual care	"Either simple risk factor counting or no formal assessment of risk"	Not pre-specified	Control or usual care arm	Not pre-specified	No "provision of a CVD risk model estimate"
Country of Primary Review	United Kingdom	United State of America	United States of America	United Kingdom	The Netherlands	United Kingdom
AMSTAR Eligible Study Designs	4/11 RCTs	4/11 Any design	7/11 Any design	5/11 'Any quantitative design'	0/11 Not specified	5/11 Randomised and non-randomised primary studies
Databases Searched	CENTRAL, MEDLINE, EMBASE, CINAHL, PsycINFO, ZETOC, ISI Proceedings	MEDLINE	MEDLINE, PsycINFO, CINAHL, Cochrane Database	ASSIA, CINAHL, EMBASE, MEDLINE, PsycINFO, Science Citation Index Expanded	MEDLINE	MEDLINE, PubMed
Date of Database Search	2004	2007	2008	2008	2011	2013
Language Restriction?	None	English	English	English	English, Dutch	None
Meta-Analysis?	No	No	No	No	No	Yes
Review Method of Quality Assessment	No formal assessment	Criteria adapted from the U.S. Preventive Services Task Force	Criteria adapted from the U.S. Preventive Services Task Force	Downs and Black checklist	Quality not assessed	Followed Critical Appraisal Skills Programme guidelines
Review Authors' Conclusions	"Evidence supporting the use of cardiovascular risk scores for primary prevention is scarce."	"We found surprisingly little evidence that physician knowledge of global CHD risk currently translates into improved clinical outcomes"	"The effect of global risk presentation on more distal outcomes is less clear and seems to be related to the intensity of accompanying interventions."	"Better quality trials are needed that compare different risk presentation formats before conclusions can be drawn"	"The impact of applying these risk scores in clinical practice is almost completely unknown, but their use is recommended in various national guidelines."	"There seems evidence that providing CVD risk model estimates to professionals and patients improves perceived CVD risk and medical prescribing, with little evidence of harm on psychological well-being."

that the effect of risk information on patients may improve proximal outcomes, such as accuracy or risk perception, in those who are high risk but the effect on distal outcomes was not clear.

Waldron 2011 (AMSTAR 5/11) reviewed studies of any quantitative design that used communication interventions for individualised cardiovascular risk and compared them to a control or usual care and assessed their impact on patient-related outcomes (Table 3.1).[72] Although the authors performed a comprehensive search, only three of the 15 primary studies identified were in actual patients—the rest were of analogue patients and therefore were not relevant to this study. The authors were unable to draw strong conclusions citing the need for better quality trials.

Van Dieren 2012 (AMSTAR 0/11) conducted a two-part review; the first part sought to identify risk scores that had been developed or validated for people with type two diabetes, and the second part sought to find studies aimed at assessing the impact on patient outcomes when these scores were implemented in practice (Table 3.1).[73] The authors therefore only searched for impact studies on the risk scores that had been identified in the former half of their review. Although the authors identified 45 primary studies, only three studies were identified from the latter half of the review and were relevant for inclusion. They concluded that “the impact of applying these risk scores in clinical practice is almost completely unknown.”[73]

Usher-Smith 2015 (AMSTAR 5/11) conducted the most recent and most comprehensive review, although the searches were conducted in 2013.[74] The authors considered randomised or non-randomised studies of interventions consisting of the provision of a CVD risk estimate to patients, or their providers, in patients with no history of CVD (Table 3.1). Searching MEDLINE and PubMed, they identified 17 primary studies, the vast majority of which had previously been reported by one of the aforementioned systematic reviews. However, this review was the first and only review to conduct meta-analyses, which helped draw stronger conclusions about impact. The authors concluded that global risk assessment could improve prescribing and perceived risk, but not smoking, and their meta-analyses showed no significant effect on systolic blood pressure or pooled total cholesterol and LDL cholesterol.

Table 3.2: Results of quality appraisal of included systematic reviews using AMSTAR criteria

AMSTAR Question	Review ID					
	Brindle 2006	Sheridan 2008	Sheridan 2010	Van Dieren 2012	Waldron 2011	Usher- Smith 2015
Was an a priori design provided?	NO	CA	CA	NO	NO	YES
Was there duplicate study selection and data extraction?	YES	NO	YES	CA	NO	YES
Was a comprehensive literature search performed?	YES	NO	YES	NO	NO	YES
Was the status of publication used as an inclusion criterion?	NO	NO	YES	NO	NO	NO
Was a list of studies (included and excluded) provided?	NO	YES	NO	NO	YES	NO
Were the characteristics of included studies provided?	YES	YES	YES	NO	YES	YES
Was the scientific quality of the included studies assessed and documented?	NO	YES	YES	NO	YES	YES
Was the scientific quality of the included studies used appropriately in formulating conclusions?	YES	YES	YES	NO	YES	NO
Were the methods used to combine the findings of studies appropriate?	NO	NO	YES	NO	YES	NO
Was the likelihood of publication biased assessed?	NO	NO	NO	NO	NO	NO
Was the conflict of interest included?	NO	NO	NO	NO	NO	NO
AMSTAR Score	4/11	4/11	7/11	0/11	5/11	5/11

CA = can't answer

3.5.2 Effects of Interventions and Quality of Evidence

Since the included reviews were of variable, but generally low, quality and only one attempted meta-analysis, I conducted a post hoc analysis of the primary studies reported by included systematic reviews that met the inclusion criteria to gain further insight from the reported data. Furthermore, some of the reviews insufficiently described included primary studies. Therefore in addition to meta-analysis, I tabulated the characteristics of included primary studies, including quality ratings for each study as reported by review authors (Table 3.3). Most (10/16) interventions used Framingham or a Framingham-derived risk score; these interventions and their controls are summarised in detail in Appendix B. The median follow-up of all included primary studies reported by reviews was 12 months, but ranged from two to 36 months (Appendix B). Table 3.4 reports the pooled estimates and GRADES for each outcome meta-analysed.

Table 3.3: Primary studies reported by included systematic reviews and included in data synthesis

Primary Study ID	Sample Size	Location	Target of Intervention	Study Design	Follow-up Time (months)	Systematic Review					Outcome						Quality as Reported by Systematic Review
Montgomery 2000[75]	614	UK	Provider	Cluster RCT	6-12	◆	◆	◆	◆		◆	◆	◆	◆	◆	◆	Fair[70]
Hanon 2000[76]	1,268	France	Provider	RCT	2	◆					◆	◆	◆	◆	◆	◆	Medium[74]
Lowenstein 1998[77]	958	Canada	Patient and Provider	RCT	3-6	◆	◆	◆	◆		◆	◆	◆	◆	◆	◆	Low[74]
Van Steenkiste 2007[78]	623	Netherlands	Patient and Provider	Cluster RCT	6	◆										◆	Fair[70]
Grover 2007[79]	2,356	Canada	Provider Patient and	RCT	12		◆		◆		◆	◆	◆	◆	◆	◆	Medium to High[74]
Hanlon 1995[80]	868	UK	Patient	RCT	5		◆					◆	◆	◆	◆	◆	Medium[74]
Emmett 2005[81]	216	England	Patient	Observational follow-up of RCT	36		◆				◆	◆	◆	◆	◆	◆	Good[71]
Family Heart Study Group 1994[82]	12,472	UK	Patient and Provider	RCT	12		◆				◆	◆	◆	◆	◆	◆	Fair[71]
Lovibond 1986[83]	75	Australia	Patient	RCT	6-12		◆				◆	◆	◆	◆	◆	◆	Fair[71]
OxCheck 1995[84, 85]	3,121	England	Patient	RCT	36		◆				◆	◆	◆	◆	◆	◆	Fair[71]
Turnbull 2006[86]	371	Australia	Patient and Provider	Cluster RCT	6-12		◆				◆	◆	◆	◆	◆	◆	Fair[71]
Williams 2006[87]	1,006	US	Patient	RCT	18		◆				◆	◆	◆	◆	◆	◆	Good[71]
Wister 2007[88]	315	Canada	Patient and Provider	RCT	12		◆				◆	◆	◆	◆	◆	◆	Good[71]
Bucher 2010[89]	3,316	Switzerland	Provider	RCT	12-18		◆				◆	◆	◆	◆	◆	◆	High[74]
Persel 2013[90]	435	USA	Patient	RCT	9-18		◆				◆	◆	◆	◆	◆	◆	Medium[74]
Price 2011[91]	185	UK	Patient	RCT	12		◆				◆	◆	◆	◆	◆	◆	Medium to High[74]

Table 3.4: Meta-analysis of the impact of global cardiovascular risk scoring on CVD morbidity or mortality, systolic blood pressure, total cholesterol, LDL cholesterol, and smoking cessation. Subgroup analyses were performed by interventions targeting the patient, the provider, or both.

Outcome		Patient Directed	Provider Directed	Patient and Provider Directed	Overall Effect Estimate
CVD Morbidity or Mortality	Effect Estimate	-	-	-	-
	I ² (%)	-	-	-	-
	Quality (GRADE)	-	-	-	-
Systolic Blood Pressure (mmHg)	Effect Estimate (MD) [95% CI]	-4.88 [-8.57,-1.19]	-1.14 [-2.09,-0.19]	-2.77 [-5.91,0.37]	-2.22 [-3.49,-0.95]
	I ² (%)	0	46	76	66
	Quality (GRADE)	very low	low	very low	very low
Total Cholesterol (mmol/L)	Effect Estimate (MD) [95% CI]	-0.07 [-0.13,-0.02]	-0.01 [-0.08,0.06]	-0.26 [-0.38,-0.15]	-0.11 [-0.20,-0.02]
	I ² (%)	0	single study	0	72
	Quality (GRADE)	very low	very low	very low	very low
LDL Cholesterol (mmol/L)	Effect Estimate (MD) [95% CI]	-0.15 [-0.27,-0.03]	-	-0.23 [-0.47,0.01]	-0.15 [-0.26,-0.05]
	I ² (%)	58	-	single study	47
	Quality (GRADE)	very low	-	very low	very low
Smoking Cessation (Risk of Quitting)	Effect Estimate (RR) [95% CI]	1.53 [1.07,2.19]	1.90 [0.43, 8.29]	0.30 [0.01, 7.07]	1.62 [1.08,2.43]
	I ² (%)	0	57	single study	17
	Quality (GRADE)	low	very low	moderate	low

Primary Outcomes

CVD-related Morbidity or Mortality

No reviews included studies reporting CVD-related morbidity or mortality (Table 3.4).

Secondary Outcomes

Systolic Blood Pressure

Five reviews reported a total of 12 unique primary studies (n=23,346) reporting SBP (Table 3.3). Of the 12 primary studies, three were cluster RCTs, eight were RCTs, and one was an observational follow-up of an RCT. Nine of the controlled trials (n=7,537) were reported with sufficient data to meta-analyse, resulting in a mean difference of mean change of SBP of -2.22 mmHg (95% CI: -3.49, -0.95; I²=66%; GRADE: very low) (Figure 3.2) (Table 3.4). Sub-group analyses by studies

of interventions targeting the patient (n=3), provider (n=3), or both (n=3), resulted in mean differences of -4.88 mmHg (95% CI -8.57, -1.19; $I^2=0\%$; GRADE: very low), -1.14 mmHg (95% CI -2.09, -0.19; $I^2=46\%$; GRADE: low), and -2.77 mmHg (95% CI -5.91, 0.37; $I^2=76\%$; GRADE: very low), respectively, in the intervention group relative to control (Figure 3.2) (Table 3.4). The standard error of Lovibond 1986 was imputed; excluding this study from the meta-analysis did not significantly change the results of the subgroup analysis or overall estimate: -4.82 mmHg (95% CI -9.36,-0.27; $I^2=0\%$) and -2.12 mmHg (95% CI -3.41,-0.83; $I^2=68\%$), respectively.

Two additional patient-directed studies were identified. The first, an RCT,[84] evaluated the impact of health checks which was comprised of a Framingham-derived risk score and counselling about risk, relative to usual care, in middle-aged adults. The study found a difference in SBP of -2.5mmHg (95% CI -3.7, -1.3) between the intervention and control group after three years; however, this was not adjusted to baseline values.[71] The second, an observational follow-up of an RCT,[81] found no significant difference between patients who received their risk score along with a decision analysis tool, relative to usual care, after three years: adjusted difference of SBP between intervention and control at follow-up was 0.94 mmHg (95% CI -3.2, 5.1, p-value 0.65).

Finally, one RCT targeting patients and providers, trained nurses on risk factor measurement and counselling, and provided patients with a CVD risk score and two to six sessions of counselling.[82] Compared to usual care after one year, unadjusted differences in SBP between intervention and control were -7.3 mmHg (p-value not reported) and -6.2 mmHg (p-value not reported), in men and women, respectively.[71]

Cholesterol

Six reviews reported a total of nine RCTs and one cluster RCT (Table 3.3). Both total cholesterol and LDL cholesterol were considered, and were analysed separately.

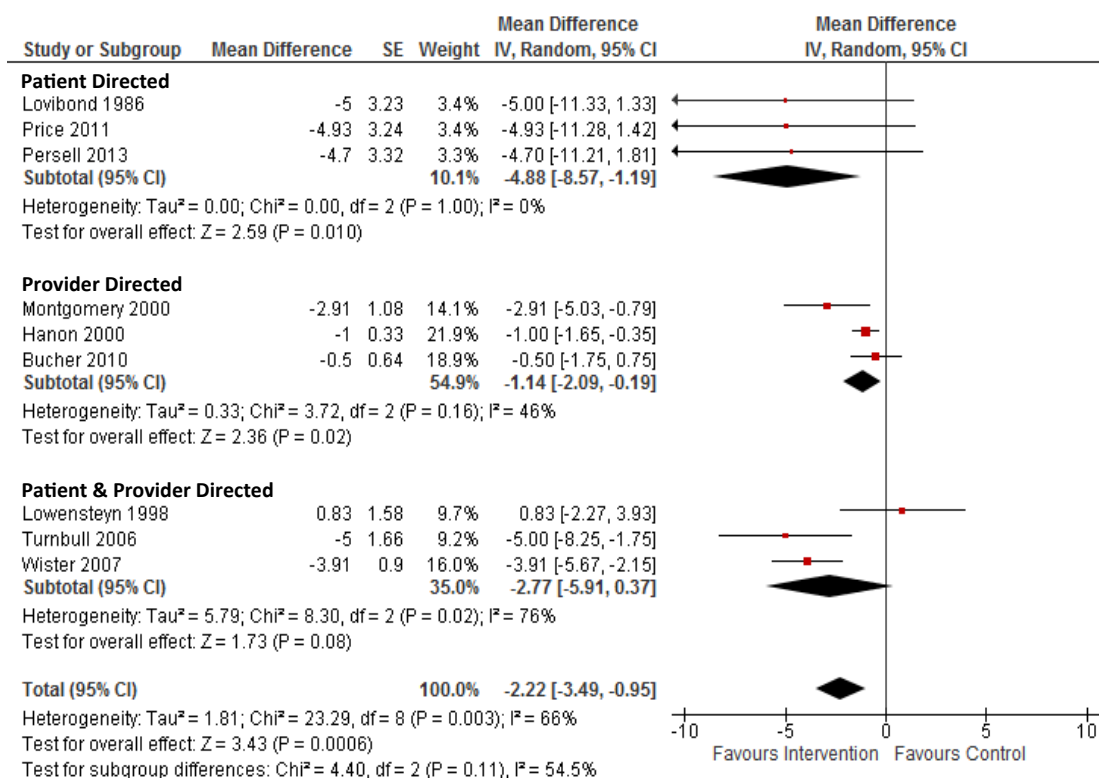


Figure 3.2: Forest plot and meta-analysis of the mean difference of mean change in systolic blood pressure (mmHg) from baseline to follow-up between intervention and control groups

Total Cholesterol

Of the seven trials ($n=23,406$) reporting total cholesterol, five ($n=7,813$) were reported with sufficient data to meta-analyse, resulting in a mean difference of -0.11 mmol/L (95% CI -0.20 , -0.02 ; $I^2=72\%$; GRADE: very low) (Figure 3.3)(Table 3.4). Sub-group analyses by studies of interventions targeting the patient ($n=2$), provider ($n=1$), or both ($n=2$), resulted in mean differences of -0.07 mmol/L (95% CI -0.13 , -0.02 ; $I^2=0\%$; GRADE: very low), -0.01 mmol/L (95% CI -0.08 , 0.06 ; GRADE: very low), and -0.26 mmol/L (95% CI -0.38 , -0.15 ; $I^2=0\%$; GRADE: very low) (Figure 3.3) (Table 3.4).

Two additional RCTs were reported, one targeting patients and one targeting both patients and providers. The former,[84] evaluated the impact of health checks which was comprised of a Framingham-derived risk score and counselling about risk, relative to usual care, in middle-aged adults. The study found a difference in total

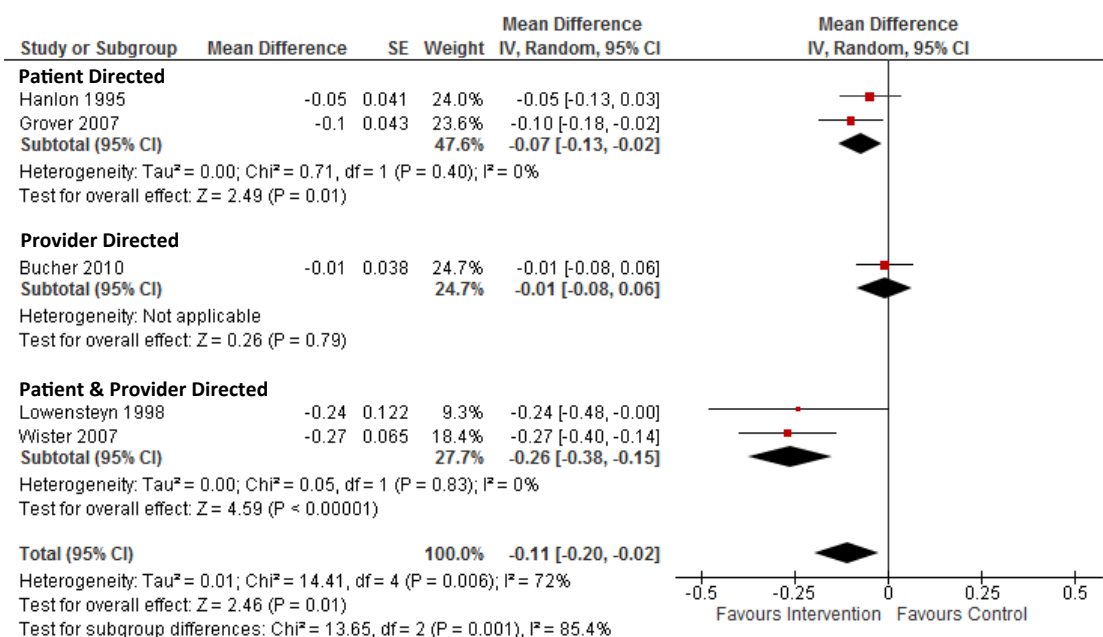


Figure 3.3: Forest plot and meta-analysis of the mean difference of mean change in total cholesterol (mmol/L) from baseline to follow-up between intervention and control group

cholesterol of -0.18 mmol/L (95% CI -0.26, -0.12) between the intervention and control group after three years, however this was not adjusted to baseline values.[71]

The latter,[82] targeting patient and providers, trained nurses on risk factor measurement and counselling, and provided patients with a CVD risk score and two to six sessions of counselling.[82] Compared to usual care after one year, unadjusted differences in total cholesterol between intervention and control were -0.13 mmol/L (p-value not reported) and -0.09 mmol/L (p-value not reported), in men and women, respectively.[71]

LDL Cholesterol

Five trials (n=4,940) reported data on LDL cholesterol, four of which (n=4,505) when meta-analysed yielded a greater reduction in LDL cholesterol in the intervention group compared to the control group: mean difference of -0.15 mmol/L (95% CI -0.26, -0.05, $I^2=47\%$; GRADE: very low) (Figure 3.4) (Table 3.4). Sub-group analyses by studies of interventions targeting the patient (n=3) and both the patient and provider (n=1), resulted in mean differences of -0.15 mmol/L (95%

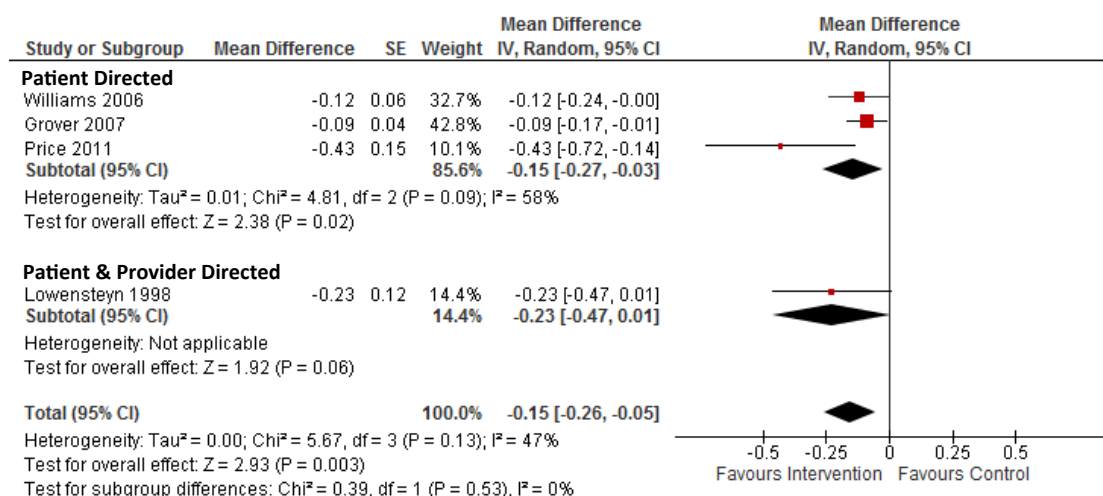


Figure 3.4: Forest plot and meta-analysis of the mean difference of mean change in LDL cholesterol (mmol/L) from baseline to follow-up between intervention and control group

CI -0.27,-0.03; $I^2=58\%$; GRADE: very low) and -0.23 mmol/L (95% CI -0.47, 0.01; GRADE: very low), respectively (Figure 3.4) (Table 3.4).

One additional RCT targeting patients assessed the impact of mailing personalised CVD risk assessment and encouraging discussion with their primary care physician, compared to usual care.[90] The primary outcome was the occurrence of an LDL cholesterol measurement of at least 0.78 mmol/L (30 mg/dL) lower than the baseline measurement during a nine month follow-up. The trial showed no significant difference between intervention and control, intention-to-treat analysis resulted in an odds ratio of 0.99 (95% CI 0.56, 1.74, p-value=0.96).[90]

Smoking

Three reviews reported a total of eight RCTs and one cluster RCT ($n=19,873$) (Table 3.3). Seven of these trials ($n=4,131$) were reported with sufficient data to meta-analyse, resulting in a risk ratio for quitting smoking of 1.62 (95% CI 1.08, 2.43; $I^2=17\%$; GRADE: low) (Figure 3.5) (Table 3.4). Sub-group analyses by studies of interventions targeting the patient ($n=4$), provider ($n=2$), or patient and provider ($n=1$) resulted in risk ratios of 1.53 (95% CI 1.07, 2.19; $I^2=0\%$; GRADE: low), 1.90 (95% CI 0.43, 8.29; $I^2=57\%$; GRADE: very low), and 0.30 (95% CI 0.01, 7.07; GRADE: moderate), respectively (Figure 3.5) (Table 3.4).

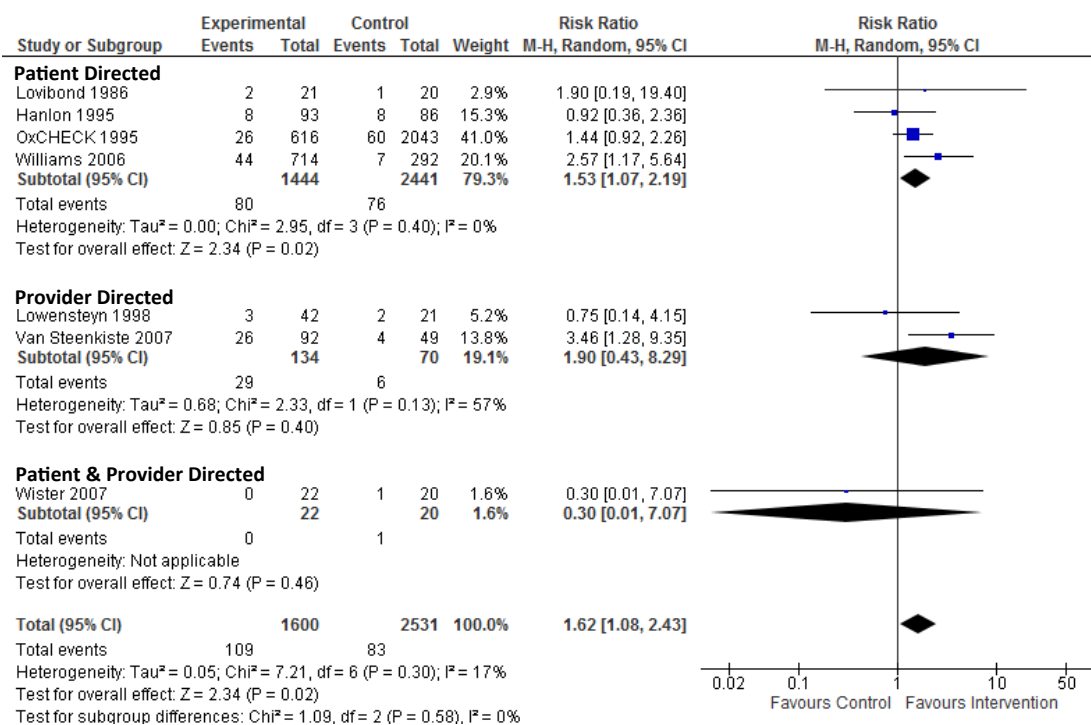


Figure 3.5: Forest plot and meta-analysis of the risk ratio of quitting smoking from baseline to follow-up between intervention and control group

Two additional RCTs were reported by included reviews, one targeted patients and one targeted patients and providers. Of the former, one RCT targeting patients assessed the impact of mailing personalised CVD risk assessment and encouraging discussion with their primary care physician to usual care.[90] As a secondary outcome, the trial sought to record the number of smokers who quit after nine months, but failed to provide the actual data stating, “non-smoking [among smokers] was rare and did not vary by group.”[90]

The other, an RCT targeting patient and providers, trained nurses on risk factor measurement and counselling, and provided patients with a CVD risk score and two to six sessions of counselling.[82] Compared to usual care after one year, unadjusted differences in smoking prevalence between intervention and control were -4.1% (p-value not reported) and -2.9% (p-value not reported), in men and women, respectively.[71]

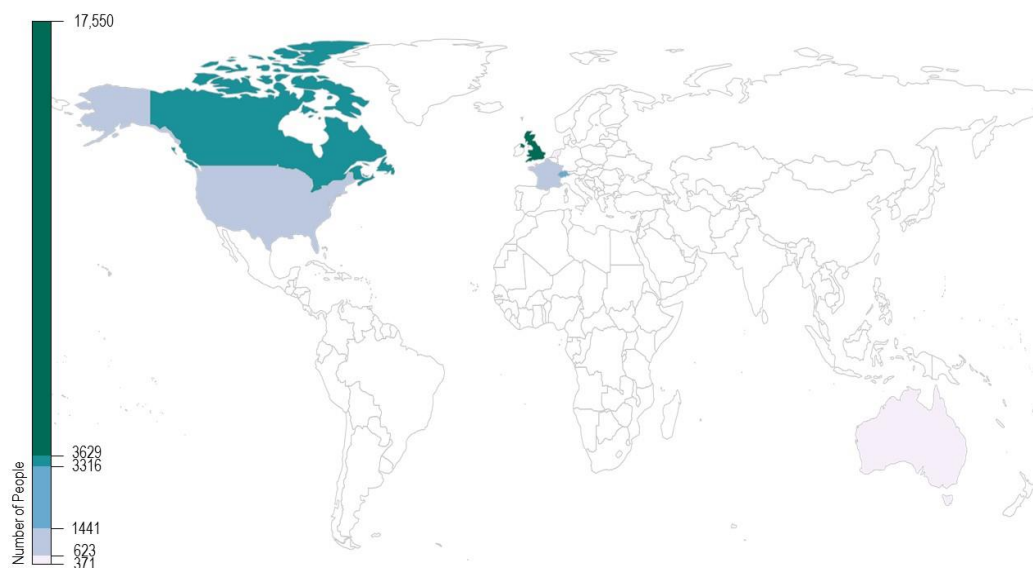


Figure 3.6: Map of the world illustrating the spatial distribution of participants included in the primary studies identified in included systematic reviews

3.5.3 Quality of Evidence

Table 3.5 reports the GRADE scores and quality parameters for all meta-analysis effect estimates. All studies meta-analysed were RCTs; risk of bias was affected for some estimates by concerns about randomisation procedures, allocation concealment, inadequate blinding, industry sponsorship and lack of intention-to-treat analysis. Indirectness was scored as serious for all because participants were only from high-income countries; three estimates were further scored as very serious because patients had existing conditions.

3.5.4 Spatial and Epidemiological Origins of Data

Included participants were from a total of seven countries: Canada, United States, France, The Netherlands, Switzerland, United Kingdom, and Australia (Figure 3.6).

Classifying by epidemiological subregion, the seven countries fell within three unique subregions (Americas A, Europe A, Western Pacific A) that together represent only 14.2% of the global population (Table 3.6).

Table 3.5: GRADE score and quality assessment parameters for meta-analysis effect estimates

Number of Studies	Quality Assessment					GRADE
	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	
Systolic Blood Pressure (mmHg)						
9	randomised trials	serious ^{1,2}	serious ³	serious ⁴	not serious	very low
Systolic Blood Pressure (mmHg) - Patient Directed						
3	randomised trials	serious ¹	not serious	serious ⁴	serious ⁵	very low
Systolic Blood Pressure (mmHg) - Provider Directed						
3	randomised trials	serious ¹	not serious	serious ⁴	not serious	low
Systolic Blood Pressure (mmHg) - Patient & Provider Directed						
2	randomised trials	serious ^{2,6}	not serious ⁷	serious ⁴	serious ⁵	very low
Smoking Cessation						
7	randomised trials	serious ^{1,2,6,8}	not serious	serious ⁴	not serious	low
Smoking Cessation - Patient Directed						
4	randomised trials	serious ^{1,2,8}	not serious	serious ⁴	not serious	low
Smoking Cessation - Provider Directed						
2	randomised trials	not serious	serious ⁹	serious ⁴	serious ⁵	very low
Smoking Cessation - Patient & Provider Directed						
1	randomised trials	not serious	not serious	serious ⁴	not serious	very low
Total Cholesterol (mmol/L)						
5	randomised trials	serious ^{1,2,6,8}	very serious ³	very serious ^{4,10,11}	serious ⁵	very low
Total Cholesterol (mmol/L) - Patient Directed						
2	randomised trials	serious ^{1,2,8}	not serious	very serious ^{4,10}	not serious	very low
Total Cholesterol (mmol/L) - Provider Directed						
1	randomised trials	serious ^{2,8}	not serious	very serious ^{4,11}	serious ⁵	very low
Total Cholesterol (mmol/L) - Patient & Provider Directed						
2	randomised trials	serious ^{1,2,6,8}	not serious	serious ⁴	serious ⁵	very low
LDL Cholesterol (mmol/L)						
4	randomised trials	very serious ^{1,2,6,8}	not serious	serious ⁴	not serious	very low
LDL Cholesterol (mmol/L) - Patient Directed						
3	randomised trials	serious ^{1,2,8}	serious ³	serious ⁴	not serious	very low
LDL Cholesterol (mmol/L) - Patient & Provider Directed						
1	randomised trials	very serious ⁶	not serious	serious ⁴	not serious	moderate

¹concerns about randomisation; ²concerns about blinding; ³variation in magnitude of intervention effect; ⁴all participants from high-income countries; ⁵wide confidence interval; ⁶Lowensteyn (1998) had industry funding and did not perform intention-to-treat analysis; ⁷removal of Lowensteyn (1998) reduces heterogeneity to 0%, Lowensteyn (1998) had a small sample size; ⁸concerns about allocation concealment; ⁹variation in direction of intervention effect; ¹⁰Grover (2007): 23% with existing CVD and 50% with diabetes; ¹¹Bucher (2010): all participants had HIV

Table 3.6: Number of participants in primary studies reported by included systematic reviews by country and epidemiological subregion

Epidemiological Sub-Region (Percent of Total Participants)	Country	Number of Participants	Percent of Global Population in Epidemiological Sub-Region
Americas A (18%)	Canada	3,629	5.3%
	United States of America	1,441	
Europe A (81%)	France	1,268	6.5%
	The Netherlands	623	
	Switzerland	3,316	
	United Kingdom	17,550	
Western Pacific A (1%)	Australia	371	2.4%

3.6 Discussion

3.6.1 Summary of Findings

Six systematic reviews were identified. Reviews on this topic varied in the databases searched, search strategies used, and the specific populations and interventions of interest, and their quality was generally poor (mean AMSTAR 4.2/11, range 0/11 to 7/11). However, they have consistently reported uncertainty about the effectiveness of global CVD risk scoring. The results show that to date no reviews have reported CVD-related morbidity or mortality. Post hoc analysis of data reported by included reviews illustrated very low quality evidence for small reductions in SBP, total cholesterol, LDL cholesterol, and low quality evidence for small increases in smoking cessation.

The meta-analysis of SBP added five additional RCTs compared to the previously reported meta-analysis[74] and revealed for the first time a statistically significant small reduction in SBP. Statistically significant, but small, reductions in total cholesterol, LDL cholesterol, and smoking were also observed.

The post hoc analysis of data reported by included systematic reviews was conducted to compensate for the poor evidence synthesis of some of the included reviews and to reduce research waste. Several of the included reviews highlighted a need for better quality trials, and the quality appraisal using GRADE corroborated

these conclusions. The post hoc analysis illustrated that all effect estimates were of low or very low GRADE quality.

All participants in the trial data were from only seven countries, of which all were high-income and represented only three epidemiological subregions of the world.

3.6.2 Interpretation of Findings

Reductions in SBP, LDL cholesterol, and smoking tended to be greatest when cardiovascular risk information was directed at patients. The delineation between patient-directed and provider-directed interventions is not well resolved, since patients may discuss risk information with their provider and vice versa. This phenomenon may contaminate the subgroup analysis. A previous review[71] concluded that greater effects were seen in patients with increased baseline CVD risk.

Reductions in blood pressure, cholesterol, and smoking could lead to reductions in overall risk and eventual reduction in CVD events. However, the observed reductions were small in magnitude and the median follow-up of all eligible studies reported by included systematic reviews was only 12 months. It is unclear if such reductions for short duration may translate to meaningful reductions in CVD events, or if the observed risk factor modifications can be sustained longterm.

The paucity of data may partly be explained by the assumption that accuracy of risk scores is a proxy for effectiveness, therefore undermining rationale for further study. While mechanical prediction, such as the use CVD risk scores, is generally a superior method of data combination than clinical judgment,[92] it is unknown whether this holds true for cardiovascular risk. Moreover, clinicians still rely on clinical judgment to integrate risk scores within the broader context of the patient—especially for risk factors that are not included in the risk score—therefore risk stratification is not strictly a practice that can be replaced with mechanical prediction. The uncertainty around the clinical utility of this practice has been highlighted by UK general practitioners, who expressed that broad implementation created considerable confusion, and emphasised the need for simplification and for guidance to be updated to reflect how risk scores are actually used.[54]

3.6.3 Findings in the Context of Existing Research

Several months after this Chapter was accepted for publication in BMJ Open,[1] a Cochrane review was published on this topic whose search included up to 15 March 2016.[93] Overall, the findings of the review were consistent with the findings of this Chapter, including the effect estimates from meta-analysis. Despite identifying additional RCTs, the Cochrane review’s pooled effect estimates for SBP (MD -2.77 mmHg 95% CI -4.16, -1.38), total cholesterol (MD -0.10 mmol/L 95% CI -0.20, 0.00), LDL cholesterol (MD -0.03 mmol/L 95% CI -0.10, 0.04), and smoking cessation (RR 1.38 95% CI 1.13, 1.69) were not significantly different from the estimates reported herein. While the review did identify three RCTs which reported CVD events as outcomes,[89, 94–96] these studies were underpowered to measure CVD events. None of the trials showed an impact on CVD events as outcomes.[97]

The lack of high quality systematic reviews reporting hard patient outcomes might partly be explained by seemingly widespread acceptance, including among several guidelines, of the impact total cardiovascular risk scoring. Neither the National Institute of Health and Care Excellence (NICE)[42] nor WHO[98] currently acknowledge this evidence gap. However, the 2013 American College of Cardiology/American Heart Association Guideline on the Assessment of Cardiovascular risk acknowledges that “none of the risk assessment tools... have been formally evaluated in randomised controlled trials... with clinical events as outcomes.”[99] NICE does go so far as to make recommendations for research, but overlooks the need to evaluate the global CVD risk approach.[100] Further, global cardiovascular risk assessment is included in the Quality and Outcomes Framework in the UK as an incentive for general practitioners to be compliant with guidance for primary prevention.[101]

There is evidence, from studies retrospectively risk scoring patients, that the absolute reduction in CVD events from cholesterol-lowering and blood pressure-lowering treatment is associated with baseline CVD risk.[32, 40] It is important to distinguish, however, that these data do not illustrate that the prospective use of CVD risk scores improves patient outcomes, but suggest that targeting high risk

patients is an efficient way to allocate resources to reduce CVD events. Nor do studies of calibration and discrimination imply effectiveness.

One may speculate the potential pathway of impact on patient outcomes from the use of risk scores. Risk scoring could help improve the accuracy of risk assessment, adherence to clinical guidance, prescription of risk factor modifying medications, accuracy of patient risk perception, and adherence of patients to risk modifying interventions, ultimately impacting modifiable risk factor levels and CVD-related morbidity and mortality. Existing evidence shows that many of these surrogate outcomes along the prevention pathway can be measured, but their findings are mixed. Interventions to train general practitioners on CVD risk scoring in addition to the use of decision support tools do not appear to improve adherence to treatment guidance.[70, 78, 102] Even when documented risk scores are placed in clinical notes, without the need for physicians to calculate it, it does not appear to change prescribing habits amongst relatively low-risk patients, but may in some higher risk patients, such as diabetics.[103] One may hypothesise that CVD risk information could improve the accuracy of patient risk perception, leading to adherence and acceptance to treatment, but RCTs measuring patient accuracy of CVD risk perception show no effect, while some lower quality studies showed an increase in accuracy of risk perception.[70, 71, 78, 104–106] This is similar for patient intent to start therapy,[107–109] despite improvements in prescription of drug treatment.[74] Further, some RCTs show reductions in CVD risk when CVD risk scores are used[70, 71, 77, 79, 82, 88, 107]; others show no effect.[69–71, 75, 76, 80, 83, 86, 104, 110, 111] While these are surrogate outcomes for reductions in risk factor levels and CVD-related morbidity and mortality, given the mixed effects and feasibility to measure, they should be considered in future studies of the use of CVD risk scoring.

3.6.4 Strengths and Limitations

This systematic review of systematic reviews was strengthened by its broad inclusion criteria, which reduced the chance relevant literature was missed. This method provided quality appraised systematic reviews and their primary studies and

therefore can help inform policy and practice, in addition to providing new insight from rigorous data synthesis from a breadth of sources. It also highlighted trends in the systematic review literature. While there was heterogeneity in the risk scores used, the exact nature of the interventions, comparisons, follow-up time, and patient demographics, such heterogeneity may approximate the reality of clinical practice. The meta-analyses of data reported by systematic reviews advanced the state of knowledge on the impact of total cardiovascular risk assessment beyond what was reported by the individual included systematic reviews. The consistency of the findings of this Chapter and those reported by a recent Cochrane review on the same topic highlight the methodological potential of systematic reviews of systematic reviews, in addition to taking six years less to complete than the analogous Cochrane review.[97]

Whilst an exhaustive search was undertaken, it is possible some systematic reviews were missed. The post hoc analysis of primary studies reported by included systematic review should be interpreted with caution. Its purpose was to better appraise and synthesise the primary studies which were already available in the systematic review literature, and therefore it did not represent the conclusions from a systematic review of individual primary studies, and it is possible that further primary studies exist. Given that these data were not appraised and synthesised to a high standard in the included systematic reviews, I felt it necessary to do so. Sensitivity analyses were not conducted due to a paucity of data. Authors of primary studies were not contacted, which may have allowed for the adjustment of some study results which were reported narratively. However, as these studies were reported in systematic reviews, some of which contacted study authors, the likelihood of further data becoming available may be minimal, and the findings of these studies did not contradict the overall findings of the meta-analyses. Publication bias and reporting bias were not assessed, not least because of the small number of studies, which may have led to overestimations of the effect sizes. Data was imputed for the standard error of one study,[83] which may underestimate heterogeneity; however, sensitivity analysis revealed only a 2% absolute increase in I^2 for the overall effect

estimate when this study was excluded. The current evidence base is limited in that all patients were from high-income countries, many were hypertensive, and most interventions used a Framingham-derived risk score. The bias toward high-income countries may partially be accounted for by the fact that only two of the six included reviews did not apply language restrictions.

As systematic reviews of systematic reviews are an emerging methodology, slight deviations from the registered protocol occurred and are reported here in the spirit of transparency.[63] While the original plan was to explore many different outcomes, I decided to focus on the most important outcomes as they relate to CVD-related morbidity and mortality. I therefore focused the secondary outcomes to systolic blood pressure, cholesterol, and smoking because together these account for the majority of premature CVD and there are effective interventions to modify them.[13, 14] It was expected that systematic reviews would have conducted meta-analyses. However, only one of the six included systematic reviews did so, and I therefore felt it was necessary to conduct my own meta-analyses. These provided invaluable insight in to the direction and magnitude of the intervention effect, and presented the results of each individual study in a transparent and easy-to-interpret way.

3.6.5 Implications for Research and Practice

The findings of the meta-analyses should be interpreted with caution given the scarcity of evidence and its low quality. Policy-makers worldwide should take care when implementing global cardiovascular risk scoring, especially in an era where prevention efforts are expanding worldwide, as there was no systematic review evidence to suggest that the prospective use of global cardiovascular risk scores in clinical practice reduces CVD events. Although the most recent systematic review was published in 2015, its literature search was conducted in 2013, and researchers may considering updating high quality systematic reviews. Since the effect estimates arising from reported RCTs were of low or very low quality, high-quality primary studies may also be needed. Given that all studies were from high-resource settings,

trials are especially needed in low-resource settings and these should be done before the widespread implementation of CVD risk scoring, or, if not possible, in concert.

3.7 Conclusions

In this Chapter, six systematic reviews on the use of CVD risk scores for primary prevention of CVD in adults were identified. These reviews showed that there was no evidence that the prospective use of global cardiovascular risk scoring translated to reductions in CVD-related morbidity or mortality. Systematic reviews, which were generally of poor quality, had consistently reported uncertainty about the impact of this practice on meaningful patient outcomes, and primary studies appeared to focus on intermediate outcomes. Reductions in SBP, cholesterol, and smoking may not be clinically significant given their small effect size and short duration. Despite the widespread popularity of global cardiovascular risk scoring in high-resource settings, resources need to be directed to conduct further RCTs powered to measure CVD-related morbidity and mortality, particularly in countries outside of Europe, North America, and Australia.

3.8 Chapter Summary

- Six systematic reviews on the impact of cardiovascular risk scores were identified, which were generally poor in quality and did not report primary studies showing effects on CVD-related morbidity or mortality
- There was very low quality evidence for small reductions in SBP, total cholesterol, LDL cholesterol, and low quality evidence for small increases in smoking cessation when risk scores were used in asymptomatic adults
- The evidence available in systematic reviews originated from seven high-income countries, which together represented only three epidemiological subregions of the world

- Further primary RCTs are likely needed in low-resource settings since these regions have the highest burden of CVD and a paucity of evidence for risk scoring
- Trials should be done before the widespread implementation of CVD risk scoring in low-resource settings, or, if not possible, in concert

4

whoishRisk: an R Package to Calculate WHO/ISH Cardiovascular Disease Risk Scores

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4.1 Publication Statement

Features of this chapter have been published in F1000 Research.[2]

4.2 Introduction

The findings of the previous chapter (Chapter 3) demonstrated a need for research on the implementation and effectiveness of cardiovascular disease (CVD) risk scores,

not least in low- and middle-income countries (LMIC). This chapter (Chapter 4) therefore developed the software required to study World Health Organisation/International Society of Hypertension (WHO/ISH) risk scores used in LMIC, and this was subsequently used in Chapter 5.

In 2007 the WHO and the ISH published the WHO/ISH CVD risk charts for all WHO epidemiological subregions of the world.[112] These charts were to be used as part of the WHO's Package of Essential Non-Communicable Disease (NCD) Interventions for Primary Health Care in Low-Resource Settings (WHO PEN) in jurisdictions that did not have their own population-derived risk scores. While these charts provided a starting point for many health systems, little was known about their validity or their development.[113]

There are two paper-based versions of WHO/ISH charts for each epidemiological subregion: one that requires measured total cholesterol and one that does not. The latter was made available for use in settings with limited access to laboratory testing or where the cost of cholesterol testing is prohibitive. Both charts require information on age, gender, diabetes status, smoking status, and systolic blood pressure to stratify people into one of five risk categories of 10-year risk of a fatal or non-fatal CVD event. Further instructions for their use have been published.[21]

One of the main barriers to researching WHO/ISH CVD risk scores was that they had to be calculated by hand because they were only published as paper or PDF risk charts, making large-scale evaluations of their implementation impractical. Since the methodology of their development was never fully published, there was no underlying equation that could be implemented in a statistical computing environment. This is a marked divergence from other mainstream risk scores such as Framingham, QRISK2, and European Society of Cardiology SCORE, which have prognostic model equations that can be implemented in a statistical computing environment.[113]

Previously, as part of a larger project, a MatLab implementation of WHO/ISH risk charts was published so that WHO/ISH CVD risk scores could be calculated for a large cohort. This implementation was insufficient because: (1) it could only calculate risk scores for epidemiological subregion South-East Asia D (SEAR D);

(2) it was developed in an expensive statistical computing environment (MatLab) not suitable for researchers in low-resource settings; (3) it was not validated; (4) it lacked user-friendliness because it was not in the form of a package. It was therefore necessary to develop new software that addressed these limitations, and to make it freely available.

4.3 Aim and Objectives

4.3.1 Aim

The aim of this chapter was to develop a standardised, open-source computational method (i.e. software) to calculate WHO/ISH CVD risk scores.

4.3.2 Objectives

To achieve this aim, the objectives of this chapter were to:

1. Extract by hand the component data from published WHO/ISH CVD risk scores for all epidemiological subregions of the world
2. Write an R function that automates the calculation of WHO/ISH CVD risk scores
3. Validate the R function by comparison to an existing implementation
4. Develop an R package to document and distribute the software

4.4 Methods

There were three main steps in the development of the package. The first step involved extracting the component information from the paper WHO/ISH CVD risk charts into an electronic format. The second was developing a function which could take risk factor values as inputs and with these determine the corresponding risk score. The last step was validating the package by comparison with an alternate implementation.

4.4.1 Extraction of WHO/ISH Cardiovascular Risk Charts

A standardised Microsoft Excel template was developed that included all possible combinations ($n=640$) of the six parameters of WHO/ISH risk charts (i.e. age, gender, smoking, systolic blood pressure, diabetes status, total cholesterol) for all epidemiological subregions of the world ($n=14$). This file was called “WHO_ISH_Risk.csv” and the first six columns specified the risk factor values, and the last 14 columns specified the corresponding risk category for a given subregion. For each unique combination of parameters, the corresponding WHO/ISH score was extracted from paper-based WHO/ISH CVD risk charts, independently and in duplicate (DC and one of JL or NB). This equated to 21,504 extractions by hand. R was used to compare the duplicate extractions and to calculate Cohen’s kappa coefficient for inter-rater reliability using the irr package.[114, 115] Cohen’s kappa coefficient was chosen as a measure agreement because it accounts for possibility that two extractions agreed by chance.[116] Discrepancies in extraction were reviewed by the same two extractors (DC and one of JL or NB) and resolved by referring to the original paper chart.

4.4.2 whoishRisk Package Development

First, I learned the R language, which was done as described in Chapter 1. I wrote the R function code and developed the R package, including all documentation, in accordance to the Comprehensive R Archive Network guidelines.[117] The R function code was reviewed by a person experienced in the R language (CK). Two additional people new to the R language, reviewed the code to ensure the syntax was simple (NB, JL). Simple syntax was prioritised so as to foster collaboration once the package was published. To check the completeness and functionality of the package, the “check” function in the build capacity of RStudio was used to ensure all package requirements, including documentation and dependencies, were met.[114]

4.4.3 R Package Validation

Comparison of SEAR D with published MatLab implementation

A MatLab implementation of WHO/ISH risk charts for epidemiological subregion SEAR D was previously published as part of a larger study.[118] This allowed for a direct comparison of results between the *whoishRisk* package and the MatLab implementation for one epidemiological subregion. Octave (version 8.3.2)[119] was used to calculate the SEAR D WHO/ISH risk score for every possible combination of risk factors (n=640) using the previously reported MatLab implementation (JL).[118] These results were compared with the results obtained from *whoishRisk* to identify any discrepancies.

4.5 Results

4.5.1 Extraction of WHO/ISH Cardiovascular Risk Charts

Cohen's kappa for initial agreement between the independent extractors was 0.97. All remaining discrepancies were resolved by consensus. The finalised "WHO_ISH_Scores.csv" file was included within the *whoishRisk* package and is not accessible to the user, although it has been published in an open access journal to promote collaboration.[2]

4.5.2 Development of the *whoishRisk* Package

whoishRisk is an R package that can be used with any computer operating system and was designated a GPL-3 license, officially making it free software. The four foundations of this license are the freedom to (1) use the software for any purpose, (2) change the software to suit user-specific needs, (3) share the software with anyone, and (4) share any changes that are made by users.[120] It contains a single function, `WHO_ISH_Risk()`, which calculates the WHO/ISH CVD risk score for any epidemiological subregion of the world based on the parameter values passed to it. It can be downloaded and installed directly from github using the `install_github()` command in the *devtools* package, with the argument

Table 4.1: Description of the WHO_ISH_Risk() function parameters

Function parameter	Full parameter name	Parameter class	Possible parameter input values	Discretisation of continuous values
age	Age	numeric	Continuous (years)	40 (≤ 49), 50 (50-59), 60 (60-69), 70 (≥ 70)
gdr	Gender	numeric	Dichotomous (0=female; 1=male)	-
smk	Smoking	numeric	Dichotomous (0=non-smoker; 1=smoker)	-
sbp	Systolic blood pressure	numeric	Continuous (mmHg)	120 (≤ 139), 140 (140-159), 160 (160-179), 180 (≥ 180)
dm	Diabetes mellitus status	numeric	Dichotomous (0=non-diabetic, 1=diabetic)	-
chl	Total cholesterol	numeric	Continuous (mmol/L); 0=unknown cholesterol	0 (unknown), 4 (>0 & ≤ 4.5), 5 (4.6-5.5), 6 (5.6-6.5), 7 (6.6-7.5), 8 (≥ 7.6)
subregion	WHO epidemiological subregion	character	“AFR_D”, “AFR_E”, “AMR_A”, “AMR_B”, “AMR_D”, “EMR_B”, “EMR_D”, “EUR_A”, “EUR_B”, “EUR_C”, “SEAR_B”, “SEAR_D”, “WPR_A”, “WPR_B”	-

“DylanRJCollins/whoishRisk”.[121] The package passed the build check assessment with zero warnings, notes, or errors indicating that it met all standards of the Comprehensive R Archive Network guidelines.[117]

4.5.3 Development of the WHO_ISH_Risk() Function

whoishRisk contains a single function, called WHO_ISH_Risk(), which calculates the WHO/ISH risk score for any epidemiological subregion. WHO_ISH_Risk() requires seven parameters: age, gender, smoking status, diabetes status, systolic blood pressure, total cholesterol, and the appropriate WHO epidemiological subregion. The function format in the workspace is: WHO_ISH_Risk(age, gdr, smk, sbp, dm, chl, subregion). These parameters and their abbreviations are summarised in Table 4.1; no default values were specified for any parameter. The WHO epidemiological subregion taxonomy used for calculating WHO/ISH risk scores is described in Table 4.2. The code for the function is included in Appendix C.

Internally, WHO_ISH_Risk() requires access to the “WHO_ISH_Scores.csv”

Table 4.2: Epidemiological region and subregion taxonomy of countries used by WHO/ISH risk charts

Region	Subregion	Countries
Africa	AFR D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome And Principe, Senegal, Seychelles, Sierra Leone, Togo
	AFR E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of The Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania, Zambia, Zimbabwe
Americas	AMR A	Canada, Cuba, United States of America
	AMR B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts And Nevis, Saint Lucia, Saint Vincent and The Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela
	AMR D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru
Eastern Mediterranean	EMR B	Bahrain, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates
	EMR D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen
Europe	EUR A	Andorra, Austria, Belgium, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom
	EUR B	Albania, Armenia, Azerbaijan, Bosnia And Herzegovina, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Serbia and Montenegro, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan
	EUR C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine
South-East Asia	SEAR B	Indonesia, Sri Lanka, Thailand
	SEAR D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal
Western Pacific	WPR A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore
	WPR B	Cambodia, China, Cook Islands, Democratic People's Republic of Korea, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam

file containing the extracted risk scores. The file is called automatically from within the package, but it is also publicly available.[2] The `WHO_ISH_Risk()` function creates an internal data frame of the risk factor values passed to it. Parameters can be single values or vectors of equal length. It then categorises the continuous parameters age, systolic blood pressure, and total cholesterol. Age and systolic blood pressure were categorised according to WHO guidance (Table 4.1).[112] Total cholesterol was categorised according to common clinical practice, rounding up from 0.5 to the nearest integer (Table 4.1).

Internally, a unique identification code is generated corresponding to the combinations of risk factors for each individual. This code is matched to a reference code from the “WHO_ISH_Scores.csv” file. The function stores the risk scores in a data frame that includes the risk factors, and ultimately returns a vector containing the risk scores. The output of the function is one of five different character strings, corresponding to the five different WHO/ISH risk categories: “<10%”, “10 to <20%”, “20 to <30%”, “30 to <40%”, “≥40%”.

Warning messages were included when parameters appear out of range. These messages, their conditions, and their intended interpretation are described in Table 4.3. Out of range continuous parameters (i.e. age, systolic blood pressure, total cholesterol) are non-fatal and a risk score is generated with a warning message. Out of range dichotomous parameters (gender, smoking status, diabetes status) are fatal errors and the output (NA) is generated with a warning.

4.5.4 Comparison with MatLab Implementation

Comparison with the published MatLab implementation of the SEAR D risk charts showed 100% agreement with the results obtained from `whoishRisk`, for all possible combinations of risk factors.[10]

4.5.5 Worked Examples

`whoishRisk` can be installed in one step using `install_github()` from the `devtools` package.[121] A worked example of how to install `whoishRisk` and use

Table 4.3: WHO_ISH_Risk() warning messages, their conditions, and intended Interpretation

Condition of Warning	Output if Condition Met	Warning Message	Interpretation of Warning
age <19	Non-fatal	At least one age is 18 or younger	WHO/ISH risk scores are meant for use in adults. At least one age value is equal to 18 or younger. Check for errors in age values.
age >100	Non-fatal	At least one age is greater than 100	Age values greater than 100 may indicate a data error. Check to ensure age values over 100 are correct.
gdr >1	Fatal	Gender must be equal to 0 or 1	A value for gender other than 0 or 1 is included. Check gender values.
smk >1	Fatal	Smoking must be equal to 0 or 1	A value for smoking other than 0 or 1 is included. Check smoking values.
sbp <90	Non-fatal	At least one systolic blood pressure is below 90 mmHg	SBP values below 90 mmHg may indicate a data error. Check to ensure values under 90 mmHg are correct.
sbp >250	Non-fatal	At least one systolic blood pressure is over 250 mmHg	SBP values over 250 mmHg may indicate a data error. Check to ensure values over 250 are correct.
dm >1	Fatal	Diabetes status must be equal to 0 or 1	A value for diabetes status other than 0 or 1 is included. Check diabetes status values.
chl >10	Non-fatal	At least one total cholesterol is greater than 10 mmol/L. Ensure all values are in units of mmol/L	Total cholesterol values over 10 mmol/L may indicate a data error. Check to ensure values over 10 mmol/L are correct in units of mmol/L.

the WHO_ISH_Risk() function to calculate the risk score for five individuals is shown below.

```
#Step 1: Install whoishRisk package
> library(devtools)
> install_github("DylanRJCcollins/whoishRisk")

#Step 2: Load whoishRisk package into workspace
> library(whoishRisk)

#Step 3: Load risk factor data
> Age <- c(40, 87, 65, 53, 71) #Age in years
> Gender <- c(0,0,0,1,1) #0=female, 1=male
> Smoking <- c(1,1,0,1,0) #0=non-smoker 1=smoker
> Systolic_Blood_Pressure <- c(129, 157, 134, 189, 141) #SBP in
  mmHg
> Diabetes <- c(1,1,1,0,1) #0=not diabetic 1=diabetic
> Total_Cholesterol <- c(0, 5.1, 4.5, 0, 8.3) #Total
  cholesterol (mmol/L, 0=unknown cholesterol)

#Step 4: Pass the risk factor vectors to the WHO_ISH_Risk()
  function, and set subregion equal to the name of the
  appropriate epidemiological subregion (e.g. "EMR_B"). This
```

will return a vector of WHO/ISH risk scores.

```
> WHO_ISH_Risk(Age, Gender, Smoking, Systolic_Blood_Pressure,
  Diabetes, Total_Cholesterol, "EMR_B")
[1] "<10%" ">=40%" "<10%" ">=40%" ">=40%"
```

Values not equal to zero or one cause fatal errors for the dichotomous parameters gender, diabetes status, and smoking status. This results in an output of “NA” and a corresponding warning message.

```
#Calculate the risk score using the following parameters: 57
  year old woman, non-smoker, diabetic, systolic blood
  pressure of 132 mmHg, type-two diabetes, with unknown
  cholesterol from Jordan. Recall that when total cholesterol
  is unknown a value of zero is used. Jordan falls under the
  EMR B epidemiological subregion.
```

```
> WHO_ISH_Risk(age=57, gdr=0, smk=0, sbp=132, dm=1, chl=0, "
  EMR_B")
[1] "<10%"
```

```
#The output is a WHO/ISH risk of <10%, meaning the individual
  has a <10% probability of having a fatal or non-fatal CVD
  event in the next 10 years.
```

```
#Let's intentionally introduce an incorrect value of 2 for the
  diabetes status in the above example.
```

```
> WHO_ISH_Risk(age=57, gdr=0, smk=0, sbp=132, dm=2, chl=0, "
  EMR_B")
[1] NA
```

Warning message:

```
In WHO_ISH_Risk(age = 57, gdr = 0, smk = 0, sbp = 132, dm = 2,
  chl = 0, : Diabetes status must be equal to 0 or 1
```

```
#Since 2 is not a possible value for diabetes status, the
  output of the function is NA (a fatal error), and a warning
  message is generated with the result indicating where the
  error was: "Diabetes status must be equal to 0 or 1."
```

Warning messages are also produced for continuous variables (age, systolic blood pressure, total cholesterol) when variables appear out of range as described in Table 4.3. These are non-fatal messages and a risk score will be generated along with the message.

```

#If we use the same vignette as the above example; recall that
  a risk score of <10% was produced:

> WHO_ISH_Risk(age=57, gdr=0, smk=0, sbp=132, dm=1, chl=0, "
  EMR_B")
[1] "<10%"

#Now, let's set systolic blood pressure (sbp) to 67 mmHg, an
  unusually low systolic blood pressure
> WHO_ISH_Risk(age=57, gdr=0, smk=0, sbp=67, dm=1, chl=0, "
  EMR_B")
[1] "<10%"

Warning message:
In WHO_ISH_Risk(age = 57, gdr = 0, smk = 0, sbp = 67, dm = 1,
  chl = 0, : At least one systolic blood pressure is below 90
  mmHg

#A risk score of <10% is produced, but it's accompanied by a
  warning message stating that "At least one systolic blood
  pressure is below 90 mmHg"

```

4.6 Discussion

4.6.1 Summary of Findings

whoishRisk is a free, open-source R package that calculates WHO/ISH CVD risk scores for all epidemiological subregions of the world. It contains a single function, `WHO_ISH_Risk()`, which when passed values for age, gender, systolic blood pressure, smoking status, diabetes status, total cholesterol, and epidemiological subregion, outputs one of five WHO/ISH risk categories: <10%, 10 to <20%, 20 to <30%, 30 to <40%, or $\geq 40\%$. Comparison of whoishRisk with a previously reported MatLab implementation of WHO/ISH risk charts for epidemiological subregion SEAR D showed perfect agreement.

4.6.2 Interpretation of Findings

This package is ideally suited for analyses of cardiovascular risk when electronic patient data is available. For large amounts of data, it would be efficient to store risk factor data for each individual in a data frame with a single row for each

individual. A new column can be added to the data frame to store the output of `WHO_ISH_Risk()` and data frame columns can be passed directly as arguments to the function. The benefit of doing this is that all function inputs and the risk score output are then organised as “tidy data” in a data frame with one individual per row, easily facilitating trace-back for fatal errors. While the risk score values are returned as character strings (e.g. “10 to <20%”), a user could simply convert these to a numeric or factor class. Character strings were chosen so as to produce a literal implementation of the risk charts. With respect to independent extraction of risk scores in duplicate, the Cohen’s kappa was 0.97 indicating almost perfect agreement, and the identified discrepancies were corrected through consensus by referring to the original paper chart. Comparison with the MatLab implementation of WHO/ISH scores for SEAR D showed perfect agreement, validating the chart extractions for SEAR D and the R code for computing the score.

4.6.3 Findings in the Context of Existing Research

To my knowledge, this is the first electronic implementation of WHO/ISH risk charts for all epidemiological subregions. It is also the first implementation in R. While an implementation had been previously published in MatLab, it was only for one epidemiological subregion (SEAR D) and was not in the form of a package, making it difficult for novice users.

4.6.4 Strengths and Limitations

The strengths of this implementation are that it has been developed into a complete R package that meets the Comprehensive R Archive Network guidelines and includes all epidemiological subregions.[117] This allows it to be downloaded directly into R from github using a standard computer and can be updated and maintained to incorporate new versions. The inclusion of warning messages helped increase the user-friendliness of the package and identify errors in data input so as to improve the quality of the results generated. It should be noted, however, that the warning messages do not contain warning messages for negative values. An

additional limitation of the package is the inability to change the threshold at which total cholesterol is discretised. While the paper-based chart extractions were done independently and in duplicate, and the few discrepancies were resolved, it is possible that some extraction errors exist. Cohen's kappa was used as a measure for the reliability of data extraction, although it was designed for comparing the agreement between two raters when raters may sometimes guess on the value of a variable because of uncertainty.[116] In this sense Cohen's kappa is limited because while it accounts for possible agreements by chance, there was an objectively correct answer for the raters and no need to guess based on uncertainty.

4.6.5 Implications for Research and Practice

whoishRisk is the first freely available software to calculate WHO/ISH risk scores from routine patient data. It is intended to help facilitate, but also standardise future research on WHO/ISH risk scores. For example, it could help facilitate research into the implementation of WHO/ISH risk scores, including auditing the correctness of documented risk scores in patient records. It may also be used to underpin web applications to facilitate rapid calculation of risk scores. Future versions of the package may seek to include outputs of the `WHO_ISH_Risk()` function that help locate datum that result in a fatal error, and should include warning messages for erroneous negative values.

4.7 Conclusions

whoishRisk is a validated and freely available R package that can be used for the calculation of WHO/ISH CVD risk charts for all WHO epidemiological subregions of the world. It can be downloaded directly from github and contains complete documentation. Its function, `WHO_ISH_Risk()`, requires seven parameters: age, gender, systolic blood pressure, smoking status, diabetes status, total cholesterol, and epidemiological subregion. The function includes warning messages when input parameters appear out of range to help diagnose fatal errors and check the accuracy of data. In the next chapter (Chapter 5) *whoishRisk* will be used to

study the implementation of WHO/ISH risk charts by Médecins Sans Frontières for Syrian Refugees in Jordan.

4.8 Chapter Summary

- An R package, called `whoishRisk`, was developed and validated to calculate WHO/ISH risk scores for any epidemiological subregion of the world
- `whoishRisk` is freely available and can be downloaded directly from github using `install_github("DylanRJCcollins/whoishRisk")`
- `whoishRisk` contains one function, called `WHO_ISH_Risk()`, which requires seven parameters: age, gender, systolic blood pressure, smoking status, diabetes status, total cholesterol, and epidemiological subregion
- `whoishRisk` enables and standardises research on the implementation of WHO/ISH risk charts

5

Cardiovascular Risk and Prevention Amongst Syrian Refugees in Jordan: quantitative strand of a mixed methods study

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5.1 Publication Statement

Features of this chapter were published in BMC Conflict and Health[3] and the textbook, An Introduction to Population-Level Prevention of Non-Communicable Diseases.[4]

5.2 Introduction

This Chapter builds on the need for primary trials of cardiovascular disease (CVD) risk scores (as described in Chapter 3) in low-resource settings by first examining the implementation of total CVD risk scoring in a model low-resource setting. After several scoping missions to Jordan, where I met with the Ministry of Health, Academic Institutions, and Non-Governmental Health Organisations, I discovered that Médecins Sans Frontières (MSF) had recently opened two primary health care clinics focused on non-communicable diseases (NCDs) amongst Syrian refugees. I was able to track down the clinics, in the Northern city of Irbid about 20 km from the Syrian border, and this first interaction eventually lead to a tripartite research collaboration with MSF, the Ministry of Health of the Hashemite Kingdom of Jordan, and myself (University of Oxford) (Appendix D) (Figure 5.1). This work is a result of that research collaboration.

As of April 2016, the United Nations High Commissioner for Refugees had registered 4.8 million Syrian refugees,[122] one million of who resided in Jordan.[123] The humanitarian crisis in Syria and by extension, northern Jordan, resulted in an unprecedented burden of NCDs, borne primarily by primary care services. Almost half (46%) of adult deaths in Syria were attributable to NCDs in 2012, and CVD was the leading cause of death before the age of 70 (premature death).[124] A cross-sectional survey of Syrian refugees (2014) estimated that more than half of Syrian refugee households in Jordan had at least one member with an NCD and although care seeking was high, cost was identified as the main barrier to seeking health care.[125]

Because of this disease burden, and the magnitude of need, MSF launched an ‘NCD Mission’ in Irbid in collaboration with the Jordanian Ministry of Health with the goal of providing free primary health care for patients with or at risk of NCDs. Since chronic disease care in Jordan had been historically provided at secondary level, MSF developed their own NCD guidance for this mission. Many aspects of MSF’s guidance were based on the World Health Organisation’s (WHO) Package of Essential NCD Interventions for Primary Health Care in Low-Resource



Figure 5.1: MSF's two primary health care clinics for patients with refugees were located in Irbid, Jordan, approximately 20 km from the Syrian border

Settings (WHO PEN);[21] most notably from Protocol One for the prevention and management of CVD.[126] This protocol included WHO/ISH CVD risk charts, and guidance for their use.[112, 126] While two versions of the charts are available, one that requires measured total cholesterol and one that does not, MSF implemented the charts which require cholesterol as they were generally regarded as superior. Herein I refer to these two versions as the laboratory-dependent (LD) and laboratory-independent (LI) WHO/ISH CVD risk charts, respectively.

In summary, MSF's NCD mission in Irbid, Jordan, was chosen as a model setting to study for several reasons:

1. The remit of the clinics was specifically to provide primary health care to patients at risk of NCDs, which meant that many patients were eligible for CVD risk scoring

2. MSF had adapted WHO PEN guidance, including WHO/ISH risk scores, for use in these clinics, which allowed me to study the implementation of WHO/ISH risk scores
3. MSF employed local (i.e. Jordanian) clinical staff, which meant that the clinicians were unlikely to have experience with total CVD risk assessment
4. MSF clinics provided free medications needed for NCD management to patients, which reduced the chance that prescribing decisions would be influenced by issues of drug access
5. MSF collected routine clinical data from paper charts into an electronic format, making a large sample size feasible
6. The security and political environment, although dynamic and not without risk, was such that I could conduct an in-depth qualitative field study (Chapter 6)

5.3 Aim and Objectives

5.3.1 Aim

The aim of this chapter was to evaluate the implementation of total CVD risk scoring and risk-based management in MSF's NCD mission in Irbid, Jordan and explore opportunities for improvement.

5.3.2 Objectives

To achieve this aim, the objectives of this chapter were to determine the:

1. Completeness of CVD risk factor measurements
2. Prevalence and correctness of documented CVD risk scores
3. Prescribing pattern of lipid-lowering treatment (LLT) and its concordance with total CVD risk-based guidance

4. Performance of LI WHO/ISH CVD risk charts relative to LD WHO/ISH CVD risk charts across three different risk thresholds used to define high CVD risk

5.4 Methods

5.4.1 Setting

MSF's NCD mission was comprised of two primary health care clinics in Irbid, Jordan, targeting urban, community-based Syrian refugees. Both clinics were included in this study. The clinics primarily accepted Syrian Refugees living with one of five conditions: CVD, hypertension, diabetes, COPD, or asthma. Initial patients were referred by the Jordanian Ministry of Health and subsequent patients through word of mouth. If patients were found to not have any of the eligible conditions they were transitioned out of the clinic's care.

5.4.2 Study Design

An exploratory sequential mixed methods design was used. The findings of the quantitative strand helped inform the qualitative strand, which was in turn used to help explain the quantitative findings (Figure 5.2). This chapter (Chapter 5) reports the quantitative strand; Chapter 6 reports the qualitative strand and integrates the strands. The quantitative and qualitative strands were given equal priority and were mixed during data collection, analysis, and interpretation (Figure 5.2).

5.4.3 Data Source and Management

While paper records were used in the clinics, a copy of the routine patient data was also entered into an electronic database designed and maintained by MSF. This was done daily by MSF staff and the database was managed and cleaned to identify out-of-range values and incorrect entries. The contents of the database were exported to Microsoft Excel, searched from inception (15/12/2014) until 01/11/2015, and all patients were screened for inclusion into the quantitative analysis.

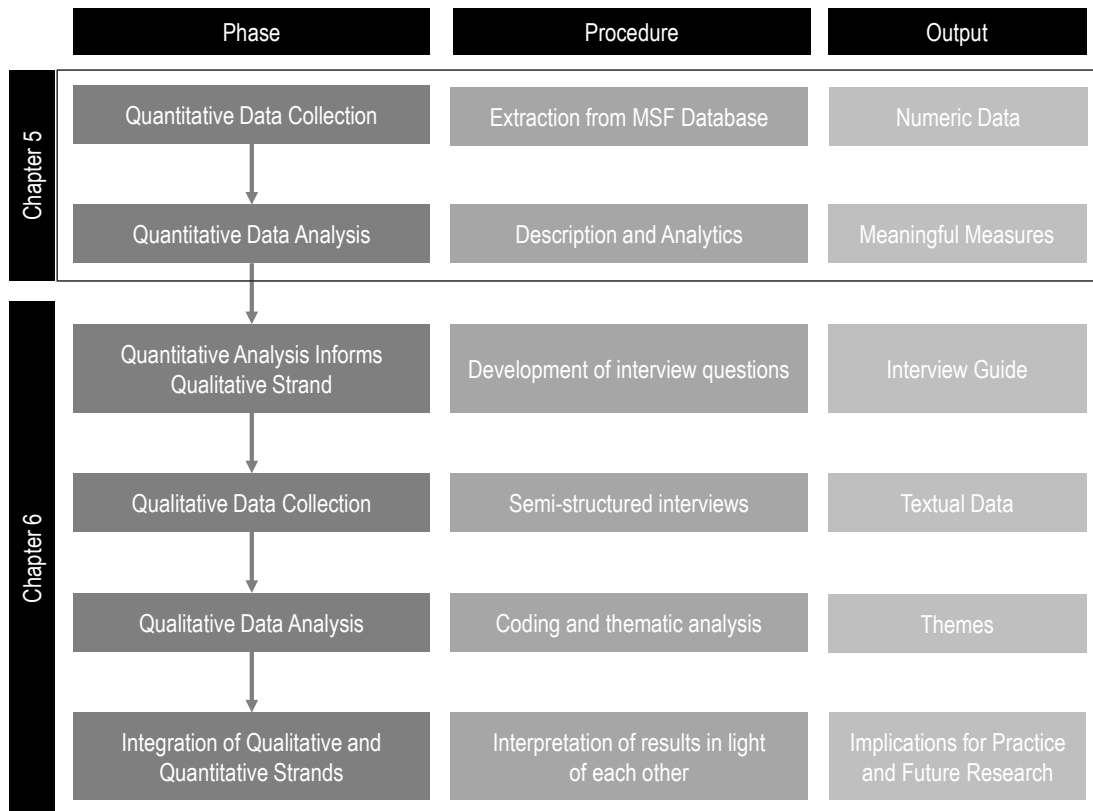


Figure 5.2: Mixed methods study design illustrating the output and procedure of each phase of the quantitative strand (Chapter 5) and qualitative strand (Chapter 6)

5.4.4 Inclusion Criteria

To be included in the analysis, patients in the electronic database had to be ≥ 18 years of age, have at least one systolic blood pressure measurement, and meet at least one of the following criteria:

- ≥ 40 years old; or
- Smoker (current or quit within 12 months); or
- Diabetic; or
- Family history of CVD or diabetes in first or second degree relative; or
- High waist circumference (Men ≥ 100 cm; Women ≥ 90 cm)

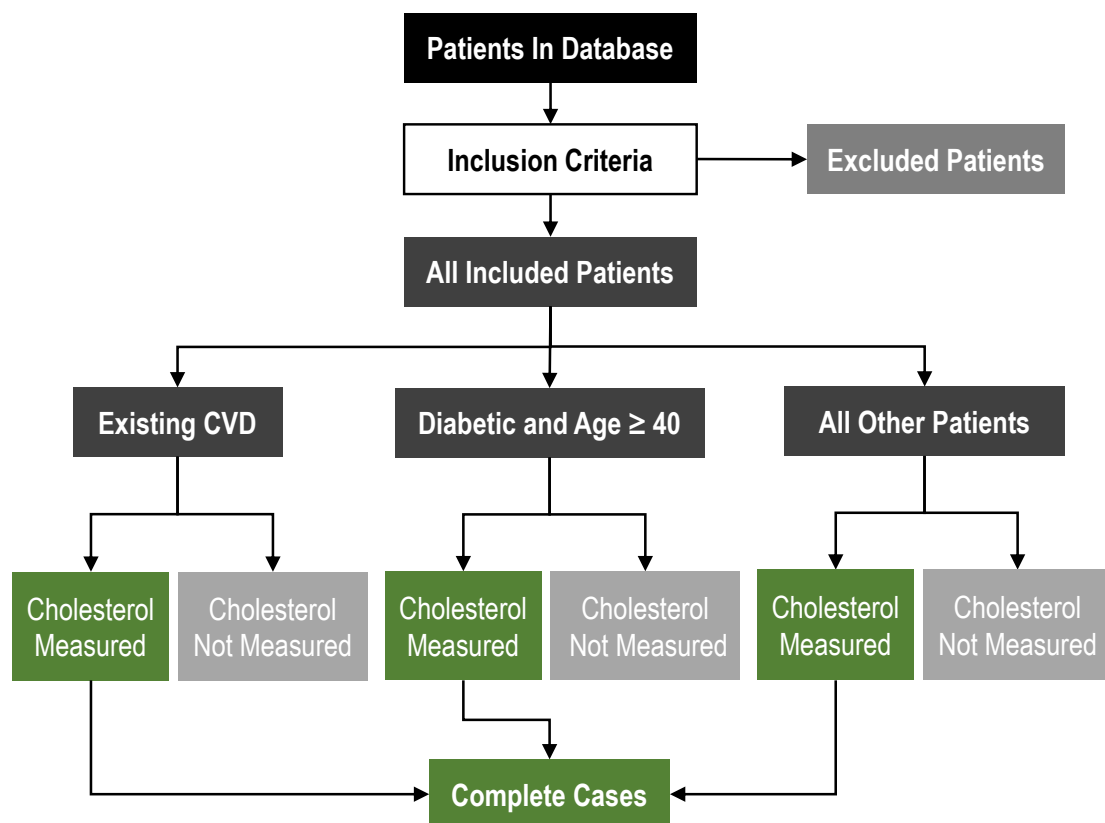


Figure 5.3: Flow chart showing the relevant analytic categories: all included patients, patients with existing CVD, people aged 40 or older with diabetes, all other patients, and complete cases

After applying the above inclusion criteria to all patients in the database, complete cases were defined as patients who had all data required to calculate a LD CVD risk score, which included at least one total cholesterol measurement (Figure 5.3).

5.4.5 Standards and Indicators

Based on MSF-adapted WHO PEN, the following two standards were used to compare clinical practice against. First, all patients were expected to have a documented and correct LD WHO/ISH CVD risk score using risk charts for epidemiological subregion Eastern Mediterranean B (EMR B). The risk scoring algorithm is depicted in Figure 5.4.

Second, LLT prescribing was expected to be concordant with guidance. Based on MSF-adapted WHO PEN, patients with a previous history of CVD, diabetics aged

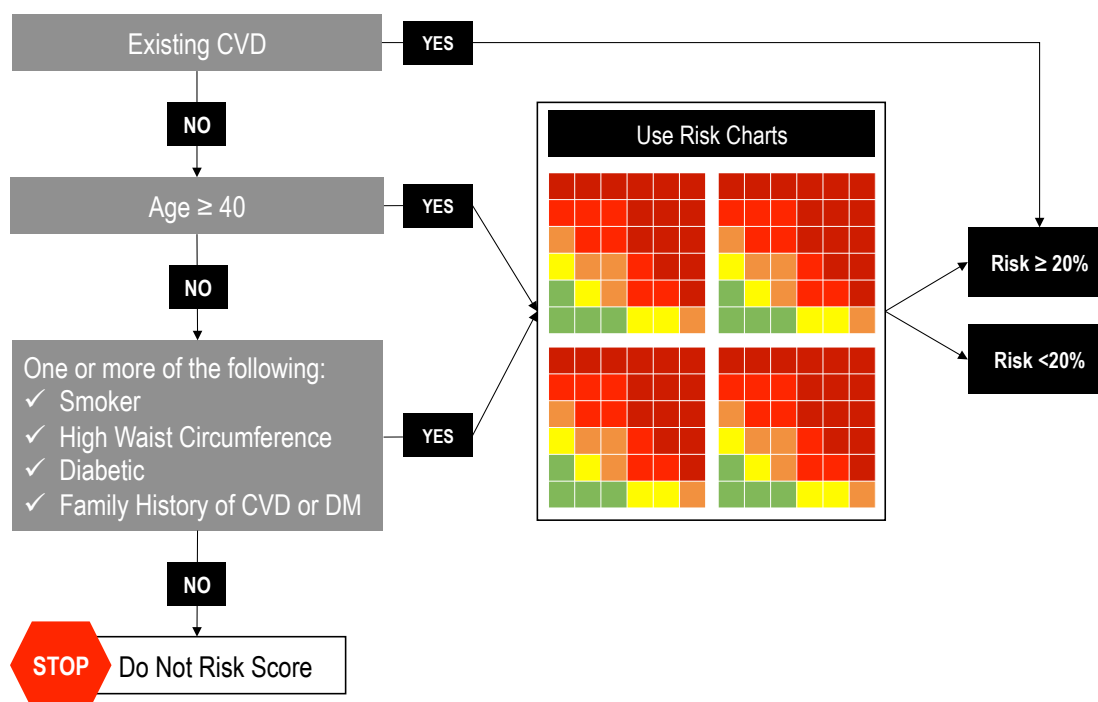


Figure 5.4: Risk assessment algorithm showing the use of laboratory-dependent WHO/ISH CVD risk scores in the context of primary and secondary prevention



Figure 5.5: Prescribing pathway for lipid-lowering treatment based on WHO PEN Protocol One and laboratory-dependent WHO/ISH risk charts

40 or older, patients with total cholesterol of 8 mmol/L or more, or a WHO/ISH risk of 20% or more were eligible for LLT (Figure 5.5).

Indicators were developed to assess the clinical workflow required to achieve the above two standards. These included assessing inputs (i.e. measuring risk factors), process (i.e. calculating risk score), and outputs (i.e. taking action based on risk) of CVD risk scoring (Table 5.1). LLT was chosen to assess the outputs of risk scoring because the decision to prescribe could be done at the same time as risk assessment. The population used to evaluate each indicator is described in Table 5.1, using terminology shown in Figure 5.3.

Table 5.1: Quantitative indicators and populations used to calculate each indicator

Domain	Question	Indicator	Population Used for Analysis
Input	Do patients eligible for risk assessments have a documented cholesterol measurement?	Proportion of patients eligible for risk assessment who have at least one documented cholesterol measurement	All included patients
	Are risk factor measurements converted to risk scores?	Proportion of patients with a documented total cholesterol measurement with a documented risk score	Complete Cases
Process	Are documented risk scores correct?	Agreement between documented and calculated risk score	Complete cases with a documented risk score
	Is LLT prescribed correctly according to risk scores documented in patient charts?	Concordance of LLT prescriptions with eligibility based on risk score documented in patient chart	All included patients with a documented risk score
Output	Is LLT prescribed correctly according to true eligibility?	Concordance of LLT prescriptions with eligibility based on true eligibility	Complete cases, all patients with existing CVD, and all diabetic patients aged 40 or older

5.4.6 Data Analysis

All data management and analysis was done using R.[127] Sensitivity, specificity, and positive and negative likelihood ratios were calculated with 95% confidence intervals using the epiR package.[128] The irr package was used to calculate Cohen's kappa.[115] The whoishRisk package developed in Chapter 4 was used to calculate WHO/ISH risk scores.[2]

Accuracy of Electronic Database

To estimate the accuracy of the electronic database, 200 data points were randomly selected from the database and compared to the original paper record. This was done by using a random number generator in R to specify the cell in the Microsoft Excel spread sheet of electronic patient data. The chart was then found, the data point was located, and if the data agreed it was coded as a match. If the data was missing it was coded as a mismatch. The percent which were correct was calculated with 95% confidence intervals using a binomial distribution.

Coding

Existing CVD was coded as positive if the patient had a history of stable or unstable angina, myocardial infarction, angioplasty, congestive heart failure, peripheral vascular disease, any other CVD condition (e.g. atrial fibrillation), or documented cardiovascular or cerebrovascular complications. High waist circumference was defined as ≥ 90 cm in women and ≥ 100 cm in men, and smoking status was coded as positive if the patient was a current smoker or had quit in the previous 12 months, as per WHO PEN.[21] All other parameters were already coded in the correct format in the database.

Selection of Risk Factor Values

To determine the distribution of CVD risk in the patient population, the CVD risk scores at the time of enrolment to the clinic were calculated. The index date was set to the date of enrolment and the first prospectively available systolic blood pressure and total cholesterol measurement was used to calculate the risk score.

To determine the risk score of patients prescribed LLT, the index date was set to the date of first LLT prescription and the first retrospectively available systolic blood pressure and total cholesterol measurement prior to the date of the LLT prescription was used. For patients not prescribed LLT, their risk score at enrolment was used to determine eligibility for LLT.

To determine the accuracy of documented CVD risk scores, the index date was set to the date of the first documented CVD risk score and the first retrospectively available systolic blood pressure and total cholesterol measurement was used. The inter-rater reliability was calculated using Cohen's kappa. Patients with existing CVD who had a recorded risk of $\geq 20\%$ were coded as a match for the calculation of Cohen's kappa.

Performance of LI WHO/ISH Risk Assessment

Complete cases were used to determine the performance of LI WHO/ISH risk scores but patients with exiting CVD were excluded from the analysis because

they did not qualify for risk scoring (Figure 5.4). For the remaining patients, the LD WHO/ISH risk score (reference test) and the LI WHO/ISH risk score (index test) was calculated using enrolment risk factor values. The performance of LI risk charts relative to LD was measured using sensitivity, specificity, and positive and negative likelihood ratios at three different definitions of high risk: 10%, 20%, and 30%. Subgroup analysis was done excluding diabetics aged 40 or older because these patients qualify for LLT without risk scoring.

Since only complete cases were used for this analysis, the impact of excluding patients with a missing cholesterol was estimated by imputing a total cholesterol measurement for the cases with missing cholesterol and including these patients in the analysis. A linear regression model was used to impute missing cholesterol values, using age, systolic blood pressure, gender, diabetes status, and smoking status. Residual plots were visually inspected to check linear model regression assumptions. Comparison of the sensitivity, specificity, and positive and negative likelihood ratios derived from complete cases with complete cases plus patients with imputed cholesterol was done to assess the impact of missing data.

5.4.7 Ethical Approval

This Chapter was reviewed and approved by the Oxford Tropical Research Ethics Committee (OxTREC Reference 576-15), MSF Operational Centre Amsterdam, and by the Ministry of Health of the Hashemite Kingdom of Jordan (Appendix D).

5.5 Results

5.5.1 Accuracy of Database

From a random sample of 200 data in the electronic database, three errors were identified relative to the original paper charts. The accuracy of the database was therefore estimated to be 98.5% (95% CI 95.7, 99.7).

5.5.2 Included Patients

There were 3,086 patients in the electronic database, from which 158 patients below the age of 18 were excluded. All patients 40 years or older were included ($n=2,577$); of those aged less than 40, 22 patients were excluded who did not meet the further inclusion criteria. Of the remaining 2,907 patients, 15 were excluded because they were missing a systolic blood pressure measurement and 2,892 patients were included in the analysis of which 2,316 were complete cases (Figure 5.6).

Figure 5.7 illustrates the subgroups of all included patients used for each analysis, and the key results of these analyses.

5.5.3 Description of Complete Cases

Of the 2,892 included patients, 2,316 were complete cases. The vast majority (93%) were included because they were aged 40 or older, of which 60% were female. In both age categories, smoking was much more prevalent in men than women; the prevalence of smoking was higher in younger men than older men (Table 5.2). Mean total cholesterol and systolic blood pressure was not significantly different between genders or age groups; the mean total cholesterol was 5.14 mmol/L (SD 1.26). Women aged 40 or older were more likely to have a high waist circumference and have a family history of diabetes, otherwise they did not differ from men in this age group (Table 5.2).

Patients missing a cholesterol measurement tended to be younger than patients with a cholesterol measurement: median age 50 (IQR 26, 60) and 57 (IQR 49, 64), respectively (Table 5.3). Those missing a cholesterol measurement were less likely to be diabetic or have a high waist circumference, otherwise they were not significantly different from included patients with a cholesterol measurement (Table 5.3).

5.5.4 What was the risk profile of the population?

Of the 2,316 complete cases, 21.9% (95% CI 20.2, 23.6) had existing CVD therefore placing them in the risk category of $\geq 20\%$. Most patients (52.6%, 95% CI 50.6, 54.7) fell into the $<10\%$ risk category or 10% to $<20\%$ category (12.6% 95%

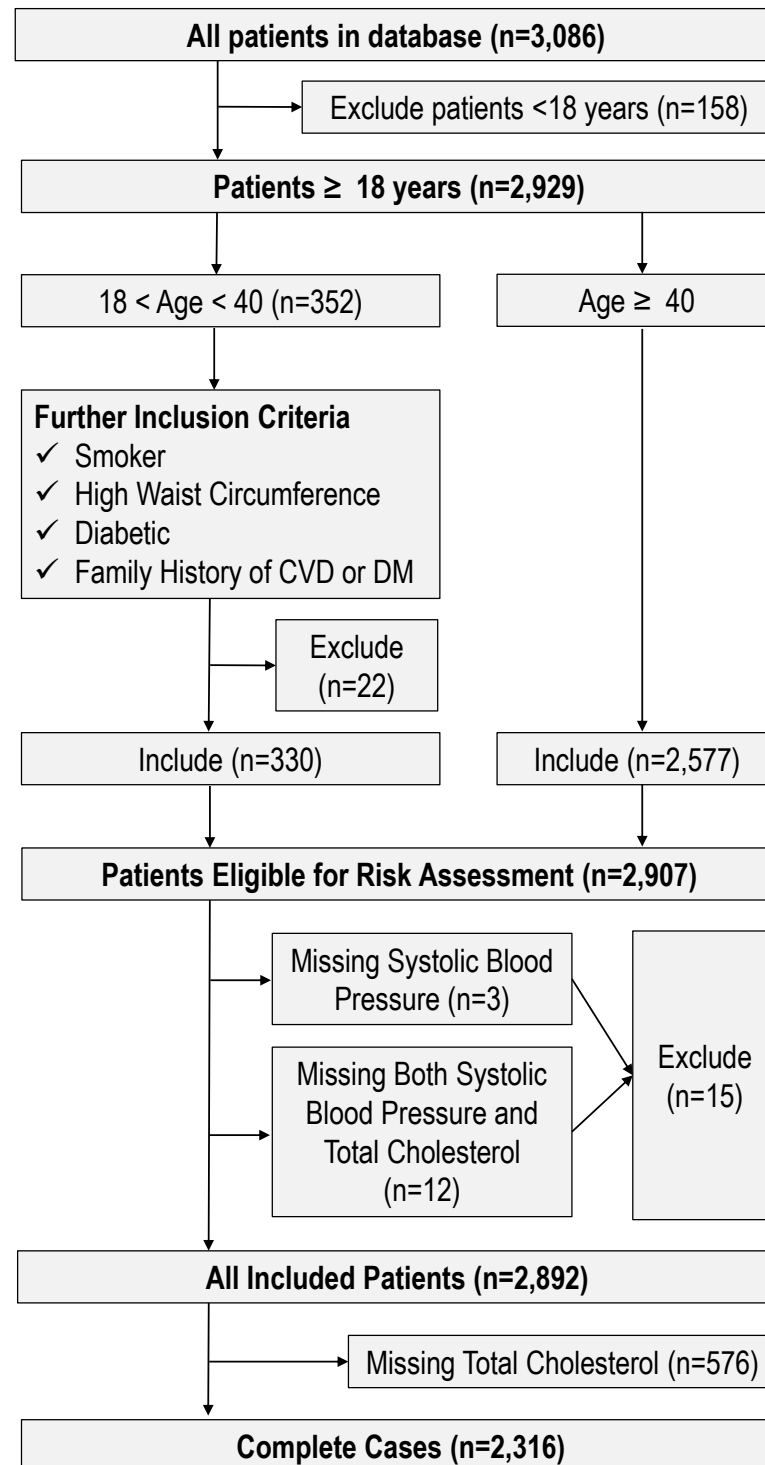


Figure 5.6: Flow chart of all included patients after applying inclusion criteria, and complete cases after excluding patients with a missing total cholesterol measurement

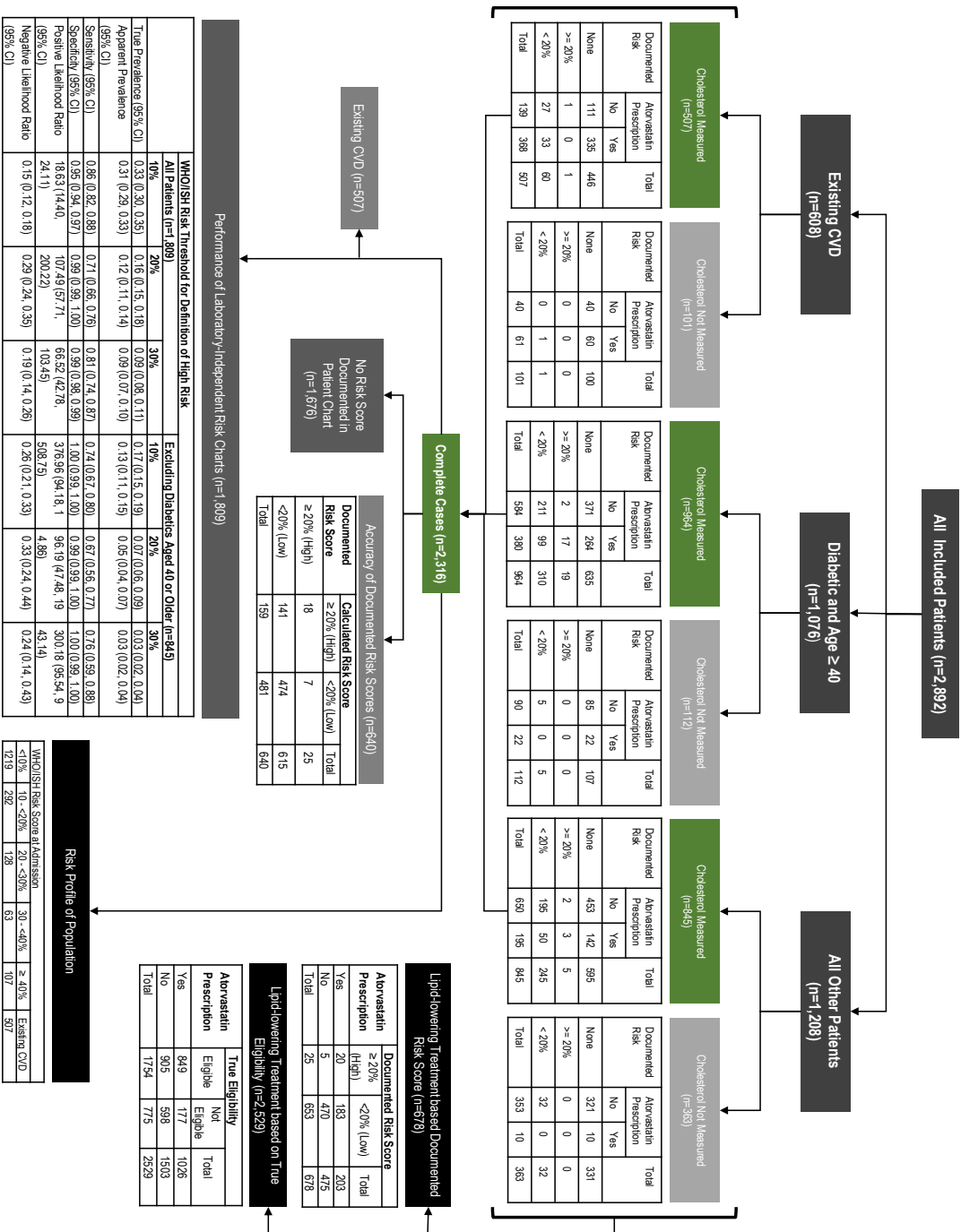


Figure 5.7: Illustration of the organisation of all included patients into their analytic populations and summary of key findings derived from each analytic population

Table 5.2: Summary of salient patient characteristics of complete cases

	18 <Age <40 (n=165)		Age ≥ 40 (n=2,151)	
	<i>Male (n=69)</i>	<i>Female (n=96)</i>	<i>Male (n=861)</i>	<i>Female (n=1,290)</i>
Median Age (IQR)	36 (32, 38)	35 (31, 38)	60 (52, 66)	57 (50, 64)
Mean SBP (mmHg) (SD)	126 (19)	120 (20)	132 (23)	135 (22)
Mean Total Cholesterol (mmol/L) (SD)	5.2 (1.0)	4.9 (0.97)	4.8 (1.3)	5.4 (1.3)
Percent who smoke (95% CI)	63.8 (52.5, 74.7)	6.25 (2.57, 13.6)	43.1 (39.8, 46.5)	12.7 (11.0, 14.7)
Percent with high waist circumference (95% CI)	59.4 (46.9, 70.9)	78.1 (68.3, 85.7)	66.3 (63.0, 69.5)	91.7 (90.0, 93.1)
Percent with Diabetes Type 1 (95% CI)	13.0 (6.50, 23.8)	14.6 (8.49, 23.6)	0.465 (0.149, 1.27)	0.155 (0.0269, 0.623)
Percent with Diabetes Type 2 (95% CI)	47.8 (35.8, 60.1)	31.3 (22.4, 41.6)	56.4 (53.1, 59.8)	57.7 (54.9, 60.4)
Percent with history of premature CVD (below 60) in first degree relative (95% CI)	40.6 (29.1, 53.1)	45.8 (35.7, 56.3)	32.1 (29.0, 35.3)	37.9 (35.3, 40.6)
Percent with history of DM in first or second degree relative (95% CI)	68.1 (55.7, 78.5)	78.1 (68.3, 85.7)	59.0 (55.6, 62.3)	68.8 (66.1, 71.3)

Table 5.3: Characteristics of complete cases in comparison to cases missing cholesterol

	Missing Cholesterol Measurement	
	No	Yes
Total Number of Patients	2,316	591
Median Age (IQR)	57 (49, 64)	50 (28, 60)
Mean SBP (mmHg) (SD)	133 (22.2)	122 (20.1)
Percent who smoke (95% CI)	25.2 (23.5, 27.1)	26.7 (23.2, 30.5)
Percent with high waist circumference (95% CI)	80.7 (79.1, 82.3)	67.9 (63.9, 71.6)
Percent with diabetes (95% CI)	57.1 (55.0, 59.1)	31.1 (27.4, 35.0)
Percent with history of premature CVD (below 60) in first degree relative (95% CI)	36.1 (34.2, 38.1)	40.8 (36.8, 44.9)
Percent with history of DM in first or second degree relative (95% CI)	65.5 (63.5, 67.4)	67.7 (63.7, 71.4)

CI). The remainder of patients (12.8%, 95% CI 11.5, 14.3) fell into categories of 20% risk or above. The salient features of patients in each risk category are summarised in Table 5.4.

5.5.5 Do patients eligible for risk assessment have a documented cholesterol measurement?

Of the included patients, 2,316 (80.1% 95% CI 78.6, 81.5) had a total cholesterol measurement (Figure 5.7). The proportion was highest amongst diabetic patients aged 40 or older: 89.6% (95% CI 87.6, 91.3). The proportion was 83.4% (95% CI 80.1, 86.2) and 70.0% (95% CI 67.3, 72.5) amongst patients with existing CVD and all other patients, respectively.

5.5.6 Are risk factor measurements converted to a risk score?

Of the 2,316 patients with complete risk factor measurements, 640 had a documented risk score (27.6%, 95% CI 25.8, 29.5) (Figure 5.7). The highest rate of risk score documentation was amongst diabetics aged 40 or older (34.1%, 95% CI 31.2, 37.2) and lowest amongst patients with existing CVD (12.0%, 95% CI 9.4, 15.3). Amongst the remaining patients, 29.6% (95% CI 26.5, 32.8) had a documented risk score.

Some patients without cholesterol measurements had a documented risk score; the rates were not significantly different in patients with existing CVD, diabetics aged 40 or older, or all other remaining patients: 0.99% (95% CI 0.052, 6.2), 4.5% (95% CI 1.7, 10.6), and 8.8% (95% CI 6.2, 12.3), respectively (Figure 5.7).

5.5.7 Are documented risk scores correct?

Cohen's kappa for agreement between calculated risk scores and documented risk scores was 0.178 ($p < 0.05$). When aggregated to above or below the WHO/ISH risk threshold for LLT prescribing (i.e. 20%), 11% (95% CI 7, 17) of high risk patients had a correctly documented high risk score and the remaining 89% had an incorrectly documented risk score below 20% (sensitivity: 0.11 (95% CI 0.07,

Table 5.4: Distribution of cardiovascular risk and summary of salient patient characteristics in each risk category

	WHO/ISH Risk Category (n=1,809)				Existing CVD (n=507)
	<10% (n=1,219)	10 to <20% (n=292)	20 to <30% (n=128)	30 to <40% (n=63)	≥40% (n=107)
Proportion of complete cases (95% CI)	52.6 (50.6, 54.7)	12.6 (11.3, 14.0)	5.5 (4.6, 6.6)	2.7 (2.1, 3.5)	4.6 (3.8, 5.6)
Percent Male (95% CI)	34.9 (32.3, 37.7)	40.1 (34.4, 46.0)	41.4 (32.9, 50.5)	34.9 (23.6, 48.1)	41.1 (31.8, 51.1)
Median Age (IQR)	51 (45, 57)	64 (60, 70)	66 (61, 72)	64 (62, 71)	66 (62, 71)
Mean SBP (mmHg) (SD)	127 (17)	140 (19)	146 (21)	156 (16)	172 (21)
Mean Total Cholesterol (mmol/L) (SD)	5.2 (1.1)	5.2 (1.2)	5.4 (1.7)	5.7 (1.3)	6.4 (1.6)
Percent who smoke (95 % CI)	23.5 (21.1, 26.0)	19.2 (14.9, 24.3)	32.8 (24.9, 41.7)	25.4 (15.6, 38.2)	26.2 (18.4, 35.7)
Percent with Diabetes (95% CI)	52.7 (49.8, 55.5)	64.0 (58.2, 69.5)	65.6 (56.6, 73.6)	77.8 (65.2, 86.9)	80.4 (71.3, 87.2)
Percent who are Diabetic and Age ≥40	45.9 (43.1, 48.8)	63.4 (57.5, 68.8)	65.6 (56.6, 73.6)	77.8 (65.2, 86.9)	80.4 (71.3, 87.2)
Percent with history of premature CVD (below 60) in first degree relative (95% CI)	37.7 (34.9, 40.4)	27.1 (22.1, 32.6)	29.7 (22.1, 38.5)	20.6 (11.9, 33.0)	28.0 (20.0, 37.7)
Percent with high waist circumference (95% CI)	82.9 (80.6, 84.9)	79.5 (74.3, 83.8)	75.0 (66.4, 82.0)	84.1 (72.3, 91.7)	84.1 (75.5, 90.2)
Percent with history of diabetes in first or second degree relative (95% CI)	69.6 (67.0, 72.2)	64.7 (58.9, 70.1)	46.9 (38.1, 55.9)	63.5 (50.4, 75.0)	61.7 (51.7, 70.8)
					76.7 (72.8, 80.3)
					61.7 (57.3, 66.0)

Table 5.5: Lipid lowering treatment prescribing patterns based on true eligibility and calculated cardiovascular risk

	Existing CVD (n=608)	Diabetic and Age ≥ 40 (n=1,076)	Total Cholesterol ≥ 8 mmol/L (n=11)	Risk $\geq 20\%$ (n=59)	Risk $< 20\%$ (n=775)
Number prescribed LLT	429	402	7	11	177
Proportion Prescribed LLT (95% CI)	70.6 (66.7, 74.1)	37.4 (34.5, 40.3)	63.3 (31.6, 87.6)	18.6 (10.1, 31.3)	22.8 (20.0, 26.0)

0.17); specificity: 0.99 (95% CI 0.97, 0.99)) (Figure 5.7). The risk ratio for having a documented high risk score if truly high risk was 7.78 (95% CI 3.31, 18.28).

5.5.8 Is LLT prescribed correctly according to true eligibility?

Of all included patients, eligibility for LLT could be determined for 2,529 patients. Of these patients, 1,754 were eligible for LLT prescription and 849 of those eligible were prescribed LLT at least once (Figure 5.7). Of the 775 patients not eligible for LLT, 177 were prescribed LLT at least once (Figure 5.7). The sensitivity and specificity of LLT prescribing relative to true eligibility was therefore 0.48 (95% CI 0.46, 0.51) and 0.77 (95% CI 0.74, 0.80), respectively. The proportion of patients prescribed LLT was highest amongst patients with existing CVD, followed by diabetics aged 40 or older, and prescribing amongst patients with total cholesterol ≥ 8 mmol/L was not significantly different: 70.6% (95% CI 66.7, 74.1), 37.4% (95% CI 34.5, 40.3), and 63.3% (95% CI 31.6, 87.6), respectively (Table 5.5). Prescribing was lowest amongst the remaining patients, and the proportion of patients prescribed LLT did not differ amongst patients above or below 20% risk: 18.6% (95% CI 10.1, 31.3) and 22.8% (95% CI 20.0, 26.0), respectively (Table 5.5).

5.5.9 Is LLT prescribed correctly according to the risk scores documented in the patient chart?

Of all included patients, 678 had a documented risk score. The sensitivity and specificity of LLT prescribing relative to the documented risk scores was 0.80 (95% CI 0.59, 0.93) and 0.72 (95% CI 0.68, 0.75), respectively. The proportion of patients

Table 5.6: Lipid lowering treatment prescribing patterns based on eligibility as documented in patient charts, subset by those with existing CVD, diabetics aged 40 or older, and all other patients

Documented Risk Score	Existing CVD (n=62)		DM & ≥ 40 (n=334)		All Other Patients (n=282)	
	$\geq 20\%$ (n=1)	$< 20\%$ (n=61)	$\geq 20\%$ (n=19)	$< 20\%$ (n=315)	$\geq 20\%$ (n=5)	$< 20\%$ (n=277)
Number prescribed LLT	0	34	17	99	3	50
Number not prescribed LLT	1	27	2	216	2	227
Proportion prescribed LLT (95% CI)	0 (0.00, 94.5)	55.7 (42.5, 68.2)	89.5 (65.5, 98.2)	31.4 (26.4, 36.9)	0.66 (17.0, 92.7)	18.1 (13.8, 23.2)

with a documented risk score $\geq 20\%$ who were prescribed LLT was not significantly different between patients with existing CVD, diabetics 40 or older, or all other remaining patients (Table 5.6). The proportion of patients with a documented risk score of $< 20\%$ prescribed LLT was highest amongst patients with existing CVD, followed by diabetic patients 40 or older, and was lowest amongst all other patients: 55.7% (95% CI 42.5, 68.2), 31.4% (95% CI 26.4, 36.9), and 18.1% (95% CI 13.8, 23.2), respectively (Table 5.6).

5.5.10 What is the performance of laboratory-independent WHO/ISH risk scores?

After removing patients with existing CVD (n=507) from the complete cases, 1,809 patients were used to determine the performance of LI WHO/ISH risk scores. Cohen's kappa for agreement between LI and LD WHO/ISH risk charts was 0.663 (p=0). At a 20% threshold of high risk, the sensitivity and specificity of LI risk scores was 0.71 (95% CI 0.66, 0.76) and 0.99 (95% CI 0.99, 1.00), respectively (Table 5.7). Sensitivity was highest at a 10% threshold, but did not differ significantly from the sensitivity when a 30% definition was used. In the subgroup analysis after removing diabetics aged 40 or older, sensitivity did not significantly change across risk thresholds (Table 5.7). Specificity at the 20% threshold was 0.99 (95% CI 0.99, 1.00) and reduced slightly to 0.95 (95% CI 0.94, 0.97) at the 10% threshold; otherwise it did not significantly change at 30% threshold or in the subgroup analysis (Table 5.7).

Table 5.7: Performance of laboratory-independent WHO/ISH risk scores relative to laboratory-dependent WHO/ISH risk scores at risk thresholds of 10, 20, and 30%

	WHO/ISH Risk Threshold for Definition of High Risk					
	All Patients (n=1,809)			Excluding Diabetics Aged 40 or Older (n=845)		
	10%	20%	30%	10%	20%	30%
True Prevalence (95% CI)	0.33 (0.30, 0.35)	0.16 (0.15, 0.18)	0.09 (0.08, 0.11)	0.17 (0.15, 0.19)	0.07 (0.06, 0.09)	0.03 (0.02, 0.04)
Apparent Prevalence (95% CI)	0.31 (0.29, 0.33)	0.12 (0.11, 0.14)	0.09 (0.07, 0.10)	0.13 (0.11, 0.15)	0.05 (0.04, 0.07)	0.03 (0.02, 0.04)
Sensitivity (95% CI)	0.86 (0.82, 0.88)	0.71 (0.66, 0.76)	0.81 (0.74, 0.87)	0.74 (0.67, 0.80)	0.67 (0.56, 0.77)	0.76 (0.59, 0.88)
Specificity (95% CI)	0.95 (0.94, 0.97)	0.99 (0.99, 1.00)	0.99 (0.98, 0.99)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)
Positive Likelihood Ratio (95% CI)	18.63 (14.40, 24.11)	107.49 (57.71, 200.22)	66.52 (42.78, 103.45)	376.96 (94.18, 1508.75)	96.19 (47.48, 194.86)	300.18 (95.54, 943.14)
Negative Likelihood Ratio (95% CI)	0.15 (0.12, 0.18)	0.29 (0.24, 0.35)	0.19 (0.14, 0.26)	0.26 (0.21, 0.33)	0.33 (0.24, 0.44)	0.24 (0.14, 0.43)

5.5.11 What is the potential effect of missing data?

A linear model was used to impute missing cholesterol values of the 576 included patients with a missing cholesterol. In the linear model, three predictor variables showed statistically significant (p-value <0.05) correlations with cholesterol: age, gender, and systolic blood pressure. Diabetes and smoking status were not significantly correlated. Residual plots appeared consistent with linear regression assumptions. After excluding all patients with existing CVD and including cases with missing but imputed cholesterol, 2,284 patients were used to test the performance of LI risk charts. Performance at all three thresholds did not differ significantly from the values derived from complete cases (i.e. no imputed cholesterol) (Table 5.8).

5.6 Discussion

5.6.1 Summary of Findings

As part of a mixed methods study, routine patient data from MSF's NCD mission for Syrian refugees in Jordan was analysed to evaluate the implementation of total CVD risk assessment and risk-based management. Of the 3,086 patients in the electronic database, 2,316 (82%) were complete cases. The accuracy of the electronic database used for the analyses was estimated at 98.5%. Patients missing a cholesterol measurement tended to be younger and were less likely to be diabetic or have a high waist circumference.

Cholesterol testing was highest amongst diabetic patients aged 40 or older, followed by patients with existing CVD and all other patients. Despite this, only 28% of patients with a cholesterol measurement had a documented risk score and this ranged from 12% amongst patients with existing CVD to 34% amongst diabetic patients aged 40 or older. Moreover, many documented risk scores were incorrect; Cohen's kappa for agreement between documented and recalculated risk scores was 0.178 and only 11% of high-risk patients had a correctly documented risk score of $\geq 20\%$.

Table 5.8: Comparison of the performance of laboratory-independent WHO/ISH risk scores relative to laboratory-dependent WHO/ISH risk scores when patients with imputed cholesterol are included in the analysis relative to when only complete cases are used

	WHO/ISH Risk Threshold for Definition of High Risk					
	10%		20%		30%	
	With Imputed Data (n=2,284)	Complete Cases (n=1,809)	With Imputed Data (n=2,284)	Complete Cases (n=1,809)	With Imputed Data (n=2,284)	Complete Cases (n=1,809)
Sensitivity (95% CI)	0.87 (0.84, 0.89)	0.86 (0.82, 0.88)	0.73 (0.67, 0.77)	0.71 (0.66, 0.76)	0.81 (0.75, 0.86)	0.81 (0.74, 0.87)
Specificity (95% CI)	0.96 (0.95, 0.97)	0.95 (0.94, 0.97)	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)
Positive Likelihood Ratio (95% CI)	22.51 (17.64, 28.73)	18.63 (14.40, 24.11)	142.16 (76.33, 264.75)	107.49 (57.71, 200.22)	77.36 (50.75, 117.91)	66.52 (42.78, 103.45)
Negative Likelihood Ratio(95% CI)	0.14 (0.11, 0.17)	0.15 (0.12, 0.18)	0.28 (0.23, 0.33)	0.29 (0.24, 0.35)	0.19 (0.14, 0.26)	0.19 (0.14, 0.26)

Analysis of LLT prescribing showed that about half (48%) of patients eligible for LLT were prescribed it. LLT prescribing was highest amongst patients with existing CVD but amongst the remaining patients prescribing rates did not differ based on CVD risk score. When LLT prescribing was compared against documented risk scores, irrespective of the correctness of the documented score, 4/5th of patients with a document risk score of $\geq 20\%$ were prescribed LLT. The proportion of patients with a documented risk score of $< 20\%$ prescribed LLT was highest amongst patients with existing CVD, followed by diabetics 40 or older, and was lowest amongst all remaining patients.

At a threshold of 20% risk, the sensitivity and specificity of LI WHO/ISH risk charts compared to LD WHO/ISH risk charts was 0.71 and 0.99, respectively. The performance did not significantly change when diabetics aged 40 or older were removed from the analysis. Including patients with imputed cholesterol, who were initially excluded from the analysis, did not significantly change the results.

5.6.2 Interpretation of Findings

It was possible to use routine clinical data to meaningfully assess the use of WHO/ISH CVD risk charts in MSF's NCD mission for Syrian refugees in Irbid, Jordan. Few patients eligible for CVD risk scoring had a documented risk score, even though the rate of cholesterol testing was relatively high. Even fewer had documented risk scores which were correct. This may suggest that in practice cholesterol testing was uncoupled from CVD risk assessment. The rate of cholesterol testing was lowest amongst patients who required risk scoring for LLT decisions. The fact that patients missing a cholesterol measurement tended to be younger and were less likely to be diabetic or have a high waist circumference, appears consistent with a single risk factor approach to cholesterol measurement. The very low rate of risk score documentation amongst patients with existing CVD may be because of ambiguity around the need to document a risk score in the patient chart, but not use the risk chart to calculate the risk score.

Looking more closely at documented risk scores illustrated two findings that suggest the incorrect use of risk charts. First, all but one patient with existing CVD and a documented risk score, had a documented risk score of $<20\%$, which meant that one or more of the following may have been true: (1) doctors were using risk charts to calculate a risk score, rather than assuming a risk of $\geq 20\%$; or (2) doctors were not using the risk charts but recording a risk score just to complete the patient record. Second, some, although few, patients without existing disease who did not have a documented cholesterol score had a documented risk score. As with the former, this may have been because doctors were recording a risk score without calculating it, or possibly trying to calculate it without a cholesterol measurement.

LLT prescriptions were also discordant from guidance. Just under half of the patients eligible for LLT and one-in-five patients not eligible for LLT were prescribed it. LLT prescription rates were the same in patients above and below the 20% risk threshold for prescribing which suggested that risk scoring was not mediating LLT prescriptions. However, in the small subpopulation of patients with a documented risk score, 80% of patients who had documented risk score $\geq 20\%$ were prescribed LLT, indicating that whilst the risk score may be incorrect, prescribing based on documented risk score was better than when compared to the patient's true risk. Interestingly, amongst diabetic patients aged 40 or older with a documented risk score, most had a documented risk score $<20\%$ and were not prescribed LLT despite being eligible. While risk scores of $<20\%$ are possible in many of these patients, they were all eligible for LLT and in these cases it appeared prescribing may have been based on risk score alone, not taking into account diabetic status or age.

Whilst MSF's NCD mission chose to use LD WHO/ISH risk charts, an important question was whether these charts could be replaced with the LI WHO/ISH risk charts. At a 20% threshold for high risk, the sensitivity and specificity was 0.71 and 0.99 respectively. This meant that for every 100 patients who are categorised as high risk by LD WHO/ISH risk charts, 29 of them would be categorised as low risk by the LI WHO/ISH risk charts. The implications of this would therefore be that for every 100 patients eligible for LLT, 29 of them would not be offered

it. With respect to specificity, at a 20% risk threshold, 1 patient per 100 low-risk patients would be classified as high risk, and therefore would be seen as eligible for LLT therapy and other interventions. Some of these patients, however, may benefit from therapy given that reductions of cholesterol in patients with very low absolute risk can reduce major vascular events.[40] Further, given the level of social deprivation and stress amongst refugee populations, these patients may have underestimated absolute risk.[129–131]

5.6.3 Findings in the Context of Existing Research

Whilst it is difficult to find similar evaluations of CVD risk assessment and management in other low-resource settings, the findings are broadly consistent with what has been observed in high-income countries. In primary health care in Australia, audits of CVD risk assessment and management showed that approximately 20% of patients eligible for risk assessment did not have the lipid measurements required to do so.[132] Further, the authors concluded that despite risk-based guidance, use of LLT was more consistent with single risk factor approach, and only 60% of patients with existing CVD were prescribed LLT. These patterns were also seen in a lower-resource, rural and Indigenous settings in Australia.[133] In the United Kingdom, amongst patients without CVD or diabetes in primary care, audits show that half of patients eligible for LLT based on QRISK are not prescribed LLT. The sensitivity and specificity of LLT prescribing with respect to eligibility based on QRISK score was 0.50 and 0.93 respectively.[134] In Southern Thailand, studies examining LLT prescribing against American Diabetes Association criteria amongst outpatient diabetic patients showed that only 22% of those eligible for LLT were prescribed it.[135]

I was unable to find any other published comparisons of LI and LD WHO/ISH risk charts for epidemiological subregion EMR B. However, comparisons of WHO/ISH risk charts for other epidemiological subregions are consistent with performance observed in the MSF NCD mission population. A comparison of LI and LD WHO/ISH SEAR D charts in Bangladesh resulted in a Cohen's kappa of 0.705

($P < 0.001$) and at 20% threshold, a sensitivity and specificity of 0.86 (95% CI 0.73, 0.95) and 0.95 (95% CI 0.93, 0.97), respectively.[136] Another examination of SEAR D charts, but in India, showed similar performance at a 20% threshold: sensitivity and specificity of 0.86 (95% CI 0.78, 0.92) and 0.97 (95% CI 0.95, 0.98), respectively.[118] In a Cuban population using the AMR A charts, the LI charts had a sensitivity and specificity of 0.84 (95% CI 0.68, 0.94) and 0.98 (95% CI, 0.97, 0.99), respectively.[137] Whilst the sensitivity of the EMR B charts in the MSF NCD population was slightly lower than that of other WHO/ISH risk charts in other populations, this variance may be because WHO/ISH risk charts vary for each subregion and the performance would be affected by the distribution of risk factors in the sample population.

The prevalence of existing CVD was 21.9% (95% CI 20.2, 23.6) amongst the clinical population. This was substantially higher than that observed in other Eastern Mediterranean populations, although the sample was not meant to be representative of the population.[16, 138] The clinical population was enrolled in clinic if they had or were at risk for developing an NCD, therefore it was expected the prevalence would be higher than in the general population. Due to this selection bias, it was expected that the prevalence of CVD risk factors amongst the clinic population would be larger than those derived from population studies in other LMIC. The prevalence of smoking was much higher in men than women, whereas the prevalence of high waist circumference was higher in women. This is consistent with population studies from other LMIC in the Eastern Mediterranean Region.[138]

5.6.4 Strengths and Limitations

This work was strengthened by its large sample size of complete cases and the accuracy of the electronic database. It was also the first study, to my knowledge, to analyse the use of WHO/ISH risk scores and the total-CVD risk approach in a low-resource setting in an LMIC, not least a humanitarian setting. The findings are topical given the scale of the Syrian refugee community, the growing

provision of NCD health care in low-resource settings, and the increasing use of WHO/ISH CVD risk charts globally.

By selecting risk factor measurements (i.e. total cholesterol, systolic blood pressure) based on the date of prescription of a LLT or the date of CVD risk assessment, I was able to more accurately approximate the measurements that the clinician would have used for risk assessment. For example, to determine if LLT prescriptions were correct, it was possible to calculate the patient's CVD risk score using the risk factor measurements immediately prior to the prescription of LLT. This reduced the chances that prescribing or accuracy of documented risk scores were misclassified as incorrect.

Absolute risk may have been underestimated in some patients who were already on risk factor lowering medication. However, given the humanitarian nature of the setting, it seemed unlikely that many patients would be taking blood pressure or cholesterol-lowering medications. If this were the case, the estimations of under-prescribing of LLT based on risk may be underestimated. It was also not possible to determine the proportion of patients who were offered but refused treatment, or to assess the number of cholesterol measurements or risk scores not recorded.

Although the findings are broadly consistent with studies of similar types in higher-resource settings, this study should be replicated in other low-resource settings in LMIC. Moreover, since the patient population study was recruited for care because of their increased risk of NCDs, their risk factor levels should not be generalised to the entire Syrian refugee population in the Eastern Mediterranean.

5.6.5 Implications for Practice and Research

Many patients were eligible for LLT prescriptions even without cholesterol testing. These patients were those with a history of CVD, diabetics aged 40 or older, and those with a risk score over 20% regardless of their total cholesterol. Clinicians should pay particular attention to these simple parameters for LLT eligibility—as these patients made up 58% of all patients in the clinical population. Moreover,

clinicians need to pay particular attention to ensure that risk scores are calculated correctly and documented in patient risk charts.

Setting a risk threshold for treatment is a common challenge for health services using total CVD risk-based guidance, and this threshold can range from 10 to 40% using WHO/ISH risk scores. This decision is largely a consideration of resource-level: as the threshold decreases the benefits increase, but so too do costs.[21]

That being said, the performance of LI risk assessment depends on the threshold set for classifying individuals as high risk (i.e. being equal to or above the risk threshold). Although the performance of LI risk charts varies slightly between risk thresholds, this variance may partly be because of the change in prevalence of the underlying “condition” (i.e. risk above the threshold). Altering the risk threshold changes the prevalence of people who are high risk, altering the spectrum of patients in the sample, and these parameters are known to alter the sensitivity and specificity of a test.[139]

Specificity of LI assessment was stable at all risk thresholds, ranging from 0.95 (10% threshold) to 1.00 (20% and 30% threshold), indicating that few patients would be incorrectly classified as high risk. At a 20% risk threshold, 1 patient per 100 low-risk patients would be classified as high risk, and therefore would be eligible for LLT therapy and other interventions. Some of these patients, however, may benefit from therapy given that there is evidence that reductions of cholesterol in patients with very low absolute risk reduces major vascular events.[40] Further, given the level of social deprivation and stress amongst refugee populations, these patients may have underestimated absolute risk.[129–131] Sensitivity is a more critical measure of the performance of LI assessment in this setting, as reductions in sensitivity result in false negatives—meaning patients who would potentially benefit from treatment would not be given access to treatment. Choosing a treatment threshold should not, however, be based on sensitivity alone. The prevalence of the condition, the sensitivity and specificity of the test, and the resources available should all be considered.

The potential harm (i.e. false negatives) associated with using the LI charts should be contextualised in light of the fact that under the current use of LD charts, less than half of patients eligible for LLT were prescribed it. If using the LI charts simplified the clinical workflow and could increase adherence, it may actually increase the number patients eligible for LLT who are prescribed it relative to the current standard.

Future research should focus on validating the WHO/ISH CVD risk charts in terms of their calibration and discrimination amongst the intended population and assessing the impact of their use on patient outcomes. This would also require research to explain the observed gaps in screening and treatment and ways to improve implementation. With respect to the undocumented or incorrect risk scores and the discordant use of LLT, the clinical workflow and health system factors should be more closely considered. This includes assessing the degree to which risk scoring is actually done and why, the actions taken based on the risk score, and other factors that would influence the utility of a CVD risks score, such as the availability of risk-reducing interventions. Through a qualitative study of MSF clinicians, possible health system factors will be examined in the next Chapter (Chapter 6).

5.7 Conclusions

This chapter provided a detailed examination of the use of WHO/ISH CVD risk scores from MSF's NCD mission for Syrian refugees in Jordan, as part of a mixed methods study. This analysis showed that it was possible to use routine clinical data from a low-resource setting to assess clinical practice in a meaningful way. While cholesterol testing rates were high amongst patients eligible for CVD risk assessment, few patients had a documented risk score and many of the documented risk scores were incorrect. LLT did not appear to follow a total risk approach and just under half of eligible patients and one-fifth of ineligible patients were prescribed LLT. Use of the LI WHO/ISH risk charts in this setting would result in 29 patients per 100 high risk patients being classified as low risk, and therefore would not be offered LLT. However, the use of LI may be of net benefit given the

under-prescribing of LLT. In light of these findings, the qualitative strand should seek to explain the observed screening (i.e. undocumented or incorrect risk scores) and treatment (i.e. discordant use of LLT) gaps.

5.8 Chapter Summary

- Routine data in low-resource settings can be used to meaningfully assess the implementation of WHO/ISH risk scores
- Analysis of 2,892 patients from MSF's NCD mission for Syrian refugees in Jordan showed that 80.1% (95% CI 78.6, 81.5) of patients who required risk assessment had a cholesterol measurement
- Only 27.6% (95% CI 25.8, 29.5) of patients with a cholesterol measurement had a documented risk score, and many of the documented risk scores were incorrect
- Just under half of eligible patients and one-fifth of ineligible patients were prescribed LLT
- Use of the LI WHO/ISH risk charts in this setting would result in 29 patients per 100 high risk patients being classified as low risk
- The qualitative strand should seek to explain the undocumented or incorrect risk scores and the discordant use of LLT

6

Cardiovascular Disease Risk and Prevention Amongst Syrian Refugees in Jordan: qualitative strand of a mixed methods study

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6.1 Publication Statement

Features of this chapter were published in BMC Conflict and Health[3] and the textbook, An Introduction to Population-Level Prevention of Non-Communicable Diseases.[4]

6.2 Introduction

This Chapter is a continuation of the mixed methods study introduced in Chapter 5. Whereas the previous Chapter reported the findings of the quantitative strand, this Chapter reports the findings of the qualitative strand and integrates the findings of the two strands. The main quantitative findings from Chapter 5 were that cardiovascular disease (CVD) risk scores were often undocumented and incorrectly calculated, and the prescribing of lipid-lowering treatment (LLT) did not follow a total CVD-risk approach.

I travelled to Médecins Sans Frontières (MSF's) non-communicable disease (NCD) mission in Irbid, Jordan and conducted interviews in the field. Due to the unique security risks, I completed the University of Oxford's Overseas Field Work Safety and Security Course (February 2015), in addition to MSF's own security training. Given the relevance of this research to MSF's work, MSF funded all expenses related to the field work and publishing of the findings.

Upon arrival to Jordan I was embedded in the MSF organisation – offices, housing, transportation, uniform, et cetera – which allowed me to gain a deeper understanding of the context of the NCD mission. A crucial component of the field work that is not captured directly in the findings of this Chapter was the diplomatic work involved in conducting research with a non-governmental organisation which was foreign to the host country. Through MSF's extensive engagement with local partners, and through direct meetings between me, MSF, and senior officials of the Ministry of Health in Jordan, this work and its findings were approved by the Honourable Dr. Mahmoud Al Sheyab, Minister of Health, Jordan (Appendix D).

6.3 Aim and Objectives

6.3.1 Aim

The aim of this chapter was to evaluate the implementation of total CVD risk scoring and risk-based management in MSF's NCD mission in Irbid, Jordan and explore opportunities for improvement.

6.3.2 Objectives

The objectives of the qualitative strand were to:

1. Explain trends observed in the quantitative strand;
2. Integrate the findings of the quantitative strand (Chapter 5) and the qualitative strand
3. Identify opportunities to improve the implementation of CVD risk scoring and associated guidance

6.4 Methods

6.4.1 Study Design

An exploratory sequential mixed methods design was used, as described in Chapter 5 (Figure 6.1).

6.4.2 Participants and Recruitment

Participants eligible for inclusion were primarily clinicians who worked directly in patient care (e.g. nurses, pharmacists, and doctors), but also those involved in the organisation and administration of the health service. At the time of the study, there were five doctors, eight nurses, and two pharmacists employed between the two clinics. Given the unique context, I sought to interview all clinical staff, and purposively sample non-clinical staff who may be able to provide insight on clinical practice and organisation of care. Participants were required to speak and read English, but as this was a requirement for employment at MSF, it was not anticipated to be a barrier to the study.

Potential participants were notified of the project by MSF before my arrival. Upon arrival, I met the staff at the morning team meetings in the field clinics and presented information about the project and scheduled interviews. The participant information sheets and participant consent forms used are included in Appendix E.

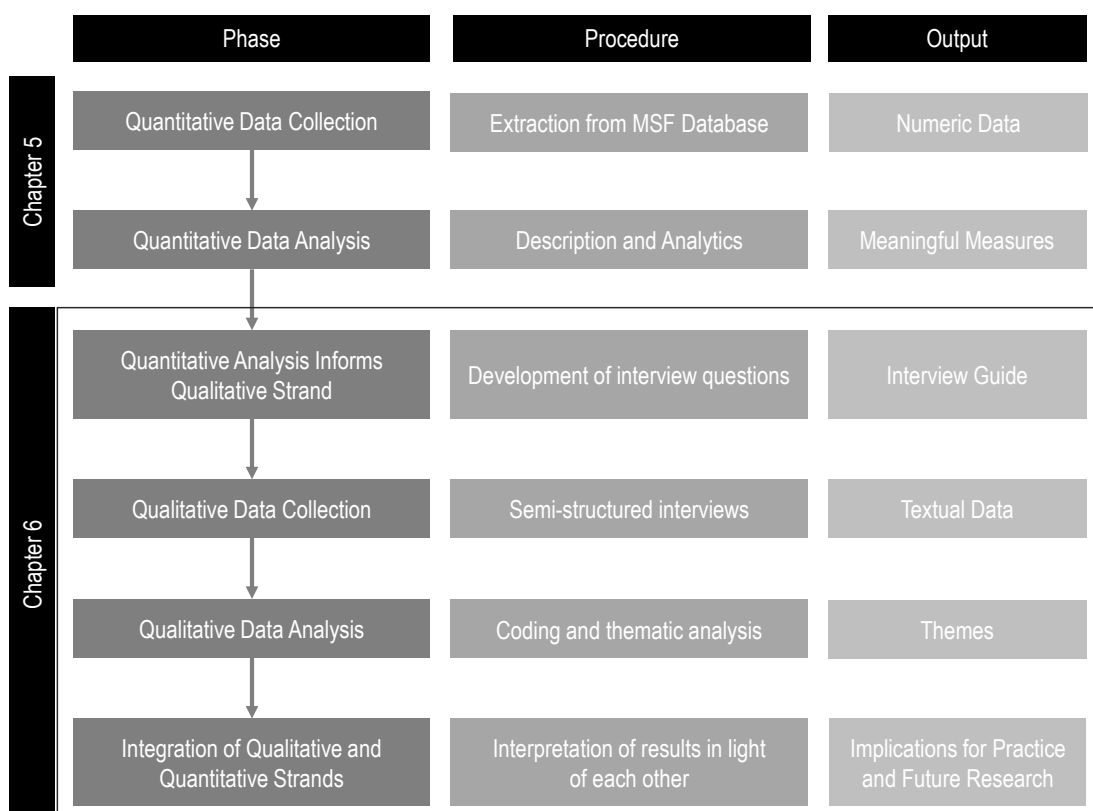


Figure 6.1: Mixed methods study design illustrating the output and procedure of each phase of the quantitative strand (Chapter 5) and qualitative strand (Chapter 6)

6.4.3 Data Collection and Management

Demographic information was not collected from the participants so as to protect the identity and confidentiality of participants. Given the identifiability of MSF's NCD mission as a whole, not collecting demographic information on the participants was the main ethical consideration to protect the identity of participants. Participants were given a generic label based on their clinical role (e.g. Doctor 1, Nurse 5, Pharmacist 3, etc.); however, I decided a priori that if any category had only one participant that I would create an aggregated generic category to protect the identity of the participants. This is described in the protocol approved by OxTREC ethical review (Appendix D).

One-on-one, face-to-face, semi-structured interviews were conducted in the workplace, but in locations that ensured privacy (e.g. office). The value of using semi-structured interviews was that it allowed for direct interrogation of anticipated

themes from the quantitative strand whilst also allowing new themes to emerge. The interview guide was adapted from a previously published guide on a similar topic, and informed by the findings of the quantitative analysis.[140]

The interviewer had no relationship with the interview participants before the interviews were conducted. After collecting written informed consent, 30 to 60 minute interviews were conducted. Because English was the second language of the interview participants, the interviewer adopted a technique to summarise or repeat information to clarify or confirm the meaning of statements from the participants as needed.

Interviews were redundantly recorded using two audio recorders and transcribed verbatim by a professional transcribing service. The transcriber confidentiality agreement can be found in Appendix E.

6.4.4 Data Analysis

Analytic Approach

Thematic analysis was used because it is a rigorous and flexible methodology of qualitative analysis but does not subscribe to a specific theoretical or epistemological worldview.[141] The analysis was based on the explicit meanings of the data rather than examining the underlying ideologies that shape what people say, and in this way borrowed concepts from semantic and realist approaches.[141] Analysis was primarily deductive and was guided by the fact that the purpose of the qualitative data was to help explain the quantitative findings. However, this was balanced by also allowing for an inductive approach whereby open coding could be used for the identification of relevant but unanticipated themes. Key themes were then selected based on their meaning and value to the overall mixed methods approach, and this helped ensure that both anticipated and unanticipated themes were captured. Coding was done in an integrated approach where a deductive framework for codes was first developed and new inductive codes were allowed.[142] The analytic approach can be summarised in six steps.

1. **Data Familiarisation** I re-read the transcripts to re-familiarise myself with the interviews and to check the accuracy of the transcription. The second analyst (TF) read the transcripts.
2. **Developing the Analytical Framework** A provisional analytic framework was developed based on the overall research question. The framework was divided into three domains: pre-consultation, consultation, and post-consultation to broadly organise qualitative data. The definitions of these domains and their categories are described in Table 6.1. The framework categories (n=7) acted as the initial codes.[143] A miscellaneous domain and subset of codes were also used to capture important information that did not fit the framework.
3. **Piloting of the Provisional Analytic Framework** The provisional framework was piloted on three interviews, independently and in duplicate, using NVivo 11. At this stage both coders (DC, TF) were able to create new codes as they saw fit. Both coders then compared and contrasted the coding, clarified meanings, and decided by consensus on new codes. This process was repeated on three new interviews to develop the working framework.
4. **Indexing Interviews** The working analytical framework was used to code the remaining interviews and re-code the initial six interviews. This was done independently and in duplicate (DC, TF) and discrepancies were resolved through consensus.
5. **Thematic Development** Through thorough interpretation and discussion of the coded interviews, key themes in relation to the research question were selected, interrogated, and compared back to the coded data.

Table 6.1: Provisional analytic framework

Domain	Category/Code	Description
Pre-Consultation Does not depend on a consultation taking place in order to be brought into existence or occur	Provider Context	The circumstances of the provider which together form the setting for an event, statement, or idea, and in terms of which it can be fully understood
	Patient Context	The circumstances of the patient which together form the setting for an event, statement, or idea, and in terms of which it can be fully understood
Consultation Anything that depends on interaction between a patient and any part of the health service	Structural Context	Relating to the arrangement of and relations between the parts or elements of the health system
	Invisible Aspects	Actions by the provider that are not openly displayed to the patient
	Visible Aspects	Interactions between the provider and patient
Post-Consultation Depends on a consultation having taken place in order to be brought into existence or occur	Outputs	The products of the consultation
	Outcomes	The results (benefits/harms) of the products of the consultation
Miscellaneous Any noteworthy text that does not appear to fit into one of the above domains	Recommendation	When an interviewee provides an explicit recommendation
	Miscellaneous	Any noteworthy text that does not appear to fit into one of the above codes

Reflexivity

An outgrowth from the acknowledgement that objectivity is not possible in qualitative research, “reflexivity is the self-appraisal in research.”[144] There are three ways in which the position of the researcher can impact the research process: access to the field, nature of the researcher-researched relationship, and the worldview and background of the researcher.[144] It is therefore important to consider the degree to which these positions affect the research process and impact the conclusions.

I was the only person to interview the participants. Since I had also conducted the quantitative analysis, I incorporated previously reported and more general questions about the topic in the interview guide to help ensure that any ‘leads’ I had did not entirely consume the interviews. I am not a clinician, but my training is in biomedical science and clinical epidemiology, and I have a particular interest in evidence-based medicine.

I was familiar with the setting and the refugee crisis, as I had previously lived in Jordan. Before data collection, I studied Arabic language at the Oxford University Language Centre. Although I could not speak Arabic, I was able to read and write the alphabet and exchange pleasantries in Arabic, helping me to build rapport with participants. I also had previously visited the clinics and local medical universities, and attended a regional public health conference in Aqaba (Jordan) to gain a better understanding of the local context of research and medical practice.

Throughout the research process I adopted a practice of critical self-reflection. During data collection, for example, I tried to remain cognisant of questions or topics that I was shying away from and likewise the ones I was emphasising, and responded appropriately.

During the analysis phase, an additional analyst (TF; a medical student from the University of Oxford) played an important role in coding and interpretation so as to promote further reflection about my own worldview and background and its influence on the analysis.

6.4.5 Ethical Approval

This Chapter was reviewed and approved by the Oxford Tropical Research Ethics Committee (OxTREC Reference 576-15), MSF Operational Centre Amsterdam, and by the Ministry of Health of the Hashemite Kingdom of Jordan (Appendix D).

6.5 Results

6.5.1 Participants

All doctors (n=5) and nurses (n=8) working in the clinics were interviewed. The remaining participants (n=3) were a mix of pharmacists or those involved in the management of the clinics (Table 6.2). The median interview time was 44 minutes (IQR 31.5, 54.5). The doctors had a range of past work experience and postgraduate education. For example, one had completed a family medicine residency, whilst the rest had only partially completed or not completed postgraduate training.

Table 6.2: Number of participants interviewed and their role at MSF

MSF Role	Number Interviewed
Medical Doctor	5
Nurse	8
Staff - Other	3
Total	16

6.5.2 Final Analytic Framework

The final analytic framework, codes, and the frequencies of use and sources are enumerated in Appendix E. These type of prevalence data should not be used to infer meaning or priority to the codes.[143]

6.5.3 Thematic Analysis

Provider-Centered Themes

Use of Risk Charts by Doctors

Doctors used risk charts in a variety of ways, but none described their use in relation to the clinical guidance. Generally, doctors had a limited understanding of total cardiovascular risk, which affected their ability to use the risk charts. One doctor viewed risk charts as an objective and systematic tool for decision making and used it routinely with patients.

Doctor B: “I think I’m using it with most of patients because the score gives you a clear idea about the risk and how to react so I depend on it a lot.”

Others, however, relied more routinely on their clinical judgment, but described using the charts when there was ambiguity about the patient’s risk, failing to understand the delineation between risk factors that are and are not included in the risk score itself.

Doctor D: “But if there is no risk factor sometimes I go to this [the risk chart] just to decide if I give him or I don’t give him the medications.”

In addition to such passive reliance on the risk chart, there were a further two reasons why risk scores may not be calculated for all eligible patients. First, one doctor misunderstood how to categorise risk factor values and thought that because the risk charts do not cover systolic blood pressures above 180 mmHg, patients with blood pressures above 180 mmHg could not be risk assessed; their strategy was to wait until the next visit.

Doctor D: “Some patients when we measure blood pressure it is 210. At that visit they are 210/120 something like that, so I can’t do it. I postpone the risk assessment to the next visit when we have better reading.”

The same doctor believed that for patients over 70 years old, the risk charts could also not be used because the upper bound of the age category was 70.

Doctor D: “Yes, they are 90 years old. When I look at them, “Okay, we will not do the risk assessment for this patient.” Because I don’t know how.”

The second reason, which affected all patients, was that doctors had to wait for a follow-up visit to know the patient’s cholesterol before they could calculate their risk. This meant that during the first consultation with patients, doctors were unable to perform the risk assessment until patients completed a requisition at an offsite laboratory.

Doctor A: “So if it’s the first time the patient is coming I need to wait for the labs to calculate what the percentage is.”

Choosing Risk Factor Measurements for Calculation of Risk Score

There was diversity in the methods that doctors used to calculate CVD risk scores and there were four different approaches to choosing which blood pressure or cholesterol measurement to use in the calculation. These consisted of using the most recent measurements, using the highest measurements, calculating multiple scores with multiple risk factor values, or delaying the calculation to the next visit when the readings are more reasonable.

Doctor D: “I usually take the most recent blood pressure reading and the most recent cholesterol reading.”

Doctor D: “Some patients when we measure blood pressure it is 210. At that visit they are 210/120 something like that, so I can’t do it. I postpone the risk assessment to the next visit when we have better reading.”

Doctor B: “Sometimes I have patients with multiple blood pressure readings and they are different. One of them 160, one of them 120 so which one I will use, most of the time I use the highest to be in the safe side.”

Doctor C: “I use both maybe it’s going to be [the] same maybe it’s not going to be [the] same and also if it’s less than 10[% risk] and 10-20[% risk] it’s similar protocol because above 20-30[% risk] you cannot change your plan.”

There was also variation in the way blood pressure was measured and recorded by nurses, before doctors review recorded vital signs to calculate a risk score. Some nurses recorded the lowest blood pressure reading and some the highest.

Nurse A: “The lower reading I take it.”

Nurse E: “Which one I write down? Sometimes I write left, right, but if they are the same hand I write the higher.”

Tendency to Favour Lifestyle Interventions as First Line Therapy

Based on the guidance implemented by the clinics, patients with total cardiovascular risk of 20% or more were eligible for LLT. However, many doctors preferred to use lifestyle interventions as first-line treatment, even in patients eligible for LLT.

Doctor E: “So it is the basics actually. It is the first line [...] doing exercise, stopping smoking, stopping maybe patients who maybe drinks alcohol, doing exercise, decreasing salt every day. Yes, so do the first line and then pharmacological treatment.”

Doctor C: “We can, [if] the cardiovascular risk is 20-30[%], we can decrease it by normalisation of blood pressure that’s high and the cholesterol level if it’s high, we can give him three months to four months diet and then recheck it. If it’s still high we can start statin to reduce it.”

Nurse D: “The patient in the first maybe refuse to take the statin. We give him a chance for three month to change the lifestyle, to change about diet, about their physical activity.”

While lifestyle interventions are indicated in patients at elevated risk, doctors favoured lifestyle intervention instead of drug intervention, rather than in addition.

Doctors' Understanding and Use of Lipid Lowering Treatment

Reliance on lifestyle intervention and under-use of LLT might also be explained partially by the limited understanding of the doctors on the use of LLT in primary prevention. Although some doctors consulted the risk charts for decision-making, their understanding of the appropriate use of risk scores for deciding eligibility for LLT was limited and they sometimes reverted to a single risk factor approach. All doctors understood that LLT lowers cholesterol, however, confusion arose for some doctors around patients with high risk but normal cholesterol levels.

Doctor B: “Nowadays, up till now, the studies said that there’s no role for statin as primary prevention that’s what I know. So no, I don’t start statin, if the cholesterol level is normal, as a primary prevention.”

Doctor C: “If it’s there any risk, yes risk above 40[%], no, just aspirin [but no statin].”

Dylan: “Just aspirin. Okay because the cholesterol is?”

Doctor C: “Normal.”

Most doctors, however, understood the role of LLT in secondary prevention of CVD.

Doctor E: “Yes, if the patient having for example a high risk and previously they’re having ischaemic heart disease or for example peripheral arterial disease, we should prescribe statin even if [cholesterol] is normal.”

Doctor A: “So what I usually try to educate the patients about it is that I tell them exactly that if your cholesterol level is 0 you’ll have to stay on the medication and that’s not probably possible but just to make it more clear for a patient that it’s preventive not only for lipids.”

Risk Communication

Although the colour-coded paper risk charts are primarily designed for the doctor to use, the charts were often used as a communication tool with patients, and many doctors avoided using numbers in their communication. The cultural associations with the colours used in the risk chart were seen as helpful, including the association of green with holiness in Islam.

Doctor C: “I’ll show this chart to the patient and explain everything about it. Here the cholesterol level, here the age. Here the blood pressure readings, DM or non-DM depending upon gender male and female, yes I explain everything about the patient and I explain I prefer to be in the yellow or green ...”

Doctors felt that communicating to a patient that they were high-risk tended to induce fear, which motivated them to reduce their own risk factors.

Doctor D: “When it is high they will be scared, “Oh no, I will try to stop smoking.””

Communicating low-risk scores to patients was sometimes helpful when de-prescribing because it reassured patients. This reassurance of low risk was also sometimes seen as counterproductive by encouraging apathy, so in these instances doctors avoided communicating the risk score so as to not promote unhealthy behaviour.

Doctor E: “So we are just, I mean showing indication that you are in the green area, [...] so you don’t need to take aspirin because you might have side effects more than the benefits from aspirin and actually a lot of them they are convinced [...]. So it is very helpful and it is convincing.”

Dylan: “If they are low risk, do you tell them that they’re low risk?”

Doctor D: “No. Because he will be comfortable and do anything he wants.”

Doctor D: “The patient don’t take everything seriously. When you talk to them there is risk 10% to have MI, or angina, or something like that, they tell us, “No, it will not happen, don’t worry,” something like that.”

Nurses and health promoters did not use cardiovascular risk charts during their sessions, but they did use colour-coded risk charts for blood pressure and glycated hemoglobin to track and communicate patient changes. Patients responded well to the visual and colour coded communication, helping to corroborate the potential of CVD risk charts as a communication tool. Nurses and health promoters also saw the potential utility of using risk charts as a motivational tool. Some nurses had a good understanding of the risk chart and how to communicate risk reduction in natural frequencies.

Nurse E: “From my experience the colours are best for our patient from numbers.”

Nurse C: “When they come here and see the blood pressure chart, they just get the blood pressure chart and start saying, “Okay. Today my blood pressure is 110/70 so I am here and I’m not in the danger zone. I’m in green zone so I’m safe.” This is also something great that when they see us using it and when we simplify this chart for them, they will do just the same. They will drop it and they will start saying, “Okay. I am 50. I was in the dark red here because my blood pressure was 180 or more so I was in the dark red zone. Now because I quit smoking, I’m here in the orange zone, for example, in the yellow zone. And after that, okay, my blood cholesterol dropped from eight to five.” So they can just put their own thoughts and as you know, the colours [are] really useful.”

Patient-Centered Themes

Patient Reaction and Adherence to Drug Intervention

The reliance of doctors on lifestyle interventions as first line therapy might be partially explained by patient preferences and reactions to drug interventions. Some patients refused new drug interventions, especially for LLT when their cholesterol measurement was normal.

Doctor C: “Many patients when you give a new medication they just [say], “No.””

Doctor A: “When any patient with I have told you before that more than 20% risk factor and we tell them that I like to add statin a new medication that’s called statin, it’s for cholesterol. And they usually react, “I don’t have any cholesterol and no I don’t have any problems with my cholesterol,” or something like that.”

De-prescribing was a common challenge faced by doctors, as some patients arrived to the clinic with unnecessary aspirin prescriptions. They also faced challenges when trying to change the types of medications, as patients often wanted to remain on the medication they had previously been using. The clinics provided free medications to the patients, but stocked only essential NCD medication of limited variety.

Doctor B: “With the nature of patients that we are dealing with, when they are started on medication it is very hard to stop.[...] Once someone tells them that “you have to take this medication”, no one, no any other one, no other doctor can convince them to stop it.”

Doctor E: “We’ll shift you for another medication. Most of them they don’t have problem with it. A small percentage they don’t want to change their medication that we got the same to you and using it for 15 years and comfortable and they are not convinced.”

Poor adherence to medications was also identified as a common challenge. Mental health challenges were one reason identified for poor adherence. Other patients would only take medication when they were not feeling well, or would stop because of side effects.

Person B: “If someone’s having mental health issues and there’s lots of depression and stuff, they tend to stop taking their medication or just not taking it regularly because there’s a lack of care for taking care of themselves.”

Person C: “I didn’t use it, [I] just give it to someone who is in need.” Why didn’t you use it? “I didn’t like it, I didn’t feel well,” or, “I felt my blood pressure was down, I didn’t have headache, so I didn’t take my drugs.””

The migration patterns of some refugees also affected adherence because they were unable obtain medication during extended trips to Syria.

Nurse B: “They move to Syria because they want to see their sons or their beloved people. They are going without medication for two months, three months, four months, six months as they can to come to Jordan, to come back to Jordan.”

Antagonistic Role of Health Myths

Health myths— popular but untrue anecdotes about health— were commonly perpetuated through the Syrian community and there was often a greater sense of trust in peers than in healthcare providers.

Doctor C: “They are taking an aspirin because they are told that every patient above 40 must take aspirin as prophylactic, yes. They are told not by doctor [but] by neighbours, by relatives, yes.”

Nurse A: “They believe their neighbours, although their neighbours they did not understand the [diabetes], but sometimes they accept the neighbours’ opinion more than us.”

Many of the health claims perpetuated by the community antagonised the goals of the clinicians. Some myths induced fear in patients about adverse reaction of medications, such as insulin.

Nurse E: “She want to stay on oral hypoglycaemic [instead of insulin]. The people told her that if she take insulin she will lose the kidney function and I told her and talked with her many time and many time and many time and she didn’t want to.”

Facebook was noted as a medium for sharing myths, especially about alternative therapies such as drinking vinegar to reduce cholesterol.

Person A: ““If I drink a cup of water plus one tablespoon of vinegar, it’s bad on the cholesterol?” This is a common question.” // “It’s something usually in Facebook. Use the vinegar or if you bought some lemon in cup of water and drink it early morning, burn the fat.”

Patients’ Ability to Reduce Risk

Although some participants felt that patient outcomes were improving, despite intensive and dedicated time for health education, many patients were not interested or able to exercise. Specifically, security concerns were a common challenge for patients to perform regular exercise, especially for undocumented refugees.

Nurse E: “So many of them refuse to walk, they say we are stranger here and we cannot [...]. We have many male, they have a fear of walking outside because they didn’t have an ID or an UNHCR paper so they refuse walking.”

Women were seen to face greater challenges to conduct exercise, because of security and sometimes cultural restraints of exercising outdoors. In such cases, nurses would recommend gentle exercise indoors.

Nurse E: “In our culture maybe women have, in this they have a conflict about women outside and if she walk or go to gym or running or something like this. So she said that my husband refuse to walk outside even if he walk with her or he refuse to go to sport or something like this, so we have a difficult – on this point.”

Dylan: “So then what advice do you give women who need to lose weight?”

Nurse E: “I advise them to choose a corridor or something high in their home and walk 50 minutes in the morning and 50 minutes at night, like a running or something like this. And many of them do that.”

Many patients were embarrassed to fully disclose their socioeconomic status or context, and therefore during clinical consultations clinicians had limited or biased information to base their recommendations on.

Nurse F: “I will give you an example, when we talk the patients, “You must when you wake up in the morning, you must bend on the bed, will be for your legs and you can move your leg in order to enhance circulation.” When we are go to their home maybe he sleep on the earth. There is no bed.”

Nurse F: “Sometimes our patients are ashamed to tell you about that. Just you hear “you must take vegetables, fruit just one time a week.” They are still silent, because sometimes they do not have anything. That is the problem. It is better, I think, in the home visit to give a good picture or clear picture about that.”

There were mixed views on the ability to make dietary changes.

Nurse G: “Most of them eat cheap food which is high carbohydrate and maybe high fat. We advise them to concern about for high fibre vegetables. It’s not expensive, most of the time in Jordan not expensive and they can get that easily to change their habits.”

Person B: “And food – access to food is an issue because when we’re in Jordan there’s lots of food everywhere but they don’t have the money. . . ”

Stress or psychological distress related to the war frequently affected the ability of patients to reduce tobacco use, in addition to becoming the dominant narrative of individual health education sessions.

Nurse B: “Some patients gradually decrease their cigarettes, but suddenly when they come “I increased my consumption.” “Why?” “Because my brother left away in Syria, because my son died, because I need more money.”

Nurse G: “Some of them, not most of them, when we focus on smoking cessation or quit smoking, they always answer that, “We have stress situation and we have bad news from our relatives and Syria.””

Health Education

Given that many doctors used lifestyle interventions as first line therapy, health education by nurses was a core component of the clinical care. These sessions,

although designed to help patients reduce their risk factors through lifestyle changes, were often directed by the patients' more immediate needs and therefore the health education objectives were not met. Nurses often found themselves with no time to discuss lifestyle changes because patients were in psychological or emotional distress.

Person B: "They're just continually thinking about that their son was killed and that's all they can think about. And then they're telling the story about what happened to the nurses and – they're crying in the health education because of everything that's happened. And then so then the health education portion gets pushed aside because they need to sit and just listen to the patient."

Nurse C: "They just keep telling us about what happened in Syria and after they finish, we start our health coaching sessions."

Nurse B: "We go away from health education, listen for their problems, for their traumatic stories in Syria, or for their experiences in the world. We must respect that and we listen for them"

One nurse noted that because of the stressful environment, it sometimes took up to three sessions with a patient until rapport was established and patients started to openly discuss lifestyle changes.

Nurse C: "They live in stress because of news that they're here and this affects everything, the stress affects the blood glucose, their hypertension, and their psychological – so the first session and the second, the third might start just to speak more and to be wide open to speak more"

Person A: "...or because they are refugee they feel we are strange."

Despite these challenges, most clinicians felt that many patients were able to make positive changes.

Nurse C: "So we succeeded to make lots of people to quit smoking and decrease their weight and increase their physical activity and change their diet habits. So it is improving."

Nurse C: "So we start telling them to decrease the sugar in their meals, for example, tea or candy or biscuit or anything to protect themselves instead of taking medication, to start taking medication. Just change yourself and it will drop. So lots of them decreased and they stick to their diet without taking medication."

Person A: "We have a lot of patient quit smoking, a lot of patient increased the physical activity. A lot of patient decreased smoking.[...]We are having a lot of improvement now."

6.5.4 Integration with Quantitative Findings

Nine themes were identified which together helped explain the quantitative stand and identify opportunities for improvement. An integration map of the findings is illustrated in Figure 6.2, which theorises the interrelatedness of qualitative themes and quantitative findings.

With respect to providers, inability (i.e. no immediate access to cholesterol information) or lack of knowledge to use risk charts may have led directly to not using risk charts and therefore either undocumented or incorrect (i.e. guessed) risk scores documented in patient charts. Or, if the risk charts were used, this may have led to incorrect calculation of a risk score and subsequently incorrectly documented risk scores (Figure 6.2).

The discordant use of treatment identified in Chapter 5 may be partially explained by two provider-centred themes. Some doctors lacked the knowledge and understanding of the indication for LLT, and this may have led directly to discordant use of LLT. Or, indirectly, this may have contributed to the tendency of providers to rely on lifestyle interventions, which sometimes took the place of drug intervention even in high risk patients.

The reluctance of patients to start, stop, or change medication may have also been a contributing factor to the tendency of providers to favour lifestyle interventions. Popular health myths, often spread on Facebook, may have contributed to this reluctance, as patients were sometimes more easily persuaded by their peers than their health care provider. Health myths also distracted health education sessions from their intended goals.

Unfocused health education and counselling sessions may have also contributed directly to the observed discordant use of treatment. Sessions were often co-opted by the needs of patients to discuss the challenges of living as refugee, including the emotional and stressful aspects of their life. While this was relevant to the goal of health education, it meant that less time was available to directly discuss risk reduction interventions.

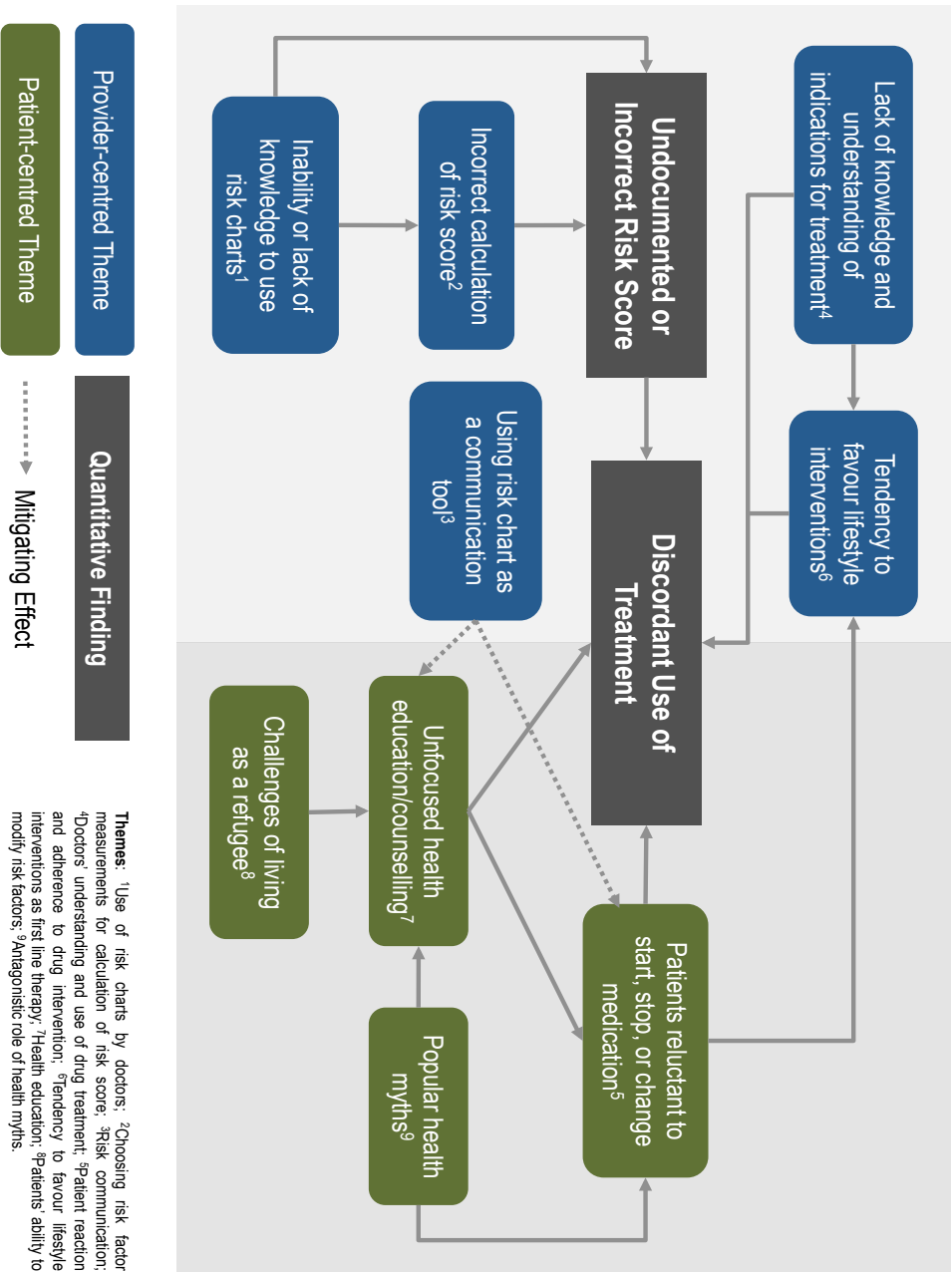


Figure 6.2: Integration map illustrating the explanatory nature of qualitative themes in relation to the key quantitative findings

The potential of judiciously using risk charts as a communication tool to help persuade patients to start, stop, or change medication, or to help focus health education, was also noted. Whilst nurses did not use risk charts in their work, they did use similar colour-coded charts to discuss blood pressure and blood sugar control which they found to be useful.

6.6 Discussion

6.6.1 Summary of Findings

This chapter reported the qualitative strand of a mixed methods study aimed to evaluate the implementation of CVD risk scoring in MSF's NCD mission in Irbid, Jordan and explore opportunities for improvement. Sixteen interviews were conducted, which included interviews with all five doctors and eight nurses working in the clinics. The interviews were analysed using thematic analysis to help explain the findings of the quantitative strand. The main findings of the quantitative strand were that few patients had a documented and correct CVD risk score, and that LLT prescriptions were discordant with guidance.

Nine key themes were identified that together helped theorise the quantitative findings, which were broadly organised into five provider-centred themes and four patient-centred themes.

With respect to provider-centred themes, although some doctors used the risk charts correctly, there was generally confusion about when to use the charts, and an inability to calculate a risk score during the first consultation because total cholesterol measurements were not available. There were also diverse and incorrect methods used when recording and choosing risk factor measurements for the calculation of a risk score. Doctors tended to favour lifestyle interventions over drug interventions even in patients where drug intervention was indicated. They also had a good understanding of the use of LLT in secondary, but not primary, prevention. Risk charts were used by doctors to help communicate with patients and make decisions; nurses did not use the CVD risk charts but felt that they could be helpful during counselling sessions.

With respect to patient-centred themes, patients were reluctant to start, stop, or change medication and were sometimes not adherent because of disruptions in access to medicine when patients travelled. Many health myths existed amongst the Syrian community and these myths were influential and antagonised the advice of clinicians. Facebook was noted a popular vector for health myths. Security concerns, socioeconomic deprivation, shame, and stress reduced the ability of patients to modify their risk factors. While health education was sometimes seen as successful, these sessions were often co-opted by more immediate needs of the patients, such as discussion of traumatic experiences.

6.6.2 Interpretation of Findings

The qualitative strand helped theorise explanatory reasons for the quantitative observations and therefore identify opportunities for improvement. There was a tension between the need to use drug intervention for primary prevention and the tendency of doctors to prefer lifestyle interventions without drug intervention. There was significant variability between clinicians in the way that risk charts were used; this was sometimes the result of misunderstandings of the potential benefits of LLTs and uncertainties about when to prescribe them, but in some cases reflected a reliance on clinical judgement and a preference for lifestyle over drug interventions. This was noted especially amongst individuals with high risk but normal cholesterol, but also may be because some patients were reluctant to start new medication and were influenced by health myths. This became problematic because individual health counselling sessions were often co-opted by psycho-social counselling rather than lifestyle education, resulting in patients not adhering to lifestyle interventions and also not on drug treatment. The fact that the risk assessment approach was laboratory-dependent (LD) meant that doctors had to defer use of the risk charts until the second visit, when the test result would normally be available; however the second visit was typically a 15 minute follow-up visit, and risk assessment may have been forgotten or overlooked.

6.6.3 Findings in the Context of Existing Research

With respect to provider-centred themes, the inability or lack of knowledge to use risk charts and the incorrect calculation of risk scores are consistent with findings from other studies. Earlier (2002) in the implementation of risk scores in the United Kingdom, for example, lack of documented risk factor measurements was a barrier for the calculation of a risk score.[145] GPs are also known to underestimate total risk when not using a risk chart, and this may lead to incorrectly documented risk score.[145–147] Other known barriers to using risk charts include lack of knowledge of risk charts, difficulty of risk communication, and the scales on the charts being too crude.[148] Lack of time and volume of work load have also been noted in the literature as a barrier, however this was not an explanatory theme in this setting.[149]

An important finding was that patients were often more trusting of their peers than the health care providers. Nurses noted that it may take up to three education sessions to build rapport with the patients and that patients perceived them as “strange” (i.e. Jordanian rather than Syrian). Some patients were also undocumented refugees which may have contributed to difficulty building trust. Trust is an important aspect of the clinician-patient relationship, and it has been shown that patients are unlikely to take advice from clinicians unless they trust them.[150, 151] Challenges building trust therefore may have contributed to the reluctance of patients to start, stop, or change medication on the recommendation of clinicians. To that end, patients are also known to be inappropriately optimistic in their own estimations of CVD risk.[152] This was noted by some of the clinicians, who in response to communicating a CVD risk score to a patient, the patient responded, “No, it will not happen, don’t worry.”

These patient-related themes are consistent with the health behaviour model, which was developed to explain why people fail to accept preventive interventions.[153] The model consists of four dimensions: perceived susceptibility, perceived severity, perceived benefits, and perceived barriers. Doctors reported that patients’ perceived susceptibility was an important factor, noting that patients who did not perceive their risk as a threat were less likely to take treatment. Likewise when

risk induced fear, patients were described as motivated to take action.[154] With respect to LLT, some patients did not understand the benefit of treatment when their cholesterol was normal (but overall risk was high) and refused treatment. The unfocused health education sessions were partly due to the patient's perceived barriers, such as the negative consequences of exercising outdoors because of security concerns and not having United Nations High Commissioner for Refugees (UNHCR) documentation. Using the risk chart as a communication tool emerged as an important mitigating factor, and was described in a way that directly targeted the patient's perception of susceptibility and benefit. For example, nurses saw potential in using the risk charts as colour coded visual aid to help communicate susceptibility, but also to show the benefits of risk factor reduction.

Using the risk charts as a communication tool is also corroborated by many other studies. Use of risk charts in this fashion is consistent with current practice in some settings; GPs in Australia have been shown to use CVD risk assessment for the purposes of patient education, rather than for decision making.[155] Visual aids, including the strong use of colour, are also known to be helpful in fostering good relationships between clinicians and patients.[150, 152, 156]

6.6.4 Strengths and Limitations

This study was strengthened by its mixed methods approach and to my knowledge was the first in this way to look at the use of CVD risk scores in primary health care in a low-resource setting in a LMIC, not least a humanitarian setting. Focusing on this setting as a model setting helped to control for the issue of access to medicines, allowing for the interrogation of other explanatory themes for the observed screening and treatment gaps. The fact that I conducted the interviews and the data analysis, meant that I was able to gain greater depth in the qualitative data, and having a second analyst (TF) helped mitigate my biases. I was also able to interview all clinical staff of both clinics. The use of deductive and inductive approach allowed me to examine both anticipated and unanticipated themes, which

reduced the chance that the deductive framework would exclude important but unanticipated information.

Data saturation, a highly debated concept in qualitative research, is a term used to describe the point during data collection at which additional interviews add no new information.[157] This concept relates to the confidence in which a sample population represents the theoretical population as a whole. Since I was able to interview all clinical staff, the sample population was the same as the theoretical population with respect to the mixed methods study aim, and in this way the concept of data saturation is limited. Furthermore, data saturation is a concept initially developed for studies using grounded theory.[158] However, in doing the interviews, I felt confident that no new information was emerging by the end and my purposive interviews with non-clinical staff corroborated this. A more useful concept than data saturation is that of information power.[158]

Information power has five items, each with two dimensions: aim (narrow/broad), specificity (dense/sparse), theory (applied/none), dialogue (strong/weak), and analysis (case/cross case).[158] The amount of information power in a sample is inversely related to sample size. Given the narrow aim, the dense specificity, strong dialogue, and case analysis used, the qualitative findings are based on relatively high information power. Nonetheless, this study should be repeated in other settings, and the explanatory themes used to theorise the use of CVD risk charts in this setting could provide the basis for further deductive implementation research.

This study was not without limitations. Since interviews were conducted in the second language of the participants, it is possible that there were misunderstandings or miscommunications, despite my interviewing strategy to summarise and review content for clarification. In terms of reflexivity, my position as a non-clinician researcher affected my access to the field. While during the interviews it seemed beneficial that I was not a clinician, because I was able to ask for explanations of practices or concepts, my affiliation with MSF may have affected the content of the interviews. During the introduction of the interviews I made it clear that I did not work for MSF, however it is reasonable to assume that MSF staff may

hesitate to be critical of themselves or their workplace. Furthermore, my position as a foreign researcher from a prestigious institution may have made participants less comfortable disclosing their own challenges or questions about the topic.

6.6.5 Implications for Research and Practice

First, the findings are consistent with others showing that the implementation of guidelines alone is not effective at changing practice[159] and recent systematic review evidence show that health care provider education is an important component of improving adherence to CVD guidelines.[160] Given the lack of familiarity of the health care providers with CVD risk scoring, training of clinicians should include detailed practical exercises on calculating risk scores and measurement of risk factors.

Second, there is potential for greater integration of a total CVD risk approach with the role of nurses and health promoters. Although there is limited evidence on task sharing for CVD management in LMIC,[161] the WHO has recently published guidance on task sharing for total CVD risk assessment in low-resource settings,[162] and there is evidence to support the role of non-physician health workers conducting CVD risk assessments.[163]

Third, risk scoring should be contextualised in a broader risk assessment algorithm that can be conducted within a single consultation that reinforces the identification of patients with existing disease and diabetics over the age of 40. Broadly speaking, patient can be stratified into three groups: individuals with existing CVD, diabetics over the age of 40, and otherwise asymptomatic. For each group, there is a different approach to management based on their total CVD risk level. Patients with existing disease are at highest risk for a subsequent CVD event and thus should be treated aggressively and comprehensively with risk factor lowering interventions. These patients do not require CVD risk scoring. Diabetic patients aged 40 or older are also at elevated total CVD risk and do not require risk scoring to initiate risk factor lowering interventions, for example, based on WHO PEN, statin therapy. The last category, patients asymptomatic for CVD, requires the use of CVD risk scores to risk stratify the population and target interventions

to those at relatively high risk. In this respect, the level of intervention should positively correlate with the level of total risk, and it is important to note that many high risk patients do not require CVD risk scoring. Ideally, based on this risk assessment algorithm, all patients should be risk stratified in one single consultation. Risk scores without measured cholesterol, such as those published by WHO, are less complex and allow single consultation risk scoring.[112] Those in charge of implementation must determine whether to optimise adherence to simple clinical protocols before adding additional complexity, such as cholesterol testing, with potentially marginal returns for patient outcomes.[164]

Fourth, greater engagement with patients in the organisation and planning of care may help build trust between the community and health care provider. Although further research is needed for its use in this context, facilitated participatory learning and action may help engage the community in identifying and correcting health myths and misconceptions.[165, 166] Since Facebook was an important vector of health myths, social media should be closely considered for corrective health promotion.

Particular attention should be given to the simplification of clinical guidance to help ensure their successful acceptance and adoption. Although the LD WHO/ISH risk assessment is generally regarded as superior, it introduces additional cost and complexity. By requiring measured cholesterol for risk assessment, clinicians must delay risk assessment until the laboratory results are returned, and this delay may prevent decision making based on risk. Consistent contact with patients cannot be guaranteed, and therefore clinicians may naturally be more inclined to make decisions (i.e. prescribe) before risk assessment and must balance expectations from patients. The LI model should therefore be closely considered as it allows clinicians to perform real-time risk assessment without laboratory measurements. Furthermore, in instances where patient follow-up is challenging, it may be best to use LI assessment rather than delay risk assessment until laboratory results are obtained. Clinicians also favoured lifestyle interventions as first line therapy, even amongst high risk individuals, despite the inability of many patients to

sustain lifestyle changes. Clinicians should be aware that while lifestyle changes are important for all patients, those who are very high risk for CVD are likely to benefit from drug intervention.

Future research should focus on single consultation risk assessment that can be done in real-time with the patient, and does not cause any delays in risk assessment or communication. This would require further examination of CVD risk models that do not require laboratory measurements, and the use of these models in clinical practice. Such models may allow for more focus from the clinicians on the aspects that can improve calculation and communication of risk, including trust building and shared decision making.

6.7 Conclusions

Considerable challenges existed when implementing CVD risk scoring and risk-based management in MSF's NCD mission for Syrian refugees in Jordan. Mixed methods analysis of the first year of implementation was a powerful approach that identified and explained a low prevalence of documented and correct CVD risk scores and discordant prescribing of LLT. A total CVD risk approach for the management of CVD in primary health care should be simplified toward a model that can be used in a single consultation and clearly contextualises the role of risk scoring in a broader risk assessment algorithm, emphasising secondary prevention and the identification of older diabetic patients. Training of health staff on a total cardiovascular risk approach and context-specific patient considerations, such as the role of health myths, the increased need for building rapport with patients, and the psycho-social-occupational context of patients is likely to be necessary to enable effective implementation. These approaches should be developed and studied further in low-resource settings.

6.8 Chapter Summary

- Semi-structured interviews were conducted with sixteen MSF staff and included all clinical staff
- Thematic analysis identified five provider-centred themes and four patient-centred themes that helped to theorise the undocumented or incorrect risk scores and discordant use of treatment in the NCD mission
- Providers had confusion about when and how to use the risk charts, tended to favour lifestyle intervention over drug treatment, and had uncertainty about the role of LLT in primary but not secondary prevention. Patients were reluctant to start, stop, or change medication and were less able to modify risk factors and benefit from health education because of their social and economic context
- Integration of the quantitative and qualitative findings helped identify opportunities to improve implementation, including:
 - detailed practical training on calculating risk scores and measurement of risk factors
 - integration of a total CVD risk approach with the role of nurses
 - contextualising risk scores in a broader risk assessment algorithm that can be conducted within a single consultation
 - greater engagement with patients in the organisation and planning of care

7

Towards Simplified Cardiovascular Disease Risk Scores: prognostic modelling study

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7.1 Introduction

Chapter 3 illustrated a paucity of evidence on the impact of cardiovascular (CVD) risk scoring and the need to conduct high quality randomised controlled trials (RCTs) in low-resource settings. Chapters 5 and 6 identified some of the challenges of CVD risk scores in low-resource settings, which included the need for single-consultation risk scoring that does not require cholesterol or other laboratory testing.

While there was precedent for non-laboratory CVD risk scores,[167, 168] I was interested to build on this work in a way that might address some of the challenges identified in Chapters 5 and 6. Past work done by others was limited

in three main ways. Firstly, given that total cholesterol (TC) is less predictive than TC to high-density lipoprotein (HDL) ratio (TC:HDL), past studies only examined models with TC.[169] Secondly, previous cohorts used were from the 1950's and 1970's, and these may not be representative of CVD risk in contemporary populations. Lastly, previous work focused on the performance of the models from a statistical standpoint and less from a clinical perspective, such as examining net reclassification improvement (NRI).[170]

I decided to address these gaps by developing and comparing two CVD risk scores: a laboratory-dependent model using TC:HDL as a covariate, rather than total cholesterol, with a laboratory-independent model that replaced this lipid covariate with body mass index (BMI). I chose to leave diabetes status in the non-laboratory model given the elevated risk of diabetic patients and the ability to diagnose diabetes at the point of care in low-resource settings.[15, 171]

This chapter was possible through the support of Professor Rod Jackson and the use of the New Zealand PREDICT dataset. It involved me travelling to Auckland, New Zealand, to establish the research collaboration and to study under Professor Jackson and his team.

7.2 Aim and Objectives

7.2.1 Aim

The aim of this chapter was to determine the degree to which replacement of TC:HDL with BMI in a CVD prognostic model affected clinically meaningful performance.

7.2.2 Objectives

To achieve this aim, the objectives of this chapter were to:

1. Develop two CVD risk prediction models using a contemporary cohort:
 - Laboratory-based Risk Assessment (LaRA) with the following predictor variables: age, gender, smoking, blood pressure lowering treatment

(BPLT), systolic blood pressure (SBP), diabetes status, and TC:HDL ratio

- Consultation-based Risk Assessment (CoRA) with the following predictor variables: age, gender, smoking, BPLT, SBP, diabetes status, and BMI

2. Comparatively evaluate their statistical and clinical performance

7.3 Methods

This chapter followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[172] Specifically, this study was a multivariable prognostic modelling study type 2b whereby a single cohort was non-randomly split into two groups for developing and ‘validating’ the models.[172]

7.3.1 Source of Data

The PREDICT Cardiovascular Disease Cohort in New Zealand Primary Care, described elsewhere, was used for the development and comparative evaluation of the risk scores.[173] The cohort was established in 2002 to research CVD risk assessment and management in primary care, and in particular to develop and validate CVD risk scores for New Zealand. Recruitment into the cohort occurs when doctors conduct a CVD risk assessment at their own discretion, and the parameters of the risk score are captured as the baseline risk factor measurements. These baseline data are linked through a national unique patient identifier (National Health Index number) to medication dispensing, laboratory testing, hospitalisations, and deaths. Patients with existing or incident CVD are identified through a combination of general practice data, hospitalisations, and pharmaceutical dispensing information.[173] Since recruitment into the cohort requires a completed CVD risk assessment, there are nearly no missing data for Framingham-risk factors. Cohort accrual and follow-up remains ongoing to at least 2020.

7.3.2 Participants

As described above, participants originate from participating general practices. Approximately 40% of all New Zealand general practices are recruitments sites, and the cohort is seen to be representative of New Zealanders eligible for CVD risk assessment.[173] Using the PREDICT database, adult patients aged 30-74 were included if they were free from CVD at baseline and had a recorded BMI measurement. Since BMI was not included as part of the baseline CVD risk assessment, not all patients in the cohort have a documented BMI.

Previous CVD was determined through a mix of general practice data, hospitalisation records, and medication dispensing information, and was defined as a history of: angina, ischaemic heart disease, transient ischaemic attack, cerebrovascular disease, or peripheral vascular disease.

7.3.3 Outcome

The outcome was a composite of fatal and non-fatal atherosclerotic-related CVD events. This was determined from national hospitalisation and mortality datasets using the International Classification of Diseases, version 10 Australian Modification (ICD-10 AM).[173] The exact list of these ICD-10 AM codes are included in Appendix F. The broad categories which defined a CVD event were: myocardial infarction, unstable angina, other coronary heart disease, ischaemic stroke, hemorrhagic stroke, transient ischaemic attack, peripheral vascular disease, congestive heart failure, and other ischaemic CVD-related deaths (Appendix F).

7.3.4 Predictors

Predictor variables were specified a priori. Both models (LaRA and CoRA) included the following predictor variables: age, gender, smoking, BPLT within the last six months, SBP, and diabetes status. The laboratory-dependent risk assessment model (LaRA) included TC:HDL; the consultation-dependent risk assessment model (CoRA) included BMI (Table 7.1).

Table 7.1: Predictor variables used in the laboratory-dependent (LaRA) and consultation-dependent (CoRA) risk models

Model	Predictor Variables							
	Age	Gender	Smoking	BPLT	SBP	Diabetes	TC:HDL	BMI
LaRA	◆	◆	◆	◆	◆	◆	◆	
CoRA	◆	◆	◆	◆	◆	◆		◆

Age in units of years (continuous); Gender in binary options of male or female; Smoking in binary options of current smoker or non-smoker; BPLT = blood pressure-lowering treatment, in binary options of yes or no; SBP = systolic blood pressure, in units of mmHg (continuous); Diabetes in binary options of diabetic or non-diabetic, TC:HDL = total cholesterol to high-density lipoprotein ratio, no units (continuous); BMI = body mass index in units of kg/m² (continuous)

All predictors except BMI were captured from the initial risk assessment done at the time of recruitment into the cohort. BMI was recorded by dividing the most recent body mass (kg) by the square of height (m) at the time of index assessment. Age in years (continuous) was determined from the participant's date of birth using the National Health Index dataset, which was linked to PREDICT. Current smokers or those who had quit within 12 months were coded as smokers; those who had never smoked or had quit for longer than 12 months were coded as non-smokers. Current BPLT was defined as a participants who had been dispensed BPLT within the previous six months. SBP in mmHg was the mean of the two most recent measurements at the time of the index assessment for recruitment into the cohort. Participants were coded as diabetic if they had type one or two diabetes, or if they had a documented hospitalisation for diabetes or were prescribed diabetic medications prior to the index assessment. TC:HDL ratio was determined from the most recent fasting or non-fasting measure at the time of index assessment; the measurements were done in community laboratories. The management and cleaning of these and other data was done by the PREDICT data management team.

7.3.5 Sample Size

All patients in the PREDICT cohort that met inclusion criteria on 31 December 2015 were selected for inclusion. There was no minimum follow-up time required for inclusion in the cohort.

7.3.6 Missing Data

Only complete cases were used; participants with one or more missing value for any required predictor were excluded.

7.3.7 Train and Test Cohorts

After applying inclusion criteria, the cohort was non-randomly geographically split into a ‘train’ and ‘test’ cohort based on the District Health Board area in which a participant resided. District Health Boards were allocated in their entirety to either the train or test cohort on the basis of achieving an approximately equal number of participants in each cohort. The train cohort was used to develop the models and the test cohort was used to assess their performance.

7.3.8 Statistical Analysis

All statistical analyses were done using R.[127] Cox proportional hazard models were used to model the time to first fatal or non-fatal CVD event.[174] Participants who died before experiencing a fatal or non-fatal CVD event were censored at the time of death. Participants who did not experience a CVD event were censored at the time of last observation. Covariates were not centred for the model.

Interaction terms were tested based on known possible interactions and clinical plausibility. Interactions were included in the final models if the statistical significance of their interaction was $p < 0.001$, except for the interaction between diabetes and sex due to a well-established precedent for inclusion.[168, 175, 176]

Non-linearity was assessed by visual inspection of LOWESS smoothed plots of martingale residuals versus the respective continuous variable.[177] The proportional hazard assumption was assessed by visual inspection of scaled Schoenfeld residual plots.[178]

Five-year absolute risk was calculated by estimating the baseline survival function at five years (using non-centred covariates). I chose five-year risk scores because it is a clinically relevant timeframe and because it was known that few patients in the cohort would have 10 or more years of follow-up time.

Model discrimination was assessed using Harrell's C statistic[179] and by plotting proportion of all observed 5-year CVD events by decile of predicted risk. Calibration plots were made by grouping all participants in the test cohort by decile of predicted 5-year risk and plotting the predicted vs observed 5-year risk by decile.

Reclassification tables stratified by individuals who did and did not have an event (within 5 years) were constructed to comparatively assess model discrimination. In such an analysis a model 'performs' better if it reclassifies individuals who had an event ('E=1') into higher risk categories ('up') and those who did not ('E=0') into lower categories ('down'). The net movement of individuals can be summarised by net reclassification improvement (NRI), which is the sum of the event NRI (NRI_e) and non-event NRI (NRI_{ne}). NRI_e is defined as the difference in proportions of individuals up-classified and down-classified, amongst those who had CVD events. Likewise, NRI_{ne} is the difference in proportions of individuals down-classified and up-classified, amongst those who did not have CVD events.[27] NRI is therefore defined[180] as:

$$NRI = NRI_e + NRI_{ne}$$

$$NRI = [P(\text{up} | E=1) - P(\text{down} | E=1)] + [P(\text{down} | E=0) - P(\text{up} | E=0)]$$

Sensitivity and specificity was calculated by dichotomising the testing cohort into 'high' and 'low' predicted 5-year risk (index test) and categorising into individuals who did and did not have an event within 5 years (reference test). This was done at three clinically meaningful thresholds of 5, 10, and 15% 5-year risk.

7.3.9 Ethical Approval

This study fell within the remit of the PREDICT research programme, which was approved by the Northern Region Ethics Committee Y in 2003 (AKY/03/12/314) with subsequent annual approval by the National Multi Region Ethics Committee since 2007 (MEC07/19/EXP). When I was not in New Zealand, all analyses were done using a virtual private network and secure virtual machine which was accessed remotely from Oxford, so as to ensure no patient data were at risk.

7.4 Results

7.4.1 Participants

After excluding participants with existing CVD ($n=55,260$), missing risk factor measurements ($n=60$), those aged <30 or >74 years ($n=21,299$), or those with no recorded BMI ($n=90,548$), a total of 326,827 participants were included in the study (Figure 7.1).

Non-random geographical splitting into the train and test cohorts achieved two groups of similar size: 163,644 and 163,183 individuals, respectively (Figure 7.1). The geographical distribution of the District Health Boards are illustrated in Figure 7.2. Important non-random differences were observed between the test and train cohorts. There were fewer men but more events in the test cohort, and a larger proportion of Maori, Pacific, and Indian individuals (Table 7.2). In terms of risk factors, the test cohort had a greater proportion of diabetic individuals and smokers, and those on BPLT. Systolic blood pressure, BMI, and TC:HDL ratio were similar between the train and test cohorts (Table 7.2). The train and test cohorts had a crude CVD incidence of 9.79% (95% CI 9.57, 10.0) and 11.6% (95% CI 11.3, 11.8) per 1000 person-years, respectively (Table 7.2).

7.4.2 Model Development and Specification

The unadjusted associations between each predictor variable and outcome are reported in Table 7.3. All continuous variables were positively associated with the outcome. With respect to binary variables, male sex, smoking, BPLT, and diabetes were positively associated with the outcome.

The full models for LaRA and CoRA, including interaction terms, are reported in Table 7.4. No continuous variables were transformed based on satisfactory visual inspection of martingale residual plots. Visual inspection of scaled Schoenfeld residual plots provided strong evidence to support the proportional hazard assumption. Martingale residual plots and scaled Schoenfeld residual plots for each model are included in Appendix F. The baseline survival function at five years for LaRA

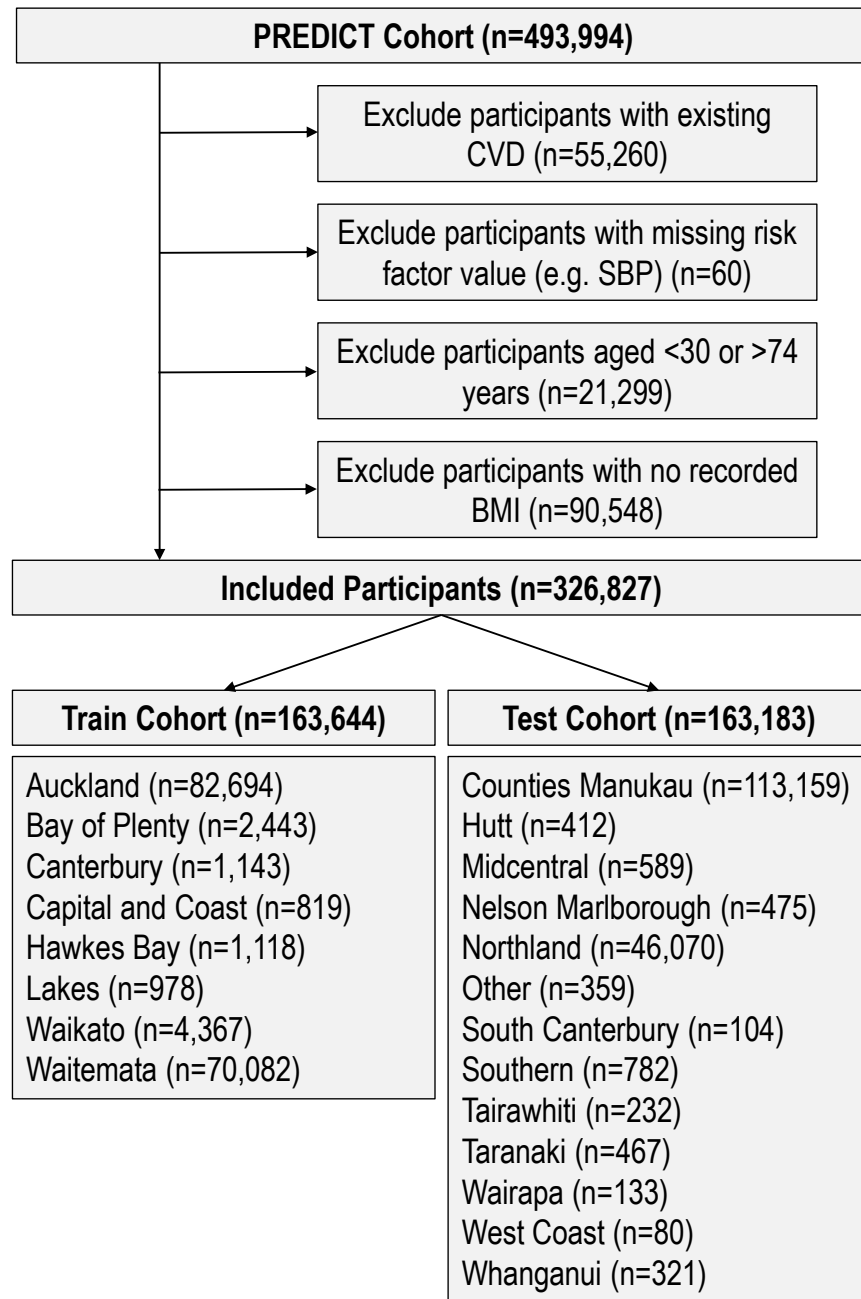


Figure 7.1: Flow chart of included participants and allocation of District Health Boards to either the train or test cohort

Table 7.2: Description and summary statistics of the train and test cohorts

	Train Cohort (n=163,644)	Test Cohort (n=163,183)
Men (% [95% CI])	94,287 (57.6 [57.4, 57.9])	90,325 (55.4 [55.1, 55.6])
Incident CVD events (% [95% CI])	7,053 (4.31 [4.21, 4.41])	8,070 (4.9 [4.8, 5.1])
Total person-years observation	720,067	697,820
Crude incidence per 1000 person-years (95% CI)	9.79 (9.57, 10.0)	11.6 (11.3, 11.8)
Mean follow-up time in years (SD)	4.4 (2.85)	4.23 (2.50)
Median Age (IQR)	54 (46-61)	53 (46-61)
Ethnicity (% [95%CI])		
European/Other	93,661 (57.2 [57.0, 57.5])	79,861 (48.9 [48.7, 49.2])
Maori	15,023 (9.2 [9.0, 9.3])	29,736 (18.2 [18.0, 18.4])
Pacific	19,165 (11.7 [11.6, 11.9])	27,355 (16.8 [16.6, 16.9])
Indian	14,135 (8.6 [8.5, 8.8])	15,099 (9.3 [9.1, 9.4])
Asian	9,140 (5.6 [5.5, 5.7])	5,326 (3.3 [3.2, 3.4])
Chinese	12,520 (7.7 [7.5, 7.8])	5,806 (3.6 [3.5, 3.6])
Smoking (% [95% CI])	21,044 (12.9 [12.7, 13.0])	29,236 (17.9 [17.7, 18.1])
Diabetes (% [95% CI])	28,245 (17.3 [17.1, 17.4])	33,443 (20.5 [20.3, 20.7])
Mean SBP (SD)	129 (17)	130 (17.4)
Mean BMI (SD)	28.7 (6.46)	30.2 (7.10)
Mean TC:HDL (SD)	4.10 (1.23)	4.18 (1.28)
Current or prior BPLT in last six months (% [95% CI])	38,435 (23.5 [23.3, 23.7])	44,200 (27.1 [26.9, 27.3])

Table 7.3: Univariate association of each predictor variable with the outcome

Variable	Coefficient	Hazard Ratio (95% CI)	p-value
Age (per year)	0.05700	1.059 (1.056, 1.061)	p <0.001
Sex Male	0.2710	1.311 (1.249, 1.376)	p <0.001
Smoker	0.4656	1.593 (1.502, 1.690)	p <0.001
BPLT	0.9183	2.505 (2.388, 2.628)	p <0.001
BMI (per kg/m ²)	0.02687	1.027 (1.024, 1.030)	p <0.001
SBP (per mmHg)	0.01933	1.020 (1.018, 1.021)	p <0.001
Diabetes	0.7805	2.183 (2.079, 2.291)	p <0.001
TC:HDL (per 1 unit)	0.09305	1.098 (1.079, 1.116)	p <0.001

Table 7.4: Coefficients, hazard ratios, and interaction terms for LaRA and CoRA

Variable	LaRA			CoRA		
	Coefficient	Hazard Ratio (95%CI)	p-value	Coefficient	Hazard Ratio (95% CI)	p-value
Age (per year)	0.146	1.16 (1.14, 1.18)	<0.001	0.159	1.17 (1.15, 1.20)	<0.001
Sex Male	0.507	1.66 (1.56, 1.77)	<0.001	0.577	1.78 (1.67, 1.89)	<0.001
Smoker	0.621	1.86 (1.75, 1.98)	<0.001	0.65	1.92 (1.80, 2.03)	<0.001
BPLT	1.44	4.23 (2.93, 6.12)	<0.001	1.32	3.73 (2.58, 5.39)	<0.001
SBP (per mmHg)	0.0485	1.05 (1.04, 1.06)	<0.001	0.0446	1.05 (1.04, 1.05)	<0.001
Diabetes	1.834	6.27 (4.52, 8.68)	<0.001	1.59	4.92 (3.54, 6.85)	<0.001
TC:HDL Ratio (per 1 unit)	0.125	1.13 (1.12, 1.15)	<0.001	-	-	-
BMI (per kg/m ²)	-	-	-	0.0625	1.06 (1.05, 1.08)	<0.001
Interactions						
Age:SBP	-0.0006	0.9994 (0.9993, 0.9995)	<0.001	-0.00055	0.9995 (0.9993, 0.9996)	<0.001
Age:DM	-0.0202	0.9801 (0.9749, 0.9852)	<0.001	-0.01722	0.9829 (0.9777, 0.9882)	<0.001
Male:DM	-0.178	0.8372 (0.7570, 0.9260)	<0.001	-0.1519	0.8591 (0.7768, 0.9501)	0.00312
BPLT:SBP	-0.00678	0.9932 (0.9906, 0.9959)	<0.001	-0.0063	0.9937 (0.9911, 0.9964)	<0.001
Age:BMI	-	-	-	-0.00068	0.9993 (0.9990, 0.9996)	<0.001
Baseline Survival Function						
At 5 years	LaRA	0.9999995		CoRA	0.9999998	

and CoRA was 0.9999995 and 0.9999998, respectively (when all covariates equal to zero). An example calculation of 5-year risk is included in Appendix F. The median predicted risk for the test cohort using LaRA and CoRA was 2.93% (IQR 1.49, 5.78) and 2.98% (IQR 1.54, 5.88), respectively.

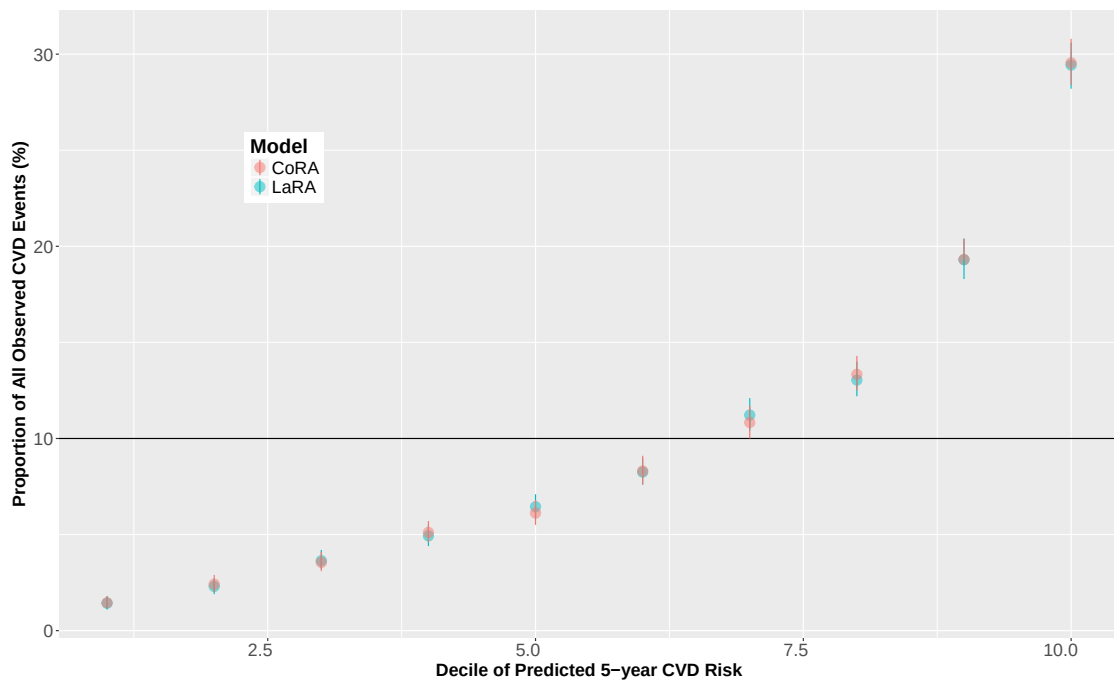
7.4.3 Model Performance

The Harrell's C measure of discrimination showed good model discrimination for both LaRA and CoRA, and this measure was not significantly different between the two models: 0.722 (95% CI 0.714, 0.730) and 0.721 (95% CI 0.713, 0.729), respectively. Discrimination of LaRA and CoRA in the test cohort was assessed visually by plotting the proportion of all observed CVD events by decile of predicted risk (Figure 7.3). For both LaRA and CoRA, half of all observed events occurred in the top two deciles of predicted risk and the proportion of all events was positively correlated with decile of predicted risk (Figure 7.3). Visual inspection also showed no significant difference in the discrimination of LaRA and CoRA. The number of participants, the mean predicted risk, expected number of events, and observed number of events are summarised in Table 7.5.

Visual inspect of model calibration showed no significant difference in calibration between LaRA and CoRA (Figure 7.4). Both models tended to overestimate

Table 7.5: Values used for calibration and discrimination plots

Laboratory-based Risk Assessment - LaRA					
Decile of Predicted Risk (n)	Predicted Data		Number of Observed Events (N=5,658)	Observed Data (5-year Outcome)	
	Mean Predicted 5-year Risk	Number of Expected Events (N=7,070)		Percent of All Observed Events (95%CI)	Observed 5-year risk (95% CI)
1 (16,319)	0.618	101	81	1.43 (1.10, 1.80)	0.50 (0.40, 0.60)
2 (16,319)	1.08	176	130	2.30 (1.90, 2.70)	0.80 (0.70, 0.90)
3 (16,317)	1.50	244	206	3.64 (3.20, 4.20)	1.26 (1.10, 1.40)
4 (16,318)	1.98	323	279	4.93 (4.40, 5.50)	1.71 (1.50, 1.90)
5 (16,319)	2.58	422	365	6.45 (5.80, 7.10)	2.24 (2.00, 2.50)
6 (16,319)	3.35	546	467	8.25 (7.60, 9.00)	2.86 (2.60, 3.10)
7 (16,317)	4.37	713	635	11.2 (10.40, 12.1)	3.89 (3.60, 4.20)
8 (16,320)	5.81	949	738	13.0 (12.2, 14.0)	4.52 (4.20, 4.90)
9 (16,316)	8.08	1,318	1,092	19.3 (18.3, 20.4)	6.69 (6.30, 7.10)
10 (16,319)	14.0	2,278	1,665	29.4 (28.2, 30.6)	10.2 (9.70, 10.7)
Consultation-based Risk Assessment - CoRA					
Decile of Predicted Risk (n)	Predicted Data		Number of Observed Events (N=5,658)	Observed Data	
	Mean Predicted 5-year Risk	Number of Expected Events (N=7,070)		Percent of All Observed Events (95%CI)	Observed 5-year risk (95% CI)
1 (16,320)	0.632	103	82	1.45 (1.20, 1.80)	0.50 (0.40, 0.60)
2 (16,317)	1.11	182	137	2.42 (2.00, 2.90)	0.84 (0.70, 1.00)
3 (16,318)	1.54	251	201	3.55 (3.10, 4.10)	1.23 (1.10, 1.40)
4 (16,319)	2.03	331	289	5.11 (4.60, 5.70)	1.77 (1.60, 2.00)
5 (16,318)	2.63	430	346	6.12 (5.50, 6.80)	2.12 (1.90, 2.40)
6 (16,318)	3.40	555	470	8.31 (7.60, 9.10)	2.88 (2.60, 3.20)
7 (16,318)	4.44	724	613	10.8 (10.0, 11.7)	3.76 (3.50, 4.10)
8 (16,318)	5.91	964	755	13.3 (12.5, 14.3)	4.63 (4.30, 5.00)
9 (16,318)	8.23	1,343	1,093	19.3 (19.3, 20.4)	6.70 (6.30, 7.10)
10 (16,319)	14.2	2,313	1,672	29.6 (28.4, 30.8)	10.3 (9.80, 10.7)

**Figure 7.3:** Proportion of all observed events (with 95% CIs) by decile of predicted 5-year risk. The solid black line at $y=10\%$ indicates a model with no discrimination

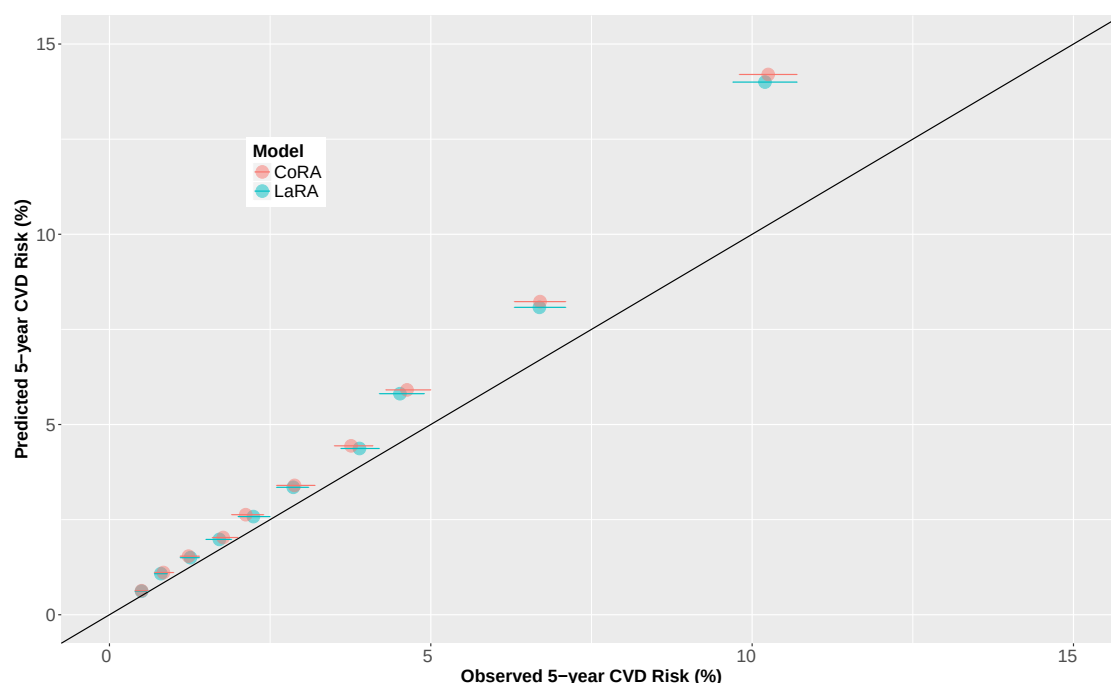


Figure 7.4: Observed 5-year risk (with 95% CIs) plotted against predicted 5-year risk, by decile of predicted risk. The solid black line indicates perfect calibration

risk by a similar magnitude.

There were no significant differences in sensitivity or specificity between LaRA and CoRA at all risk thresholds, with the exception of specificity at a 10% threshold definition which differed by 0.01 between the two models (Table 7.6). Sensitivity decreased with increasing 5-year risk threshold definitions for high-risk. The sensitivity at 5, 10, and 15% risk thresholds for LaRA and CoRA was 0.63 (95% CI 0.62, 0.63), 0.28 (95% CI 0.27, 0.29), 0.10 (95% CI 0.10, 0.11) and 0.64 (95% CI 0.63, 0.65), 0.30 (95% CI 0.29, 0.31), 0.12 (95% CI 0.11, 0.12), respectively (Table 7.6). Specificity showed the opposite trend; the specificity at 5, 10, and 15% risk thresholds for LaRA and CoRa was 0.72 (95% CI 0.71, 0.72), 0.92 (95% CI 0.92, 0.92), 0.98 (95% CI 0.97, 0.98) and 0.71 (95% CI 0.71, 0.71), 0.91 (95% CI 0.91, 0.91), 0.97 (95% CI 0.97, 0.97), respectively (Table 7.6).

Amongst individuals who had events ($n=5,658$) and who did not have events within 5 years ($n=157,525$), the NRI_e of CoRA in reference to LaRA was 2.19% (95% CI 1.83, 2.62) and the NRI_{ne} was -0.97% (95% CI -1.02, -0.93)(Table 7.7). The overall NRI of CoRA was 1.22% (95% CI 0.93%, 1.60%).

Table 7.6: Sensitivity and specificity of LaRA and CoRA at clinically relevant thresholds of 5, 10, and 15% predicted 5-year risk of a fatal or non-fatal CVD event

Performance Measure	5-year Risk Threshold		
	5%	10%	15%
Sensitivity (95% CI)			
LaRA	0.62 (0.61, 0.63)	0.28 (0.27, 0.29)	0.10 (0.10, 0.11)
CoRA	0.63 (0.62, 0.64)	0.29 (0.28, 0.30)	0.11 (0.10, 0.12)
Specificity (95% CI)			
LaRA	0.71 (0.71, 0.71)	0.91 (0.91, 0.91)	0.97 (0.97, 0.98)
CoRA	0.71 (0.70, 0.71)	0.91 (0.91, 0.91)	0.97 (0.97, 0.97)

Table 7.7: Reclassification table and net reclassification improvement (NRI) of CoRA with respect to LaRA in the test cohort (n=163,183)

CVD Event?	LaRA	CoRA				Net Reclassification (95% CI)	
		<5%	6-10%	11-15%	≥15%		
Yes (n=5,658)	<5%	1894	257	8	2	P(up)	0.122 (0.114, 0.131)
	6-10%	205	1452	249	21	P(down)	0.100 (0.0920, 0.108)
	11-15%	1	214	620	153	NRI _e	0.0219 (0.0183, 0.0262)
	≥15%	0	4	142	436		
No (n=157,525)	0-4%	107309	4567	84	48	P(up)	0.0548 (0.0537, 0.0559)
	5-9%	3815	25294	2606	156	P(down)	0.0451 (0.0440, 0.0461)
	10-14%	10	2223	6215	1171	NRI _{ne}	-0.00974 (-0.0102, -0.00927)
	≥15%	8	87	954	2978	NRI	0.0122 (0.00903, 0.0160)

7.5 Discussion

7.5.1 Summary of Findings

Two 5-year prognostic CVD risk models, Laboratory-based Risk Assessment (LaRA) and Consultation-based Risk Assessment (CoRA), were developed and comparatively evaluated to determine the degree to which replacement of cholesterol information (TC:HDL ratio) with BMI affected clinically meaningful performance of risk prediction. Data from the PREDICT New Zealand primary care database were used; after inclusion of patients aged 30-74 who were asymptomatic for CVD, 326,827 individuals were included in the analysis. The included population was spatially split into a train (n=163, 644) and test (n=163,183) cohort in which a crude incidence of CVD per 1,000 person-years of 9.79 (95% CI 9.57, 10.0) and 11.6 (95% CI 11.3, 11.8) was observed, respectively.

The median predicted risk for the test cohort using LaRA and CoRA was 2.93% (IQR 1.19, 5.78) and 2.98% (IQR 1.54, 5.88), respectively. Harrell's C and visual

inspection of discrimination plots showed good discrimination; for both LaRA and CoRA half of all observed events occurred in the top two deciles of predicted risk, and there was no difference in discrimination between the two models. There was no difference in calibration between the models: both similarly overestimated risk by the same magnitude, and the magnitude of over estimation was positively correlated with decile of predicted risk.

Sensitivity ranged from 0.64 to 0.10 and specificity ranged from 0.71 to 0.98 at threshold definitions of high risk of 5 and 15%, respectively. Overall the NRI of CoRA with respect to LaRA was 1.22% (95% CI 0.83%, 1.69%).

7.5.2 Interpretation of Findings

The significant demographic differences observed between the train and test cohort were expected. The purpose of spatially (i.e. non-randomly) splitting the cohort was to reduce the chance of over-estimating the performance of the prediction models. While the mean SBP, BMI, and TC:HDL were not significantly different between the two cohorts, the increased incidence of CVD in the test cohort might be attributed to the larger proportion of Maori, Pacific, and Indian peoples and significantly higher rates of smoking and diabetes.

The hazard ratios for BPLT and for diabetes in LaRA and CoRA were relatively high in comparison to the univariate analysis. This was attributed to the addition of interaction terms in the final models. It is also important to note that the hazard ratios are not based on centred covariates and therefore should be interpreted as the hazard ratio when all other covariates are equal to zero. Similarly, the baseline survival function was estimated when all covariates are equal to zero, rather than using centred variables.

The demographic differences between the train and test cohort may explain miss-calibration of LaRA and CoRA in the test cohort, and in this way may help approximate more closely an external validation. The relative discrimination and calibration of LaRA and CoRA showed that replacement of TC:HDL with BMI did not significantly attenuate model performance.

Comparison of the clinical performance of LaRA and CoRA also showed no significant difference between the two models. Sensitivity decreased and specificity increased equally for both models as the threshold definition of high risk increased from 5 to 15%, as would be expected by the change in relative proportion of those who were defined as high and low risk. Although not different between the two models, the range in sensitivity was quite large: from 0.10 to 0.63. This translates to anywhere from 90% to 37% of patients who had an event being defined as low risk, which may lead to under-treatment in practice. The range in specificity, which would relate to the amount of unnecessary treatment as a result of false positive definitions of high risk, was smaller: 0.71 to 0.97.

The NRI, which is a better measure of clinical performance than sensitivity and specificity, showed a slight increase in performance of CoRA in reference to LaRA. Although small in magnitude, the overall NRI of +1.22% meant that a greater proportion of individuals who had a CVD event were up-classified at least one risk category relative to individuals who did not have an event, when CoRA was used for risk classification, relative to LaRA.

7.5.3 Findings in the Context of Existing Research

While other studies have developed and evaluated non-laboratory based CVD risk scores, this study is unique from the existing literature for three main reasons.[34, 168, 170, 181–183] First, the cohort used is the largest and most contemporary to date. Previous studies of non-laboratory risk scores have ranged in size from 689 to 65,560 individuals with baseline measurements ranging from 1968 to 2001.[170] This study included five times that of the largest previous study (n= 326,827) and was the first to use data from New Zealand. Second, previous studies have compared models which replace total cholesterol with BMI, but not replacement of TC:HDL ratio.[167] Given that TC:HDL is a better predictor than total cholesterol, it was novel and relevant to comparatively assess its replacement with BMI.[169] Third, previous studies assessed the predictive performance from a statistical and population level, using metrics such as C-statistic and calibration and discrimination

plots. While these measures are standard performance metrics, this study extended previous work by also evaluating the differences between the models using measures of NRI, sensitivity, and specificity.

In comparison to non-laboratory 5-year CVD risk scores developed by Gaziano et al., which replaced total cholesterol with BMI, the sensitivity of LaRA and CoRA were markedly lower. For example, at a 10% 5-year risk definition of high risk, the sensitivity of the non-laboratory Gaziano score in women and men was 0.54 (95% CI 0.50, 0.57) and 0.60 (95% CI 0.57, 0.64), respectively.[167] The sensitivity of LaRA and CoRA at the same threshold definition was 0.28 (95% CI 0.27, 0.29) and 0.29 (95% CI 0.28, 0.30). The difference in sensitivity could be attributed to several causes. First, the populations used were not directly comparable. Gaziano et al. used a population of 6,186 individuals from the National Health and Nutrition Examination Survey Follow-up Study (NHEFS) cohort in America, whose baseline risk factors were measured in the early 1970's.[167] Second, it was unclear how some of the predictor variables were defined (e.g. history of blood pressure treatment) and therefore how they compare to the predictor variables used in LaRA and CoRA. Third, differences in the outcome definition may have affected the performance; it is possible that the methods used to defined outcomes in the PREDICT cohort were less crude than those used in NHEFS.

7.5.4 Strengths and Limitations

In addition to being strengthened by its sample size, complete case analysis, and contemporary data, this study was also strengthened by the number of CVD events observed. In the train cohort, there were a total of 7,053 events, which equated to just over 1,000 events per predictor variable. This was two orders of magnitude greater than the generally accepted adequacy of 10 outcome events per predictor variable.[184] An additional strength was the assessment of the models using NRI, which had previously not been reported for non-laboratory CVD risk scores in the literature.[170] That being said, no single measure is sufficient to assess performance and there are several limitations to NRI. First, the definitions of categories used

to make reclassification tables are not necessarily clinically relevant, and therefore movement between these categories may likewise not be relevant.[185] For example, if the CVD risk threshold for treatment is 20% movement between categories above or below 20% are not relevant with respect to treatment. For this reason, I have also reported sensitivity and specificity as measures of performance because they use a single threshold which can be chosen based on clinical relevance. Second, NRI, unlike other measures of discrimination, is influenced by model miscalibration.[185]. Third, NRI on its own does not give a direct measure of false-positive rate and false-negative rate, and it weights both equally. For this reason it may be more useful to report event NRI and non-event NRI separately, as done in this Chapter.[186]

While external validation was not performed, it was not necessary for the primary purpose of the study, which was to comparatively evaluate the performance of the two risk models. Given the large sample size and number of events, it was possible to spatially split the cohort into two distinct populations, which reduced the chance of over-estimating the performance of the models. None-the-less it is unknown whether the relative performance of the two models would be similar in an external cohort, not least in a low-resource population.

Temporal, rather than spatial, splitting may have provided more distinct differences between the two cohorts, and therefore possibly a less optimistic estimation of model performance. Temporal splitting was not done because the cohort grew exponentially since its inception. Therefore, splitting the cohort into two groups of equal size based on the date of inception into the cohort would have left one cohort with relatively short (e.g. three years) follow-up. Spatial splitting of the cohort was seen as sufficient for the comparative assessment of the two models.

CVD risk scores, in general, have limitations, and do not perform risk prediction well.[187] Existing scores, including the ones developed here, assume the effect of a risk factor is constant through time and that the interaction terms are likewise constant through time, which may not be true.[26] Most, if not all CVD risk scores, also do not account for treatment initiated during the follow-up period.[188] By their nature, CVD risk scores have an inherent element of time, and there is

also no consensus on the relative meaningfulness of various follow-up times, for example five, ten, or lifetime risk scores. Furthermore, risk scores are limited in the sense that they need to be understood and used by clinicians, which is a known barrier to their implementation.[140]

Lastly, the characteristics of participants excluded from the analysis because of a missing BMI measurement were not described, which may limit the generalisability of the findings.

7.5.5 Implications for Research and Practice

LaRA and CoRA were not developed for use in clinical practice. The purpose of this study was to examine more fundamentally the ability to simplify TC:HDL-dependant risk scores with BMI. The findings of this study may, however, support the use of existing CVD non-laboratory risk scores which replace total cholesterol with BMI. Future research should aim to externally validate the risk scores using a cohort from a low-resource population, and compare them to existing models using NRI. More broadly, future research on simplifying CVD risk scores could explore self-assessment models which do not require medical consultation, and their role in a staged risk assessment approach. From my experience working with refugees (Chapters 5 and 6), I saw a role for very basic self-assessment or lay-person-mediated assessment which could be done as a first step before consulting primary care. This would likely require simplification of risk scores to not include blood pressure and diabetes; the impact of which is currently unknown. It is possible that the relative clinical utility of simplified risk scores depends on the definition of high risk, so future work may consider exploring the net benefit at thresholds used in clinical practice.[189, 190]

7.6 Conclusions

Laboratory-dependent CVD risk scores can be simplified by replacing TC:HDL ratio with BMI without significant attenuation in statistical or clinical performance. While previous studies have shown the ability of BMI to replace total cholesterol, this is the first to show its ability to replace the more relevant predictor of TC:HDL ratio.

Overall this work supports the use of other non-laboratory CVD risk scores which use BMI, and an overall approach which can be done in a single consultation using routine clinical data.

7.7 Chapter Summary

- Two CVD risk scores, Laboratory-dependent Risk Assessment (LaRA) and Consultation-based Risk Assessment (CoRA), were developed and comparatively evaluated to determine the effect of replacing TC:HDL ratio with BMI on clinically meaningful performance
- Data from 326, 827 individuals from the New Zealand PREDICT cohort were included in the analysis and spatially split into a train (n=163, 644) and test (n=163,183) cohort
- CoRA performed equally as well or better than LaRA in all statistical and clinical measure of performance: discrimination, calibration, NRI, sensitivity, and specificity
- Overall, this Chapter provided support for the simplification of CVD risk scores by using BMI to replace a TC:HDL covariate; future studies should compare the clinical performance of CoRA with other non-laboratory in an external cohort from a low-resource setting

8

Discussion and Conclusions

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8.1 Introduction

Due to its immense contribution to the global burden of disease,[6–9] the United Nations continues to prioritise the prevention of cardiovascular disease (CVD). CVD risk stratification in primary health care to manage those with high CVD risk is central to the World Health Organisation’s (WHO’s) global strategy on non-communicable diseases (NCDs).[191–193] In their first global assessment of national capacity for the prevention and control of NCDs, the WHO specifically assessed the implementation of CVD risk assessment in primary health care. The report found large implementation gaps in low- and middle-income countries (LMIC): 79% of countries reported that fewer than 25% of primary health care facilities offered CVD risk assessment, with over half of these countries having no facilities offering risk

assessment.[192] The large implementation gaps, magnitude of the disease burden, and the WHO's mandate and endorsed strategy for using CVD risk assessment in primary health, means that huge efforts are underway to implement CVD risk assessment in low-resource settings.[21, 162, 192–194] It is within this context that the findings of my thesis are situated today. At its outset, the aim of this thesis was to examine the use of total cardiovascular risk scoring for the prevention of CVD in low-resource settings. The overarching hypothesis was that cardiovascular risk scoring was sub-optimal for the prevention of CVD in low-resource settings.

8.2 Summary of Findings

Chapter 1 presented the structure and overview of this thesis, and highlighted key accomplishments. Chapter 2 provided background information and set the foundation of the thesis by discussing and summarising key concepts, existing work, and overall rationale.

The aim of Chapter 3 was to determine the impact of cardiovascular risk scores on meaningful patient outcomes when used for primary prevention in adults, as reported by existing systematic reviews. Six systematic reviews were identified, but when quality assessed they were generally poor in quality. None of the reviews reported CVD-related morbidity or mortality as outcomes and none of the primary studies were done in low-resource settings. Studies did report improvements in systolic blood pressure (SBP), total cholesterol, low-density lipoprotein (LDL) cholesterol, and smoking but when meta-analysed and quality assessed using GRADE, the findings did not appear to be clinically significant. Moreover, when looking at the populations from which the evidence was derived, all studies were from seven high-income countries, which together represented only three (of 14) epidemiological subregions of the world. The main conclusion of this chapter was that further RCTs are likely needed in low-resource settings since the evidence from high-income settings was of low-quality and not generalisable to low-resource settings.

The aim of Chapter 4 was to develop a standardised, open-source software to calculate WHO/International Society of Hypertension (WHO/ISH) CVD risk

scores. An R package, called `whoishRisk`, was developed and validated to calculate WHO/ISH risk scores for any epidemiological subregion of the world.[2] `whoishRisk` contains one function, called `WHO_ISH_Risk()`, which requires seven parameters: age, gender, systolic blood pressure, smoking status, diabetes status, total cholesterol, and epidemiological subregion. `whoishRisk` is freely available and can be downloaded directly from github using `install_github("DylanRJCollins/whoishRisk")`.

The aim of chapter 5 was to quantitatively evaluate the implementation of total CVD risk scoring and risk-based management using routine clinical data in Médecins Sans Frontières (MSF's) NCD mission. The study setting was in Irbid, a city in Northern Jordan on the border with Syria, where MSF had been asked by the Jordanian Ministry of Health to set up two NCD-focused primary health care clinics for Syrian refugees. Over the first year of implementing WHO/ISH CVD risk scores and risk-based guidance, significant screening and treatment gaps existed amongst the eligible patient population. Although 80.1% of patients who required risk assessment had a cholesterol measurement, only 27.6% of patients with a cholesterol measurement had a documented risk score, and many of the documented risk scores were incorrect. Just under half of eligible patients and one-fifth of ineligible patients based on their WHO/ISH risk were prescribed lipid-lowering treatment (LLT), despite it being freely available from MSF.

The aim of Chapter 6 was to explain the quantitative findings of Chapter 5 and identify opportunities to improve the implementation of WHO/ISH CVD risk scores. To do this I conducted in-person one-on-one semi-structured interviews with MSF staff in the primary health care centres in Jordan. Providers had confusion about when and how to use the risk charts, tended to favour lifestyle intervention over drug treatment, and had uncertainty about the role of LLT in primary but not secondary prevention. Patients were reluctant to start, stop, or change medication and were less able to modify risk factors and benefit from health education because of their social and economic context. Integration of the quantitative and qualitative findings helped identify opportunities to improve implementation, including: detailed practical training on calculating risk scores

and measurement of risk factors; integration of a total CVD risk approach with the role of nurses; contextualising risk scores in a broader risk assessment algorithm that can be conducted within a single consultation; and greater engagement with patients in the organisation and planning of care.

The aim of Chapter 7 was to determine the degree to which replacement of a contemporary measure of cholesterol – TC:HDL ratio – with BMI in a CVD prognostic model affected the performance of risk prediction. To do this I developed and comparatively evaluated two CVD risk scores, Laboratory-dependent Risk Assessment (LaRA) and Consultation-based Risk Assessment (CoRA). Data from 326,827 individuals from the New Zealand PREDICT cohort were included in the analysis and spatially split into a train (n=163, 644) and test (n=163,183) cohort. CoRA performed equally as well or better than LaRA in all statistical and clinical measure of performance: discrimination, calibration, sensitivity, specificity, and net reclassification improvement. Overall, this work provided initial support for the simplification of CVD risk scores using BMI rather than TC:HDL as a predictor variable without attenuation of performance. In the future this may be extended to simplify laboratory-dependent scores such that they can be used in a single consultation without laboratory measurements.

8.3 Implications for Policy, Practice, and Patients

8.3.1 Policy

Given the paucity of evidence for the effectiveness of CVD risk scoring in low-resource settings, my recommendations for policy-makers are focused on the generation and judicious use of local evidence.[1] I propose five-steps for policy-makers to consider if they choose to implement CVD risk assessment for the prevention of CVD in a low-resource setting (Figure 8.1). These five steps expand on the principles of pragmatic trials, which involve testing interventions in routine clinical practice settings that are diverse and representative of the 'real world.'[195]

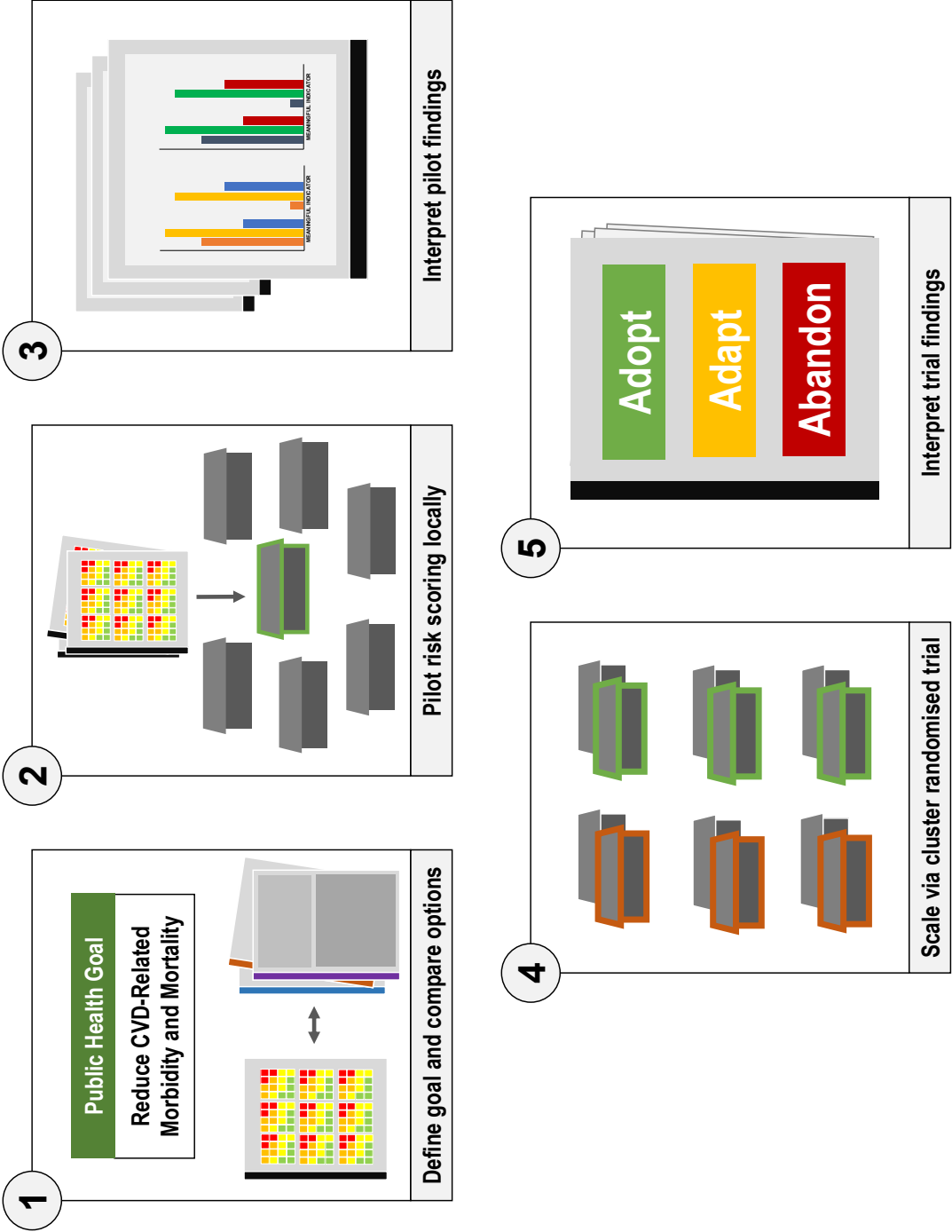


Figure 8.1: Five steps for policy-makers to consider when implementing cardiovascular risk scoring for the prevention of cardiovascular disease in low resource settings

Step One: Define goal and compare options

Policy-makers should clearly define their intended public health goal (i.e. to reduce CVD-related morbidity and mortality) and compare CVD risk assessment with other clinical and public health interventions, taking into consideration the entire health system and the unique context of their setting. Given that there are many cost effective interventions, including various forms of pharmacological interventions, tobacco control, mass media interventions, and legislative interventions, each option needs to be carefully considered in relation to the intended outcome and to each other.[196] Although a comprehensive approach may be ideal, it may not be feasible given resource levels.[197] Furthermore, there are many stakeholders of implementation, including governments, non-governmental organisations, and donors – each potentially with their own agendas. Having clearly defined objectives and public health policy goals can help policy-makers direct implementation and avoid ineffective interventions.[198]

Step Two: Pilot risk scoring locally

Before trialling or scaling up, interventions should be piloted and optimised for the local context.[199, 200] This allows for the early determination of how and why the intervention might fail, and provides an opportunity for corrective action.[201] There are many existing resources to facilitate implementation research and to plan pilot studies, including the Medical Research Council’s complex intervention guidance,[200] the WHO’s implementation research toolkit,[202] and more specifically the WHO’s guide to implementation research in the prevention and control of NCDs.[203] In my experience working with representatives from Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan, Turkey, Ukraine, and Uzbekistan on WHO PEN implementation, many found these resources abstract and look to detailed published examples

of how to evaluate a pilot study.¹ The continued development of the WHO HEARTS technical package may help to provide more detailed criteria for meaningful evaluation of pilot studies of CVD risk scores in low-resource settings, in addition the use of Chapters 5 and 6 of this thesis as a methodological case study.[204] Based on the findings of this thesis, those piloting CVD risk scoring may wish to consider the need for detailed practical training on calculating risk scores and measurement of risk factors, integration of a total CVD risk approach with the role of nurses, and contextualising risk scores in a broader risk assessment algorithm that can be conducted within a single consultation.

Step Three: Interpret pilot findings

Interpreting the findings of a pilot study is a nuanced task that requires expertise and there is a risk of misinterpretation of the findings, potentially causing the inappropriate cancellation or scale-up of the project. Since pilot studies are used to test and adapt an intervention to a local context, they typically use surrogate outcomes, are of short duration, and/or are under-powered.[201] This presents a risk that the findings are interpreted as evidence of effectiveness, and decisions to scale or cancel made on this basis. It is important for those in charge of the pilot study to be careful in the communication of the findings and the purpose of the pilot, and the use of significance testing or claims of effectiveness. It is also important to consider stakeholder views in decision making, including patients, providers, donors, and other partners; however, attempts should be made to mitigate the impact of conflicts of interest.[205] This can be done through the systematic declaration of conflicts of interest – a policy which is sometimes lacking in organisations responsible for guideline development.[206]

¹Through lecturing and facilitating at the “Workshop on Implementation of a Package of Essential Interventions for Noncommunicable Diseases (PEN) for Primary Health Care in Eastern Europe and Central Asia” in Helsinki, Finland (24-25 March 2017) and Samarkand, Uzbekistan (17-19 May 2016)

Step Four: Scale via cluster randomised trial

If the decision is made to scale-up, policy-makers may consider using a cluster-RCT given the need for evidence of effectiveness. There are three potential benefits to this approach: the ability to test the effectiveness of the intervention, limiting the initial cost of scaling up (relative to full national scale-up), and reducing the ethical risk of scaling an intervention that does not work.[207, 208] There is existing guidance from the WHO on how to develop a scale-up strategy which could be adapted to a cluster-randomised approach.[209] It is important to consider the need for check-points for de-adoption (or ‘reversal’) as evidence of effectiveness is generated, so as to limit harm if the intervention is not effective.[207] There are many strategies used to de-adopt ineffective practices in health care but no consensus approach.[210] In the context of a cluster-randomised scale-up this would involve stopping scale-up and reversing implementation, of which there are ethical grounds to do so if the intervention is ineffective.[207, 208]

Step Five: Interpret trial findings

The findings of the cluster randomised trial can be used to make an evidence-based decision on whether to adopt or abandon the intervention. This would involve comparing CVD risk scoring with other interventions to achieve reductions in CVD-related morbidity and mortality in light of the trial findings, with an eye for unintended consequences at a system-level.[211] In addition to the evidence itself, thorough decisions for adopting the intervention would take into account the expertise of the policy-makers and the perspectives of frontline clinicians. Policy-makers need be aware that the interpretation of scientific evidence requires specific expertise,[212] and may consider actively involving those with this expertise, such as academics, in key decisions. As in Step 3, those involved in decision making should declare their conflicts of interest to mitigate the bias of vested interests.

8.3.2 Investing in Information and Communications Technology

In order to enact the aforementioned five steps, and more broadly to conduct pragmatic clinical trials in low-resource settings, the role of information and communications technology (ICT) can not be overlooked. A major challenge in low-resource settings is the use of paper medical records and therefore the impractical nature of collecting large amounts of routine data. Given that pragmatic trials of CVD risk scoring would require the collection, management, and use of routine clinical data over a long period of time, electronic systems are needed. The aforementioned five steps should be interpreted in the context of needing significant investments in health care ICT.

8.3.3 Practice

In general, the implementation of risk scoring should not distract from the overall high-risk strategy for prevention of CVD events. There are potential unintended consequences that the implementation of CVD risk scoring distracts from simple but important forms of CVD risk assessment, such as the identification and management of secondary prevention patients who are at the highest risk and do not require risk scoring systems for risk assessment.[27] While the findings of this thesis call into question the impact of the prospective use of CVD risk assessment on important patient outcomes, they should not be misinterpreted as questioning the importance of total-risk based management. The question arising from these findings are not whether total-risk based management is effective, but if CVD risk assessment helps clinicians achieve this. In light of the findings of this thesis, clinicians may wish to consider using audit and feedback to improve the quality of risk assessment and adherence to CVD guidelines, pay closer attention to CVD risk communication, and task sharing with non-physicians staff, as henceforth described.

Audit and Feedback

Chapter 5 and 6, consistent with other studies, showed that many patients eligible for risk assessment were never risk assessed, and even of those risk assessed, most were done incorrectly.[132–135] Audit and feedback is one method clinicians may consider to improving quality of care, especially early in implementation.[213] Although the impact of this practice is potentially limited,[160] it may be effective when performance is initially low, the audit and feedback cycle is done more than once, with clear targets and action plans.[213] It is also a method that practitioners can do on their own with few resources, and in this sense may be a pragmatic choice in low-resource settings.

Risk Communication

Risk communication, and using CVD risk charts as a communication tool, was an important theme identified in Chapter 6. This is consistent with GPs in Australia, for example, who have been shown to use CVD risk assessment for the purposes of patient education, rather than for decision making.[155] A greater focus on the communication of risk in simple ways may improve the clinical utility of risk assessment.[55] Visual aids, including the strong use of colour and visualisations of natural frequencies, can help improve communication.[150, 152, 156] Otherwise, strategies include using numeric terms rather than descriptive terms (e.g. “high risk”), using a consistent numerical denominator for comparisons of risk, using absolute numbers but not number needed to treat, and assessing the patient’s own estimation of risk at baseline.[150, 214]

Task Sharing

Task sharing with nurses may play an important role in meaningful risk communication, given that in many settings nurses have more time with patients and are competent in health education and counselling. In MSF’s clinics, for example, nurses routinely used risk communication tools for blood sugar control, and they were eager to use the CVD risk charts to help with their health education sessions (Chapter

6). Although there is limited evidence on task sharing for CVD management in LMIC,[161] the WHO has recently published guidance on task sharing for total CVD risk assessment in low-resource settings,[162] and there is evidence to support the role of non-physician health workers conducting CVD risk assessments.[163]

8.3.4 Patients

While developing recommendations for patients was beyond the scope of this thesis, they are, of course, the beneficiaries of effective interventions to prevent CVD. In Chapter 6, there were important patient-centred themes that affected the use of total CVD-risk based guidance by clinicians. Popular health myths – untrue claims about health and treatments – were common and affected the willingness of patients to follow health advice from clinicians. This was not unexpected given the plethora of concepts that people need to understand to assess health claims,[212] but there are interventions to help, even in low-resource settings.[215–218] These include educational pamphlets on risk,[219] educational interventions to teach primary school children to assess health claims,[218] and even podcasts to teach adults to assess health claims about intervention effects.[217] Self-care for CVD is also an important up-and-coming field, but at this time there are few evidence-based self-care interventions.[220]

8.4 Future Research

Future research should focus on three main areas: randomised trials of the prospective use of CVD risk scores for the prevention of CVD in low-resource settings, external validation and head-to-head comparisons of the clinical performance of existing CVD risk scores, and the utility of risk scores at increasing clinician accuracy of risk estimation at varying threshold definitions of high risk.

With respect to the effectiveness of CVD risk assessment at reducing CVD-related morbidity and mortality; high quality cluster randomised trials are needed. Two RCTs identified by a recent Cochrane review that reported CVD events as outcomes showed no reduction in events, but these trials were underpowered and

of low GRADE quality.[93] Of the eight on-going or unpublished trials of CVD risk assessment that I am aware of, none have primary outcomes of CVD-related morbidity or mortality. [52–60] All but one of these trials were published in 2014 or later, at which point at least several systematic reviews showing a need for measuring CVD-related morbidity and mortality had been published.[1, 69, 71, 72, 221, 222] While it is challenging to measure CVD events as a primary outcome because of the sample size and follow-up time required, it is possible.[94] In their RCT of CVD risk assessment and health counselling, Jorgensen et al. estimated an intervention group sample size to detect a 15% difference in incident CVD over 10 years to be 8,140 (type 1 error rate of 0.05; power of 0.80).[94] This proved to be an impractically large sample; the trial was only able to recruit 6,091 participants and the final data were underpowered for CVD events. Despite the difficulty of such trials, they are needed, especially in low-resource settings because this is where the burden of CVD is highest and evidence of effectiveness is needed most. It is therefore worth considering a pragmatic approach which introduces randomisation to scaling-up the intervention as described in Section 8.3.1.

Despite the mass proliferation of CVD risk scores,[223] in general, CVD risk scores do not perform risk prediction well.[187] Whilst new forms of statistical computing may change this, the development of new risk scores is of lower priority relative to the need to simplify and externally validate existing scores, and to assess and compare their clinical utility. Existing comparisons of risk scores tend to use limited metrics of performance (e.g. area under a receiver operating characteristic curve); future work should seek to compare their clinical performance including net reclassification improvement and net benefit.[190] This should be done in particular for existing non-laboratory risk scores before more are developed. It will also be important to compare the net benefit of existing laboratory and non-laboratory risk scores across a range of treatment thresholds, because the performance of non-laboratory risk scores may depend on the threshold definition of high-risk.

Furthermore, there are a plethora of studies that assess the ability of clinicians to estimate total CVD risk.[145, 147, 224–227] These studies show that clinicians

do not intuitively assess total risk well, which would support the use of CVD risk scores. What is unknown, however, is whether the accuracy of total risk estimation by clinicians varies based on the risk definition of ‘high risk.’ Since treatment decisions are based on risk thresholds, the utility of CVD risk scores may depend on the risk threshold set to define high risk. For example, it may be easier for a clinician to distinguish patients above and below a 30% 10-year risk (which is the WHO-endorsed threshold for low-resource settings) than those above and below a 10% threshold, as used in the United Kingdom. This remains unknown, and in the first instance a systematic review needs to be conducted and subgroup analysis performed for varying definitions of high risk.

8.5 Overall Strengths and Limitations

This thesis is not without limitations. Whilst the methodological limitations of each study design are described in Chapters 3 to 7, more broadly there were three limitations to my thesis. First, I was only able to study the implementation of WHO/ISH CVD risk scores in one low-resource setting. It was not feasible to study more than one setting due to of the time required to broker international research agreements with multiple stakeholders, and because of limited financial resources. It is likely that studying additional low-resource settings would identify further barriers and opportunities for implementing CVD risk assessment. The mixed methods evaluation I conducted in Jordan should therefore be repeated in other jurisdictions implementing CVD risk assessment in primary care. Second, the cohort used in Chapter 7 was from New Zealand – a high-income setting. Whilst the purpose of the study was not to create new risk scores for use in low-resource settings, it is uncertain at this time if the findings would be consistent in cohorts from low-resource settings. The main challenge to doing so is the lack of high quality, prospective cohorts from these settings. Lastly, this thesis did not seek to include patients – an important stakeholder in implementation – in its assessment of CVD risk assessment for low-resource settings. Given the purpose of risk assessment is to improve patient

outcomes, research on the values and attitudes of patients towards CVD risk in different low-resource settings may shed new light on suitability of CVD risk scores.

The strengths of each study are described in their respective chapter. In general, this thesis was strengthened by its contributions of new knowledge to the field, its diverse methodological approaches, and through fieldwork. By combining evidence synthesis, a detailed mixed methods study of implementation, and an assessment of simplifying CVD risk scores, I was able to test my overarching hypothesis from various perspectives. Conducting field work in a humanitarian setting was a considerable achievement that strengthened my programme of research. It required a lengthy process of developing a tripartite research collaboration between me, MSF, and the Jordanian Ministry of Health, obtaining funding, and working within the dynamic security and political context of a humanitarian setting.

8.6 Conclusions

Cardiovascular risk assessment is a widely endorsed approach for the prevention of CVD. However, this thesis has shown that in its current form it is sub-optimal for the prevention of CVD in low-resource settings due to a lack of evidence of effectiveness, its difficulty to implement and test, and its complexity to use in clinical practice. Focus should be shifted towards conducting high quality randomised trials in low-resource settings designed to assess CVD-related morbidity and mortality as primary outcomes. This will require simplification of risk assessment algorithms so they can be completed in a single consultation and further studies of their implementation in primary health care. With this in mind, cardiovascular risk assessment as a pivotal intervention for the prevention of CVD in low-resource settings should be judiciously compared to other alternatives, and if implemented, closely monitored for its impact on health outcomes.

Throughout this thesis, given the need for primary studies in low resource settings (Chapter 3), I was conscious of the need to build capacity to conduct such studies. I felt that it was not enough to show that more primary research was needed, but that my work should also facilitate further research in low-resource

settings. I've made and published open source software, including examples of its use.[2] I published a detailed study which illustrated how routine data can be used to evaluate CVD risk assessment in low-resource settings, and the value of mixed methods in such evaluations.[3] I've shared this work by creating YouTube videos, by writing case studies for textbooks and workshops,[4] through teaching, presenting at international conferences, and through lecturing at WHO regional conferences to delegates from over ten LMICs. It is my hope that in doing so, researchers in low-resource settings can build on the new knowledge I have contributed and advance the field even further. I am already aware of two researchers who have contacted me because they are using the `whoishRisk` package.

In conclusion, this thesis has answered important questions about the role of CVD risk scoring for the prevention of CVD in low-resource settings, and has raised questions about its effectiveness and feasibility to implement and test. Although it is an endorsed strategy by the WHO, policy-makers should keep in mind the need to simplify CVD risk scoring and to generate local evidence of effectiveness before fully mainstreaming this practice.

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Appendices



Chapter 1 Appendix

Included in this appendix are the following documents in this order:

- R Programming Course Certificate (1 page)
- Data Scientist's Toolbox Course Certificate (1 page)
- Getting and Cleaning Data Course Certificate (1 page)
- Poster Presentation from Preventing Overdiagnosis Conference (September, 2016, Barcelona) (1 page)







Cardiovascular Risk Assessment and Statin Use in Medecins Sans Frontieres NCD Mission for Syrian Refugees in Jordan

Collins, D.R.J.,¹ Jobanputra, K.,² Shoaib, M.,² Ward, A.,¹ Tarawneh, M.,^{3*} Sayaydeh, A.,^{3*} Shafei, A. A.,^{3*} Fardous, T.H.,^{3*} Heneghan, C.J.¹

Introduction

- Nearly one million Syrian refugees live in Jordan, and the burden of NCDs in this population is high [1,2]
- MSF provides primary health care to Syrian refugees with NCDs in Northern Jordan
- The provision of NCD care in humanitarian emergencies is largely unprecedented and MSF developed NCD clinical guidance for use in these settings (Figure 1)
- Total cardiovascular risk assessment, based on WHO PEN, is a central component of MSF's approach [3]



Figure 1. Risk assessment pathway for statin prescribing

Objectives

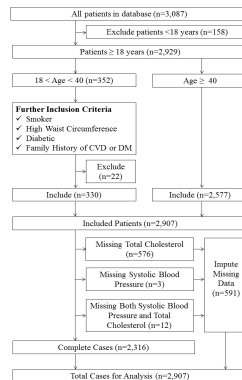
- We conducted a retrospective analysis of MSF's non-communicable disease mission for Syrian refugees in Jordan to determine the:
- degree of over- and under-prescribing of statins
 - the proportion of eligible patients with a correctly documented CVD risk score in their clinical record
 - the performance of laboratory-independent (LI) WHO/ISH CVD risk assessment relative to laboratory-dependent (LD) WHO/ISH CVD risk assessment with respect to need for statin therapy

Methods

- All patients eligible for cardiovascular risk assessment were included in the analysis (Figure 2)
- We used routinely collected electronic patient data
- We compared current practice against two standards: (1) all eligible patients should have a documented and correct CVD risk score, and (2) statin prescriptions should be concordant with guidance for statin eligibility (Figure 1)
- Ethical approval was obtained from the Oxford Tropical Research Ethics Committee (OxTREC Reference 576-15), MSF Operational Centre Amsterdam, and the Ministry of Health in Jordan

Results

Figure 2. Flowchart of included patients



Are CVD Risk Scores Documented and Correct?

- 23% (n=680) of patients eligible for CVD risk assessment (n=2,907) had a documented CVD risk score and 39% of these scores were correct
- Therefore 91% of patients did not have a correctly documented CVD risk score

Are Statins Prescribed According to Standard?

- No difference in prescribing in those below and above the risk threshold for treatment
- Half of the patients were eligible for statin prescription without risk scoring

	History of CVD	DM2 & Age ≥ 40	TC ≥ 5 mmol/L	Risk < 20%	Risk ≥ 20%
Total (n)	608	1072	11	1150	66
Number with Statin Rx (%)	429 (70.6)	401 (37.4)	7 (63.6)	188 (16.3)	11 (16.7)

Table 1. Statin prescribing based on eligibility category (Figure 1)

Can LI WHO/ISH Risk Charts Replace LD WHO/ISH Risk Charts?

	WHO/ISH Risk Treatment Threshold		
	10%	20%	30%
True Prevalence (95% CI)	0.17 (0.15, 0.19)	0.07 (0.06, 0.09)	0.03 (0.02, 0.04)
Apparent Prevalence (95% CI)	0.13 (0.11, 0.15)	0.05 (0.04, 0.07)	0.03 (0.02, 0.04)
Sensitivity (95% CI)	0.74 (0.67, 0.80)	0.67 (0.56, 0.77)	0.76 (0.59, 0.88)
Specificity (95% CI)	1.00 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (0.99, 1.00)

Table 2. True prevalence, apparent prevalence, sensitivity, and specificity of LI WHO/ISH risk assessment relative to LD WHO/ISH risk assessment

Proposed Simplified Approach

A simplified LI risk assessment pathway would result in under-treatment; 8/1,000 patients enrolled in the clinic would be incorrectly classified as ineligible for statins relative to the LD pathway (Figure 3)

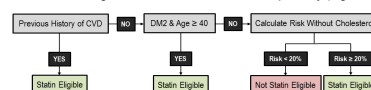


Figure 3. Simplified risk assessment pathway for statin prescribing

Conclusions

- The poor documentation of risk scores may help explain discordant statin prescribing.
- The simplified workflow of the LI process may result in improved adherence to guidance and therefore reduce over- and under-treatment, despite the attenuated performance of the LI charts
- Guideline developers should look to balance simplicity with accuracy, perhaps first fully optimising simple protocols before adding additional complexity that may reduce guideline adherence with little benefit to patient outcomes

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References

- [1] Medecins Sans Frontieres Country Operations Profile - Jordan [Internet]. 2015. Available from: <http://www.msf.org/pages/country-operations-profile>
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[3] WHO. Package of essential non-communicable (NCD) disease interventions for primary health care in low-resource settings [Internet]. Geneva, Switzerland: 2010 [cited 2014 Oct 27]. Available from: <http://apps.who.int/iris/handle/10665/44280>

B

Chapter 3 Appendix

Included in this appendix are the following documents in this order:

- MEDLINE Search Strategy
- EMBASE Search Strategy
- The Cochrane Library Search Strategy
- CINAHL Search Strategy
- Table of Additional Characteristics of Included Primary Studies from Included Systematic Reviews

MEDLINE

```
meta analysis.mp,pt. or review.pt. or search:.tw.  
Cardiovascular Diseases/pc [Prevention & Control]  
Coronary Disease/pc [Prevention & Control]  
Coronary Artery Disease/pc [Prevention & Control]  
Stroke/pc [Prevention & Control]  
myocardial ischemia/pc or myocardial infarction/pc  
2 or 3 or 4 or 5 or 6  
Cardiovascular Diseases/  
Coronary Disease/  
Coronary Artery Disease/  
Stroke/  
myocardial ischemia/ or myocardial infarction/  
((cardiovascular or cardio-vascular) adj3 (disease or disorder? or  
condition?)).ti,ab.  
((coronary or heart or cardiac or myocardi*) adj3 (disease or disorder?  
or condition? or infarct*)).ti,ab.  
stroke.ti,ab.  
8 or 9 or 10 or 11 or 12 or 13 or 14 or 15  
Primary Prevention/
```

exp Health Promotion/
 health education/ or exp consumer health information/ or exp patient
 education as topic/
 counseling/
 (prevent* or promot* or educat* or counsel*).ti,ab.
 17 or 18 or 19 or 20 or 21
 16 and 22
 7 or 23
 Risk Factors/
 Risk Adjustment/
 Risk Assessment/
 risk*.ti.
 25 or 26 or 27 or 28
 score?.ti,ab.
 framingham.ti,ab.
 (global adj3 risk*).ti,ab.
 qrisk*.ti,ab.
 (who adj3 ish).ti,ab.
 Models, Cardiovascular/
 30 or 31 or 32 or 33 or 34 or 35
 29 and 36
 (risk* adj (predict* or estimat* or level* or information or model* or
 scor* or assess*)).mp.
 (predict* adj model*).mp.
 37 or 38 or 39
 1 and 24 and 40
 limit 41 to yr="2005 -Current"

EMBASE

meta-analysis:.mp. or search:.tw. or review.pt.
 Cardiovascular Diseases/pc [Prevention & Control]
 Coronary Disease/pc [Prevention & Control]
 Coronary Artery Disease/pc [Prevention & Control]
 Stroke/pc [Prevention & Control]
 myocardial ischemia/pc or myocardial infarction/pc
 2 or 3 or 4 or 5 or 6
 Cardiovascular Diseases/
 Coronary Disease/
 Coronary Artery Disease/
 Stroke/
 myocardial ischemia/ or myocardial infarction/
 ((cardiovascular or cardio-vascular) adj3 (disease or disorder? or
 condition?)).ti,ab.
 ((coronary or heart or cardiac or myocardi*) adj3 (disease or disorder?
 or condition? or infarct*)).ti,ab.
 stroke.ti,ab.
 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
 Primary Prevention/
 exp Health Promotion/

health education/ or exp consumer health information/ or exp patient
 education as topic/
 counseling/
 (prevent* or promot* or educat* or counsel*).ti,ab.
 17 or 18 or 19 or 20 or 21
 16 and 22
 7 or 23
 Risk Factors/
 Risk Adjustment/
 Risk Assessment/
 risk*.ti.
 25 or 26 or 27 or 28
 score?.ti,ab.
 framingham.ti,ab.
 (global adj3 risk*).ti,ab.
 qrisk*.ti,ab.
 (who adj3 ish).ti,ab.
 Models, Cardiovascular/
 30 or 31 or 32 or 33 or 34 or 35
 29 and 36
 (risk* adj (predict* or estimat* or level* or information or model* or
 scor* or assess*)).mp.
 (predict* adj model*).mp.
 37 or 38 or 39
 1 and 24 and 40
 limit 41 to yr="2005 -Current"

The Cochrane Library

ID	Search
#1	MeSH descriptor: [Cardiovascular Diseases] explode all trees and with qualifier(s): [Prevention & control - PC]
#2	MeSH descriptor: [Coronary Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#3	MeSH descriptor: [Coronary Artery Disease] explode all trees and with qualifier(s): [Prevention & control - PC]
#4	MeSH descriptor: [Stroke] explode all trees and with qualifier(s): [Prevention & control - PC]
#5	MeSH descriptor: [Myocardial Ischemia] explode all trees and with qualifier(s): [Prevention & control - PC]
#6	MeSH descriptor: [Myocardial Infarction] explode all trees and with qualifier(s): [Prevention & control - PC]
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Cardiovascular Diseases] this term only
#9	MeSH descriptor: [Coronary Disease] this term only
#10	MeSH descriptor: [Coronary Artery Disease] this term only
#11	MeSH descriptor: [Stroke] explode all trees
#12	MeSH descriptor: [Myocardial Ischemia] this term only
#13	MeSH descriptor: [Myocardial Infarction] this term only
#14	((cardiovascular or cardio-vascular) near/3 (disease or disorder?

```

    or condition?)):ti,ab,kw
#15    ((coronary or heart or cardiac or myocardi*) near/3 (disease or
    disorder? or condition? or infarct*)):ti,ab,kw
#16    stroke:ti,ab,kw
#17    #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18    MeSH descriptor: [Primary Prevention] this term only
#19    MeSH descriptor: [Health Promotion] explode all trees
#20    MeSH descriptor: [Health Education] this term only
#21    MeSH descriptor: [Consumer Health Information] explode all trees
#22    MeSH descriptor: [Patient Education as Topic] explode all trees
#23    MeSH descriptor: [Counseling] this term only
#24    (prevent* or promot* or educat* or counsel*):ti,ab,kw
#25    #18 or #19 or #20 or #21 or #22 or #23 or #24
#26    #17 and #25
#27    #7 or #26
#28    MeSH descriptor: [Risk Factors] this term only
#29    MeSH descriptor: [Risk Adjustment] this term only
#30    MeSH descriptor: [Risk Assessment] this term only
#31    risk*:ti,ab,kw
#32    #28 or #29 or #30 or #31
#33    score?:ti,ab
#34    framingham:ti,ab
#35    (global near/3 risk*):ti,ab
#36    qrisk*:ti,ab
#37    (who near/3 ish):ti,ab
#38    MeSH descriptor: [Models, Cardiovascular] this term only
#39    #33 or #34 or #35 or #36 or #37 or #38
#40    #32 and #39
#41    (risk* next (predict* or estimat* or level* or information or
    model* or scor* or assess*)):ti
#42    (predict* next model*):ti,ab,kw
#43    #40 or #41 or #42
#44    #27 and #43 Publication Year from 2005 to 2015

```

CINAHL

```

    S49 & S26 AND S42 AND S45
S48 & S26 AND S42 AND S45
S47 & S26 AND S42 AND S45
S46 & S26 AND S42 AND S45
S45 & S43 OR S44
S44 & PT review OR PT systematic review
S43 & TI meta-analysis OR AB meta-analysis OR MW meta-analysis
S42 & S39 OR S40 OR S41
S41 & TX (predict* N model*) OR AB (predict* N model*) AND MW (predict* N
    model*)
S40 & TI ( (risk* N (predict* or estimat* or level* or information or
    model* or scor* or assess*)) ) OR AB ( (risk* N (predict* or estimat*
    or level* or information or model* or scor* or assess*)) ) OR MW ( (
    risk* N (predict* or estimat* or level* or information or model* or

```

```

    scor* or assess*)) )
S39 & S31 AND S38
S38 & S32 OR S33 OR S34 OR S35 OR S36 OR S37
S37 & (MM "Diagnosis, Cardiovascular") OR (MM "Attitude to Risk")
S36 & TI (who N3 ish) OR AB (who N3 ish)
S35 & TI qrisk* OR AB qrisk*
S34 & TI (global N3 risk*) OR AB (global N3 risk*)
S33 & TI framingham OR AB framingham
S32 & TI score? OR AB score?
S31 & S27 OR S28 OR S29 OR S30
S30 & TI risk
S29 & (MM "Risk Assessment")
S28 & (MM "Cardiovascular Risk Factors")
S27 & (MM "Risk Factors")
S26 & S6 OR S25
S25 & S16 AND S24
S24 & S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23 & TI ( (prevent* or promot* or educat* or counsel*) ) OR AB ( (
    prevent* or promot* or educat* or counsel*) )
S22 & (MM "Counseling")
S21 & (MH "Patient Education+")
S20 & (MM "Consumer Health Information")
S19 & (MM "Health Education")
S18 & (MH "Health Promotion+")
S17 & (MM "Preventive Health Care")
S16 & S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15
S15 & TI stroke OR AB stroke
S14 & TI ( ((coronary or heart or cardiac or myocardi*) N3 (disease or
    disorder? or condition? or infarct*)) ) OR AB ( ((coronary or heart
    or cardiac or myocardi*) N3 (disease or disorder? or condition? or
    infarct*)) )
S13 & TI ( ((cardiovascular or cardio-vascular) N3 (disease or disorder?
    or condition? or infarct*)) ) OR AB ( ((cardiovascular or cardio-
    vascular) N3 (disease or disorder? or condition? or infarct*)) )
S12 & (MM "Myocardial Ischemia")
S11 & (MM "Myocardial Infarction")
S10 & (MM "Stroke")
S9 & (MM "Coronary Arteriosclerosis")
S8 & (MM "Coronary Disease")
S7 & (MM "Cardiovascular Diseases")
S6 & S1 OR S2 OR S3 OR S4 OR S5
S5 & (MM "Myocardial Infarction/PC")
S4 & (MM "Myocardial Ischemia/PC")
S3 & (MM "Stroke/PC")
S2 & (MM "Coronary Arteriosclerosis/PC")
S1 & (MM "Cardiovascular Diseases/PC")

```

Table B.1: Characteristics of primary studies reported by included systematic reviews

Primary Study ID	Risk Score	Population	Intervention	Control	Systematic Reviews					
					Brindle 2006[69]	Sheridan 2008[70]	Sheridan 2010[71]	Van Dieren 2012[73]	Waldron 2011[72]	Usher-Smith 2015[74]
Montgomery 2000[75]	Framingham-derived risk score	“between 60 and 79 years with high blood pressure.”	“CHD risk chart alone”	“Usual care”	◆	◆		◆		
Hanon 2000[76]	10 year Framingham risk	“Adults 18–75 years with BP >140/90 without severe hypertension, secondary hypertension, heart disease, CVD, renal, pulmonary, hepatic disease or significant psychiatric or other serious illness, diabetes, pregnancy or of reproductive age without effective contraception”	“As for control group plus calculation of Framingham risk also given to physicians”	“Baseline measurement of BP and prescription of fosinopril followed by visits at 4 and 8 weeks at which physicians could add in hydrochlorothiazide”	◆					◆
Lowensteyn 1998[77]	8-year coronary risk from CHD Prevention Model and estimated ‘cardiovascular age’	“Patients 30–74 years without history of CVD in whom clinicians thought a risk profile would be clinically useful”	“Physicians—same 1 h education meeting and a monthly newsletter plus received 2 copies of patients risk profile within 10 working days. Patients—completed same questionnaire and then invited back 2 weeks later when presented with risk”	“Physicians—1 h education meeting and a monthly newsletter. Patients — completed questionnaire about attitudes and knowledge surrounding CVD prevention and assessment of their current lifestyle and medical problems”		◆				◆
Van Steenkiste 2007[78]	Framingham-derived	“men aged 40-70, women aged 40-75, without established CVD”	“4 hour interactive session on CHD risk and risk reduction for practitioners; 16 page decision support tools on CHD risk to be given to patient; 2 scheduled consultations to discuss risk”	“Written educational materials for GPs on Dutch Cholesterol Guidelines”		◆				
Grover 2007[79]	10-year Framingham risk	“Patients with diabetes or 10-year risk >30% with moderate cholesterol, 10-year risk 20–30% with high cholesterol or 10-year risk 10–20% with very high cholesterol with no hypersensitivity to statins, risk of pregnancy, breastfeeding, active liver disease, raised CK or triglycerides, a history of pancreatitis or significant renal insufficiency** ”	“Physicians attended the same full-day educational session [as control]. Patients were given a copy of their risk profile and then followed up at 2–4 weeks, 3,6,9 and 12 months”	“Physicians attended full-day educational session. Patients received usual care with follow-up at 2–4 weeks and 3,6,9 and 12 months”			◆		◆	◆
Hanon 1995[80]	Dundee risk score	“Workers at two work sites not working permanent night shifts, taking part in another coronary intervention or taking lipid-lowering medication”	“Health education plus feedback on risk score or health education and feedback on serum cholesterol plus feedback on risk score”	“Health education (interview backed up by written information) or health education and feedback on serum cholesterol”			◆			◆

Primary Study ID	Risk Score	Population	Intervention	Control	Systematic Reviews
					Brindle 2006[69] Sheridan 2008[70] Sheridan 2010[71] Van Dieren 2012[73] Waldron 2011[72] Usher-Smith 2015[74]
Emmett 2005[81]	Framingham	“30 to 80 years, not currently taking antihypertensive medication, and had sustained raised blood pressure at a level where their general practitioner (GP) would normally discuss initiation of pharmacological therapy”	“Risk + decision Analysis [tool] ”	“No intervention (usual care)”	◆
Family Heart Study Group 1994[82]	Dundee risk score	“All men aged 40-59 and their partners”[228]	Patient: “Risk + counselling” Nurse: “risk factor measurements and their quality assurance and follow up, and client centred lifestyle counselling”[72]	“No intervention (usual care)”	◆
Lovibond 1986[83]	International Coop Study Risk Score	“persons aged 30 to 60 years who were willing to undergo a thorough medical examination and who were found on examination to have a high overall risk of CHD, although free of clinical evidence of disease (subjects could be within normal limits on any particular risk measure provided overall risk was elevated).” [44]	“Regular Assessment and Feedback of Coronary Risk-Factor Status and Overall CHD Risk”[44]	“general qualitative feedback of the objective measurements of weight, blood pressure, and aerobic fitness” [44]	◆
OxCheck 1995[84, 85]	Framingham or a Framingham derived risk score.	“the entire middle aged (35-64 years) population of each of five practices.”[229]	“Risk + counselling” in health checks performed by nurses	“Usual care”	◆
Turnbull 2006[86]	CHD risk Take Heart	“18–75 years and had mild to moderate hypertension, although people with severe hypertension were eligible if they were not at very high absolute risk”	“an interactive CD-ROM program designed to enable the GP to quantify and manage risk, a CD-ROM and video for the patient, and a supporting website. A set of written and audio patient education materials are supplied and each patient is referred to a program-commissioned dietitian for at least one session on non-pharmacological approach”	“Usual care”	◆

Primary Study ID	Risk Score	Population	Intervention	Control	Systematic Reviews					
						Brindle 2006[69]	Sheridan 2008[70]	Sheridan 2010[71]	Van Dieren 2012[73]	Waldron 2011[72] Usher-Smith 2015[74]
Williams 2006[87]	Framingham or a Framingham derived risk score	"Eligible subjects were currently smoking 5 or more cigarettes per day, were 18 years of age and older, read and spoke English, had no history of a psychotic illness (depression and anxiety were allowed), and had a minimum life expectancy of 18 months."	"patients' 10-year risks for developing cardiovascular disease were reviewed, and patients were informed that lowering their cholesterol and stopping smoking could cut that risk by more than 50% within 12 months"	"National Cancer Institute booklet "You Can Quit Smoking," ²¹ a copy of their cholesterol test results, the American Dietetic Association booklet on elevated cholesterol "The New Cholesterol Countdown," ²² and a list of active area smoking cessation programs. They were encouraged to enrol in a cessation program and to meet with their physician"		◆				
Wister 2007[88]	Framingham	"age 45–64 years, residence in the Fraser Health region and cardiovascular risk profile according to the literature for primary and secondary prevention. 16–18. . . . Participants in the primary prevention group had an absolute Framingham risk score of 10% or higher over a 10-year period (considered the minimum level for effective treatment outcomes)."	"a report card (sent to the participant and his or her family doctor) showing the person's risk profile, coupled with a Telehealth-guided self-care management system."	"Usual Care"			◆			
Bucher 2010[89]	10-year Framingham risk	"Patients registered at the centres, not pregnant, aged 18 or older with continuous cART for 90 days prior to baseline and with complete data on CHD risk factors at baseline"	"Physicians received same booklet of evidence-based guidelines [as control] plus a risk profile for each patient on the patient charts"	"Physicians received booklet of evidence-based guidelines for the management of CHD risk factors and were advised in the booklet to access a website for CHD risk assessment"						◆
Persell 2013[90]	10-year Framingham risk	"Primary care physicians at an academic medical centre and patients aged 40–79 years without history of CVD, DM or PAD, not taking lipid-lowering medication who had 2 or more clinic visits in the preceding 2 years and LDL cholesterol test in previous 5 years with most recent LDL 100 mg/dL and 10-year FRS >20% or LDL 130 mg/dL and FRS 10–20% or LDL 160 mg/dL and FRS 5–10%"	"Patients were mailed a risk message containing their personal CVD risk information and encouraging them to discuss risk-lowering options with their primary care physician"	"Usual Care"						◆

Primary Study ID	Risk Score	Population	Intervention	Control	Systematic Reviews
					Brindle 2006[69] Sheridan 2008[70] Sheridan 2010[71] Van Dieren 2012[73] Waldron 2011[72] Usher-Smith 2015[74]
Price 2011[91]	10 year UKPDS V3.0 risk of cardiovascular disease	“Patients with CVD risk 20%, able to read and write English, not known to have CVD or a physical disability or other condition reducing the ability to walk”	“A 10-year cardiovascular risk estimate for current risk and ‘achievable risk’ calculated assuming current targets for systolic BP, LDL cholesterol, HbA1c and smoking cessation were met ±brief lifestyle advice intervention”	“Told their individual fasting glucose level, blood pressure and LDL cholesterol and whether they were elevated according to current guidelines ±brief lifestyle advice intervention”	◆

C

Chapter 4 Appendix

Included in this appendix are the following documents in this order:

- Code for the WHO_ISH_Risk() Function

Code for WHO_ISH_Risk() Function

```
#' Calculating WHO/ISH Risk Scores
#
# This function calculates WHO/ISH risk scores for any epidemiological
# subregion of the world.
#
# @param age age (years)
# @param gdr gender (1 = male, 0 = female)
# @param smk smoking status (1 = current smoker, 0 = non-smoker)
# @param sbp systolic blood pressure (mmHg)
# @param dm diabetes status (1 = diabetic, 0 = non-diabetic)
# @param chl total cholesterol (mmol/L)
# @param subregion epidemiological subregion (character value, one of:
#   AFR_D, AFR_E , AMR_A , AMR_B , AMR_D , EMR_B ,
#   EMR_D , EUR_A , EUR_B , EUR_C , SEAR_B , SEAR_D ,
#   WPR_A , WPR_B )
# @return A vector of WHO/ISH risk scores.
# @author Dylan R.J. Collins, Joseph Lee, Niklas Bobrovtiz, Constantinos
#   Koshlaris, Alison Ward, Carl Heneghan
# @details
# This function calculates WHO/ISH risk scores for any epidemiological
# subregion based on the values of six parameters passed to it (age,
# gender, smoking status, systolic blood pressure, diabetes status, and
# total cholesterol).
# @export

WHO_ISH_Risk<- function (age,gdr,smk,sbp,dm,chl, subregion) {
```

```

#Load required data
df<-data.frame(age,gdr,smk,sbp,dm,chl)
ref<-read.csv(file=system.file("extdata", "WHO_ISH_Scores.csv", package
  = "whoishRisk"))

#Warning Messages
if(any(df$age < 19)) warning("At least one age is 18 or younger")
if(any(df$age > 100)) warning("At least one age is greater than 100")
if(any(df$gdr > 1)) warning("Gender must be equal to 0 or 1")
if(any(df$smk > 1)) warning("Smoking must be equal to 0 or 1")
if(any(df$sbp < 90)) warning("At least one systolic blood pressure is
  below 90 mmHg")
if(any(df$sbp > 250)) warning("At least one systolic blood pressure is
  over 250 mmHg")
if(any(df$dm > 1)) warning("Diabetes status must be equal to 0 or 1")
if(any(df$chl >10)) warning("At least one total cholesterol is greater
  than 10 mmol/L. Ensure all values are in units of mmol/L")

#Age
df$age<-ifelse(df$age > 17 & df$age < 50, 40, df$age)
df$age<-ifelse(df$age >= 50 & df$age < 60, 50, df$age)
df$age<-ifelse(df$age >= 60 & df$age < 70, 60, df$age)
df$age<-ifelse(df$age >= 70, 70, df$age)

#Cholesterol
df$chl<-ifelse(df$chl > 0 & df$chl < 4.5, 4, df$chl)
df$chl<-ifelse(df$chl >= 4.5 & df$chl < 5.5, 5, df$chl)
df$chl<-ifelse(df$chl >= 5.5 & df$chl < 6.5, 6, df$chl)
df$chl<-ifelse(df$chl >= 6.5 & df$chl < 7.5, 7, df$chl)
df$chl<-ifelse(df$chl >= 7.5, 8, df$chl)

#Systolic Blood Pressure
df$sbp<-ifelse(df$sbp > 0 & df$sbp < 140, 120, df$sbp)
df$sbp<-ifelse(df$sbp >= 140 & df$sbp < 160, 140, df$sbp)
df$sbp<-ifelse(df$sbp >= 160 & df$sbp < 180, 160, df$sbp)
df$sbp<-ifelse(df$sbp >= 180, 180, df$sbp)

#Create a new variable called luv (look up value)
df$luv<-paste(df$age,df$gdr,df$dm,df$smk,df$sbp,df$chl,sep="")

#Create a new variable called refv (reference value)
ref$refv<-paste(ref$age,ref$gdr,ref$dm,ref$smk,ref$sbp,ref$chl,sep="")

#Match the look up value with the reference value
if (subregion=="AFR_D"){

```

```

df$AFR_D<-ref$AFR_D[match(df$luv,ref$refv)]
return(as.character(df$AFR_D))}

if (subregion=="AFR_E"){
df$AFR_E<-ref$AFR_E[match(df$luv,ref$refv)]
return(as.character(df$AFR_E))}

if (subregion=="AMR_A"){
df$AMR_A<-ref$AMR_A[match(df$luv,ref$refv)]
return(as.character(df$AMR_A))}

if (subregion=="AMR_B"){
df$AMR_B<-ref$AMR_B[match(df$luv,ref$refv)]
return(as.character(df$AMR_B))}

if (subregion=="AMR_D"){
df$AMR_D<-ref$AMR_D[match(df$luv,ref$refv)]
return(as.character(df$AMR_D))}

if (subregion=="EMR_B"){
df$EMR_B<-ref$EMR_B[match(df$luv,ref$refv)]
return(as.character(df$EMR_B))}

if (subregion=="EMR_D"){
df$EMR_D<-ref$EMR_D[match(df$luv,ref$refv)]
return(as.character(df$EMR_D))}

if (subregion=="EUR_A"){
df$EUR_A<-ref$EUR_A[match(df$luv,ref$refv)]
return(as.character(df$EUR_A))}

if (subregion=="EUR_B"){
df$EUR_B<-ref$EUR_B[match(df$luv,ref$refv)]
return(as.character(df$EUR_B))}

if (subregion=="EUR_C"){
df$EUR_C<-ref$EUR_C[match(df$luv,ref$refv)]
return(as.character(df$EUR_C))}

if (subregion=="SEAR_B"){
df$SEAR_B<-ref$SEAR_B[match(df$luv,ref$refv)]
return(as.character(df$SEAR_B))}

if (subregion=="SEAR_D"){
df$SEAR_D<-ref$SEAR_D[match(df$luv,ref$refv)]
return(as.character(df$SEAR_D))}

if (subregion=="WPR_A"){

```

```
df$WPR_A<-ref$WPR_A[match(df$luv,ref$refv)]  
return(as.character(df$WPR_A))}  
  
if (subregion=="WPR_B"){  
  df$WPR_B<-ref$WPR_B[match(df$luv,ref$refv)]  
  return(as.character(df$WPR_B))}  
}
```

D

Chapter 5 Appendix

Included in this appendix are the following documents in this order:

- Data Sharing Agreement with MSF (3 pages)
- Study Protocol (9 pages)
- OxtREC Approval Document (2 pages)
- OxtREC Research Sponsor Letter (1 page)
- MSF Study Approval Letter (1 page)
- Jordanian Ministry of Health Approval Letters (2 pages)

Data Sharing Agreement

between

Médecins Sans Frontières - UK

and

THE CHANCELLOR, MASTERS AND SCHOLARS OF THE UNIVERSITY OF OXFORD

This agreement between MSF-UK (disclosing party) and University of Oxford (recipient party) is entered into on 22/10/2015.

Disclosing party: MSF-UK(hereinafter referred to as "MSF")

Name of contact person: Philipp du Cros, Head of Manson Unit

Médecins Sans Frontières/Doctors Without Borders (MSF)
Lower Ground Floor, Chancery Exchange, 10 Fumival Street,
London EC4A 1AB

Recipient party: The Chancellor, Masters And Scholars Of The University Of Oxford (hereinafter referred to as "Oxford")

Name of contact person: Prof Carl Heneghan

University Offices, Wellington Square,
Oxford OX1 2JD,
England

Description/ name of data set:

MSF will be sharing a database called the "NCD Tool" and it is a patient management and medical data analysis tool for projects of MSF Operational Centre Amsterdam with non-communicable disease components.

This database includes previously collected routine clinical data on CVD care in two MSF clinics in Irbid, Ibn Sina and Ibn Rushed

The data that is shared on the basis of this agreement has been collected by MSF as routine programmatic data.

MSF is the full owner of any data related to said study/ program.

Purpose of use: To complete the programme of work as outlined in the appended protocol

Method of transferring data:

All data will be transferred as a pseudonymised export with password protection.. Each party agrees to maintain this dataset either on a secure server.

The purpose of this Agreement is to set forth the terms, conditions, and obligations concerning the sharing of data between the parties.

Therefore, MSF and Oxford agree to share the aforementioned data under the following conditions:

1. MSF certifies that no personal health identifiers are included in this data set or that appropriate patient consent has been obtained for all identifiable data.
2. Both parties agree to maintain confidentiality and privacy safeguards that were originally created as part of the protocol or data collection. Both parties agree not to release information about specific identifiable subjects to anyone. Only people mentioned in the protocol will have access to the database.
3. During handling and storage of the data, all parties agree to abide by universally recognised ethical principles. In particular, due consideration will be given to issues of individual consent, confidentiality, and involvement of concerned communities.
4. The parties to this agreement agree not to use the transferred data for commercial purpose, and not to claim any intellectual property rights on the data.
5. Both parties view dissemination of research findings, both by publication and oral presentation, as an essential objective of the research. Therefore Parties are encouraged to publish the results of their work in a collaborative fashion for the benefit of the public.
6. A copy of each manuscript or abstract shall be submitted to MSF at least 30 days before submission for publication in a journal or presentation at an international meeting. Publication shall be accompanied by an acknowledgement that MSF and the host country supplied the data. Guidelines for authorship of the International Committee of Medical Journal Editors Committee will be used to establish authorship. For the avoidance of doubt, nothing in this Agreement shall prevent or hinder any registered student of Oxford from submitting for a degree of Oxford a thesis based on the results obtained during the course of work undertaken as part of the Project, the examination of such a thesis by examiners appointed by Oxford, or the deposit of such a thesis in accordance with the relevant procedures of Oxford.
7. The ownership of the data remains with MSF.
8. The information and data provided through this agreement shall only be used for the above mentioned purpose and according to the outlined terms and conditions. Neither party shall use the personal information/ data provided under this agreement for any purpose other than that set out in this agreement.
9. This Agreement shall be in full force and effect from the first date written above for a period of one year thereafter. This Agreement may be terminated with thirty (30) days written notice by either party or mutual agreement of the parties.

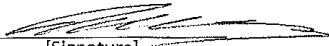
Upon completion of the agreement, the recipient party will return all copies of the collected data and the cleaned database. MSF commits to storing the data for at least 5 years.

10. In the event of the termination of this Agreement, the personal information shared under this Agreement shall be returned to the disclosing party.
11. The liability of either party for any breach of this Agreement, or arising in any other way out of the subject matter of this Agreement, will not extend to any incidental or consequential damages or losses including (without limitation) loss of profits.
12. This Agreement shall be governed by English Law, and the English Courts shall have exclusive jurisdiction to deal with any dispute which may arise out of or in connection with this Agreement.

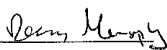
The undersigned individuals represent that they are fully authorized to execute this Agreement on behalf of the respective parties, perform the obligations under this Agreement, and make all representations, warranties, and grants as set forth herein.

MSF is willing to provide the data for use as indicated above according to the outlined conditions, and the recipient party and MSF agree to comply with those conditions.

IN WITNESS WHEREOF this Agreement has been signed on behalf of the disclosing party by the the Head of the Manson Unit of MSF UK:

Dr. Philipp du Cros 22/10/2015 
 [Name] [Date] [Signature]

IN WITNESS WHEREOF this Agreement has been signed on behalf of the recipient party by

DENIS MURPHY 23 Oct 15 
 [Name] [Date] [Signature]

Appendices (*Protocol or concept paper to be attached*)

1. Protocol



OXTREC
 Protocol_COLLINS_v6

Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

Study Design: sequential explanatory mixed methods clinical audit

Study Site: Irbid, Hashemite Kingdom of Jordan

Participating Centres: Médecins Sans Frontières (MSF) Ibn Sina Clinic and Ibn Rushed Clinic

Principal Investigator: Dylan Collins

Protocol Version No.: 07102015

Sponsor: University of Oxford

Funding: Funding for travel expenses will be provided by MSF, the Nuffield Department of Primary Care Health Sciences and Christ Church, as per allowable research expenditure of DPhil. students. No additional funding from MSF will be used, outside of their normal operational remuneration for their staff involved in this project.

OXTREC reference: 576-15

Updated by Dylan Collins on 07 October 2015

1. RESEARCH TEAM

The research team is led by Dylan Collins (Principal Investigator, Oxford) and is comprised of collaborators from MSF and the Ministry of Health of the Hashemite Kingdom of Jordan.

University of Oxford

Dylan Collins (Principal Investigator, DPhil Student)

Professor Carl Heneghan (DPhil Supervisor)

Dr. Alison Ward (DPhil Supervisor)

Médecins Sans Frontières

Dr. Kiran Jobanputra (Manson Unit, United Kingdom)

Dr. Shoaib Muhammad (Medical Coordinator, Jordan)

Dr. Ito Ken (NCD Care Project, Jordan)

Ministry of Health, Hashemite Kingdom of Jordan

Dr. Ayoub Al-Sayayedeh (Director of Non-communicable Diseases)

Dr. Abdul Razzaq Al-Shafei (Health Economy Directorate)

Dr. Taissir Fardous (Health Economy Directorate)

Local Cardiologist from Irbid Directorate (not yet recruited)

2. BACKGROUND

The Syrian Refugee Crisis

The on-going war in Syria has resulted in over 4,000,000 Syrian people seeking refuge internationally and in neighbouring countries. Over 600,000 Syrian refugees live in Jordan, many of whom have, or at risk for, cardiovascular disease (CVD).¹ This crisis has created an urgent need to adapt and simplify clinical guidance for CVD care in humanitarian settings as Médecins Sans Frontières (MSF) and service providers try to meet these unprecedented health care needs.

Médecins Sans Frontières Response

MSF operates in several countries, including Lebanon, Turkey, Iraq, and Jordan, to provide medical care to Syrian refugees. Recognising a need early in the crisis, MSF called for integration of non-communicable disease (NCD) health care for refugees and took action by developing and piloting innovative NCD guidance and programmes in Jordan. They have partnered and continue to work with the Ministry of Health in Jordan to provide care.

Amongst other operations in the country, MSF operates two clinics in Irbid, Jordan, that specialise in NCD care for urban (rather than camp-based) Syrian refugees. These clinics work to supplement care provided by the government of Jordan, especially for patients with non-communicable diseases, including cardiovascular disease.

To date, there is little precedent on the clinical management of cardiovascular disease in humanitarian or conflict settings, largely because of the historical burden of communicable diseases in these settings. In 2010, the World Health Organisation published the Package of Essential Non-communicable Disease Interventions for Low-resource Settings (WHO PEN), which includes global CVD risk assessment charts and clinical protocols for the prevention and management of CVD. WHO PEN represents the only evidence-based guidance for CVD care in low-resource settings and MSF has adapted this guidance for use in Jordan.

Rationale for Study

Given the inexperience of MSF, and other service providers, in providing cardiovascular disease management in humanitarian settings, it is necessary to audit what has currently be operationalised and develop an evidence base for the improvement of service provision. This audit will help MSF develop a plan to better achieve best practice standards in their clinics, and provide guidance to other MSF clinics looking to operationalise CVD risk management. Given the number of patients who need care from humanitarian medical organisations, we believe that the results of this audit will also be of utility to Ministries of Health and other organisations providing, or planning to provide, health care to refugees who are at risk of cardiovascular disease.

Partnership

This partnership is an initiative between Dylan Collins, University of Oxford, and Dr. Kiran Jobanputra, Deputy Head, Manson Unit, Médecins Sans Frontières. MSF Operational Centre Amsterdam developed a medical data tool for projects with non-communicable disease components that allows for patient management and medical data analysis. This tool is used in Irbid for the routine collection and analysis of clinical data. Our team will use it to audit previously collected routine clinical data on CVD care in two MSF clinics in Irbid, Ibn Sina and Ibn Rushed.

¹ UNHCR. Syria Regional Refugee Response. Inter-agency Information Sharing Portal. Accessed 20/08/2015 from <http://data.unhcr.org/syrianrefugees/regional.php>
Version 07102015

3. AIM & OBJECTIVES

Aim

To analyse the current standard of cardiovascular risk management and to develop evidence-based recommendations to improve areas of deficiency relative to best-practice clinical guidance

Objectives of Quantitative Strand

The objective of the quantitative strand is to review the current practice of cardiovascular risk management and identify areas of deficiency based on routinely collected clinical data. To do this we will

- describe the practice of CVD risk assessment as documented in routinely collected clinical data
- describe CVD risk factor modifying prescription patterns
- describe the risk distribution of the patient group based on documented and calculated risk score
- determine the discriminatory value of measured cholesterol in calculating CVD risk score
- model the cost of aligning practice more closely with best practice guidance

Objectives of Qualitative Strand

The objective of the qualitative strand is to help explain the findings of the quantitative strand and to inform the development of recommendations for improvement. To do this we seek to interview MSF staff and affiliates in order to:

- gain insight into current practices and reasons for deviations from best practice
- unearth and understand barriers and enablers to achieving best practice

4. METHODS

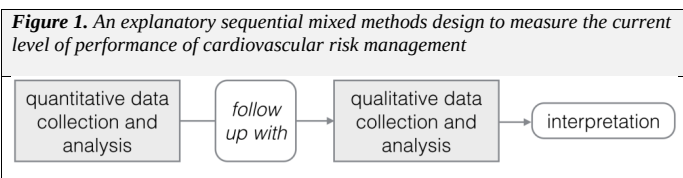
4.1 Study Sites

This project will be conducted in two Médecins Sans Frontières (Ibn Sina and Ibn Rushed) clinics in Irbid, Jordan.

4.2 Study Design

4.2.1 A Sequential Explanatory Mixed Methods Design

This study will employ both quantitative (analysis of routinely collected medical record data) and qualitative methods (semi-structured interviews) to measure the current state of cardiovascular risk management (assessment and treatment) in MSF's Irbid clinic. We will use a mixed methods sequential explanatory design, which involves first analysing and interpreting quantitative data (the *quantitative strand*), followed by qualitative interviews (the *qualitative strand*) to help explain the results of the quantitative strand (Figure 1). The strands will be mixed during data collection, with a quantitative strand priority.



Herein we will describe each component of the protocol for the qualitative and quantitative strands separately, for clarity.

4.2.2 Study subjects and recruitment

Quantitative Strand

We will perform an *a posteriori* analysis of routinely collected clinical data from patients who access care from one of the aforementioned MSF clinics. These patients are refugees (documented and undocumented) who live in and around Irbid Jordan and have, or are at risk of having, non-communicable diseases. We will not collect any additional information from, communicate, or come in contact with patients in anyway.

Qualitative Strand

We will interview MSF staff or affiliates involved with clinical care (physicians, nurses, pharmacists, etc.), administration, policy, or program development pertaining to the scope of MSF Irbid's work. Participants will be informed about the project through a staff meeting where copies of the Participant Information Sheet (Appendix 1) will be distributed. We may also distribute Participant Information Sheets by e-mail. We will ask participants and potential participants if they think we should speak to a staff or affiliate involved in their work. We will contact any additional potential participants by telephone, e-mail, or in person as appropriate.

4.2.3 Inclusion criteria*Quantitative Strand*

We will perform an *a posteriori* analysis of routinely collected clinical data using the MSF Operational Centre Amsterdam's NCD medical data analysis tool (henceforth 'NCD tool'). Participants eligible for inclusion therefore must (1) access care from Ibn Sina or Ibn Rushed clinic, (2) already be in the MSF tool database, (3) be 18 years of age or older, **and** (4) meet one of the following criteria:

- Age ≥ 40 years
- Smoker
- Waist Circumference (≥ 90 cm in women ≥ 100 cm in men)
- Known hypertension
- Known diabetes mellitus (DM)
- History of premature CVD in first degree relatives
- History of DM or kidney disease in first degree relatives

Qualitative Strand

We will use purposive sampling to interview MSF staff or affiliates involved with clinical care (physicians, nurses, pharmacists, etc.), administration, policy, or program development pertaining to the scope of MSF Irbid's work. Participants must be able to read and speak proficiently in English, which shouldn't be a challenge in this setting given most people work or were educated in English.

4.2.4 Exclusion criteria*Quantitative Strand*

Patients who are not included in MSF's NCD tool database or do not meet the aforementioned inclusion criteria.

Qualitative Strand

We will not interview patients. We will not interview people who cannot speak and read proficiently in English.

4.2.5 Informed consent*Quantitative Strand*

We will only use information already collected and maintained in MSF's clinical research database, which has been collected by MSF and made available for the purpose of this project, in line with MSF's standard operational and ethical procedures. All data used from this database will be anonymised so that no patients will be identifiable.

Qualitative Strand

We will obtain written informed consent from all qualitative strand participants. Each potential participant will obtain a copy of the participant information sheet (Appendix 1) before reading and signing the consent form (Appendix 2). All potential participants will be provided with a paper copy of the participant information sheet, have time to review the sheet, have an opportunity to ask the person taking consent questions and to discuss the project. Some of the participants will have, in addition, received an electronic copy by e-mail if e-mail was used to communicate.

4.3 Study Timeline

Below is a high-level overview of the project timeline. We anticipate the project to commence 01 September 2015.

Activity	Week																			
	01	02	03	04	05	06	07	08	09	10	11	12	13	14	15	16	17	18	19	20
<i>Quantitative Analysis</i>																				
<i>Qualitative Data Collection</i>																				
<i>Qualitative Analysis</i>																				
<i>Drafting Recommendations</i>																				
<i>Writing MSF Report</i>																				
<i>Writing Manuscript</i>																				

5. SAMPLE SIZE

Quantitative Strand

We intend to include all eligible patients currently existing in MSF's NCD tool database. We estimate this to represent data on approximately 1,000 patients.

Qualitative Strand

We seek to interview, through purposive sampling, 8-12 people, or until we reach data saturation.

6. DATA MANAGEMENT AND ANALYSIS

6.1 Data Collection

Quantitative Strand

The quantitative strand will use routinely collected clinical data previously stored in MSF's NCD tool database (Table 1), no additional data on patients will be collected.

For patients with a documented CVD risk score, we will use the most recent documented CVD risk score for the analysis and use it to set the index date. We will use the most recent previous measurement of cholesterol and systolic blood pressure from the index date to calculate CVD risk. Smoking status will be coded as positive when the patient is currently a smoker or has quit in the previous 12 months.

For patients that do not have a documented risk score we will set the index date to the time of first prescription of a statin or anti-hypertensive, whichever comes first. We will use the most recent previous measurement of cholesterol and systolic blood pressure from the index date to calculate CVD risk.

For patients without a document CVD risk score and no prescription of a statin or anti-hypertensive, the date of registration will be used as the index date and the earliest subsequent measurement of cholesterol and systolic blood pressure will be used to calculate CVD risk.

Integrity of Database

To ensure that the data captured in the database is a reliable representation of what is recorded in patient charts, we will review by hand the charts of 10% of included participants. This will be performed by the Principal Investigator in the clinic. No additional information will be extracted from patient charts. For a given patient, we will check each datum in the database included in our analysis to see if it matches the patient's chart and record discrepancies if they exist. The list of discrepancies will be made available to the database maintenance team for reconciliation at their discretion.

Qualitative Strand

Participants will be selected by purposive sampling. Non-invasive semi-structured interviews of 30 to 60 minutes will be conducted on a voluntary basis, recorded, and transcribed verbatim.

When possible and at the discretion of the participant, interviews will be scheduled for the end of the work day in a private room of the clinic so that if the participant decides not to participate, their colleagues will not be aware of whether or not they contributed to the project. Given the often chaotic environment of the clinic, we may choose to schedule the interview at a mutually agreeable alternate location. All participants' information will remain confidential and identifying information will be removed during analysis.

The development of the qualitative interview guide will be informed by the results of the quantitative strand. The interview guide will consist of two parts: (1) a core group of questions for all participants and (2) questions specific to the participants involved directly with clinical care (i.e. doctors, nurses, pharmacists, and other clinicians). The interview guide will develop and evolve as new themes emerge during data collection. A draft guide has been developed (Appendix 3) and will be finalised based on the results of the quantitative strand.

6.2 Data Analysis

Quantitative Strand

Data management and analyses will be done using Microsoft Excel 2010, except for imputation, which will be performed using R 3.2.0. The planned outputs from the quantitative analysis are listed in Table 1.

Table 1. The data input and analytical output of the quantitative strand analysis

Planned Inputs (routinely collected medical record data)	Planned Outputs
• Date of birth • Gender • Systolic blood pressure • Smoking status • Diabetes status • Total blood cholesterol • Waist Circumference (≥ 90 cm in women ≥ 100 cm in men) or BMI • Diagnosis of hypertension • Diagnosis of diabetes mellitus (DM) type 1 or 2 • History of premature CVD, DM, or kidney disease in first degree relatives • Prescription of drug interventions • CVD risk score	• Descriptive patient demographics (IBNLT age, gender, prevalence of DM, CVD, etc) • Amount of missing data • Proportion of eligible participants with documented risk score • Proportion of documented risk scores that were correct based on recorded patient data • CVD risk distribution of included patients based on <i>documented</i> risk scores • CVD risk distribution of included patients based on <i>calculated</i> risk score using measure cholesterol • CVD risk distribution of included patients based on <i>calculated</i> risk score without using measured cholesterol • Prescription of statins, anti-hypertensive (including but not limited to thiazide diuretics, ACEi, calcium channel blocker) and anti-diabetic drugs (including but not limited to metformin, sulfonyl urea) • Proportion of population reclassified for (1) risk

	category and (2) drug intervention (all drug interventions, anti-hypertensive, statins, anti-diabetics) comparing current risk and prescriptions to WHO PEN Protocol 1 with and without measured cholesterol
--	--

Qualitative Strand

The qualitative data will be transcribed verbatim by a transcriptionist, who will sign a confidentiality agreement (Appendix 4). These data will be managed using NVivo 10 and analysed using thematic framework analysis. All identifying information will be removed during the analysis to protect the confidentiality of the participants. Participants will be designated a generic labels that includes their role/occupation; for example, 'Nurse #3,' 'Administrator #4,' or 'Doctor #1.' If there is only one person in a given role, we will alter our labels so each label has more than one person. For example, if there was only one doctor and two nurses, we would label them Clinician 1, Clinician 2, Clinician 3, to mitigate any risk of the doctor being identifiable.

6.2.1 Data Storage from Quantitative and Qualitative Strand

All electronic files will be stored on the University of Oxford's network drive and behind the university firewall. All files with identifying information will be password protected. Data may sometimes be collected, temporarily stored, or analysed on the researcher's laptop. This laptop is password protected and, as property of the Nuffield Department of Primary Care Health Sciences, encrypted by the University of Oxford's IT Department. A back-up of the data files will be kept on an external USB storage device, which will be kept in a locked drawer in the Department of Primary Care Health Sciences, along with hard copy of participant consent forms and transcriptionist confidentiality agreements. Once electronic copies of paper consent forms are made and safely backed-up, we will destroy the paper records.

During data collection in the field, paper copies of participant consent forms will be kept in a locked brief case. Digital copies will be made and stored as described above.

6.3 Dissemination of Results

Results will be published in an open access peer-reviewed journal, in a public MSF report, and at academic conferences and will comprise some of Dylan Collins' doctoral thesis. All data included in these forums will be anonymised. Although clinical audits are not normally published beyond the organisation performing it, we feel that the results will be of interest and benefit to other health care providers in humanitarian settings. Therefore, we believe it is imperative that the results be published, whilst respecting the confidentiality of participants.

7. ETHICAL CONSIDERATIONS

7.1 Ethical Review

We are following MSF's Research Ethics Framework. According to this framework, this project falls within the definition of clinical audit, and it is MSF's policy for clinical audit that ethical oversight be delegated to the Medical Director responsible. The Medical Director responsible for the MSF Ibn Sina and Ibn Rushed clinics, Dr. Sid Wong, has reviewed and approved this project. Dr. Kiran Jobanputra, Deputy Head of the Manson Unit at MSF, has supplied written confirmation from Dr. Wong (Appendix 5).

As we intend to publish our results, we are seeking OxtREC review and approval.

7.2 Potential risks of participation

Quantitative Strand

Patient whose data was used in the analysis will not be identifiable in any publications. Patients will not know if their data was used in an analysis. If a patient were to read an MSF report, or a published article about the project, they may have an emotional reaction if they interpret the results as meaning they received

poor quality health care. We believe that this risk is minimal, given that (1) the patients are not the likely audience of this work, (2) many patients cannot read English, and (3) many patients will already be aware that the quality of care may be attenuated given the humanitarian emergency setting. We feel that the benefit to service improvement deriving from this project is ultimately more beneficial to the patient, and other refugees in need of cardiovascular disease management and prevention.

Qualitative Strand

We believe there is minimal risk of participants being identified given the number of MSF staff and clinics operating in Jordan and because of the steps we are taking to remove identifying information. This risk is clearly explained in the Participant Information Sheet. We will choose and/or edit direct quotations such that they do not reveal identifying information. Our qualitative work is focused on seeking explanations about general practices and areas for improvement, rather than focusing on the habits or behaviour of specific individuals. The questions we are asking are not controversial and are about improving routine patient care. Therefore, we do not anticipate documenting information that may jeopardize a participants if, in the unlikely chance, that confidentiality is breached.

We have designed the question guide to mitigate any feelings of incompetency. It is possible that the interview might inspire, however, some questions from clinicians about how they should manage cardiovascular risk. Dylan Collins (the interviewer) will indicate that because he is not a clinician he is unable to provide advice on this topic. He will refer them to the established MSF guidance and, if they choose, to Dr. Kiran Jobanputra, who will be able to answer any such concerns about clinical care or provide them with further resources.

7.3 Benefits of Study Participation

Participants will benefit as their input will be directly used to improve the guidance, processes, cost modelling, and tools they use to provide refugees with health care. Those participants not directly involved in patient care, namely those working in administration and planning, will benefit from having local evidence that they can use for further funding or research opportunities.

Patients will potentially benefit from the improvement of health care services towards evidence-based, best practice standards.

7.4 Payments or Inducements

No participants will receive payment or inducements of any kind.

7.5 Legal Liability

This research will be appropriately covered through the University of Oxford's legal liability insurances.

8. FUNDING

Funding for travel expenses will be provided by MSF, the Nuffield Department of Primary Care Health Sciences and Christ Church, as per allowable research expenditure of DPhil. students. No additional funding from MSF will be used, outside of their normal operational remuneration for their staff involved in this project.

Oxford Tropical Research Ethics Committee

University of Oxford
Research Services, University Offices
Wellington Square, Oxford OX1 2JD
Tel. +44 (0)1865 (2)82106
E-mail: oxtrece@admin.ox.ac.uk



Mr Dylan Collins
Department of Primary Care Health Sciences
New Radcliffe House
Radcliffe Observatory Quarter
Woodstock Road
Oxford OX2 6GG

09 September 2015

Dear Mr Collins

Full Title of Study: Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

OXTREC Reference: 576-15

Thank you for your email of the 4th September, and for your minimal risk application form. Other documents reviewed were:

Documents:	Version:	Date:
Protocol	03092015	3/9/15
PIS	07082015	7/8/15
Interview Participant Consent Form	20082015	20/8/15
Interview guide	20082015	20/8/15
Confidentiality agreement	20082015	20/8/15
Letter from Sid Wong		13/8/15

The OxtREC executive team reviewed the above application on the 7th September and gave approval for this study.

Approval is given for the first five years and is subject to receiving the local ethical approval (if this approval has not yet been received).

Any subsequent changes to the application must be submitted to the Committee as an Amendment. This should include a letter to give the reasons for the proposed modifications and all revised documents with changes tracked.

Direct Line Tel: +44 (0)1865 (2)82106
Email: oxtrece@admin.ox.ac.uk
Web: www.admin.ox.ac.uk/rso/

2



Please ensure that you submit a completed Annual Report form on every anniversary of this approval and a final End of Study Report. The relevant forms can be found on the OXTREC website: <http://www.tropicalmedicine.ox.ac.uk/oxtrec>.

Yours sincerely

A handwritten signature in black ink that reads 'Mary Warrell'.

Dr Mary Warrell
OxTREC Chairman

Oxford Tropical Research Ethics Committee

University of Oxford
Research Services, University Offices
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To whom it may concern

09 September 2015

Dear Sir/Madam

Title: Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

OxTREC Ref: 576-15

The above study has been designed by Mr Dylan Collins and colleagues at the University of Oxford. It is funded by the University of Oxford. I confirm that the University will accept the role of Research Sponsor in so far as it takes overall organisational responsibility for the management of the study.

The University maintains Clinical Trial Professional and "no-fault" Insurance which, to the extent that a claim is made against the Sponsor, will apply to this study.

Sponsorship is confirmed subject to the condition that should any substantial amendments or reports be submitted to the Local Ethics Committee, these should also be copied to OxTREC.

Yours faithfully

A handwritten signature in black ink, appearing to read 'Rebecca Bryant'.

Dr Rebecca Bryant
Research Ethics Manager (OxTREC)



Dylan Collins
Nuffield Department of Primary Care Health Sciences
New Radcliffe House
Radcliffe Observatory Quarter
Woodstock Road
Oxford OX2 6GG

13 August 2015

Dear Dylan,

Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

I am writing to confirm that we would be happy to proceed with the above mentioned clinical audit, as a collaborative activity between MSF (Operational Centre Amsterdam), the Ministry of Health of Jordan, and yourself as Principal Investigator.

Clinical audit is considered as a routine quality improvement activity within MSF, and as such we do not normally submit audit proposals to our institutional ERB. I am therefore happy to give approval for this work to commence, and will take direct responsibility for ethics oversight.

Please note that we would still advise you to obtain ethics approval from your institutional ERB, in view of the intention to publish the results of the analysis. We are also seeking to obtain an authorisation letter from the Ministry of Health of Jordan to this effect.

Sincerely,

Dr Sid Wong
Medical Director

Médecins Sans Frontières - Artsen Zonder Grenzen
Operational Centre Amsterdam
Plantage Middenlaan 14
1018 DD Amsterdam

Tel: +31 (0) 20 520 8945
Mobile: +31 (0) 61 179 3031
E: sidney.wong@amsterdam.msf.org

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الرقم
التاريخ
الموافق ١٥/٢٠١٥

السادة منظمة أطباء بلا حدود- هولندا

تحية طيبة وبعد ،،،

إشارة إلى كتابكم تاريخ ٢١ / ٩ / ٢٠١٥ بخصوص إجراء دراسة في المراكز الصحية التابعة للمنظمة في محافظة اربد حول الأمراض غير السارية (تحسين معالجة عوامل اختطار الأمراض القلبية والوعائية)

أرجو العلم بأنه لا مانع لدينا من إجراء هذه الدراسة، دون أي التزام مالي من وزارة الصحة وتزويدنا بتقرير الدراسة بعد تنفيذها.

وتفضلوا بقبول فائق الاحترام ،،،

وزير الصحة


الدكتور علي حياصات



المملكة الأردنية الهاشمية

هاتف: ٢٢٠٠٢٢٠ ٦ ٩٦٢٢ فاكس: ٥٦٨٨٢٧٢ ٦ ٩٦٢٢ ص.ب. ٨٦ عمان ١١١١٨ الأردن. الموقع الإلكتروني: www.moh.gov.jo



الرقم
التاريخ
الموافق ١٧/١/٢٥

السادة منظمة أطباء بلا حدود/ هولندا

تحية طيبة وبعد،،،

إشارة إلى كتابكم رقم ٢٠١٦٠٧١٤ تاريخ ٢٠١٦/٧/١٤ بخصوص النتائج النهائية
لدراسة سريرية لتقييم الممارسات التي تعمل على وقاية إدارة العوامل المؤدية لأمراض القلب
(القلبية الوعائية).

يرجى العلم انه لا يوجد لدينا أية ملاحظات أو تعليقات على نتائج الدراسة المرفقة.

وتفضلوا بقبول فائق الاحترام،،،

\ وزير الصحة

الأستاذ الدكتور محمود الشيباب

معلمة امارة التخطيط
الدكتور بشير القصير

س.أ

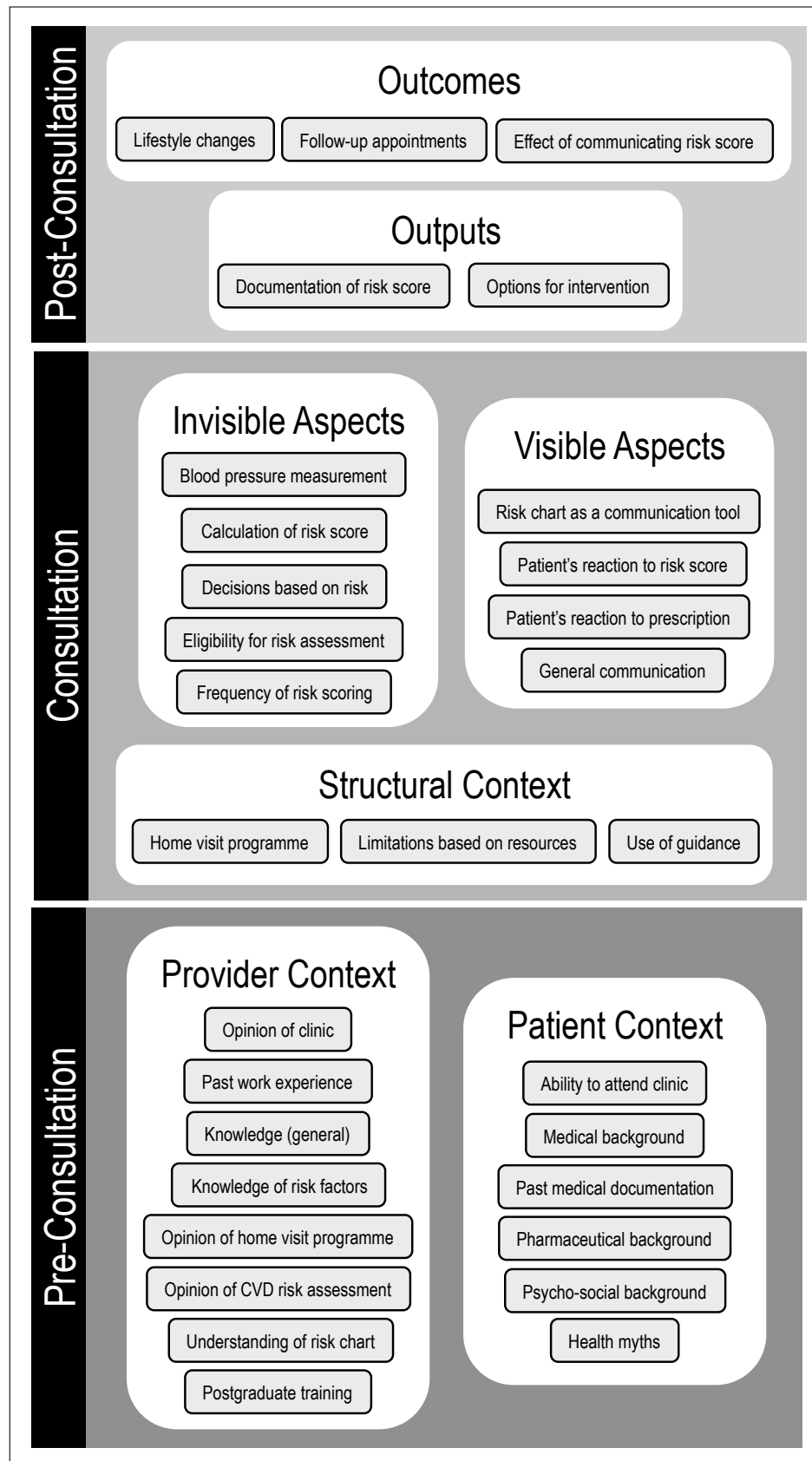
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Chapter 6 Appendix

Included in this appendix are the following documents in this order:

- Final Coding Framework (1 page)
- Interview Participant Information Sheet (2 pages)
- Interview Participant Consent Form (1 page)
- Interview Guide (1 page)
- Transcriber Confidentiality Agreement (1 page)
- Table of Coding Frequencies



Participant Information Sheet

OxTREC reference number: 576-15

Project Title

Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

What's the project about?

We are trying to improve MSF's clinical guidance on cardiovascular disease prevention and management. To do this, we want to further understand the current level of care provided by MSF to urban Syrian refugees in Irbid who have, or at risk of having, cardiovascular disease. We want to understand how care is currently provided so that we can improve our guidance to be simpler and easier to use, so that we have a better chance of achieving best-practice standards. We are conducting this project in two MSF clinics.

Why have I been invited to take part?

You have been invited to take part because we think that you may be able to help us improve cardiovascular disease health care guidance for MSF. We are interested to learn more about your opinions and experiences with this topic.

What's involved for me?

You are invited to take part in an informal, confidential, interview that is expected to take between 30 and 60 minutes. In this interview we will discuss your experience with, and opinions about, cardiovascular disease care for refugees. We will audio record the interviews so that we do not miss any important information, but these recordings will be kept private and confidential. Your name will be kept anonymous and will not be shared with anyone but the interviewer.

What will happen to my interview?

The recording of the interview will be stored securely on a University of Oxford computer and server and will be protected. We will type-out the interviews so that we can analyse them. The information from all of the interviews we conduct will be analysed together so that we can understand how cardiovascular disease care is currently provided and how it might be improved. You will **never** be identified by name, but you will be identified by role (e.g. Doctor #1, Nurse #3, Administrator #2). We may use direct quotations from your interview, but **we will not include any information that would identify you or someone else**. The following is an example of what a quotation might look like in any publications resulting from this study:

"Patients often come to us already knowing what prescription they want—prescriptions they had when they were in Syria. This makes it difficult for us, in a limited amount of time, to manage patient demands and use clinical guidance." - Nurse #3

We will only use the information you provide for this project and it will not be used for additional research. The analysed interviews will be published in public reports and scientific documents.

Are there any risks in taking part?

There are minimal risks to participating and you should be comfortable with us using the information you tell us in the interview as described above.

The interview will take 30 to 60 minutes, which might cause you an inconvenience. To reduce this inconvenience, we will schedule the interview at a time that works best for you, in a mutually agreeable place such as your office. Should you need to leave during the interview, you can stop the interview at any time.

It is very unlikely that your confidentiality will be breached, and if it does, we do not believe the result would be very harmful. Your participation will remain confidential; we will not publish your name in any report. The interviewer will not disclose to anyone whether you did or did not participate. People who participate will



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HEALTH SCIENCES

only be identified by their generic role (e.g. Nurse, Doctor, Administrator) and given the number of MSF staff, and the rotation of MSF staff, in Jordan, we do not believe that you will be identifiable. If we take direct quotes from your interview, we will choose ones that protect your identity. If, however, your confidentiality was breached, we do not believe the results would be very harmful because the questions we will ask you are not controversial and are about improving routine patient care. If you are uncomfortable with what you've said in the interview, you can ask us to not use the information.

The questions we ask might inspire your own questions about how to assess and manage cardiovascular risk. If this did occur, we can provide you with resources to answer your questions. The interviewer is not a clinician, and will not be able to answer these questions, but they can refer you to an MSF staff member who will be able to.

What are the benefits of taking part?

By taking part, you're helping us improve our clinical guidance for MSF's mission in Irbid. Your participation will directly help us create better quality, more user-friendly, clinical guidance—which might benefit you if you end up using it. This project will also create an evidence base of information for cardiovascular risk management in refugee settings—in the form of a report—which you might be able to use to rationalise new programmes or apply for programme funding. We also believe that this guidance, developed with your contribution, will help other health care professionals, and their patients, provide high quality care for the prevention and management of cardiovascular disease.

Do I have to take part?

You do not have to take part. Please be aware that:

- You can ask questions about the study before deciding whether to participate;
- It is your choice whether to take part or not and this choice will not affect your employment or relationship with MSF;
- If you agree to take part, you can withdraw from the project without penalty at any time;
- If you withdraw, we will ask if we can use the information already collected. If you do not agree, we will delete all information we have collected from you.

Has the project been reviewed by an ethics committee?

This project adheres to the ethical standards of the MSF Research Ethics Framework and oversight is held by Dr. Sid Wong, MSF Medical Director. This project has also been reviewed and approved by the Oxford Tropical Research Ethics Committee (OxTREC).

What if I have any questions or want to raise a concern?

You can ask questions, or raise concerns, at any time, by contacting Dylan Collins or Kiran Jobanputra.

Dylan Collins,	Kiran Jobanputra
Principal Investigator, University of Oxford dylan.collins@phc.ox.ac.uk +44 (0)747 968 2338	Deputy Head, MSF Manson Unit Kiran.Jobanputra@london.msf.org +44 (0)207 067 4249



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Interview Participant Consent Form

Project Title Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

OxTREC Reference Number: 576-15

Instructions

If you wish to take part in this study, please read the following points and sign your name at the bottom.

- I confirm that I have read the information sheet for the above mentioned project and have had time to consider the information and ask questions, and have had these questions answered satisfactorily
- I understand that my interview will be audio recorded, that my name **will not** be used in publications but my generic occupation will be (e.g. 'Doctor', 'Nurse', 'Administrator), and that direct quotations might be used in publications (with identifying information removed)
- I agree to be interviewed for the above mentioned project

Participant's Name

Signature

Date

Person Taking Consent

Signature

Date



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Interview Participant Consent Form Version 20082015

Interviewer Guide

Project Title Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

OxTREC Reference Number: 576-15

This script will be modified slightly as new themes emerge during interviewing and with the results of the quantitative strand analysis. It is a *guide* for semi-structured interviews, which may be deviated from depending on the relevant tangents of the interview.

Interviewer Preamble

My name is Dylan Collins; I'm a PhD student at the University of Oxford and am leading this project. I'd like to remind you that you can stop the interview at any point and I can delete things you've said if you do not want me to use them. Do you have any questions before we start?

Core Questions (for all participants)

1. Can you please tell me about your role with the clinic?
2. We've reviewed some of the patient files and medications and I'd like to share some of the results with you: they're aggregated together and we won't be discussing individual cases or patients. What do you think about these results?
 - a. Probes, based on results
3. Do you think we could improve CVD care for our patients?
 - a. How?
 - b. Why?
4. What might some challenges be to making improvements?
5. What do you think would help an organisation or someone doing your job make these changes?
6. We think that the WHO guidance might be useful in our clinic. I'd like to show it to you now and know your thoughts.
 - a. Probe for thoughts on global cardiovascular risk assessment
 - b. Probe for thoughts on outputs of protocol
 - c. Probe for thoughts on the ease of use/complexity of protocol
7. Is there anything else that you would like to share with me or think I should have asked?
8. Is there anyone you think I should speak to who might be able to help with the project? I will not tell them that you referred me so they will not know if you participated or not.

Additional Questions for Clinicians

1. What do you understand by the term 'cardiovascular risk score'?
2. We are interested in your experience in using CVD risk scores. Have you used the risk scores in practice?
 - a. (If yes) When was the last time you used a CVD risk score with a patient?
 - b. (If yes) Can you describe the experience to me?
3. What role does CVD risk play in the decision making process?
4. In your opinion, what are the advantages of using CVD risk scores?
5. What are the disadvantages of using CVD risk scores?
6. What lead, or might lead, you to using CVD risk scores?
7. What does, or might, prevent you from using CVD risk scores?
 - a. What could help you overcome these?
8. Have you heard of recommendations or guidelines about CVD risk scores use in clinical practice?
 - a. (If yes) What do you think about these?
9. How would you communicate risk to a patient? (Ask participant for a real example or use given scenario if participant is unable to give an example)
10. Which group of patients would you use the CVD risk score on? Why?
11. Anything else that you would like to tell me or think that I should have asked?



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Confidentiality Agreement

Project Title: Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit

OxTREC Reference Number: 576-15

I, _____, of _____ (name of organisation) agree that our organisation will maintain full confidentiality in regards to any and all audiotapes and documentations received from Dylan Collins related to his work on the project entitled *Improving the clinical management of cardiovascular risk in Médecins Sans Frontières mission in Irbid, Jordan: a mixed methods clinical audit*

Furthermore, we agree:

1. To hold in strictest confidence the identification of any individual that may be inadvertently revealed during the transcription of audio-taped interviews, or in any associated documents.
2. To not make copies of any audiotapes or computerized titles of the transcribed interview texts, unless specifically requested to do so by Dylan Collins.
3. To store all study-related audiotapes and materials in a safe, secure location as long as they are in my possession.
4. To return all audiotapes and study-related materials to Dylan Collins in a complete and timely manner.
5. To delete all electronic files containing study-related documents from my computer hard drive and any back-up devices.

I am aware that _____ (name of organisation) can be held legally responsible for any breach of this confidentiality agreement, and for any harm incurred by individuals if I disclose identifiable information contained in the audiotapes and/or files to which I will have access.

Representative's Name

Representative's Signature

Date



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Confidentiality Agreement Version 30112015

Table E.1: The number of sources (participants) and number of references for each code of the final analytic framework

Domain	Category	Code	Number of Sources	Number of References
Pre-Consultation	Provider Context	Knowledge (general)	3	8
		Knowledge of risk factors	4	15
		Opinion of CVD risk assessment	5	16
		Opinion of home visit programme	2	4
		Opinion of clinic	1	2
		Past work experience	5	9
		Postgraduate education	3	3
		Understanding of risk chart	6	21
	Patient Context	Health myths	8	14
		Ability to attend clinic	3	8
		Medical background	4	10
		Past medical documentation	1	3
		Pharmaceutical background	5	18
		Psycho-social background	11	30
Consultation	Structural Context	Home visit programme	4	8
		Limitations based on resources	4	10
		Use of guidance	5	17
	Invisible Aspects	Blood pressure measurement	5	17
		Calculation of risk score	5	31
		Decisions based on risk	5	26
		Eligibility for risk assessment	3	8
		Frequency of risk scoring	4	8
	Visible Aspects	General communication	4	9
		Patient's reaction to risk score	4	9
		Patient's reaction to prescription	5	13
		Risk chart as a communication tool	9	27
Post-Consultation	Outputs	Documentation of risk score	3	3
		Options for intervention	7	12
	Outcomes	Effect of communicating risk score	4	9
		Follow-up appointments	3	5
		Lifestyle changes	6	17
Miscellaneous		Recommendation	7	12
		Miscellaneous	7	13

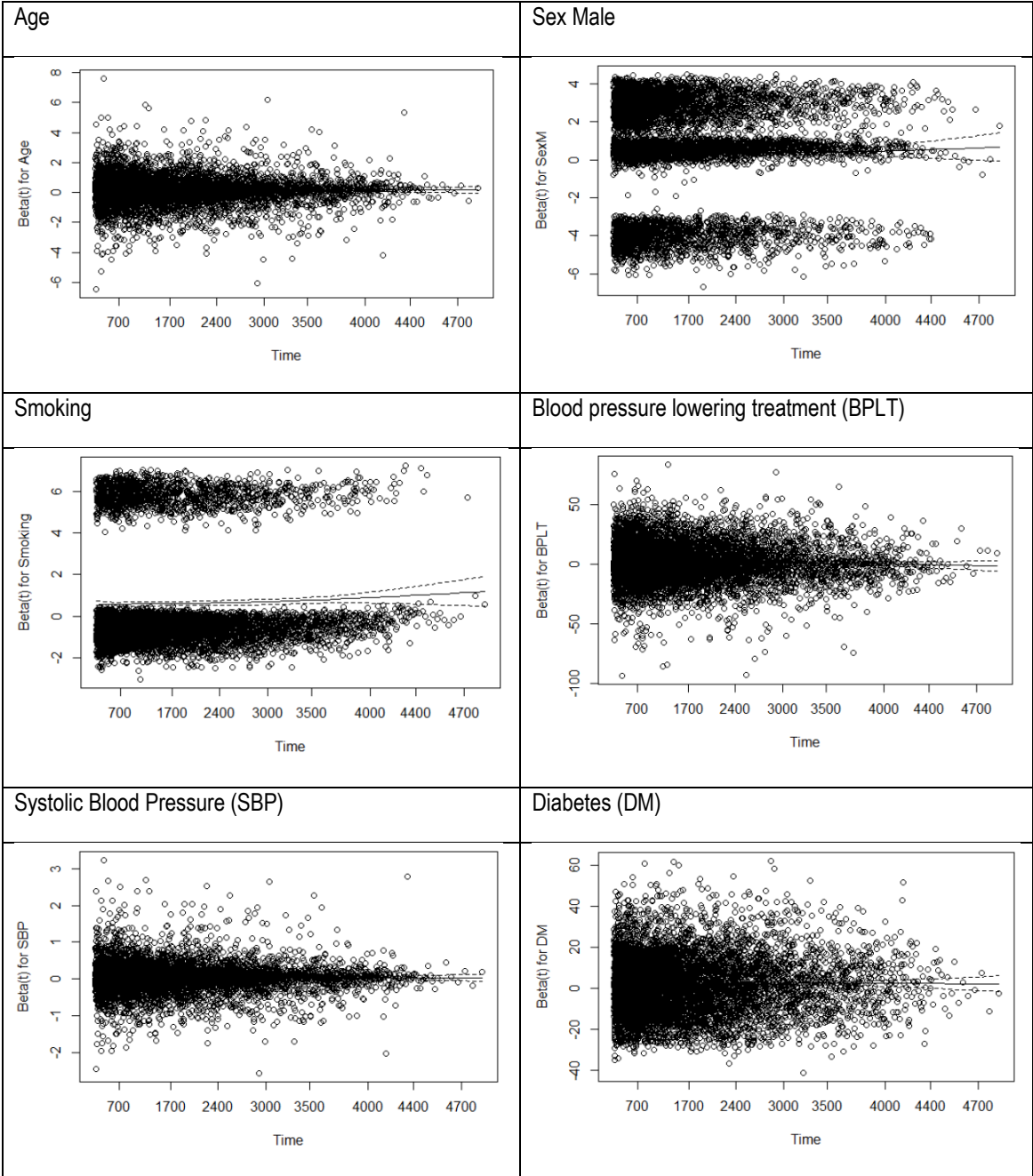
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Chapter 7 Appendix

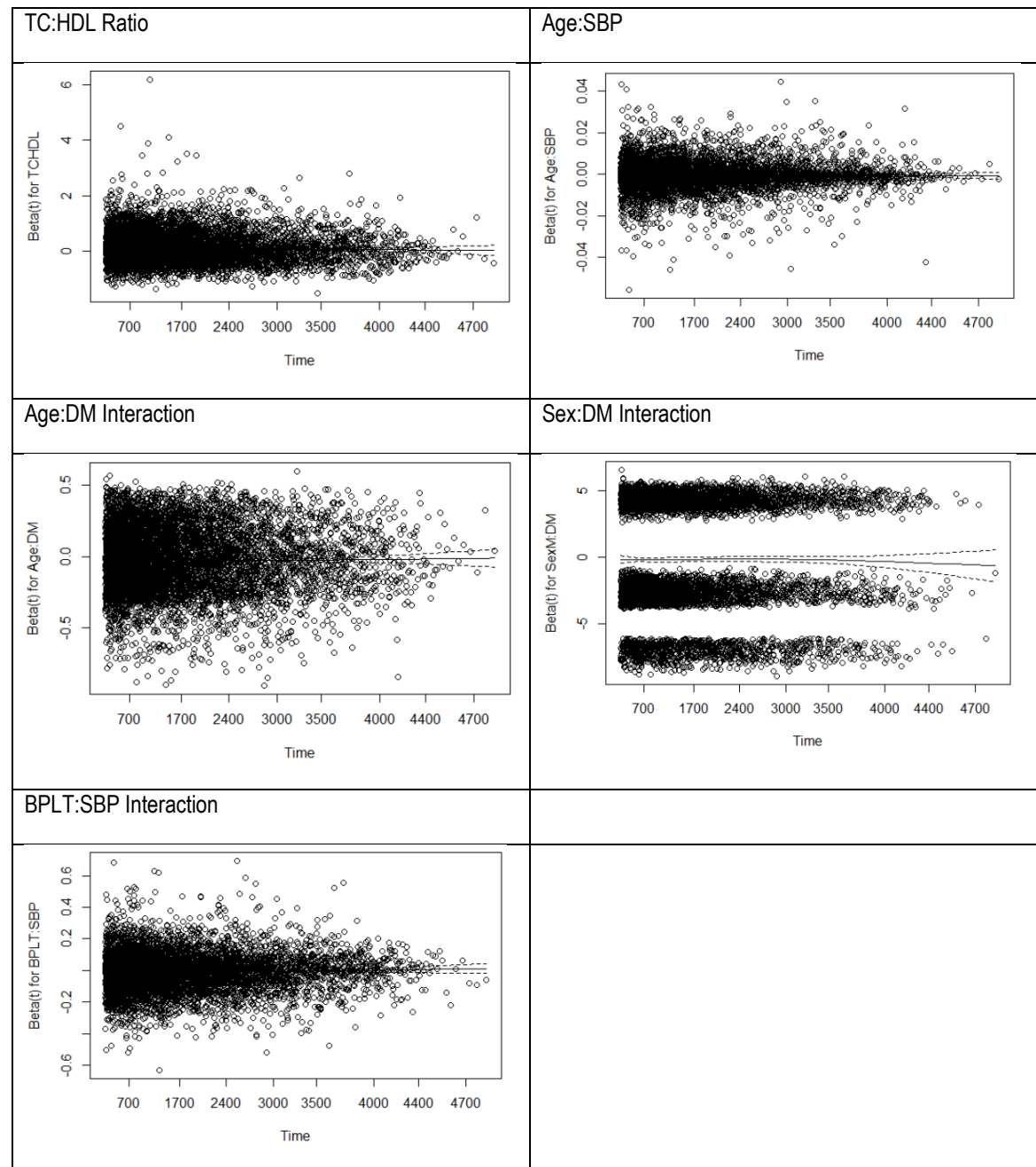
Included in this appendix are the following documents in this order:

- Scaled Schoenfeld Residual Plots for LaRA (2 pages)
- Scaled Schoenfeld Residual Plots for CoRA (2 pages)
- Martingale Residual Plots (1 page)
- International Classification of Disease 10 Australian Modification (ICD-10-AM) Codes Used to Define a CVD Event
- Example Calculation of 5-year Risk using LaRA and CoRA

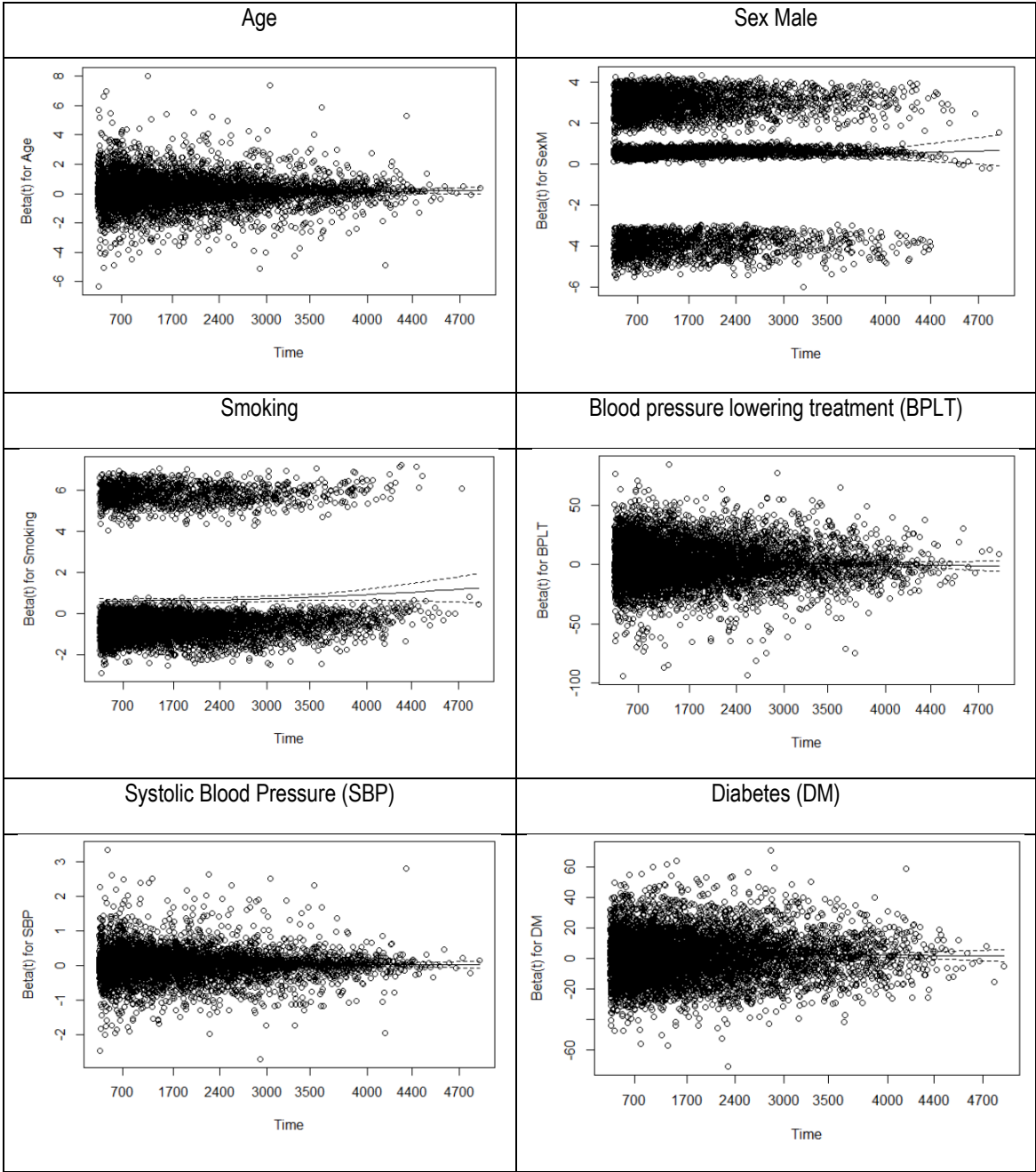
Scaled Schoenfeld Residuals - LaRA

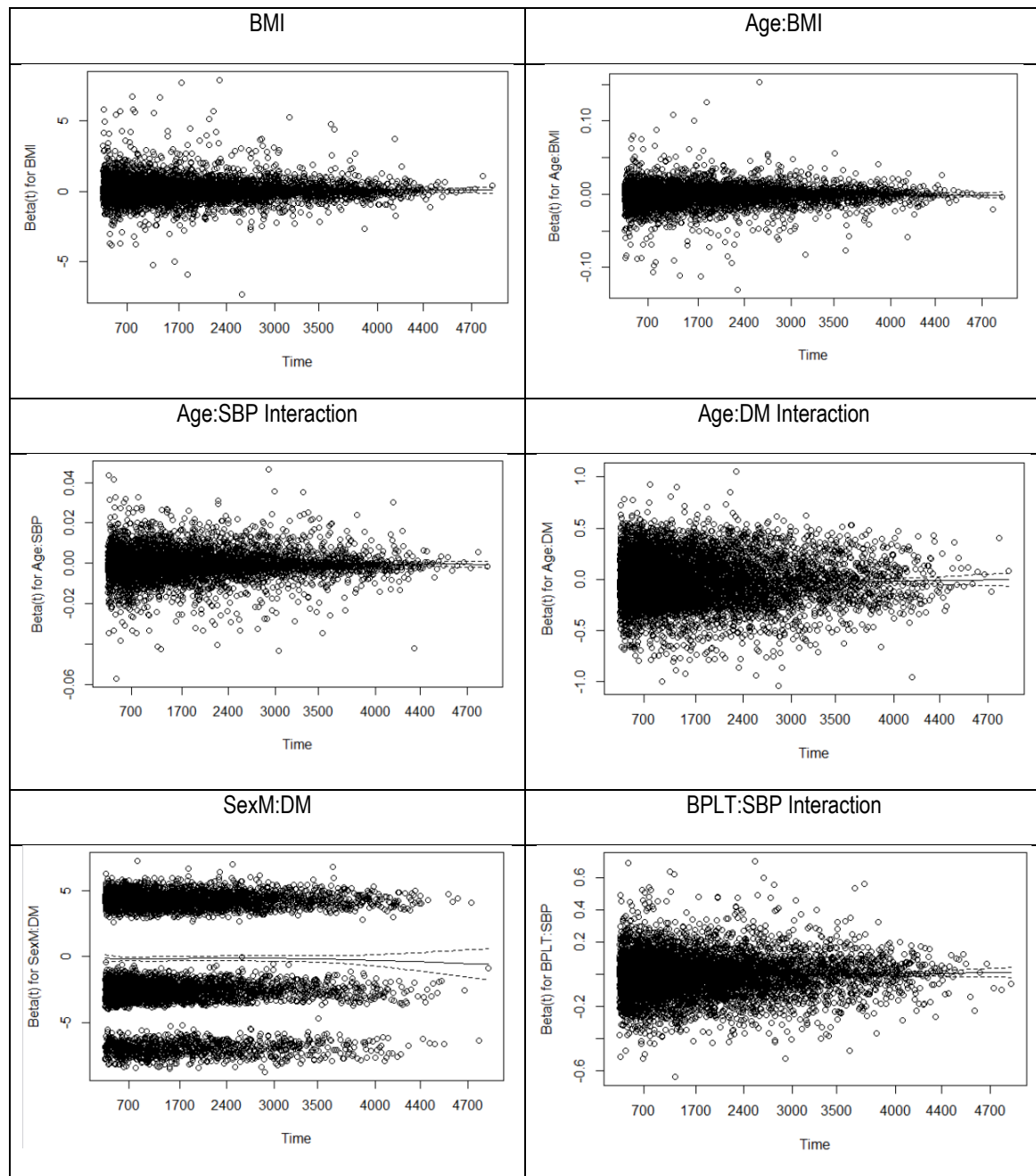


Scaled Schoenfeld Residuals - LaRA



Scaled Schoenfeld Residuals - CoRA



Scaled Schoenfeld Residuals - CoRA

Martingale Residual Plots

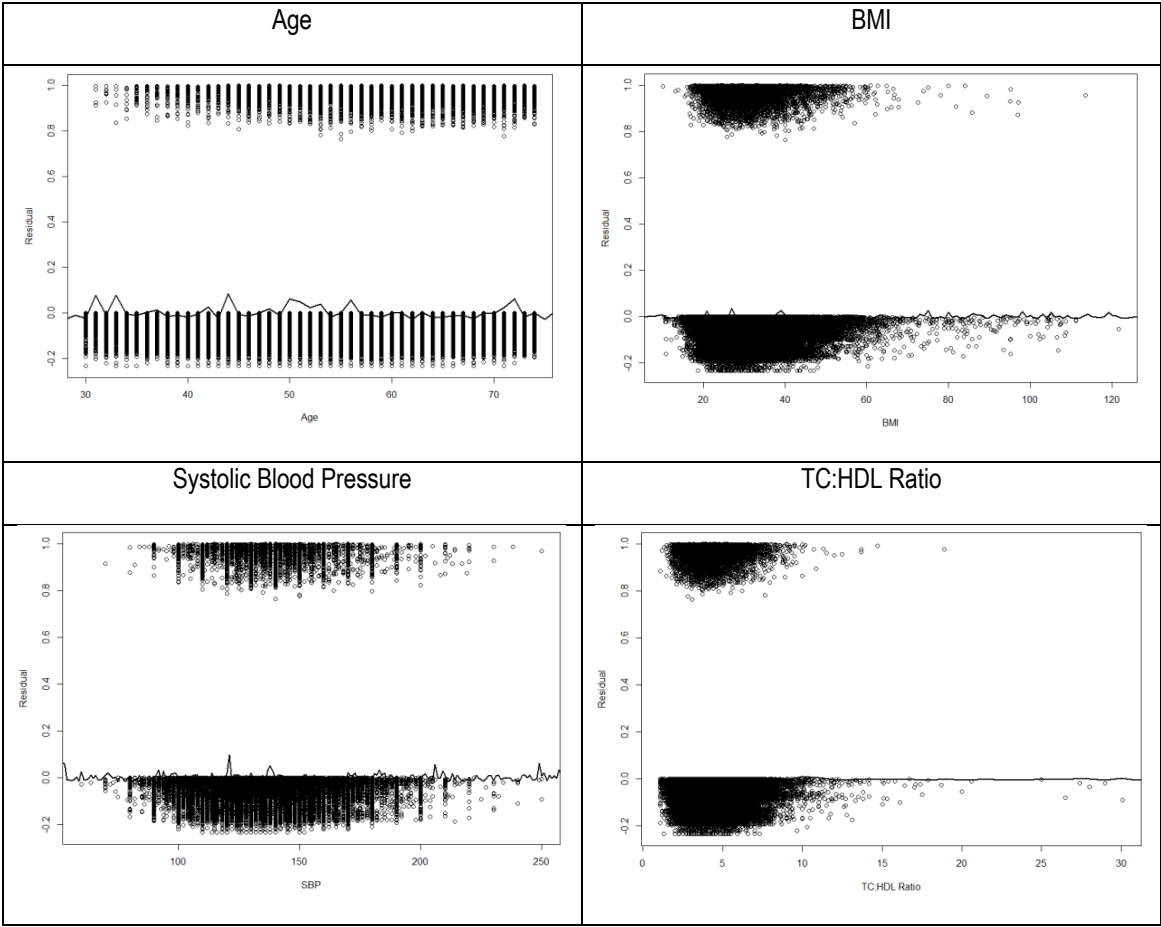


Table F.1: International Classification of Disease 10 Australian Modification (ICD-10-AM) codes used to define a cardiovascular event

Outcome	ICD-10-AM codes
Myocardial infarction	I210, I211 - I214, I219 - I221, I228, I229
Unstable angina	I200
Other coronary heart disease	I236, I248, I249, I255, I469, I460, I235, I209, I201, I234, I256, I253, I252, I232, I230, I254, I233, I208, I240, I238, I231
Ischaemic stroke	I630 - I636, I638, I639, I64
Haemorrhagic stroke	I600 - I616, I618, I619
Transient ischaemic attack	G450 - G453, G458 - G468
Peripheral vascular disease	E1050 - E1052, E1150 - E1152, E1451, E1452, I7021 - I7024, I7100 - I7103, I711, I713, I715, I718, I739 - I745, I748, I749
Congestive heart failure	I110, I130, I132, I50, I500, I501, I509
Other ischaemic CVD-related deaths	3270000 - 3270011, 3270300, 3270800 - 3270803, 3271200, 3271201, 3271500 - 3271503, 3271800, 3271801, 3273000, 3273001, 3273300, 3273301, 3273600, 3273900, 3274200, 3274500, 3274800, 3275100, 3275101 - 3275103, 3275400 - 3275402, 3275700, 3275701, 3276300 - 3276314, 3276316, 3276316 - 3276319, 3305000, 3305500, 3307500, 3308000, 3310000, 3311200, 3311500, 3311800, 3312100, 3312400, 3312700, 3313000, 3315100, 3315400, 3315700, 3316000, 3316300, 3317800, 3318100, 3350000, 3350600, 3350601, 3350900, 3351200, 3351500, 3351501, 3351800, 3352100, 3352400, 3352700, 3353000, 3353001, 3353300, 3353600, 3353900, 3354200, 3354800, 3354801, 3354802, 3354803, 3355100, 3355400, 3530306, 3530307, 3530400, 3530401, 3530500, 3530501, 3530906, 3530907, 3530908, 3530909, 3531000, 3531001, 3531002, 3531003, 3531004, 3531005, 3531200, 3531201, 3531500, 3531501, 3845619, 3849700, 3849701, 3849702, 3849703, 3849704, 3849705, 3849706, 3849707, 3850000, 3850001, 3850002, 3850003, 3850004, 3850300, 3850301, 3850302, 3850303, 3850304, 3850500, 3850700, 3850800, 3850900, 3863700, 9020100, 9020101, 9020102, 9020103, 9022900, 9023000, E1059, E1159, E1459, I250, I2510 - I2513, I252, I258, I259, I461, I650 - I653, I658 - I664, I668 - I670, I672, I690, I691, I693, I694, I698, I700, I701, I7020, I708, I709, I714, Z951, Z955, Z958, Z959

Table F.2: Example calculation of 5-year CVD risk using LaRA and CoRA for a 66 year old diabetic woman, who does not smoke, is on blood-pressure lowering treatment, has systolic blood pressure of 200 mmHg, a TC:HDL ratio of 5.2, and BMI of 30.9 kg/m²

Parameter	Model Coefficient		Example Data	Product of Coefficient and Variable	
	LaRA	CoRA		LaRA	CoRA
Age (per year)	0.1457	0.1589	66	9.61620	10.48740
Sex Male	0.5074	0.5765	No (0)	0	0
Smoker	0.6206	0.6499	No (0)	0	0
BPLT	1.442	1.316	Yes (1)	1.44200	1.31600
SBP (per mmHg)	0.04845	0.04456	200	9.69000	8.91200
Diabetes	1.835	1.594	Yes (1)	1.83500	1.59400
TC:HDL Ratio (per 1 unit)	0.1245	-	5.2	0.64740	0
BMI (per 1 kg/m ²)	-	0.06249	30.9	0	1.93094
Age:SBP	-0.0006	-0.00055	N/A	-7.94112	-7.22040
Age:DM	-0.02015	-0.01722	N/A	-1.32990	-1.13652
Male:DM	-0.1776	-0.1519	N/A	0	0
BPLT:SBP	-0.00678	-0.0063	N/A	-1.35540	-1.25960
Age:BMI	N/A	-0.00068	N/A	0	-1.38985
Sum of Products of Coefficient and Variables				12.60418	13.23397
Baseline Survival Function at 5 years		Calculation of 5-year Risk			
LaRA	0.9999995	1-0.9999995exp(12.60418)= 13.83450896			
CoRA	0.9999998	1-0.9999998exp(13.23397)= 10.57834391			